WHO treatment guidelines for drug-resistant tuberculosis

2016 update

Annexes 4, 5 and 6

THE END TB STRATEGY

World Health Organization

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2016 update

Annexes 4, 5 and 6

World Health Organization

These guidelines were developed in compliance with the process for evidence gathering, assessment and formulation of recommendations, as outlined in the WHO Handbook for Guideline Development (version March 2014; available at http://www.who.int/kms/handbook_2nd_ed.pdf).

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Contents: Web Annex 4: GRADE tables – Web Annex 5: Evidence to decision tables – Web Annex 6: Summaries of unpublished data used for the recommendations

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Contents

ANNEX 4

GRADE tables

The GRADE tables are ordered as follows:[1]

1. Shorter regimens for MDR-TB (PICO 3)
2. MDR-TB regimen composition – systematic reviews of individual medicines in adults (PICO 1)
3. MDR-TB regimen composition – paediatric individual patient data meta-analysis (PICO 1)
4. The role of surgery (PICO 4)

[1] Evidence from studies identified during the reviews performed to answer PICO question 2 (treatment of isoniazid-resistant TB and *Mycobacterium bovis*) as well as part of PICO question 4 (delay in starting MDR-TB treatment) could not be summarized as GRADE tables and thus are not included here. See also Annex 6 for a summary of findings from studies that were not published at the time of the release of these guidelines.

1. 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 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 "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 longer regimens from aggregate meta-analysis using data from 31 studies of longer 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	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 longer regimen studies relapse was ascertained in 14 cohorts overall (reference 7).

[b] Six studies of shorter regimens, 31 studies of longer 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 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 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 "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 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	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	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 longer 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 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 longer 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 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 "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 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	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	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 longer 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 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 longer 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 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 "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 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	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	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 longer 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 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 longer 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 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 "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 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	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

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	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)[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]	19/28 (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 longer 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 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 longer 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%).

2. MDR-TB regimen composition – systematic reviews of individual medicines in adults (PICO 1)

Author(s): Bastos M, Lan Z, Menzies R (11 November 2015)

Question: A later generation fluoroquinolone compared to no later generation fluoroquinolone for adults with rifampicin-resistant TB or MDR-TB[a]

Setting: Treatment of adults with rifampicin-resistant TB/MDR-TB/XDR-TB using conventional regimens lasting about 24 months, in low and high resource settings, within hospital or ambulatory models of care

Bibliography: 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	A LATER GENERATION FLUOROQUINOLONE	NO LATER GENERATION FLUOROQUINOLONE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in patients on later generation fluoroquinolone versus no fluoroquinolone, as part of a MDR-TB regimen (assessed with: individual patient data meta-analysis (Ahuja SD, et al. PLOS Med. 2012)												
32	observational studies	serious[b]	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	691/833 (83.0%)	301/678 (44.4%)	**OR 2.5** (1.0 to 5.9)[c]	**390 more per 1,000** (from 30 fewer to 640 more)	⨁⨁◯◯ LOW	CRITICAL
Treatment success versus failure/relapse/death in patients on later generation fluoroquinolone versus ofloxacin, as part of a MDR-TB regimen (assessed with: individual patient data meta-analysis (Ahuja SD, et al. PLOS Med. 2012)												
32	observational studies	serious[b]	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	691/833 (83.0%)	3386/4624 (73.2%)	**OR 1.9** (1.0 to 3.6)[c]	**100 more per 1,000** (from 15 fewer to 240 more)	⨁⨁◯◯ LOW	CRITICAL
Treatment success versus failure/relapse in patients on later generation fluoroquinolone versus no fluoroquinolone or ciprofloxacin or ofloxacin, as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)[d]												
48	observational studies	serious[e]	not serious	not serious	not serious	none	4270/4978 (85.8%)[f]	3397/4046 (84.0%)[g]		**10 fewer per 1,000** (from 78 fewer to 57 more)	⨁◯◯◯ 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	A LATER GENERATION FLUOROQUI-NOLONE	NO LATER GENERATION FLUOROQUI-NOLONE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in patients on later generation fluoroquinolone versus no fluoroquinolone or ciprofloxacin or ofloxacin, as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)												
47	observational studies	serious[e]	not serious	not serious	not serious	none	4270/5474 (78.0%)[h]	3397/4958 (68.5%)[i]		**23 more per 1,000** (from 60 fewer to 108 more)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (Grade 3 or 4, or drugs stopped due to adverse events) in patients on later-generation fluoroquinolone												
13	observational studies	serious	not serious	not serious	not serious	none[j]	10/827 (1.2%)[k]		not estimable[j]		⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (Grade 3 or 4, or drugs stopped due to adverse events) in patients on ofloxacin or ciprofloxacin (assessed with: aggregated data meta-analysis 2015)												
9	observational studies	serious	not serious	not serious	not serious	none[j]	401/1408 (28.5%)[l]		not estimable[j]		⨁◯◯◯ VERY LOW	CRITICAL

CLs: confidence limits; FE: fixed effects; OR: odds ratio

[a] Use of later generation fluoroquinolones (moxifloxacin, gatifloxacin or levofloxacin) is compared with use of ofloxacin or no fluoroquinolone alongside other drugs in the MDR-TB regimen; one outcome related to severe adverse events of ofloxacin also included in this table.

[b] In the individual patient data analysis (Ahuja SD, et al.), most patients received individualized treatment, with substantial risk of confounding by indication (as well as selection bias).

[c] Odds ratio adjusted for age, HIV status, sputum smear positivity, cavitation on chest radiograph, and prior treatment with first-line and second-line TB drugs.

[d] Adjustment for individual patient characteristics not possible; the adjusted values of the pooled proportions (with their 95% CL) shown in footnotes below.

[e] In 20 studies the patients were given standardized regimens, but in the remaining studies therapy was individualized, leading to risk of confounding by indication.

[f] Adjusted proportion: 91% (95% CL: 85%–95%).

[g] Adjusted proportion: 92% (95% CL: 87%–96%).

[h] Adjusted proportion: 80% (95% CL: 74%–85%).

[i] Adjusted proportion: 78% (95% CL: 74%–85%).

[j] Serious adverse events (SAEs) reported in patients were attributed to a medicine by the authors who were unblinded and used non-standardized methods to define, ascertain and report SAEs. No valid comparisons are possible with patients not on the target medicine, because SAEs in these patients could be due to other drugs received.

[k] Pooled proportion: FE 95% CL: 0.6%–2.4%.

[l] Pooled proportion: FE 95% CL: 1.9%–4.1%.

Author(s): Bastos M, Lan Z, Menzies R (11 November 2015)

Question: Gatifloxacin compared to no gatifloxacin for the treatment of adults with rifampicin-resistant TB or MDR-TB

Setting: Treatment of adults with rifampicin-resistant TB/MDR-TB/XDR-TB using conventional regimens lasting about 24 months and shorter MDR-TB regimens, in low and high resource settings, within hospital or ambulatory models of care

Bibliography: (1) Van Deun A, Maug AKJ, Salim MAH, Das PK, Sarker MR, Daru P, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 2010;182(5):684–92. (2) Butov DA, Efremenko YV, Prihoda ND, Yurchenko LI, Sokolenko NI, Arjanova OV, et al. Adjunct immune therapy of first-diagnosed TB, relapsed TB, treatment-failed TB, multidrug-resistant TB and TB/HIV. Immunotherapy 2012;4(7):687–695. (3) Xu HB, Jiang RH, Xiao HP. Clofazimine in the treatment of multidrug-resistant tuberculosis. Clin Microbiol Infect. 2012;18(11):1104–1110. (4) Xu HB, Jiang RH, Li L, Xiao HP. Linezolid in the treatment of MDR-TB: a retrospective clinical study. Int J Tuberc Lung Dis. 2012;16(3):358–363. (5) Carroll MW, Lee M, Cai Y, Hallahan CW, Shaw PA, Min JH, et al. Frequency of adverse reactions to first- and second-line anti-tuberculosis chemotherapy in a Korean cohort. Int J Tuberc Lung Dis. 2012;16(7):961–966. (6) Jawahar MS, Banurekha VV, Paramasivan CN, Rahman F, Ramachandran R, Venkatesan P, et al. Randomized clinical trial of thrice-weekly 4-month moxifloxacin or gatifloxacin containing regimens in the treatment of new sputum positive pulmonary tuberculosis patients. PLoS One 2013;8(7):e67030. (7) Jo KW, Lee SD, Kim WS, Kim DS, Shim TS. Treatment outcomes and moxifloxacin susceptibility in ofloxacin-resistant multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2014:18(1):39–43. (8) Rustomjee R, Lienhardt C, Kanyok T, Davies GR, Levin J, Mthiyane T, et al. A Phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. Int J Tuberc Lung Dis. 2008;12(2):128–138.

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	GATIFLOXACIN	NO GATIFLOXACIN	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death (assessed with: Van Deun 2010; Butov 2011; Xu 2012a, 2012b)[a]												
4	observational studies	very serious[b]	serious	not serious	serious	strong association	189/225 (84.0%)	174/268 (64.9%)		**191 more per 1,000** (116 more to 265 more)	⨁◯◯◯ VERY LOW	CRITICAL
Death versus all other outcomes (assessed with: Van Deun 2010, Butov 2011, Xu 2012a, 2012b)[a]												
4	observational studies	very serious[b]	serious	not serious	serious	none	6/225 (2.7%)	23/268 (8.6%)		**59 fewer per 1,000** (20 fewer to 99 fewer)	⨁◯◯◯ 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	GATIFLOXACIN	NO GATIFLOXACIN	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Serious adverse events (Grade 3 or 4, or drugs stopped due to adverse events) in patients on gatifloxacin versus no gatifloxacin (assessed with: comparative observational studies: Caroll 2012; Jawahar 2013; Jo 2014; Rustomjee 2008; Van Deun 2010)[a]												
5	observational studies	very serious	serious	not serious	serious	none[c]	15/422 (3.6%)[d]	137/1711 (8.0%)[e]	not estimable[c]		⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; FE: fixed effects

[a] In the no gatifloxacin group the other fluoroquinolone used was either ofloxacin, levofloxacin or moxifloxacin.

[b] Small observational studies using individualized regimens with substantial potential for bias; in the Van Deun, et al. study gatifloxacin was used as part of shorter MDR-TB regimens reserved for patients selected upon specific criteria.

[c] Serious adverse events (SAEs) reported in patients were attributed to a medicine by the authors who were unblinded and used non-standardized methods to define, ascertain and report SAEs. No valid comparisons are possible with patients not on the target medicine, because SAEs in these patients could be due to other drugs received.

[d] Pooled proportion: FE 95% CL: 2.0%–5.8%.

[e] Pooled proportion: FE 95% CL: 6.8%–9.4%.

Author(s): Bastos M, Lan Z, Menzies R (11 November 2015)

Question: A second-line injectable compared to no second line injectable for adults with rifampicin-resistant TB or MDR-TB[a]

Setting: Treatment of adults with rifampicin-resistant TB/MDR-TB/XDR-TB using conventional regimens lasting about 24 months and shorter MDR-TB regimens, in low and high resource settings, within hospital or ambulatory models of care

Bibliography: (1) 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):e1001300. (2) Bastos M, Lan Z, Menzies R. An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis, 2016 (under review, 28 May 2016).

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	A SECOND-LINE INJECTABLE	NO SECOND LINE INJECTABLE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in patients on kanamycin or amikacin, as part of a MDR-TB regimen (assessed with: individual patient data meta-analysis (Ahuja SD, et al. PLOS Med. 2012)												
32	observational studies	serious[b]	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	2572/3467 (74.2%)	557/981 (56.8%)	**aOR 1.6** (1.2 to 2.0)[c]	**170 more per 1,000** (from 55 more to 280 more)	⨁⨁◯◯ LOW	CRITICAL
Treatment success versus failure/relapse/death in patients on capreomycin, as part of a MDR-TB regimen (assessed with: individual patient data meta-analysis (Ahuja SD, et al. PLOS Med. 2012)												
32	observational studies	serious[b]	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	733/1018 (72.0%)	557/981 (56.8%)	**aOR 1.3** (0.5 to 3.7)[c]	**150 more per 1,000** (from 75 fewer to 310 more)	⨁⨁◯◯ LOW	CRITICAL
Treatment success versus failure/relapse in patients on kanamycin or amikacin, as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)[d]												
43	observational studies	serious[e]	not serious	not serious	not serious	none[f]	3336/3935 (84.8%)[g,h]	3378/3942 (85.7%)[g,i]	not estimable	**36 more per 1,000** (from 38 fewer to 110 more)	⨁◯◯◯ 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	A SECOND-LINE INJECTABLE	NO SECOND LINE INJECTABLE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in patients on kanamycin or amikacin, as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)												
43	observational studies	serious[e]	not serious	not serious	not serious	none[f]	3336/4741 (70.4%)[g,j]	3378/4282 (78.9%)[g,k]	not estimable	**21 more per 1,000** (from 90 fewer to 131 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/relapse in patients on capreomycin versus no other second-line injectable drug, as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)												
43	observational studies	serious[e]	not serious	not serious	not serious	none[f]	3960/4658 (85.0%)[l]	2754/3219 (85.6%)[m]	not estimable	**5 fewer per 1,000** (from 73 fewer to 62 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/relapse/death in patients on capreomycin versus no other second-line injectable drug, as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)												
43	observational studies	serious[e]	not serious	not serious	not serious	none[f]	3960/5141 (77.0%)[n]	2754/3882 (70.9%)[o]	not estimable	**69 more per 1,000** (from 31 fewer to 168 more)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (Grade 3 or 4, or drugs stopped due to adverse events) in patients on amikacin, capremycin or kanamycin (assessed with: aggregated data meta-analysis 2015)												
19	observational studies	serious[f]	not serious	not serious	not serious	none[p]	184/2538 (7.2%)[q]	-	not estimable[p]	-	⨁◯◯◯ VERY LOW	CRITICAL

CLs: confidence limits; FE: fixed effects

[a] In this analysis, the use of a specific injectable agent (amikacin, kanamycin or capreomycin) is compared with no use of that particular agent, although another second-line injectable agent may have been used as part of the MDR-TB regimen.

[b] Individual patient data taken from 32 observational studies in which most patients received individualized treatment. Risk of selection bias, and confounding by indication.

[c] aOR: Odds ratio adjusted for age, HIV, positivity on sputum-smear microscopy, chest radiograph cavitation, and prior treatment with first-line and second-line TB drugs.

[d] In the aggregated data meta-analysis patients with XDR-TB were excluded where possible.

[e] In total, 61 cohorts provided end-of-treatment outcome information: in 23 cohorts the patients were given standardized regimens and in 38 cohorts therapy was individualized, leading to risk of confounding by indication. Of the 61 cohorts, 18 cohorts did not specify which second-line injectable agent was used, and therefore only the remaining 43 cohorts were retained for this analysis.

[f] Potential confounding from preferential inclusion of capreomycin in the individualized regimens of patients with more advanced resistance patterns or disease.

[g] Given that amikacin or kanamycin were used in almost all studies, the comparison is made between studies in which 72%–100% of patients received the injectable agent (intervention group) versus a comparator group of studies in which 0%–71% of patients received one of these agents.

[h] Adjusted proportion: 94% (95% CL: 90%–97%).

[i] Adjusted proportion: 89% (95% CL: 83%–96%).

[j] Adjusted proportion: 82% (95% CL: 75%–88%).

[k] Adjusted proportion: 78% (95% CL: 70%–86%).

[l] Adjusted proportion: 92% (95% CL: 87%–97%).

[m] Adjusted proportion: 93% (95% CL: 86%–97%).

[n] Adjusted proportion: 77% (95% CL: 69%–84%).

[o] Adjusted proportion: 83% (95% CL: 76%–89%).

[p] Serious adverse events (SAEs) reported in patients were attributed to a medicine by the authors who were unblinded and used non-standardized methods to define, ascertain and report SAEs. No valid comparisons are possible with patients not on the target medicine, because SAEs in these patients could be due to other drugs received.

[q] Pooled proportion: FE 95% CL: 6.2%–8.4%.

Author(s): Menzies R, Bastos M, Lan Z (11 November 2015)

Question: Ethionamide/prothionamide compared to no ethionamide/prothionamide for adults with rifampicin-resistant TB or MDR-TB

Setting: Treatment of adults with rifampicin-resistant TB/MDR-TB/XDR-TB using conventional regimens lasting about 24 months and shorter MDR-TB regimens, in low and high resource settings, within hospital or ambulatory models of care

Bibliography: (1) 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):e1001300. (2) Bastos M, Lan Z, Menzies R. An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis, 2016 (under review, 28 May 2016).

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	ETHIONAMIDE/ PROTHIONA-MIDE	NO ETHIONAMIDE/ PROTHIONA-MIDE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in patients on ethionamide/prothionamide as part of a MDR-TB regimen (assessed with: individual patient data meta-analysis (Ahuja SD, et al. PLOS Med. 2012))[a]												
32	observational studies	serious[b]	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	4101/5667 (72.4%)	878/1487 (59.0%)	**aOR 1.9** (1.5 to 2.3)[c]	**130 fewer per 1000** (from 65 more to 185 more)	⨁◯◯◯ LOW	CRITICAL
Serious adverse events (Grade 3 or 4, or drugs stopped due to adverse events) in patients on ethionamide/prothionamide as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)												
17	observational studies	serious	not serious	not serious	not serious	none[d]	173/2106 (8.2%)[e]	-	not estimable[d]		⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limit; FE: fixed effects

[a] In this analysis, use of ethionamide is combined with prothionamide, and compared to results in patients who did not get either of these drugs, but received multiple other drugs.

[b] This is individual patient data taken from 32 observational studies in which most patients received individualized treatment. There is risk of selection bias and confounding by indication.

[c] aOR: Odds ratio adjusted for age, HIV, acid fast bacillus smear, chest radiograph cavitation, and prior treatment with first-line, and second-line TB drugs.

[d] Serious adverse events (SAEs) reported in patients were attributed to a medicine by the authors who were unblinded and used non-standardized methods to define, ascertain and report SAEs. No valid comparisons are possible with patients not on the target medicine, because SAEs in these patients could be due to other drugs received.

[e] Pooled proportion: FE 95% CL:7.0%–9.6%.

Author(s): Menzies R, Bastos M, Lan Z (11 November 2015)

Question: Cycloserine/terizidone compared to no cycloserine/terizidone for adults with rifampicin-resistant TB or MDR-TB

Setting: Treatment of adults with MDR-TB regimens, in low and high resource settings, within hospital or ambulatory models of care

Bibliography: (1) 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):e1001300. (2) Hwang TJ, Wares DF, Jafarov A, Jakubowiak W, Nunn P, Keshavjee S. Safety of cycloserine and terizidone for the treatment of drug-resistant tuberculosis: a meta-analysis. Int J Tuberc Lung Dis. 2013;17(10):1257–66. (3) Bastos M, Lan Z, Menzies R. An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis, 2016 (under review, 28 May 2016).

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	CYCLOSERINE/ TERIZIDONE	NO CYCLOSERINE/ TERIZIDONE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Success versus failure/relapse/death for cycloserine and terizidone from Individual patient data meta-analysis (Ahuja SD, et al. PLOS Med 2012)[a]												
32	observational studies	serious	serious	not serious	not serious	none	3115/4240 (73.5%)	1864/2914 (64.0%)	**OR 1.5** (0.9 to 2.2)[a]	**95 more per 1,000** (from 73 more to 117 more)	⨁◯◯◯ VERY LOW	CRITICAL
Success versus failure/relapse for cycloserine and terizidone (assessed with: aggregated data meta-analysis 2015)												
53	observational studies	serious	serious	not serious	serious	none	4474/5285 (84.7%)[2]	1969/2479 (79.4%)[3]	not estimable	**49 more per 1,000** (from 56 fewer to 155 more)	⨁◯◯◯ VERY LOW	CRITICAL
Success versus failure/relapse/death for cycloserine and terizidone (assessed with: aggregated data meta-analysis 2015)												
53	observational studies	serious	serious	not serious	serious	none	4474/5916 (75.6%)[4]	1969/2823 (69.7%)[5]	not estimable	**5 fewer per 1,000** (from 139 fewer to 129 more)	⨁◯◯◯ 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	CYCLOSERINE/ TERIZIDONE	NO CYCLOSERINE/ TERIZIDONE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Drug discontinued due to major psychiatric toxicity from cycloserine used to treat MDR-TB (assessed with: Hwang, et al. Int J Tuberc Lung Dis. 2012 (systematic review))[b]												
26	observational studies	serious	serious	not serious	serious	none[c]	144/1923 (7.5%)	-	not estimable[c]		⨁◯◯◯ VERY LOW	CRITICAL
Drug discontinued due to toxicity (all types) from cycloserine used to treat MDR-TB (assessed with: Hwang TJ, et al. Int J Tuberc Lung Dis. 2012 (systematic review))[b]												
27	observational studies	serious	serious	not serious	serious	none[c]	201/2164 (9.3%)	-	not estimable[c]		⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (Grade 3 or 4, or drugs stopped due to adverse events) in patients on cycloserine as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)												
16	observational studies	serious	not serious	not serious	not serious	none[c]	96/2140 (4.5%)[d]	-	not estimable[c]		⨁◯◯◯ VERY LOW	CRITICAL
Drug discontinued due to toxicity (all types) from terizidone used to treat MDR-TB (assessed with: Hwang TJ, et al. Int J Tuberc Lung Dis. 2012 (systematic review))[b]												
10	observational studies	serious	serious	not serious	serious	none[c]	111/707 (15.7%)	-	not estimable[c,e]		⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; FE: fixed effects; OR: odds ratio

[a] Adjusted for age, extent of disease, HIV, and prior treatment with first-line or second-line TB drugs. Patients on cycloserine and terizidone were combined together for this analysis.

[b] No regional differences observed.

[c] Serious adverse events (SAEs) reported in patients were attributed to a medicine by the authors who were unblinded and used non-standardized methods to define, ascertain and report SAEs. No valid comparisons are possible with patients not on the target medicine, because SAEs in these patients could be due to other drugs received.

[d] Pooled proportion: FE 95% CL: 3.6%–5.5%.

[e] Terizidone and cycloserine were compared in three of the studies. Authors reported no differences and concluded that the effect of terizidone varied from not being different to being moderately better than cycloserine.

Author(s): Menzies R, Bastos M, Lan Z (11 November 2015)

Question: Linezolid compared to no linezolid for adult patients on treatment for MDR-TB/XDR-TB

Setting: Treatment of adults with rifampicin-resistant TB/MDR-/XDR-TB using conventional regimens lasting about 24 months, in low and high resource settings, within hospital or ambulatory models of care

Bibliography: (1) Altet MN, Vidal R, Milá C, Rodrigo T, Casals M, Mir I, et al. Monitoring changes in anti-tuberculosis treatment: associated factors determined at the time of diagnosis. Int J Tuberc Lung Dis. 2013;17(11):1435–41. (2) Carroll MW, Lee M, Cai Y, Hallahan CW, Shaw PA, Min JH, et al. Frequency of adverse reactions to first- and second-line anti-tuberculosis chemotherapy in a Korean cohort. Int J Tuberc Lung Dis. 2012;16(7):961–966. (3) De Lorenzo S, Alffenaar JW, Sotgiu G, Centis R, D'Ambrosio L, Tiberi S, et al. Efficacy and safety of meropenem-clavulanate added to linezolid-containing regimens in the treatment of MDR-/XDR-TB. Eur Respir J. 2013;41(6):1386–92. (4) Jiang R-H, Xu H-B, Li L. Comparative roles of moxifloxacin and levofloxacin in the treatment of pulmonary multidrug-resistant tuberculosis: a retrospective study. Int J Antimicrob Agents. 2013;42(1):36–41. (5) Koh W-J, Kwon OJ, Gwak H, Chung JW, Cho S-N, Kim WS, et al. Daily 300 mg dose of linezolid for the treatment of intractable multidrug-resistant and extensively drug-resistant tuberculosis. J Antimicrob Chemother. 2009;64(2):388–91. (6) Lee M, Lee J, Carroll MW, Choi H, Min S, Song T, et al. Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis. N Engl J Med. 2012;367(16):1508–18. (7) Mignone F, Codecasa LR, Scolfaro C, Raffaldi I, Lancella L, Ferrarese M, et al. The spread of drug-resistant tuberculosis in children: an Italian case series. Epidemiol Infect. 2014;142(10):2049–56. (8) Padayatchi N, Mac Kenzie WR, Hirsch-Moverman Y, Feng P-J, Villarino E, Saukkonen J, et al. Lessons from a randomised clinical trial for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2012;16(12):1582–7. (9) Singla R, Caminero JA, Jaiswal A, Singla N, Gupta S, Bali RK, et al. Linezolid: an effective, safe and cheap drug for patients failing multidrug-resistant tuberculosis treatment in India. Eur Respir J. 2012;39(4):956–962. (10) Schecter GF, Scott C, True L, Raftery A, Flood J, Mase S. Linezolid in the treatment of multidrug-resistant tuberculosis. Clin Infect Dis. 2010;50(1):49–55. (11) Tang S, Yao L, Hao X, Zhang X, Liu G, Liu X, et al. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. Eur Respir J. 2015;45(1):161–70. (12) Udwadia ZF, Sen T, Moharil G. Assessment of linezolid efficacy and safety in MDR- and XDR-TB: an Indian perspective. Eur Respir J. 2010;35(4):936–938–940.

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	LINEZOLID	NO LINEZOLID	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in XDR-TB patients given linezolid (assessed with: RCT in China, 2009–2011 (Tang, et al, 2015))[a]												
1	randomized trials	serious	not serious	not serious	serious	strong association	23/29 (79.3%)[b]	11/29 (37.9%)[c]	not estimable	**414 more per 1,000** (from 184 more to 644 more)	⨁⨁⨁◯ MODERATE	CRITICAL

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	LINEZOLID	NO LINEZOLID	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus. failure/relapse/death/default in MDR-TB or XDR-TB patients given linezolid (assessed with: 1RCT + 6 observational studies combined)												
7	observational studies[d]	very serious	serious	not serious	serious	none	153/198 (77.3%)[e]	387/606 (63.9%)[f]	not estimable	**134 more per 1,000** (from 64 more to 204 more)	⨁◯◯◯ VERY LOW	CRITICAL
Death (versus all other outcomes) in MDR-TB and XDR-TB patients given linezolid (assessed with: 1RCT + 6 observational studies combined)												
7	observational studies[d]	very serious	serious	not serious	serious	none	21/212 (9.9%)	65/468 (13.9%)	not estimable	**40 fewer per 1,000** (91 fewer to 11 more)	⨁◯◯◯ VERY LOW	CRITICAL
Grade 3–4 Serious adverse events and/or drugs stopped due to linezolid (assessed with: internal comparator groups)[g,h]												
4	observational studies[h,i]	very serious	serious	not serious	serious	none	11/49 (22.4%)	112/1305 (8.6%)	not estimable	**139 more per 1,000** (21 more to 257 more)	⨁◯◯◯ VERY LOW	CRITICAL
Grade 3–4 Serious adverse events and/or drugs stopped due to linezolid 600 mg/day (assessed with: largely uncontrolled observational studies)[j]												
8	observational studies[i,j]	very serious	serious	not serious	serious	none	28/190 (14.7%)[k]		not estimable		⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limit; RCT: randomized controlled trial

[a] Method of randomization not described, hence risk of allocation bias unknown. Study was not blinded, hence risk of ascertainment bias, and small number of subjects.

[b] 95% CL: 65%–94%.

[c] 95% CL: 20%–56%.

[d] All were small studies. The 1 RCT was very small and unblinded with unclear randomization. The 6 observational had individualized regimens.

[e] 95% CL: 73%–84%.

[f] 95% CL: 46%–90%.

[g] Not showing the effects in two studies for patients receiving 1200 mg per day (9/51; 18%).

[h] Altet 2013; Carroll 2012; Mignone 2014; Padayatchi 2012 (only Padayatchi reported the dose).

[i] The intervention group was given linezolid at a start dose of 1200 mg per day for 4–6 weeks and followed by a dose of 300–600 mg per day.

[j] Koh 2009; Schecter 2010; Udwadia 2010; Singla 2012; Lee 2012; De Lorenzo 2013; Jiang 2013; Padayatchi 2012 (only Padayatchi reported SAE in group not receiving linezolid; Singla (600 mg vs 1200 mg) and De Lorenzo (600 mg vs >600 mg) compared SAE at different doses).

[k] 95% CL: 10%–21%.

Author(s): Ronald L, Cerigo H, Fox G, Menzies R (11 November 2015)

Question: Clofazimine compared to no clofazimine for the treatment of adults with rifampicin-resistant TB or MDR-TB

Setting: Treatment of adults with rifampicin-resistant TB/MDR-TB/XDR-TB using conventional regimens lasting about 24 months and shorter MDR-TB regimens, in low and high resource settings, within hospital or ambulatory models of care (as well as non-tuberculous mycobacteria (NTM) in some outcomes for SAE)

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	CLOFAZIMINE	NO CLOFAZIMINE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in MDR-TB patients on clofazimine (assessed with: individual patient data meta-analysis (2010))[a]												
31	observational studies	very serious	serious	not serious	not serious	none	459/806 (56.9%)[b]	3292/4970 (66.2%)[c]	**adjusted OR 1.4** (0.4 to 4.0)	**10 more per 1,000** (from 220 fewer to 340 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/death in non-XDR MDR-TB patients with clofazimine in their regimen (assessed with: 1 RCT 2010–2011 (Tang S, et al. 2015))												
1	randomized trials	serious[d]	not serious[e]	not serious	serious[e]	strong association	39/49 (79.6%)[f]	28/47 (59.6%)[g]	not estimable	**200 more per 1,000** (from 60 fewer to 450 more[m]	⨁⨁⨁◯ MODERATE	CRITICAL
Treatment success versus failure/relapse/death (assessed with: 1 RCT + 5 cohorts of MDR/XDR patients)[h]												
6	observational studies[i]	very serious	serious	not serious	serious	none	75/102 (73.5%)[j]	68/92 (73.9%)[k]	not estimable	**10 fewer per 1,000** (from 210 fewer to 170 more)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events resulting in drug discontinuation in MDR-/XDR-TB patients on clofazimine (assessed with: comparative studies)[l]												
5	observational studies	very serious	serious	not serious	serious	none	2/81 (2.5%)	281/658 (42.7%)	not estimable		⨁◯◯◯ 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	CLOFAZIMINE	NO CLOFAZIMINE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Serious adverse events resulting in drug discontinuation in NTM patients on clofazimine (assessed with: uncontrolled studies)[l]												
6	observational studies	very serious	serious	serious	serious	none	25/195 (12.8%)		not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events resulting in drug discontinuation in NTM patients on clofazimine (assessed with: comparative studies only)[l]												
4	observational studies	very serious	serious	serious	serious	none	6/181 (3.3%)	15/167 (9.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; RE: random effects

[a] Outcomes were compared in persons who received clofazimine versus those who received no Group 5 drugs. Adjusted estimate from propensity score matching was done, patients with clofazimine matched to patients from centres where clofazimine was not used.

[b] RE value on pooled meta-analysis: 63% (95% CL: 49%–78%).

[c] RE value on pooled meta-analysis: 62% (95% CL: 45%–79%).

[d] Method of randomization not described, and no blinding, increasing risk of allocation bias and ascertainment bias.

[e] One study in five centres in one country (China) only.

[f] 95% CL: 68%–91%.

[g] 95% CL: 46%–74%.

[h] Benefit was seen in one RCT, but in 5 small observational studies patients receiving clofazimine had worse outcomes. These regimens were individualized so there is risk of bias (confounding by indication).

[i] one randomized control trial + 5 cohorts.

[j] Adjusted proportion 73%; 95% CL: 64%–82%.

[k] Adjusted proportion 89%; 95% CL: 73%–100%.

[l] Adverse events reported in patients taking clofazimine were attributed to the drug by authors who were unblinded and used non-standardized methods to define, ascertain and report adverse events. No valid comparisons are possible with patients not taking clofazimine, because adverse events in patients not receiving clofazimine could be due to other drugs received concomitantly.

[m] P=0.04; treatment failure also significantly lower than in control (11% versus 29%; P=0.03).

Author(s): Winters N, Butler-Laporte G, Menzies D (11 November 2015)

Question: Macrolides (clarithromycin, azithromycin) compared to no macrolides for treatment of adults with rifampicin-resistant TB or MDR-TB.

Setting: Treatment of adults with rifampicin-resistant TB/MDR-TB/XDR-TB using conventional regimens lasting about 24 months, in low and high resource settings, within hospital or ambulatory models of care (as well as non-tuberculous mycobacteria (NTM) in some outcomes for SAE)

Bibliography: Winters N, Butler-Laporte G, Menzies D. Efficacy and safety of World Health Organization group 5 drugs for multidrug-resistant tuberculosis treatment. Eur Respir J. 2015;46(5):1461–70.

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	MACROLIDES (CLARITHRO-MYCIN, AZITHROMYCIN)	NO MACROLIDES	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success in MDR-TB patients on clarithromycin (HIV uninfected)												
2	observational studies[a]	serious	not serious	not serious	serious	none	20/61 (32.8%)	59/191 (30.9%)	not estimable	**19 more per 1,000** (from 10 fewer to 11 more)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events in NTM patients on clarithromycin (HIV uninfected) (assessed with: randomized controlled trials)												
3	randomized trials	not serious	serious	serious[b]	serious	none[c]	31/174 (17.8%)	26/175 (14.9%)	not estimable	**10 more per 1,000** (from 60 fewer to 70 more)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events in NTM patients on clarithromycin (HIV uninfected) (assessed with: uncontrolled cohorts)												
15	observational studies[d]	serious[e]	serious	serious[b]	not serious	none	41/615 (6.7%)	-	not estimable		⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events in NTM patients on clarithromycin (HIV infected) (assessed with: randomized controlled trials)												
8	randomized trials	not serious	not serious	serious[b]	serious	none[c,f]	108/1088 (9.9%)	118/1111 (10.6%)	not estimable	**7 fewer per 1,000** (from 20 fewer to 20 more)	⨁⨁◯◯ LOW	CRITICAL

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT			
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	MACROLIDES (CLARITHRO-MYCIN, AZITHROMYCIN)	NO MACROLIDES	RELATIVE (95% CL)	ABSOLUTE (95% CL)	CERTAINTY OF EVIDENCE	IMPORTANCE
Serious adverse events in NTM patients on clarithromycin (HIV infected) (assessed with: uncontrolled cohorts)												
6	observational studies[d]	serious[e]	not serious	serious[b]	not serious	none	122/584 (20.9%)[g]	-	not estimable[e]		⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events in NTM patients on azithromycin (HIV uninfected) (assessed with: uncontrolled cohorts)												
5	observational studies[d]	serious[e]	serious	serious[b]	not serious	none	7/197 (3.6%)[h]		not estimable[e]		⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events in NTM patients on azithromycin (HIV infected) (assessed with: randomized controlled trials)												
7	randomized trials	not serious	serious	serious[b]	serious	none[c,f]	113/1215 (9.3%)	57/1196 (4.8%)	not estimable	**40 more per 1,000** (from 30 fewer to 100 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/relapse/death in MDR-TB patients on macrolides (assessed with: individual patient data meta-analysis (Ahuja SD, et al. 2012; Fox G, et al. 2015))												
31	observational studies	very serious	serious	not serious	not serious	none[i]	254/396 (64.1%)[j]	3292/4970 (66.2%)[k]	**adjusted OR 0.7** (0.3 to 1.9)[l]	**20 more per 1,000** (from 120 fewer to 150 more)	⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; OR: odds ratio

[a] Controlled cohorts.

[b] Based on studies of patients on preventive or curative treatment for non-tuberculous mycobacterial disease.

[c] Patients with advanced HIV, and studies from pre-antiretrovirals era.

[d] Un-controlled cohorts.

[e] Unblinded studies; adverse events attributed to study drugs by authors with non-standardized methods.

[f] Serious adverse events expected to be more frequent in these patients (advanced HIV disease and no antiretroviral treatment).

[g] 95% CL: 12%–27%.

[h] 95% CL: 0%–8%.

[i] Adjusted estimates using propensity score matching.

[j] Adjusted estimate: 75% (95% CL: 69%–81%).

[k] Adjusted estimates 73% (95% CL: 66%–81%).

[l] Adjusted odds ratio estimated using propensity score matching. Reference population for this estimate is patients in centres where this drug was not used at all.

Author(s): Fox G, Menzies R, et al. (11 November 2015)

Question: Thioacetazone compared to no thioacetazone for treatment of adults with rifampicin-resistant TB and MDR-TB.

Setting: Treatment of adults with rifampicin-resistant TB/MDR-TB/XDR-TB using conventional regimens lasting about 24 months, in low and high resource settings, within hospital or ambulatory models of care.

Bibliography: (1) Fox G, et al. Group 5 drugs for multidrug-resistant tuberculosis: individual patient data meta-analysis (under review). (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):e1001300.

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	THIOACETAZONE	NO THIOACETAZONE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in patients on thioacetazone as part of MDR-TB treatment (assessed with: individual patient data meta-analysis)												
31[a]	observational studies	very serious	serious[b]	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	491/612 (80.2%)[c]	3670/5647 (65.0%)[d]	**adjusted OR 2.1** (0.8 to 5.5)[e]	**22 more per 1,000** (from 31 less to 74 more)[f]	⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; RE: random effects

[a] In 7 of these studies at least one person received thioacetazone (range: 1–671 per study).

[b] I-squared = 0% (95% CL: 0%–71%).

[c] RE adjusted % = 80% (95% CL: 77%–83%).

[d] RE adjusted % = 72% (95% CL: 63%–80%), among controls who did not receive thioacetazone in studies where thioacetazone was not given

[e] Adjusted using RE multivariable analysis with propensity score matching to adjust for potential confounding between patients taking thioacetazone and matched controls in studies where thioacetazone was not used

[f] RE analysis, only including 7 studies where thioacetazone was used.

Author(s): Bastos M, Lan Z, Menzies R (11 November 2015)

Question: *p*-aminosalicylic acid compared to no *p*-aminosalicylic acid for treatment of adults with rifampicin-resistant TB or MDR-TB.

Setting: Treatment of adults with rifampicin-resistant TB/MDR-TB/XDR-TB using conventional regimens lasting about 24 months, in low and high resource settings, within hospital or ambulatory models of care

Bibliography: (1) 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):e1001300. (2) Bastos M, Lan Z, Menzies R. An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis, 2016 (under review, 28 May 2016).

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	*P*-AMINOSALICYLIC ACID	NO *P*-AMINOSALICYLIC ACID	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in patients on *p*-aminosalicylic acid (PAS), as part of a MDR-TB regimen (assessed with: individual patient data meta-analysis (2012))												
32	observational studies	serious[a]	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	2162/2871 (75.3%)	2817/4283 (65.8%)	**aOR 1.0** (0.8 to 1.4)[b]	**105 more per 1,000** (from 110 fewer to 120 more)	⨁⨁◯◯ LOW	CRITICAL
Treatment success versus failure/relapse in patients on PAS as part of a MDR-TB regimen (assessed with: aggregate data meta-analysis (2015)												
55	observational studies	serious[c]	not serious	not serious	not serious	none[d]	4981/5744 (86.7%)[e]	2968/3595 (82.6%)[f]		**49 more per 1,000** (from 7 fewer to 107 more)[l]	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus failure/relapse/death in patients on PAS as part of a MDR-TB regimen (assessed with: aggregate data meta-analysis (2015)[g]												
55	observational studies	serious[c]	not serious	not serious	not serious	none[d]	4981/6276 (79.4%)[h]	2968/4521 (65.6%)[i]		**54 more per 1,000** (from 34 fewer to 144 more)[l]	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (Grade 3 or 4, or drugs stopped due to adverse events) in patients on PAS, as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)												
16	observational studies	serious	not serious	not serious	not serious	none[j]	208/1706 (12.2%)[k]		not estimable		⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; FE: fixed effects

[a] Individual patient data taken from 32 observational studies in which most patients received individualized treatment. Risk of selection bias, and confounding by indication.

[b] aOR: Odds ratio adjusted for age, HIV, acid-fast bacillus smear, chest radiograph cavitation, and prior treatment with first line, and second line TB drugs.

[c] Very serious limitations – all studies were observational – leading to risk of selection and information bias. In 20 studies the patients were given standardized regimens, but in the remaining 40 studies therapy was individualized, leading to risk of confounding by indication.

[d] Unadjusted analysis.

[e] Pooled proportion: 93% (95% CL: 83%–96%).

[f] Pooled proportion: 90% (95% CL: 85%–95%).

[g] From aggregate data meta-analysis: Patients with XDR-TB excluded from analyses, where possible.

[h] Pooled proportion: 81% (95% CL: 75%–87%).

[i] Pooled proportion: 78% (95% CL: 71%–85%).

[j] Serious adverse events (SAEs) reported in patients were attributed to a medicine by the authors who were unblinded and used non-standardized methods to define, ascertain and report SAEs. No valid comparisons are possible with patients not on the target medicine, because SAEs in these patients could be due to other drugs received.

[k] Pooled proportion: FE 95% CL: 10.6%–13.9%.

[l] Risk difference from adjusted analysis.

Author(s): Bastos M, Lan Z, Menzies R (11 November 2015)

Question: Pyrazinamide compared to no pyrazinamide for adults with rifampicin-resistant TB or MDR-TB.

Setting: Treatment of adults with rifampicin-resistant TB/MDR-TB/XDR-TB using conventional regimens lasting about 24 months and shorter MDR-TB regimens, in low and high resource settings, within hospital or ambulatory models of care.

Bibliography: (1) 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):e1001300. (2) Bastos M, Lan Z, Menzies R. An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis, 2016 (under review, 28 May 2016).

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	PYRAZINAMIDE	NO PYRAZINAMIDE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus failure/relapse/death in patients on pyrazinamide as part of a MDR-TB regimen (assessed with: individual patient data meta-analysis (Ahuja SD, et al. PLOS Med. 2012)												
20	observational studies	serious	not serious	not serious	not serious	none	2454/3775 (65.0%)	55/89 (61.8%)	**aOR 1.3** (1.1 to 1.6)[a]	**32 more per 1000** (from 10 more to 60 more)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (Grade 3–4 events, or drugs stopped due to adverse events) in patients on pyrazinamide as part of a MDR-TB regimen (assessed with: aggregated data meta-analysis 2015)												
19	observational studies	serious	not serious	not serious	not serious	none[b]	56/2023 (2.8%)[c]		not estimable		⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; FE: fixed effects

[a] aOR: odds ratio adjusted for age, HIV, acid-fast bacillus smear, chest radiograph cavitation, and prior treatment with first-line and second-line TB drugs.

[b] Serious adverse events (SAEs) reported in patients were attributed to a medicine by the authors who were unblinded and used non-standardized methods to define, ascertain and report SAEs. No valid comparisons are possible with patients not on the target medicine, because SAEs in these patients could be due to other drugs received.

[c] Pooled proportion: FE 95% CL: 2.1%–3.7%.

3. MDR-TB regimen composition – paediatric individual patient data meta-analysis (PICO 1)

Author(s): Elizabeth Harausz, Anthony Garcia-Prats, Simon Schaaf, Stephanie Law, Dick Menzies, Jennifer Furin, Tamara Kredo and Anneke C. Hesseling on behalf of the Paediatric MDR-TB IPD Group (11 November 2015)

Question: Later-generation fluoroquinolones compared to no later-generation fluoroquinolones for children with MDR-TB (excluding confirmed XDR-TB).

Setting: International

Bibliography: Refer to Annex 6, Section 3 for a summary of this unpublished study (Harausz E, Garcia-Prats AJ, Schaaf S, Law S, Furin J, Kredo T, et al., for The Collaborative Group for Meta-Analysis of Paediatric Individual Patient Data in MDR-TB. A systematic review and individual patient data meta-analysis of treatment and outcomes among children with multi-drug resistant tuberculosis. A preliminary report for the Guideline Development Group Meeting of the World Health Organization, November 9–11 2015).

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	LATER-GENERATION FLUOROQUINOLONES	NO LATER-GENERATION FLUOROQUINOLONES	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus fail/relapse/die – confirmed cases (IPD analysis): n = 623												
12	observational studies	serious	serious	not serious	not serious	none	480/551 (87.1%)	36/45 (80.0%)	**OR 0.710** (0.094 to 5.370)[a]	**37 fewer per 1000** (from 180 fewer to 110 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus fail/relapse/die/lost to follow up – unconfirmed cases (IPD analysis): n = 219[b]												
3	observational studies	serious	serious	not serious	not serious	none	19/21 (90.5%)	169/184 (91.8%)	**OR 0.667** (0.064 to 6.966)[a,b]	**47 fewer per 1000** (from 13 fewer to 108 more)	⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; OR: odds ratio

[a] All effect estimates shown are adjusted for age, HIV status, gender, TB disease severity and site (random effects model with clustering by site).

[b] Unconfirmed cases include lost to follow up in this analysis only.

Author(s): Elizabeth Harausz, Anthony Garcia-Prats, Simon Schaaf, Stephanie Law, Dick Menzies, Jennifer Furin, Tamara Kredo and Anneke C. Hesseling on behalf of the Paediatric MDR-TB IPD Group (11 November 2015)

Question: Second-line injectable agent compared to no second-line injectable agent for children with MDR-TB (excluding confirmed XDR-TB)

Setting: International

Bibliography: Refer to Annex 6, Section 3 for a summary of this unpublished study (Harausz E, Garcia-Prats AJ, Schaaf S, Law S, Furin J, Kredo T, et al., for The Collaborative Group for Meta-Analysis of Paediatric Individual Patient Data in MDR-TB. A systematic review and individual patient data meta-analysis of treatment and outcomes among children with multi-drug resistant tuberculosis. A preliminary report for the Guideline Development Group Meeting of the World Health Organization, November 9–11 2015).

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	SECOND-LINE INJECTABLE AGENT	NO SECOND LINE INJECTABLE AGENT	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus fail/relapse/die – confirmed cases (IPD analysis): n = 623												
25	observational studies	serious	serious	not serious	not serious	none	493/566 (87.1%)	41/57 (71.9%)	**OR 3.32** (1.53 to 7.21)[a]	**43 more per 1000** (from 107 fewer to 194 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus fail/relapse/die – unconfirmed cases (IPD analysis): n = 219												
12	observational studies	serious	serious	not serious	not serious	none	154/157 (98.1%)	58/62 (93.5%)	**OR 1.38** (0.14 to 13.50)[a]	**11 more per 1000** (from 108 fewer to 129 more)	⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limit; OR: odds ratio

[a] All effect estimates shown are adjusted for age, HIV status, gender,TB disease severity and site (random effects model with clustering by site).

Author(s): Elizabeth Harausz, Anthony Garcia-Prats, Simon Schaaf, Stephanie Law, Dick Menzies, Jennifer Furin, Tamara Kredo and Anneke C. Hesseling on behalf of the Paediatric MDR-TB IPD Group (11 November 2015)

Question: Ethionamide/prothionamide compared to no ethionamide/prothionamide for children with MDR-TB (excluding confirmed XDR-TB)

Setting: International

Bibliography: Refer to Annex 6, Section 3 for a summary of this unpublished study (Harausz E, Garcia-Prats AJ, Schaaf S, Law S, Furin J, Kredo T, et al., for The Collaborative Group for Meta-Analysis of Paediatric Individual Patient Data in MDR-TB. A systematic review and individual patient data meta-analysis of treatment and outcomes among children with multi-drug resistant tuberculosis. A preliminary report for the Guideline Development Group Meeting of the World Health Organization, November 9–11 2015).

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	ETHIONAMIDE/ PROTHIONA-MIDE	NO ETHIONAMIDE/ PROTHIONA-MIDE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus fail/relapse/die – confirmed cases (IPD analysis): n = 623												
24	observational studies	serious	serious	not serious	not serious	none	493/574 (85.9%)	41/49 (83.7%)	**OR 2.04** (0.29 to 14.60)[a]	**59 fewer per 1000** (from 180 fewer to 60 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus fail/relapse/die – unconfirmed cases (IPD analysis): n = 219												
11	observational studies	serious	serious	not serious	not serious	none	181/187 (96.8%)	31/32 (96.9%)	**OR 1.08** (0.05 to 21.90)[a]	**19 fewer per 1000** (from 139 fewer to 102 more)	⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; OR: odds ratio

[a] All effect estimates shown are adjusted for age, HIV status, gender, TB disease severity and site (random effects model with clustering by site).

Author(s): Elizabeth Harausz, Anthony Garcia-Prats, Simon Schaaf, Stephanie Law, Dick Menzies, Jennifer Furin, Tamara Kredo and Anneke C. Hesseling on behalf of the Paediatric MDR-TB IPD Group (11 November 2015)

Question: Cycloserine/terizidone compared to no cycloserine/terizidone for in children with MDR-TB (excluding confirmed XDR-TB)

Setting: International

Bibliography: Refer to Annex 6, Section 3 for a summary of this unpublished study (Harausz E, Garcia-Prats AJ, Schaaf S, Law S, Furin J, Kredo T, et al., for The Collaborative Group for Meta-Analysis of Paediatric Individual Patient Data in MDR-TB. A systematic review and individual patient data meta-analysis of treatment and outcomes among children with multi-drug resistant tuberculosis. A preliminary report for the Guideline Development Group Meeting of the World Health Organization, November 9–11 2015).

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	CYCLOSERINE/ TERIZIDONE	NO CYCLOSERINE/ TERIZIDONE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus fail/relapse/die/lost – confirmed cases only (IPD analysis): n = 701												
24	observational studies	serious	serious	not serious	not serious	none	307/339 (90.6%)	227/284 (79.9%)	**OR 1.70** (0.91 to 3.19)[a]	**3 fewer per 1000** (from 90 fewer to 97 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus fail/relapse/die – unconfirmed cases (IPD analysis): n = 219												
10	observational studies	serious	serious	not serious	not serious	none	132/134 (98.5%)	80/85 (94.1%)	**OR 0.38** (0.01 to 28.90)[a]	**13 fewer per 1000** (from 106 fewer to 81 more)	⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; OR: odds ratio

[a] All effect estimates shown are adjusted for age, HIV status, gender,TB disease severity and site (random effects model with clustering by site).

Author(s): Elizabeth Harausz, Anthony Garcia-Prats, Simon Schaaf, Stephanie Law, Dick Menzies, Jennifer Furin, Tamara Kredo and Anneke C. Hesseling on behalf of the Paediatric MDR-TB IPD Group (11 November 2015)

Question: Clofazimine compared to no clofazimine for children with MDR tuberculosis (excluding confirmed XDR-TB)

Setting: International

Bibliography: Refer to Annex 6, Section 3 for a summary of this unpublished study (Harausz E, Garcia-Prats AJ, Schaaf S, Law S, Furin J, Kredo T, et al., for The Collaborative Group for Meta-Analysis of Paediatric Individual Patient Data in MDR-TB. A systematic review and individual patient data meta-analysis of treatment and outcomes among children with multi-drug resistant tuberculosis. A preliminary report for the Guideline Development Group Meeting of the World Health Organization, November 9–11 2015).

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	CLOFAZIMINE	NO CLOFAZIMINE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus fail/relapse/die – confirmed cases (IPD analysis): n = 623												
9	observational studies	serious	serious	not serious	serious	none	18/23 (78.3%)	516/600 (86.0%)	**OR 0.46** (0.02 to 10.00)[a]	**47 more per 1000** (from 81 fewer to 170 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus fail/relapse/die – unconfirmed cases (IPD analysis): n = 219												
2	observational studies	serious	serious	not serious	serious	none	4/4 (100.0%)	208/215 (96.7%)	**OR 0.25** (0.12 to 5.30)[b]	**47 more per 1000** (from 14 fewer to 107 more)	⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; OR: odds ratio

[a] Effect estimates for the confirmed are adjusted for age, HIV status, gender, TB disease severity and site (random effects model with clustering by site).

[b] Effect estimate is not adjusted.

Author(s): Elizabeth Harausz, Anthony Garcia-Prats, Simon Schaaf, Stephanie Law, Dick Menzies, Jennifer Furin, Tamara Kredo and Anneke C. Hesseling on behalf of the Paediatric MDR-TB IPD Group (11 November 2015)

Question: Pyrazinamide compared to no pyrazinamide for children with MDR tuberculosis (excluding confirmed XDR-TB)

Setting: International

Bibliography: Refer to Annex 6, Section 3 for a summary of this unpublished study (Harausz E, Garcia-Prats AJ, Schaaf S, Law S, Furin J, Kredo T, et al., for The Collaborative Group for Meta-Analysis of Paediatric Individual Patient Data in MDR-TB. A systematic review and individual patient data meta-analysis of treatment and outcomes among children with multi-drug resistant tuberculosis. A preliminary report for the Guideline Development Group Meeting of the World Health Organization, November 9–11 2015).

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	PYRAZINAMIDE	NO PYRAZINAMIDE	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus fail/relapse/die – confirmed cases (IPD analysis): n = 623												
26	observational studies	serious	serious	not serious	not serious	none	499/582 (85.7%)	35/41 (85.4%)	**OR 0.45** (0.01 to 33.40)[a]	**66 fewer per 1000** (from 160 fewer to 26 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus fail/relapse/die – unconfirmed cases (IPD analysis): n = 219												
12	observational studies	serious	serious	not serious	not serious	none	187/194 (96.4%)	25/25 (100.0%)	**OR 0.490** (0.027 to 8.840)[b]	**50 fewer per 1000** (from 114 fewer to 14 more)	⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; OR: odds ratio

[a] Effect estimates for confirmed are adjusted for age, HIV status, gender, TB disease severity and site (random effects model with clustering by site)

[b] OR for unconfirmed cases is not adjusted.

Author(s): Elizabeth Harausz, Anthony Garcia-Prats, Simon Schaaf, Stephanie Law, Dick Menzies, Jennifer Furin, Tamara Kredo and Anneke C. Hesseling on behalf of the Paediatric MDR-TB IPD Group (11 November 2015)

Question: High dose isoniazid compared to no high dose isoniazid for children with MDR-TB (excluding confirmed XDR-TB)[a]

Setting: International

Bibliography: Refer to Annex 6, Section 3 for a summary of this unpublished study (Harausz E, Garcia-Prats AJ, Schaaf S, Law S, Furin J, Kredo T, et al., for The Collaborative Group for Meta-Analysis of Paediatric Individual Patient Data in MDR-TB. A systematic review and individual patient data meta-analysis of treatment and outcomes among children with multi-drug resistant tuberculosis. A preliminary report for the Guideline Development Group Meeting of the World Health Organization, November 9–11 2015).

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	HIGH DOSE ISONIAZID	NO HIGH DOSE ISONIAZID	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus fail/relapse/die – confirmed cases (IPD analysis): n = 623												
6	observational studies	serious[a]	serious	not serious	not serious	none	130/133 (97.7%)	404/490 (82.4%)	**OR 6.97** (2.11 to 23.00)[b]	**120 more per 1000** (from 59 more to 187 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus fail/relapse/die – unconfirmed cases (IPD analysis): n = 219[c]												
1	observational studies	serious[a]	serious	not serious	not serious	none	85/85 (100.0%)	127/134 (94.8%)	**OR 10.06** (0.56 to 178.40)[c]	–	⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; OR: odds ratio

[a] Most of the cases receiving high-dose isoniazid were from cohorts in South Africa, so despite adjusting for study site, there may still be some residual confounding.

[b] Effect estimates shown are adjusted for age, HIV status, gender, TB disease severity and site (random effects model with clustering by site).

[c] OR for the unconfirmed cases is not adjusted.

Author(s): Elizabeth Harausz, Anthony Garcia-Prats, Simon Schaaf, Stephanie Law, Dick Menzies, Jennifer Furin, Tamara Kredo and Anneke C. Hesseling on behalf of the Paediatric MDR-TB IPD Group (11 November 2015)

Question: *p*-aminosalicylic acid compared to no *p*-aminosalicylic acid for children with MDR-TB (excluding confirmed XDR-TB)

Setting: International

Bibliography: Refer to Annex 6, Section 3 for a summary of this unpublished study (Harausz E, Garcia-Prats AJ, Schaaf S, Law S, Furin J, Kredo T, et al., for The Collaborative Group for Meta-Analysis of Paediatric Individual Patient Data in MDR-TB. A systematic review and individual patient data meta-analysis of treatment and outcomes among children with multi-drug resistant tuberculosis. A preliminary report for the Guideline Development Group Meeting of the World Health Organization, November 9–11 2015).

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	*P*-AMINOSALICYLIC ACID	NO *P*-AMINOSALICYLIC ACID	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus fail/relapse/die – confirmed cases (IPD analysis): n = 623												
20	observational studies	serious	serious	not serious	not serious	none	115/135 (85.2%)	419/488 (85.9%)	**OR 0.52** (0.26 to 1.07)[a]	**5 fewer per 1000** (from 110 fewer to 95 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus fail/relapse/die/lost to follow up – unconfirmed cases (IPD analysis): n = 237[b]												
8	observational studies	serious	serious	not serious	serious	none	69/75 (92.0%)	143/162 (88.3%)	**OR 0.18** (0.02 to 1.76)[a,b]	**27 fewer per 1000** (from 60 fewer to 115 more)	⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; OR: odds ratio

[a] All effect estimates for confirmed cases are adjusted for age, HIV status, gender, TB disease severity and site (random effects model with clustering by site).

[b] OR for the unconfirmed cases includes lost to follow up in this calculation only.

Author(s): Elizabeth Harausz, Anthony Garcia-Prats, Simon Schaaf, Stephanie Law, Dick Menzies, Jennifer Furin, Tamara Kredo and Anneke C. Hesseling on behalf of the Paediatric MDR-TB IPD Group (11 November 2015)

Question: Clarithromycin compared to no clarithromycin for children with MDR-TB (excluding confirmed XDR-TB)

Setting: International

Bibliography: Refer to Annex 6, Section 3 for a summary of this unpublished study (Harausz E, Garcia-Prats AJ, Schaaf S, Law S, Furin J, Kredo T, et al., for The Collaborative Group for Meta-Analysis of Paediatric Individual Patient Data in MDR-TB. A systematic review and individual patient data meta-analysis of treatment and outcomes among children with multi-drug resistant tuberculosis. A preliminary report for the Guideline Development Group Meeting of the World Health Organization, November 9–11 2015).

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	CLARITHROMYCIN	NO CLARITHROMYCIN	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Treatment success versus fail/relapse/die – confirmed cases (IPD analysis): n = 623												
11	observational studies	serious	serious	not serious	serious	none	22/32 (68.8%)	512/591 (86.6%)	**OR 0.24** (0.04 to 1.51)[a]	**24 fewer per 1000** (from 220 fewer to 170 more)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success versus fail/relapse/die – unconfirmed cases (IPD analysis): n = 219												
2	observational studies	serious	serious	not serious	serious	none	3/3 (100.0%)	209/216 (96.8%)	not estimable	–	⨁◯◯◯ VERY LOW	CRITICAL

CL: confidence limits; OR: odds ratio

[a] All effect estimates shown are adjusted for age, HIV status, gender, TB disease severity and site (random effects model with clustering by site).

4. The role of surgery (PICO 4)

Author(s): Harris RC, Khan MS, Allen V, Moore DAJ, Fielding K, Grandjean L, and the LSHTM MDR-TB surgery systematic review group (11 November 2015)

Question: Surgery compared to no surgery for treatment of MDR or XDR TB

Setting: Georgia, Latvia, Russia, South Africa, South Korea and Turkey

Bibliography: (1) Harris RC, Khan MS, Martin LJ, Allen V, Moore DAJ, Fielding K, et al. and the LSHTM MDR-TB surgery systematic review group. The effect of surgery on the outcome of treatment for multidrug-resistant tuberculosis: a systematic review and meta-analysis. BMC Infect Dis. 2016;16(1). (2) Dravniece G, Cain KP, Holtz TH, Riekstina V, Leimane V, Zaleskis R. Adjunctive resectional lung surgery for extensively drug-resistant tuberculosis. Eur Respir J. 2009;34(1):180–183. (3) Gegia M, Kalandadze I, Kempker RR, Magee MJ, Blumberg HM. Adjunctive surgery improves treatment outcomes among patients with multidrug-resistant and extensively drug-resistant tuberculosis. Int J Infect Dis. 2012;16:e391–396. (4) Karagöz T, Yazicioğlu Moçin O, Pazarli P, Senol T, Yetiş Duman D, Duman G, et al. The treatment results of patients with multidrug resistant tuberculosis and factors affecting treatment outcome. Tuberk Toraks. 2009;57:383–392. (5) Keshavjee S, Gelmanova IY, Farmer PE, Mishustin SP, Strelis AK, Andreev YG, et al. Treatment of extensively drug-resistant tuberculosis in Tomsk, Russia: a retrospective cohort study. Lancet 2008;372:1403–1409. (6) Kim H-R, Hwang SS, Kim HJ, Lee SM, Yoo C-G, Kim YW, et al. Impact of extensive drug resistance on treatment outcomes in non-HIV-infected patients with multidrug-resistant tuberculosis. Clin Infect Dis. 2007;45(10):1290–1295. (7) Kim DH, Kim HJ, Park S-K, Kong S-J, Kim YS, Kim T-H, et al. Treatment outcomes and long-term survival in patients with extensively drug-resistant tuberculosis. Am J Respir Crit Care Med. 2008;178:1075–1082. (8) Kwak N, Kim HR, Yoo CG, Kim YW, Han SK, Yim JJ. Changes in treatment outcomes of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2015;19:525–530. (9) Kwon YS, Kim YH, Suh GY, Chung MP, Kim H, Kwon OJ, et al. Treatment outcomes for HIV-uninfected patients with multidrug-resistant and extensively drug-resistant tuberculosis. Clin Infect Dis. 2008;47:496–502. (10) Leimane V, Riekstina V, Holtz TH, Zarovska E, Skripconoka V, Thorpe LE, et al. Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. Lancet 2005;365:318–326. (11) Mitnick CD1, Shin SS, Seung KJ, Rich ML, Atwood SS, Furin JJ, et al. Comprehensive treatment of extensively drug-resistant tuberculosis. New Engl J Med 2008;359:563–574. (12) Shean KP, Willcox PA, Siwendu SN, Laserson KF, Gross L, Kammerer S, et al. Treatment outcome and follow-up of multidrug-resistant tuberculosis patients, West Coast/Winelands, South Africa, 1992–2002. Int J Tuberc Lung Dis. 2008;12(10):1182–1189. (13) Sklyuev S, Levin A, Tcheimach E, Krasnov D. PC-658–02 Complex treatment approach for patients with destructive pulmonary tuberculosis by application of endobronchial valve. Int J Tuberc Lung Dis. 2013;17(12, Supp.2):S329–330. (14) Tahaoğlu K, Törün T, Sevim T, Ataç G, Kir A, Karasulu L, et al. The treatment of multidrug-resistant tuberculosis in Turkey. N Engl J Med. 2001;345:170–174. (15) Törün T, Tahaoğlu K, Ozmen I, Sevim T, Ataç G, Kir A, et al. The role of surgery and fluoroquinolones in the treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2007;11(9):979–985.

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT			
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	SURGERY	NO SURGERY	RELATIVE (95% CL)	ABSOLUTE (95% CL)	QUALITY	IMPORTANCE
Cured (follow up: range 0.5 to 10 years; assessed with: WHO definition)												
5	observational studies	serious[a-g]	not serious[h]	not serious[i]	not serious	none[j]	118/157 (75.2%)	308/561 (54.9%)	**OR 3.03** (1.59 to 5.78)	**238 more per 1,000** (from 110 more to 327 more)	⨁◯◯◯ VERY LOW	CRITICAL
Successful outcome (follow up: range 0.25 to 7 years; assessed with: cure or treatment success, WHO definition)												
14	observational studies	serious[a-g,k,l]	not serious[m]	not serious[n]	not serious	none[i,o]	371/453 (81.9%)[p]	1197/2006 (59.7%)	**OR 2.62** (1.94 to 3.54)[p]	**198 more per 1,000** (from 145 more to 243 more)	⨁◯◯◯ VERY LOW	CRITICAL
Death (follow up: range 0.5 to 10 years; assessed with: all-cause mortality or TB mortality)												
5	observational studies	serious[a-f,k,q-s]	not serious[m]	serious[t]	serious[s]	none[j]	11/191 (5.8%)	52/720 (7.2%)	**OR 0.82** (0.41 to 1.64)	**12 fewer per 1,000** (from 41 fewer to 41 more)	⨁◯◯◯ VERY LOW	CRITICAL
Loss to follow up (previously default) (follow up: range 0.5 to 10 years; assessed with: WHO definition)												
4	observational studies	serious[a-f,u]	not serious[m]	not serious[v]	not serious	none[j,w]	6/156 (3.8%)	77/613 (12.6%)	**OR 0.35** (0.15 to 0.81)[x]	**78 fewer per 1,000** (from 21 fewer to 105 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment failure (follow up: range 0.5 to 10 years; assessed with: WHO definition)												
5	observational studies	serious[a-g,k]	not serious[m]	not serious[v]	not serious	none[j,w]	8/191 (4.2%)	82/720 (11.4%)	**OR 0.38** (0.18 to 0.81)	**67 fewer per 1,000** (from 20 fewer to 91 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Transfer out (follow up: not reported)												
2	observational studies	serious[a-c,f,y,z]	not serious[aa]	not serious	not serious[aa]	none[z,bb]	0/139 (0.0%)	6/305 (2.0%)	not estimable		⨁◯◯◯ VERY LOW	CRITICAL

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT			
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	SURGERY	NO SURGERY	RELATIVE (95% CL)	ABSOLUTE (95% CL)	QUALITY	IMPORTANCE
Relapse or relapse/failure – not reported												
-	-	-	-	-	-	-	-	-	-	see comment	-	
Adverse events from surgery (follow up: range 1.5 to 10 years)												
1	observational studies	serious[a,b,f]	not serious[cc]	not serious	not serious[cc]	publication bias strongly suspected[dd]	2/66 (3%) surgical patients died due to surgical complications.				⨁◯◯◯ VERY LOW	CRITICAL

CL: Confidence limits; OR: Odds ratio

[a] Do not address or adjust for confounders and some studies do not fully describe the population – Dravniece, et al. 2009; Karagoz, et al. 2009; Kim et al. 2007; Kwak et al. 2015; Kwon et al. 2008; Mitnick, et al. 2008; Shean, et al. 2008; Sklyuev, et al. 2013; Tahaoglu, et al. 2001; and Torun, et al. 2007.

[b] Retrospective observational studies do not have randomization and have inherent bias in who is offered surgery – Dravniece, et al. 2009; Karagoz, et al. 2009; Keshavjee, et al. 2008; Kim et al. 2007; Kim, et al. 2008; Kwak, et al. 2015; Kwon, et al. 2008; Leimane, et al. 2005; Mitnick, et al. 2008; Shean, et al. 2008; Tahaoglu, et al. 2001; and Torun, et al. 2007.

[c] Uncertainty in representativeness of study population – Dravniece, et al. 2009; Karagoz, et al. 2009; Kim et al. 2007; Kwak, et al. 2015; Kwon et al. 2008; Shean, et al. 2008; and Tahaoglu, et al. 2001

[d] No estimate of variability given – Dravniece, et al. (2009) and Tahaoglu, et al. (2001).

[e] Number of "lost to follow-up" reported, but characteristics not described – Tahaoglu, et al. (2001).

[f] Length of follow up not described or adjusted for in analysis – Dravniece, et al. 2009; Kim, et al. 2007; Kwak, et al. 2015; Kwon, et al. 2008; Leimane, et al. 2005; Mitnick, et al. 2008; Shean, et al. 2008; Tahaoglu, et al. 2001; and Torun, et al. 2007.

[g] In surgical studies, it is not possible to blind patients or the study team. Outcome assessors could be blinded, and is somewhat important for assessing cure using smear as an outcome indicator. However, personnel other than the diagnosing physician, generally conduct laboratory assessment. For treatment success/failure there is a risk of reporting bias due to lack of blinding where data are programmatic, as there may be over-reporting due to programmatic targets and could be biased by knowledge of surgical status.

[h] Moderate I-squared (54.2%) and overlapping CLs between studies, and are thus not downgraded.

[i] Some variation in duration of follow-up in outcome definition, however it is not downgraded as alone it is not classified as serious for this outcome.

[j] All studies are cohort based, and therefore there may be some confounding due to patient allocation to surgery or no surgery. Patients who are more unwell may be more likely to be recommended for surgery (therefore causing underestimate of effect size). However, the most sick are often not offered surgery as they may be too unwell or the disease may be too disseminated to allow surgery (therefore overestimating effect size). In addition, there may be variation in the population offered surgery by setting or surgeon. As there is a specific window for surgery, these biases may have an impact on estimation of effect size, though it is unclear whether they would bias the estimation in a particular direction, and are a reflection of the reality of the patient group offered surgery. Therefore, the reviewers decided not to upgrade or downgrade the rating.

[k] Reports number, but not summary statistics or precision for this specific outcome – Leimane, et al. (2005) and Mitnick, et al. (2008)

[l] Abstract only, outcome and patient characteristics not clearly described – Dravniece, et al. (2009)

[m] Low I-squared and overlapping CLs between studies, so not downgraded.

[n] Most studies followed WHO outcome definitions. Some variation in duration of follow up to assess outcome but not downgraded as alone is not classified as serious issue for this outcome.

[o] Empty lower right quadrant of funnel plot. However, it seems that smaller (less precise) studies are reporting lower effect estimate so if publication bias were to exist this would suggest the current estimate effect measure is conservative. Per protocol, studies with <10 surgical participants were excluded, therefore the very smallest of studies were not included. Plot is not sufficiently asymmetrical to raise serious concerns, and any bias would appear to cause an underestimate of effect, therefore quality is not downgraded.

[p] n=13 for OR estimates, but n=11 for numbers of patients summarized in the table, as only two studies report effect estimate rather than the number of patients with the outcome and the denominator.

[q] In surgical studies, it is not possible to blind patients or study team. Outcome assessors could be blinded, but unimportant in mortality outcome as no subjectivity in assessment.

[r] Time period of follow up very variable, and for patients with follow up for <2 years the follow up period is potentially insufficient for mortality outcome – Shean, et al. (2008) and Torun, et al. (2007).

[s] Pooled CLs cross the null. Event rate is low and post hoc optimal information size calculation indicated number included in assessment of this outcome is too low to give sufficient power.

[t] Variation between studies in outcome definition used (all-cause versus TB-only). Unclear/variable period over which death was assessed (e.g. died during treatment, within six months of completion, or after two years).

[u] In surgical studies, it is not possible to blind patients or study team. Outcome assessors could be blinded, but where data are programmatic they are unlikely to be. This could introduce underestimate in reporting of default, but this bias is unlikely to vary between study groups.

[v] Mostly use WHO definition, minor variation in definition in some studies, but sufficiently direct not to downgrade.

[w] OR (similar to relative risk given the infrequency of the event) is <0.5 and the upper confidence limit would still provide a clinically significant benefit, therefore this would be considered a large effect size. However, the quality is not upgraded as according to GRADE methodology this should not be done if the risk of bias is serious.

[x] n=2 studies had no patients lost to follow-up in the surgery group, so 0.5 has been added to all cells in order that a CL can be calculated. The summary OR restricted to the 2 studies that had at least one patient lost to follow-up in each group is 0.47 (95% CL: 0.18, 1.24).

[y] Although reported separately, unlikely that clear differentiation has been made between “loss to follow-up” and “transfer out”.

[z] Suspected underreporting of outcome, but uncertain as to how this would impact the conclusions.

[aa] No pooled estimate, so insufficient evidence to assess.

[bb] Only two publications, so not possible to assess publication bias, but given how few report this outcome publication bias may be plausible.

[cc] One study and no comparator group so not possible to estimate.

[dd] Likely that complications occurred in other studies, but have either not been reported or have been included in all-cause deaths.

Author(s): Fox GJ, Mitnick CD, Benedetti A, Chan ED, Becerra M, Chiang C-Y, Keshavjee S, Koh W-J, Shiraishi Y, Viiklepp P, Yim J-J, Pasvol G, Robert J, Shim TS, Shin SS, Menzies R (11 November 2015)

Question: Elective partial lung resection compared to no surgery for patients on treatment for MDR-TB

Setting: Which types of surgery encompassed (lobectomy, segmentectomy, wedge resection)? Definition of non-response and adverse outcome of surgery; definition of extensive disease; how specialized were the centres/practitioners which provided surgery (external validity)? Under which conditions to indicate resection surgery and when to contraindicate; before or after culture conversion.

Bibliography: Fox GJ, Mitnick CD, Benedetti A, Chan ED, Becerra M, Chiang C-Y, et al. Surgery as an adjunctive treatment for multidrug-resistant tuberculosis: an individual patient data meta-analysis. Clin Infect Dis. 2016;62(7):887–95.

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	ELECTIVE PARTIAL LUNG RESECTION	NO SURGERY	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Success versus treatment failure or relapse (assessed with: Individual patient data meta-analysis)												
26[a]	observational studies[b]	not serious[c]	not serious[d]	not serious[e]	not serious[f]	none	185/204 (90.7%)[g]	1134/1398 (81.1%)[h]	**OR 2.4** (0.4 to 15.6)[i]	**100 more per 1000** (from 174 more to 179 fewer)	⨁⨁◯◯ LOW	CRITICAL
Success versus treatment failure or relapse or death (assessed with: Individual patient data meta-analysis)												
26[a]	observational studies[b]	not serious[c]	not serious[d]	not serious[e]	not serious[f]	none	185/214 (86.4%)[j]	1134/1702 (66.6%)[k]	**OR 2.0** (0.4 to 9.5)[i]	**133 more per 1000** (from 222 fewer to 284 more)	⨁⨁◯◯ LOW	CRITICAL
Success versus treatment failure or relapse or death or loss to follow-up (assessed with: Individual patient data meta-analysis)												
26[a]	observational studies[b]	not serious[c]	not serious[d]	not serious[e]	not serious[f]	none	185/229 (80.8%)[l]	1134/2193 (51.7%)[m]	**OR 3.5** (1.5 to 8.1)[i]	**272 more per 1000** (from 99 more to 380 more)	⨁⨁◯◯ 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	ELECTIVE PARTIAL LUNG RESECTION	NO SURGERY	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Death versus treatment failure or relapse or success (assessed with: Individual patient data meta-analysis)												
26[a]	observational studies[b]	not serious[c]	not serious[d]	not serious[e]	not serious[f]	none	10/214 (4.7%)	304/1702 (17.9%)	**OR 0.6** (0.2 to 2.2)[i]	**63 fewer per 1000** (from 137 fewer to 145 more)	⨁⨁◯◯ LOW	CRITICAL

CL: confidence limits; OR: odds ratio

[a] 26 studies include 18 studies where surgery was performed, and eight studies where surgery was not performed.

[b] *Limitations*. All data are from observational studies. The background medication regimen and the quality of surgery and other care are expected to differ between the studies. Bias expected because the decision to operate and the type of surgery are usually closely linked to prognostic factors such as severity/seriousness of the condition, the extent of resistance pattern, effectiveness of the medical options available and the patient response to treatment.

[c] *Risk of bias*. All included studies are observational, and selection bias is a substantial risk. Patient selection for surgery may be biased towards patients with more favourable prognostic factors or the opposite. Length of treatment differed substantially between surgical and non-surgical patients, suggesting that differences in the background medical regimens may also affect outcomes; although this and other measured potential confounders were included in the adjusted analysis of effect.

[d] *Inconsistency*. Based on estimated I^2_R. Estimates for the first two outcomes (success versus treatment failure or relapse +/- death) were very similar but OR for success increases when individuals who were lost to follow-up were included in the analysis.

[e] *Indirectness*. No indirectness expected given that all patients were on treatment for MDR-/XDR-TB. The outcomes (success, treatment failure, relapse and death) were among those scored as critical by the Guideline Development Group; loss to follow up was not one of the specified outcomes but is relevant to the question.

[f] *Imprecision*. 95% confidence limits for effect estimate applied with adjustment.

[g] Pooled proportion 93% (89%–97%).

[h] Pooled proportion 77% (69%–85%).

[i] *Adjusted effect estimates*. The method of adjustment was one to one propensity score matching between surgical patients and non-surgical patients, from non-surgical studies.

[j] Pooled proportion 90% (86%–94%).

[k] Pooled proportion 64% (54%–73%).

[l] Pooled proportion 66% (62%–70%).

[m] Pooled proportion 51% (40%–62%).

Author(s): Fox GJ, Mitnick CD, Benedetti A, Chan ED, Becerra M, Chiang C-Y., Keshavjee S, Koh W-J, Shiraishi Y, Viiklepp P, Yim J-J, Pasvol G, Robert J, Shim TS, Shin SS, Menzies R

Question: Elective pneumonectomy compared to no surgery for patients on treatment of MDR-TB.

Setting: Before or after culture conversion; which comparison group would have (a) failure / relapse, (b) failure / relapse / death, and (c) failure / relapse / death / loss to follow up.

Bibliography: Fox GJ, Mitnick CD, Benedetti A, Chan ED, Becerra M, Chiang C-Y, et al. Surgery as an adjunctive treatment for multidrug-resistant tuberculosis: an individual patient data metaanalysis. Clin Infect Dis. 2016;62(7):887–95.

QUALITY ASSESSMENT							NO. OF PATIENTS		EFFECT		CERTAINTY OF EVIDENCE	IMPORTANCE
NO. OF STUDIES	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	ELECTIVE PNEUMONEC-TOMY	NO SURGERY	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Success versus treatment failure or relapse (assessed with: individual patient data meta-analysis)												
26[a]	observational studies	not serious[b]	not serious[c]	not serious[d]	not serious[e]	none	72/91 (79.1%)[f]	1134/1398 (81.1%)[g]	**OR 0.8** (0.1 to 6.0)[h]	**4 fewer per 100** (from 15 more to 51 fewer)	⨁⨁◯◯ LOW	CRITICAL
Success versus treatment failure or relapse or death (assessed with: individual patient data meta-analysis)												
26[a]	observational studies	not serious[b]	not serious[c]	not serious[d]	not serious[e]	none	72/105 (68.6%)[i]	1134/1702 (66.6%)[j]	**OR 0.7** (0.1 to 3.0)[h]	**8 fewer per 100** (from 19 more to 50 fewer)	⨁⨁◯◯ LOW	CRITICAL
Success versus treatment failure or relapse or death or loss to follow-up (assessed with: individual patient data meta-analysis)												
26[a]	observational studies	not serious[c]	not serious[c]	not serious[d]	not serious[e]	none	72/117 (61.5%)[k]	1134/2193 (51.7%)[l]	**OR 1.4** (0.7 to 3.2)[h]	**83 more per 1000** (from 89 fewer to 257 more)	⨁⨁◯◯ 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	ELECTIVE PNEUMONEC-TOMY	NO SURGERY	RELATIVE (95% CL)	ABSOLUTE (95% CL)		
Death versus success or treatment failure or relapse (assessed with: individual patient data meta-analysis)												
26[a]	observational studies	not serious[b]	not serious[c]	not serious[d]	not serious[e]	none	14/105 (13.3%)	304/1702 (17.9%)	**OR 1.8** (0.6 to 5.1)[h]	**103 more per 1000** (from 63 fewer to 347 more)	⨁⨁◯◯ LOW	CRITICAL

CL: confidence limits; OR: odds ratio

[a] 26 studies include 18 studies where surgery was performed, and eight studies where surgery was not performed.

[b] *Risk of bias.* All included studies are observational, and selection bias is a substantial risk. Patient selection for surgery may be biased towards patients with more favourable prognostic factors or the opposite. Length of treatment differed substantially between surgical and non-surgical patients, suggesting that differences in the background medical regimens may also affect outcomes; although this and other measured potential confounders were included in the adjusted analysis of effect.

[c] *Inconsistency.* Based on estimated I-squared R. Estimates for the first two outcomes (success versus treatment failure or relapse +/- death) were very similar but OR for success increases when individuals who were lost to follow-up were included in the analysis.

[d] *Indirectness.* No indirectness expected given that all patients were on treatment for MDR-/XDR-TB. The outcomes (success, treatment failure, relapse and death) were among those scored as critical by the Guideline Development Group; loss to follow up was not one of the specified outcomes but is relevant to the question.

[e] *Imprecision.* 95% confidence limits for effect estimate applied with adjustment.

[f] Pooled proportion 79% (71%–88%).

[g] Pooled proportion 77% (6%–85%).

[h] *Effect estimates.* Adjusted effect estimates applying one to one propensity score matching between surgical patients and non-surgical patients from non-surgical studies.

[i] Pooled proportion 69% (60%–78%).

[j] Pooled proportion 64% (54%–73%).

[k] Pooled proportion 62% (54%–71%).

[l] Pooled proportion 51% (40%–62%).

ANNEX 5

Evidence to decision tables

1. Standardized shorter regimens versus longer regimens for the treatment of MDR-TB

Population:	Adults or children with multidrug or rifampicin-resistant TB (MDR/RR-TB)
Intervention:	Standardized shorter regimens
Comparison:	Longer regimens
Main outcomes:	Treatment success versus failure/relapse; treatment success versus failure/relapse/death; treatment success versus failure/relapse/death/loss to follow-up
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 "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 drug-resistant TB guidelines.
Perspective:	More extensive use of shorter MDR-TB regimens for patients who are eligible, with consequent improved patient quality of life through reduction of treatment duration, better adherence and outcomes, and lower resource use.

Background: The interest in reducing the duration of treatment for MDR-TB has motivated a number of initiatives to treat patients with shorter regimens under programmatic as well as trial conditions. In the past few years, results from three studies of patients on shorter regimens have been reported and other studies have begun, including both observational cohorts and RCTs in different settings. Early results from observational studies in Bangladesh, Cameroon and Niger using regimens lasting 12 months or less have shown much higher treatment success compared with longer conventional regimens when treating patients with specific inclusion criteria. Given the limited experience in the use of these shorter MDR-TB regimens, WHO's position has until now recommended such regimens to only be used within a context of operational research and under close monitoring for effectiveness and safety during and after the end of treatment. The first findings from ongoing RCTs evaluating this regimen in different countries are not expected before the end of 2017.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ◉ Yes ○ Varies ○ Don't know	An estimated half a million new cases of MDR-TB emerge each year necessitating treatment. Only about one fourth of these were reported to be placed on treatment in recent years. Outcomes of MDR-TB treatment on a global level are poor with much loss to follow up and death; only about one half of cases have a successful outcome at the end of treatment.	MDR-TB is a global challenge and access to treatment often problematic, with regimens being typically of long duration, toxic and expensive. There is clearly an interest in reducing the duration of treatment, simplifying the administration of the regimen, and providing patients with a safer combination of medicines that can cure them in the large majority of instances.
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ◉ Large ○ Varies ○ Don't know	In contrast to longer regimens, shorter MDR-TB regimens have been reported to give relapse-free cure rates of over 85% among selected patients. The evidence summarized for the update of these guidelines has shown success ratios to be statistically significantly higher among patients treated with the shorter regimen compared with those treated with longer regimens (even when adjusted for certain factors).	Very few observations are available up to now on the performance of shorter MDR-TB regimens in the presence of additional resistance. Exclusion criterion: Previously treated MDR-TB patients with second-line drugs (this may not only be a factor of drug resistance but because these patients may differ in behaviour, adherence). In eastern European/central Asian settings where resistance patterns are more wide-ranging and where DST to some of the drugs is challenging, the regimen may be expected to be less effective. So previous treatment with a regimen containing second-line drugs is an exclusion criterion (accurate information on previous drug history may be difficult to get from patient or medical files).
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ◉ Small ○ Trivial ○ Varies ○ Don't know		Use of the shorter regimens has been associated with lower levels of adverse events, even when these were collected more systematically within a framework of operational research. Gatifloxacin, the fluoroquinolone of choice for the shorter MDR-TB regimen, until recently was reported to be associated with dysglycaemia in elderly patients treated for conditions other than TB. Since then gatifloxacin was shown to not increase dysglycaemia when used as part of four-month regimens for TB treatment. The benefits for its use are expected to outweigh the risks when the drug has a mainstay role in the treatment of a condition as serious as MDR-TB. The shorter regimens do not include a number of drugs that are most often associated with serious or distressing adverse events (such as cycloserine, PAS, linezolid). These can thus be reserved to be used as part of a salvage regimen should the patient not respond to a shorter regimen.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ◉ Very low ○ Low ○ Moderate ○ High ○ No included studies	All data analysed for this update were derived from observational studies. The results of randomized controlled trial data are not expected before the end of 2017.	

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ◉ No important uncertainty or variability ○ No known undesirable outcomes		
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the comparison?** ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ◉ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know		
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ◉ Don't know	No research evidence was identified.	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ○ Moderate ○ High ◉ No included studies	No research evidence was identified.	

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favour the intervention or the comparison?** ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ◉ No included studies	No research evidence was identified.	
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ◉ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	Although no reliable data are available on the costs of shorter TB regimens, it is expected that both drug costs and programme costs would not be higher than longer regimens. This would mean that more resources would be available for the treatment of more patients.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ○ Probably yes ◉ Yes ○ Varies ○ Don't know		The shorter MDR-TB regimens have been successfully implemented in a number of settings in Africa and Asia in recent years through the efforts of a number of technical agencies and national programmes. The intervention is acceptable to clinicians and patients.

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ◉ Probably yes ○ Yes ○ Varies ○ Don't know		The intervention has been successfully implemented under a number of settings, and even supported by major donors such as the Global Fund to Fight AIDS, TB and Malaria. Supply of clofazimine, which is indicated as a leprosy drug, is a problem in Latin America and elsewhere. No quality-assured source of gatifloxacin – a cheap fluoroquinolone (which was the cornerstone of the shorter MDR-TB regimen until relatively recently), is available today. There has been a global shortage in manufacturing following the reported risk of associated dysglycaemia. This has since been shown to be much less serious and the benefits would likely outweigh risks when the drug is used to treat a condition as serious as MDR-TB. However, the WHO recommendation for the use of shorter MDR-TB regimen and an update of the WHO Model Essential Medicines List (which as yet does not feature clofazimine and gatifloxacin as TB drugs) will be expected to have a favourable impact on drug manufacturers and fuel their interest to invest in the production of these two drugs.

Conclusions

SHOULD STANDARDIZED SHORTER REGIMENS BE USED FOR THE TREATMENT OF MDR-TB INSTEAD OF LONGER REGIMENS (ALL CASES; REGARDLESS OF PYRAZINAMIDE OR FLUOROQUINOLONE SUSCEPTIBILITY)?

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	◉	○

Recommendation	In patients with rifampicin-resistant TB or MDR-TB who have not been previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely, the WHO Guideline Development Group recommends that a shorter MDR-TB regimen may be used instead of a conventional regimen (conditional recommendation, very low certainty in the evidence)
Justification	All data used to assess the shorter MDR-TB treatment regimens were derived from observational studies. Individual patient data from Bangladesh (supported by the Damien Foundation), Uzbekistan (supported by Médecins sans Frontières (MSF)) and Swaziland (MSF) as well as aggregated data from sub-Saharan African countries (supported by the UNION and Action Damien; Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, DR Congo, Niger) were included in the analysis. These were compared with the outcomes of patients without previous exposure to second-line TB drugs who were included in the adult individual patient data (aIPD) analysis. The standard outcomes used in the intervention and comparator arms largely complied with the standardized outcomes used by TB programmes. The analyses performed for the update of the guidelines showed that patients who received shorter MDR-TB treatment regimens had a statistically significant higher likelihood of treatment success than those who received longer conventional regimens. The number of relapses was very low, although this may have been the result of the relatively small number of patients followed up. As expected, treatment success was lower in patients with additional resistance to pyrazinamide and/or fluoroquinolones, even if in general it remained high and exceeded that in the patients on individualized, longer regimens (although the differences were not statistically significant).

Subgroup considerations	Until more evidence is available, WHO recommends that the shorter MDR-TB regimen not be used in patients who have been previously treated with second-line drugs for more than one month or who have known resistance to medicines in the regimen. This recommendation is subject to patients having been tested for in vitro resistance to at least fluoroquinolones and the injectable agent used in the regimen before starting treatment. In the absence of reliable testing, patients who are highly unlikely to be infected with resistant strains based on clinical or recent representative surveillance data may also be eligible for the shorter MDR-TB regimen. *People living with HIV* need to be given the same consideration for treatment with the shorter MDR-TB treatment regimen as people who are HIV seronegative. *Children* were generally excluded from studies of shorter MDR-TB treatment regimens. However, there is no plausible biological reason to believe that these regimens are less effective in children than in adults. As a result, it is recommended that children with pulmonary rifampicin-resistant TB/MDR-TB be given the same consideration for treatment with a shorter MDR-TB treatment regimen as adults. *Pregnancy* was an exclusion criterion for shorter MDR-TB treatment regimen studies. Two of the core components of the shorter MDR-TB regimens – the injectable agent and ethionamide (or prothionamide) – are usually contraindicated in pregnancy. Withholding these medicines from the shorter MDR-TB treatment regimen could however seriously compromise its effectiveness. Thus for pregnant women it is recommended that an individualized, longer regimen be used which can allow the inclusion of four or more effective medicines with no known teratogenic properties. *Extrapulmonary disease.* The findings from studies of shorter MDR-TB regimen were limited to patients with pulmonary disease, and they cannot be extrapolated directly to all different forms of extrapulmonary TB. No recommendation is thus possible at this stage to use the shorter regimen in patients with extrapulmonary MDR-TB. *Resistance additional to isoniazid and rifampicin*. In patients infected with strains known or strongly suspected of being resistant to one or more drugs in the shorter MDR-TB treatment regimen (e.g. pyrazinamide), it is recommended that the shorter regimen not be used until more evidence becomes available about its performance in such a situation.
Implementation considerations	In order to reproduce the high cure rates achieved by the studies included in the reviews for this guidance, all efforts need to be made to avoid the acquisition of additional resistance, through careful selection of patients to be enrolled, and effective patient support to enable full adherence to treatment. It is recommended that patients be tested for susceptibility or resistance to fluoroquinolones and to the second-line injectable agent used in the regimen before being started on a shorter MDR-TB regimen. Patients with strains resistant to any of the two groups of medicines should be transferred to treatment with a longer, individualised regimen. The availability of reliable and rapid tests would be valuable to decide (within a few days) which patients would be eligible for shorter MDR-TB regimens, and what modifications to longer MDR-TB regimens are necessary based on the resistance detected. In patients with confirmed rifampicin-resistant TB or MDR-TB, the MTBDR*sl* assay may be used as the initial test, over culture and phenotypic DST, to detect resistance to fluoroquinolones and to the second-line injectable drugs (conditional recommendations; certainty of evidence for direct testing of sputum from low to moderate). This applies to testing in both children and adults. Indirect testing may include biological samples from extrapulmonary sites. While resistance-conferring mutations to fluoroquinolones detected by the MTBDR*sl* assay are highly correlated with phenotypic resistance to ofloxacin and levofloxacin, the correlation with moxifloxacin and gatifloxacin is less clear and the inclusion of moxifloxacin or gatifloxacin in a MDR-TB regimen is best guided by phenotypic DST results. In settings in which laboratory capacity for DST to fluoroquinolones and injectable agents is not yet available, the clinician and the TB programme manager would need to decide on the basis of the likelihood of resistance to these medicines, informed by the patient's clinical history and recent representative surveillance data. The evidence for the effectiveness and safety of the shorter MDR-TB regimen derives from studies where this treatment was administered under fairly standardized conditions with relatively little variation in the content and duration. Thus, the recommendation on the use of the shorter MDR-TB regimen is made under the premise that it is implemented as per the composition and duration used in the observational studies. Replacement of medicines and prolongation/shortening of the duration would only be permissible within the parameters applied in these studies (e.g. gatifloxacin replaced by moxifloxacin; prothionamide replaced by ethionamide; intensive phase prolonged up to six months in case of no sputum conversion). Two staples of the regimen, clofazimine and high-dose isoniazid, may be difficult to procure in some countries. Moreover, there are no good paediatric formulations of clofazimine and dividing the capsule into smaller doses is almost impossible, making dosing in children uncertain. Given the global shortage in the supply of quality-assured gatifloxacin in recent years, the sites where observational studies have been conducted have had to substitute this agent with moxifloxacin. This has led to an important increase in the overall price of the regimen, with moxifloxacin typically accounting for about one half of overall drug costs. The implementation of these guidelines at the national level needs to ensure that sufficient quantities of these medicines are available to meet the demand and that no stock-outs occur.

Monitoring and evaluation	Patients who receive a shorter MDR-TB treatment regimen need to be monitored during treatment and after completion using schedules of relevant clinical and laboratory testing which have been successfully applied in the studies under field conditions. The WHO framework for active TB drug-safety monitoring and management (aDSM) needs to be applied to ensure appropriate action to respond promptly to adverse events and an acceptable level of monitoring for them, alongside the monitoring for treatment outcomes.
Research priorities	▪ STREAM study results will be available in a few years but the panel felt comfortable to make the conditional recommendations. ▪ The WHO Guideline Development Group discussed the research priorities for reducing the duration of MDR-TB regimens and highlighted the following priorities: – Future research needs to include the effectiveness/safety of the shorter MDR-TB treatment regimen in subgroups which have been systematically excluded from study protocols (e.g. children, patients with different forms of extrapulmonary disease) and in settings where background resistance to drugs other than fluoroquinolones and second-line injectable agents is high (e.g. pyrazinamide or high-level isoniazid resistance). – Implementation research on the introduction of the shorter MDR-TB regimen. – Studies on cost effectiveness.

2. Regimens with individualized composition and duration for adults and children with MDR-TB in whom a shorter MDR-TB regimen cannot be used

Population:	Adults and children with rifampicin-resistant TB/MDR-TB in whom a shorter MDR-TB regimen cannot be used
Intervention:	A longer regimen of individualized composition and duration
Comparison:	Other
Main outcomes:	Cured/completed by the end of treatment; culture conversion by six months; treatment failure; relapse; survival (or death); adverse reactions (severity, type, organ class)
Setting:	Treatment administered to patients in both hospital and ambulatory settings; the distribution of the studies and data was global
Perspective:	The longer regimen is reserved for adult and paediatric patients who are ineligible for the shorter MDR-TB regimen due to additional resistance, extrapulmonary disease, or other contraindications. The design of the regimen's composition is revised to optimize the use of available medicines based on available evidence and thus it maximizes the likelihood of patients having a successful outcome at its end.

Background: A number of rifampicin-resistant TB/MDR-TB patients (children and adults) are expected not to be eligible for the shorter MDR-TB regimen recommended elsewhere in these guidelines. These include patients who were previously treated with second-line TB medicines for more than one month, individuals infected with strains resistant to one or more drugs in the shorter MDR-TB regimen, and patients with extrapulmonary disease. In these patients, a longer regimen is usually indicated, with a composition and duration individualized to increase the likelihood of the regimen's effectiveness and achieve a good balance of expected benefits to harms. These regimens have been in use for several years in many different geographical settings but their use has been limited to published observational studies of patients followed up under programmatic conditions, with only solitary RCTs designed and conducted to assess the benefit / safety of the longer regimens.

For the 2016 update of these guidelines, WHO has used three different sources of evidence to summarize the effects, namely:

i) A systematic review and study-level meta-analysis for the effect of individual second-line drugs in MDR-TB treatment (see Annex 6 for summary of unpublished study).

ii) An individual-patient data analysis for 9153 MDR-TB patients nearly all of whom are adults (up to 2010) (Ahuja SD, et al. PLoS Med. 2012;9(8):e1001300).

iii) An individual-patient data analysis for 974 paediatric MDR-TB patients (see Annex 6 for summary of unpublished study).

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ○ Large ◉ Varies ○ Don't know	Treatment of MDR-TB in adults and children with longer second-line regimens is known to increase the likelihood of cure and lower the risk of chronicity and death (Ahuja SD, et al. PLoS Med. 2012;9(8):e1001300; Seddon JA, et al. Thorax. 2014;69(5):458–64.). Recent reviews have shown that success ratios averaging to about 60% in adults with MDR-TB and 90% in children are possible among patients treated under programmatic conditions.	The likelihood of success is expected to vary depending on a number of patient factors (severity of disease, resistance patterns) and health care services (access to different medications of good-quality, patient monitoring and support).
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ◉ Varies ○ Don't know	A number of the second-line medications are associated with undesirable adverse effects in both adults and children with MDR-TB, which at times lead to serious outcomes and discontinuation or substantial change in regimens (Bloss E, et al. Int J Tuberc Lung Dis. 2010;14(3):275–81; Seddon JA, et al. Journal of Infection. 2013;66(4):320–9; see also body of guidelines (including Table 7), GRADE tables in Annex 4 and summaries of unpublished studies in Annex 6 for more details on effectiveness and safety of longer MDR-TB regimens in adults and children).	The likelihood of harms is expected to vary depending on a number of patient factors (comorbidity, disease severity) and the health intervention (choice of drugs, pill-burden and drug–drug interactions, adequacy of safety monitoring and support, options to switch drugs in case of adverse reactions). The fact that longer regimens are composed of at least five medications in the intensive phase increases the likelihood of additive adverse effects and interactions. The reclassification of PAS to Group D3 implies that this medication that is often responsible for many undesirable effects would be used less often. Moreover, it is expected that a larger proportion of patients will be placed on the shorter MDR-TB regimen lasting 9–12 months, which contains less medications associated with major adverse effects (cycloserine, linezolid, PAS; ethionamide / prothionamide limited to the intensive phase which is shorter than in most longer regimens).
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ◉ Very low ○ Low ○ Moderate ○ High ○ No included studies	Most of the data reviewed for both effectiveness and safety derive from observational studies with limited possibilities of adjustment. The quality of the evidence from the few randomized trials was marked downwards because of imprecision (single studies with relatively small numbers of observations).	Efforts were made to use individual-level patient data where possible in both adults and children to adjust for covariates that could influence outcomes. However, residual confounding is very likely to have been substantial in many of the analyses.

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the comparison?** ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ◉ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	No research evidence was identified.	
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ◉ Probably yes ○ Yes ○ Varies ○ Don't know	There has been a steady increase in the number of rifampicin-resistant TB/MDR-TB patients placed on second-line treatment globally and reports to WHO show that in 2014, 111 000 patients were started on treatment (Global tuberculosis report 2015 (WHO/HTM/TB/2015.22); apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf)	Longer, individualized regimens have been successfully used to treat MDR-TB patients for the past few decades, under a variety of settings in both high- and low-resource situations. Efforts in low- and middle-income settings have been supported through domestic funding and also externally by major donors like USAID and the Global Fund to Fight AIDS, TB and Malaria. The availability of core second-line drugs required to compose the longer regimens has improved in recent years. The Global Drug Facility now includes most of the drugs on its catalogue. The price of the drugs has also decreased over time, including that of linezolid and moxifloxacin, as the generic manufacture of these agents has increased (most drugs in Groups A to D with the exception of the new drugs bedaquiline and delamanid are now off patent). There are still challenges in the procurement of certain drugs. Bedaquiline and delamanid remain expensive although initiatives have successfully donated bedaquiline in the past few years and made delamanid available at a lower cost to low-income countries. There is no quality-assured source of gatifloxacin (a cheap later-generation fluoroquinolone), which is available today given a global shortage in manufacture following a reported risk of associated dysglycemia (this risk has since been shown to be much lower in TB patients and benefits would likely outweigh risks when the drug is used to treat a condition as serious as MDR-TB). Clofazimine supplies are also limited and this drug is indicated primarily for leprosy and used "off-label" for the treatment of MDR-TB. Both clofazimine and gatifloxacin do not as yet feature on the WHO Model Lists of Essential Medicines as TB drugs. The programmatic management of drug-resistant TB has become a mainstay component of many national TB programmes and several countries have successfully introduced a sound monitoring framework to follow up patients for response to treatment and to safeguard patient safety.

Conclusions

SHOULD A REGIMEN OF INDIVIDUALIZED COMPOSITION AND DURATION BE USED IN ADULTS AND CHILDREN WITH RIFAMPICIN-RESISTANT TB/MDR-TB IN WHOM A SHORTER MDR-TB REGIMEN CANNOT BE USED?

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	◉	○
	The recommendations apply to children and adults with rifampicin-resistant TB/MDR-TB (see also under Subgroup considerations). In children without severe disease (severity defined in the paediatric individual patient data (pIPD) on the basis of poor nutritional status, extensive disease on chest radiography, presence of severe forms of extrapulmonary disease and HIV sero-positivity), the injectable agents may be excluded from the regimen.				
Recommendation	a) In patients with rifampicin-resistant TB or MDR-TB, the Guideline Development Group recommends a regimen with at least five effective TB medicines during the intensive phase, including pyrazinamide plus four core second-line TB medicines, one chosen from Group A, one from Group B, and at least two from Group C [1] (conditional recommendation, very low certainty in the evidence). If the minimum of effective TB medicines cannot be composed as above, an agent from Group D2 and other agents from Group D3 may be added to bring the total to five [2]. b) In patients with rifampicin-resistant TB or MDR-TB, the Guideline Development Group recommends that the regimen be further strengthened with high-dose isoniazid and/or ethambutol (conditional recommendation, very low certainty in the evidence). [1] Group A=levofloxacin, moxifloxaci, gatifloxacin; Group B=amikacin, capreomycin, kanamycin, (streptomycin); Group C= ethionamide (or prothionamide), cycloserine (or terizidone), linezolid, clofazimine; in children with non-severe disease Group B medicines may be excluded [2] Group D2=bedaquiline, delamanid; Group D3=*p*-aminosalicylic acid, Imipenem-cilastatin, meropenem, amoxicillin-clavulanate, (thioacetazone)				

Justification

Desirable and undesirable effects

A. Fluoroquinolones

Based on the evidence reviews, the GDG concluded that treatment with later-generation fluoroquinolones (defined for these guidelines as high-dose levofloxacin, moxifloxacin, and gatifloxacin) significantly improves treatment outcomes in adults with rifampicin-resistant TB or MDR-TB. This group of drugs is considered to be the most important component of the core MDR-TB regimen and the benefits from their use outweighs potential risks. They should therefore always be included unless there is an absolute contraindication for their use. The order of preference for the inclusion of the later-generation fluoroquinolones in MDR-TB regimens is as follows: high-dose levofloxacin, moxifloxacin and gatifloxacin. It is recommended that ofloxacin be phased out from MDR-TB regimens and that ciprofloxacin is never used due to the limited evidence for their effectiveness. Although the pIPD had high levels of confounding and insufficient numbers to adequately analyse the treatment effect of high-dose levofloxacin, moxifloxacin and gatifloxacin, data from adults with MDR-TB shows a treatment benefit. Therefore these recommendations have been extrapolated to children.

Fluoroquinolones in general have a good safety profile and considering the seriousness of rifampicin-resistant TB/MDR-TB, the potential for drug-related harms is offset by the benefits from their use. Although adverse events were poorly recorded, in the study-level meta-analysis, the frequency of SAEs (defined as Grade 3–4 adverse events or medicines stopped permanently due to adverse event) attributed to fluoroquinolones was low (1.2%–2.8%). Moxifloxacin carries a risk of QT prolongation, a cause for concern when used in combination with medications that have a similar effect (including bedaquiline and delamanid). There are fewer concerns about the cardiotoxicity of levofloxacin and gatifloxacin, an important consideration given that several other second-line drugs have QT-prolonging potential.

Concerns about dysglycaemia reported in 2006 in patients treated with gatifloxacin for conditions other than TB led the parent company to stop manufacture of the drug, and a global shortage in quality-assured formulations of this drug ensued. A trial of a four-month standardized regimen for drug-susceptible TB that included gatifloxacin (400 mg once daily) published in 2014 reported no significant risk of hyperglycaemia associated with exposure to gatifloxacin. Although adverse events were poorly recorded the data for this review showed that there was a lower risk of serious adverse events (SAEs; defined as Grade 3–4 adverse events or drugs stopped due to adverse event) in patients taking gatifloxacin (3.6%) than in those who did not, including those receiving no fluoroquinolones (8%; not statistically significant). The frequency of SAEs associated with gatifloxacin was thus comparable to the one associated with fluoroquinolones in the study-level meta-analysis.

B. Second-line injectable agents

Based on the available evidence, second-line injectable agents were associated with an increased likelihood of treatment success when included in a longer MDR-TB treatment regimen (the small size of the population not receiving an injectable agent in the aIPD limited the power to detect an impact of this class of agents). It is therefore recommended that adults with rifampicin-resistant TB or MDR-TB always receive a second-line injectable agent as part of their regimen unless there is an important contraindication. In children with mild forms of disease, however, the harms associated with this group of medications may outweigh potential benefits and therefore injectable agents may be excluded in this group. The GDG based this decision upon the observation that treatment success in children with clinically-diagnosed disease (which was associated with less severe clinical manifestations) was in general high and did not differ significantly between patients who received a Group B medication (98.1%) and those who did not (93.5%). For children with additional resistance to fluoroquinolones, Group B medication is best retained.

The choice of which of the three standard agents to use – amikacin, capreomycin or kanamycin – would be determined by the likelihood of effectiveness and implementation considerations. While streptomycin is not usually included with the second-line drugs it can be used as the injectable agent of the core MDR-TB regimen if none of the three other agents can be used and if the strain is unlikely to be resistant to it.

Adverse effects need to be carefully monitored for while using second-line injectable agents. Hearing loss and nephrotoxicity are among the most frequent and most severe side effects. However, skin rash, hypersensitivity and peripheral nephropathy may also occur. The risk of adverse effects increases with the total cumulative dose of second-line injectable agents, so caution has to be exercised when given to people who have previously received these medications, including streptomycin as part of a regimen for drug-susceptible TB. In children especially, hearing loss can have a profound impact on quality of life, affecting acquisition of language and the ability to learn at school.

Although adverse events are poorly reported, the data for this review found that 7.3% of adult patients (10.1% in children) had SAEs attributed to second-line injectable agents. In a study focused on hearing loss in children with TB, 24% of children treated for MDR-TB with an injectable agent had hearing loss and 64% of children had progression of hearing loss after completing it (in this study, 30% of the children were HIV-infected).

C. Other core second-line agents

When designing the core MDR-TB treatment regimen, two or more of the following four medicines are to be included: ethionamide (or prothionamide), cycloserine (or terizidone), linezolid and clofazimine, usually in this order of preference, unless the balance of benefits-to-harms for the individual patient demands otherwise. Group C agents are included to bring the total effective second-line TB medicines in the core regimen to at least four during the intensive phase of the regimen. In addition, if pyrazinamide cannot be included or counted upon, another agent is added. Ethionamide can be used interchangeably with prothionamide, and terizidone instead of cycloserine.

Given the lack of reliable DST for drugs belonging to Group C, the choice of which ones to include is determined by the balance of desirable to undesirable effects and by implementation considerations. The adult and paediatric IPD meta-analyses showed an increase in the likelihood of treatment success when MDR-TB treatment regimens included cycloserine (marginally statistically significant) and ethionamide/prothionamide (statistically significant only in adults; in the pIPD the vast majority of children did not receive ethionamide or prothionamide and significance testing was therefore not always possible for want of a sufficient number of controls). In contrast to cycloserine/terizidone and ethionamide/prothionamide, RCT data from a few recent studies are now available for clofazimine and linezolid. Linezolid has shown a statistically significant treatment benefit in both RCT and cohort studies in adult patients, with this benefit being most pronounced in patients with additional resistance to fluoroquinolones and with XDR-TB. Both the adult and paediatric IPD showed no significant increase in treatment success associated with the use of clofazimine, while linezolid was used too sparingly in the cohorts included to allow a conclusive analysis.

Ethionamide and prothionamide cause gastrointestinal disturbance, in particular vomiting, which can limit tolerability. Hypothyroidism may occur, especially in combination with PAS. Hypothyroidism is reversible upon cessation of drugs. Although adverse events are poorly reported, the data for this review found that 8.2% of patients had SAEs due to ethionamide or prothionamide.

Cycloserine has a well-established association with neuropsychiatric adverse effects. However, the aIPD meta-analysis revealed low levels of SAEs, although data on adverse events were poorly reported (4.5% in the study-level meta-analysis conducted for this update). A meta-analysis published in 2013 comparing the adverse effects of cycloserine with terizidone found that terizidone had little to no benefit over cycloserine with regard to adverse effects.

Adverse effects of linezolid include thrombocytopenia and anaemia. These can be severe and life threatening, although these adverse effects are reversible with cessation of drug or on some occasions with lowering the drug dose (usually from 600 mg daily to 300 mg daily). Haematologic toxicities are less common with current strategies of once-daily dosing. Peripheral neuropathy may or may not improve with cessation of drug. The outcome of optic neuropathy upon cessation of linezolid is less clear, and should be treated as a medical emergency. Given the potentially serious adverse effects of linezolid – particularly anaemia, thrombocytopenia, lactic acidosis, peripheral neuropathy and optic neuropathy – the decision to use linezolid must balance its risks and benefits and the availability of other TB medicines. Due to the potential for severe adverse events, linezolid use needs to be accompanied by close monitoring for adverse events. Where this is not possible, linezolid would best be reserved for MDR-TB patients who have additional drug resistance, or XDR-TB patients, or for those who are intolerant to other components of the core regimen.

Clofazimine probably contributes to the sterilizing function of MDR-TB regimens where pyrazinamide is not effective. The single randomized control trial, although it had serious methodological concerns, showed a statistically significant treatment benefit associated with the use of clofazimine. However, much of the evidence for its effect in MDR-TB is based on observational studies, which showed conflicting or inconclusive findings. One of the main adverse effects of clofazimine is skin discoloration/darkening, which may be distressing to patients. In the RCT, the adverse events reported were mostly limited to skin conditions and discoloration, and did not lead to discontinuation in the use of the drug. Overall, small rates of adverse events were noted in observational studies. SAEs appear to be relatively uncommon. There has been some evidence that clofazimine may prolong the QT interval, so caution is advised when using this medication in combination with other drugs also known to have the same effect.

D. Add-on agents

This group of medicines includes drugs that do not form part of the core second-line agents. It is split into three subgroups:

Group D1 consists of pyrazinamide, ethambutol and high-dose isoniazid. These agents are usually added to core second-line medications, unless the risks from confirmed resistance, pill burden, intolerance or drug–drug interactions outweigh potential benefits.

The aIPD showed improved likelihood of success (versus treatment failure, relapse or death combined) in patients who had pyrazinamide included in their regimens. This effect was significant both statistically and in absolute terms. The pIPD did not show a significant treatment effect with use of pyrazinamide. In many settings, rifampicin-resistant TB strains frequently have additional resistance to pyrazinamide (in the order of 50%–60%). While it would be desirable to avoid giving pyrazinamide to patients whose strains are resistant to the drug, it is acknowledged that reliable DST for pyrazinamide is very often unavailable in resource-constrained settings. Although adverse events are poorly reported, the data from the study-level meta-analysis showed that 2.8% of patients who received pyrazinamide had SAEs attributed to it. The balance of desirable to undesirable effects favours the addition of pyrazinamide to the core second-line MDR-TB regimen by default, unless resistance is confirmed from reliable DST, or there are well-founded reasons to believe that the strain is resistant, or there are other contra-indications for its use, particularly risk of significant toxicity. As for the drugs from the core regimen, if pyrazinamide is compromised or cannot be used, more agents from Group C and subsequently Group D are added until five effective drugs are present in the intensive phase of the regimen.

The recommendation for the inclusion of high-dose isoniazid in adult MDR-TB regimens is largely based on evidence from the analysis of pIPD. This analysis showed a statistically significant increased likelihood of treatment success (versus treatment failure, relapse or death combined) in children with bacteriologically confirmed MDR-TB, even after adjustment for age, HIV status, sex, TB disease severity and treatment centre (treatment with high-dose isoniazid was almost exclusively done in South African sites). An RCT of high-dose isoniazid therapy for MDR-TB in adults found no increased risk of hepatotoxicity. Additionally, high-dose isoniazid was very well tolerated in children with drug susceptible tuberculous meningitis in a large cohort study from the Western Cape (van Toorn R, et al. Pediatr Infect Dis J. 2014;33(3):248–52).

Isoniazid is recommended alongside a full MDR-TB regimen in patients with rifampicin-resistant TB strains confirmed or suspected to be susceptible to isoniazid. High-dose isoniazid is one of the core components of the shorter MDR-TB treatment regimen. Strains bearing mutations in the promoter region of the inhA gene may have a minimum inhibitory concentration (MIC) to isoniazid, which is low enough to be overcome by high-dose isoniazid; and in such settings the drug may still add benefit. However, this mutation has been associated with high-level ethionamide resistance and therefore, if present, ethionamide (or prothionamide) may have to be replaced in the regimen. In settings with elevated prevalence of high-level isoniazid resistance associated with katG mutations, high-dose isoniazid may be less effective and therefore its routine use may not be warranted. Susceptibility to ethionamide (or prothionamide) is not affected by these mutations and can be used in combination with high-dose isoniazid if the isoniazid resistance mutation is not known.

The aIPD did not show any statistically significant association between use of ethambutol and likelihood of success. Ethambutol may cause ocular toxicity, which can be difficult to diagnose in young children, although this risk is reduced if the dose does not exceed recommended limits (0.5% of SAEs reported associated with the meta-analysis conducted for this review although the reporting of adverse events data is often incomplete). Special care is needed when renal function is compromised. Rifampicin-resistant TB/MDR-TB strains may also be resistant to ethambutol, particularly in those patients who have been treated with this drug previously. However DST for this drug is not considered reliable and reproducible. The potential benefit that ethambutol may add to a core MDR-TB regimen needs to be balanced carefully with the inconvenience of adding another medicine to the regimen and the risks for associated harms.

Group D2 is made up of bedaquiline and delamanid, two new drugs that have been released in recent years. WHO has issued interim policy on the use of these medicines in 2013 and 2014. The current guidelines make no change to the previous recommendations on how bedaquiline and delamanid may be added to a core MDR-TB regimen in adults (no recommendation for children). The WHO policy on the role of D2 agents, including their potential use in children, was under review at the time of the production of these guidelines.

Group D3 consists of *p*-aminosalicylic acid (PAS), imipenem–cilastatin, meropenem, clavulanate and thioacetazone. These drugs are only to be used when a MDR-TB regimen with at least five effective drugs (i.e. primarily four core second-line medicines plus pyrazinamide) cannot be otherwise composed.

The aIPD, as well as the study-level meta-analysis conducted for the current guidelines revision, found no significant effect of PAS on treatment success. In addition, PAS use is associated with a high frequency of adverse effects (12.2% SAEs in the meta-analysis undertaken for this study). PAS is thus reserved for situations when there is no option to use other drugs.

Carbapenems (imipenem–cilastin or meropenem) appear to be hydrolyzed more slowly by *M. tuberculosis* when combined with clavulanic acid. Clavulanate has shown poor results in *in vitro* studies and in early bactericidal activity (EBA) studies. The aIPD showed that patients treated with clavulanate were more likely to have poor treatment outcomes, although this may be due to confounding by the higher likelihood that patients receiving this drug tended to have more severe disease (not all confounding could be adjusted for in the analysis). WHO recommends that whenever clavulanate and carbapenems are included in regimens they are to be always used together. Clavulanate is only available as combination preparations containing amoxicillin. The spectrum of adverse effects associated with amoxacillin–clavulanate and carbapenems is to a large extent identical to that associated with the penicillins.

Thioacetazone has been used extensively in the past as part of first-line combination therapy for TB, based on RCT evidence of effectiveness. Use of the drug in TB treatment has however been restricted since the early 1990s due to the severe skin reactions it causes, including Stevens-Johnson syndrome and toxic epidermal necrolysis (which can lead to death, especially in people living with HIV), and the widespread availability of safer, affordable alternatives for the combination TB regimens. If thioacetazone is being considered as part of a MDR-TB treatment regimen, close monitoring for severe skin reactions is required and it is imperative that the patient be tested for HIV, and that the drug not be used if the patient is HIV seropositive.

M. tuberculosis is intrinsically resistant to the macrolide class of antibiotics. The evidence reviews for the current guidelines showed no indication of the effectiveness of drugs of this class (clarithromycin, azithromycin), which have at times been included in MDR-TB regimens in both adults and children. In addition, the aIPD showed an increased risk, although not statistically significant, for poor outcomes in patients receiving macrolides although macrolides appeared to be safe in prolonged use. Macrolides are associated with QT prolongation, which would be of particular concern if patients are receiving other TB drugs that may have a similar risk, such as moxifloxacin, clofazimine, bedaquiline or delamanid. WHO therefore recommends that clarithromycin and azithromycin not be included in MDR-TB regimens.

Adverse effects of PAS include gastrointestinal disturbance and hypothyroidism (in particular when given in combination with ethionamide/prothionamide). Hypothyroidism is reversible upon cessation of the drugs. Although adverse events are poorly reported, the data for this review found that 12.2% of patients had SAEs (defined as Grade 3–4 adverse events or drugs stopped due to adverse event) attributed to PAS. The pIPD showed possibility of treatment harm associated with the use of PAS (not statistically significant). However, PAS is frequently given to children with few other treatment options, and therefore this effect may be due to confounding by indication (sites that had poorer outcomes with PAS also had significantly higher rates of children who were HIV seropositive, malnourished, had severe pulmonary disease and who had additional resistance to fluoroquinolones and the second-line injectable medicines).

Subgroup considerations	***Rifampicin-resistant TB/MDR-TB with additional resistance to fluoroquinolones, second-line injectable agents and XDR-TB*** In rifampicin-resistant TB/MDR-TB patients with confirmed or well-founded belief of resistance to medications from Group A (fluoroquinolones) or Group B (second-line injectable), substitution of drugs from these classes proceeds as detailed below. If any of the components of the regimen – the four core second-line medicines and pyrazinamide – is considered not to be effective, additional agents from Groups D2 or D3 are added. This is almost always necessary when resistance to both Groups A and B drugs (i.e. XDR-TB) is present. An analysis of individual data collected for the update of the WHO drug-resistant TB treatment guidelines of 2011 concluded that regimens containing more drugs were associated with the highest odds of success for MDR-TB patients who had additional resistance to fluoroquinolones and/or second-line injectable agents. The current WHO advice when designing regimens for patients with resistance to fluoroquinolones, second-line injectable medications and XDR-TB continues to apply. Access to rapid diagnostic testing which could reliably identify resistance to fluoroquinolones or injectable medications would help clinicians to decide how to modify longer MDR-TB regimens. The GenoType MTBDRs*l* line probe assay may now be used as an initial test, over phenotypic culture-based DST, to detect resistance to fluoroquinolones and second-line injectable drugs (conditional recommendation; certainty of evidence low to moderate for direct testing). GenoType MTBDRs*l* can be used in both children and adults and as a direct and indirect test (for extrapulmonary samples). While resistance-conferring mutations to fluoroquinolones detected by the MTBDRsl assay are highly correlated with phenotypic resistance to ofloxacin and levofloxacin, the correlation with moxifloxacin and gatifloxacin is less clear and the inclusion of moxifloxacin or gatifloxacin in a MDR-TB regimen is best guided by phenotypic DST results. ***TB of the central nervous system*** The treatment of tuberculous meningitis related to rifampicin-resistant or MDR strains is best guided by drug susceptibility results and the known properties of TB drugs to penetrate the central nervous system (CNS). In patients with rifampicin-resistant TB/MDR-TB meningitis, it is recommended that the medications selected for the regimen have good CNS penetration properties. The fluoroquinolones recommended by these guidelines have good CNS penetration, as do ethionamide (or prothionamide), cycloserine (or terizidone) and linezolid. Pyrazinamide has good CNS penetration, although caution should be exercised, as a large percentage of MDR-TB strains may be resistant. Isoniazid penetrates the CNS very well, with higher doses reaching adequate MICs in the cerebrospinal fluid. Due to its good CNS penetration, high-dose isoniazid is recommended as part of the treatment regimen unless high-level resistance is known to exist. PAS and ethambutol do not penetrate the CNS well and should not be counted upon among the number of effective drugs to treat MDR-TB meningitis. Kanamycin, amikacin and streptomycin only penetrate the cerebrospinal fluid in the presence of meningeal inflammation. There are little data on the CNS penetration of capreomycin, clofazimine, bedaquiline or delamanid. ***People living with HIV*** The composition of the treatment regimen for MDR-TB does not differ for people living with HIV. However, thioacetazone should not be given to patients who are HIV positive. If thioacetazone is being considered as part of a treatment regimen HIV infection needs to be reliably excluded in the patient.

Implementation considerations

The implementation of MDR-TB chemotherapy is feasible under programmatic conditions, as has been amply shown by the global expansion in the use of longer MDR-TB regimens worldwide, particularly in the past decade. Changes made by the current revision to the grouping of the medicines and to the composition of the longer regimen are not expected to have major impact on their continued use. Most of the fluoroquinolones and the injectable agents are readily available, as are the majority of the Group C and Group D agents. The latest WHO Model Lists of Essential Medicines (August 2015) includes most of the agents in Groups A to D except for gatifloxacin and thioacetazone. However, clofazimine, meropenem, imipenem–cilastatin and amoxicillin–clavulanate are listed for indications other than TB, while bedaquiline and delamanid are only included in the adult list. Other specific factors important for implementation are discussed in the respective sections below.

Where possible a patient with rifampicin-resistant TB/MDR-TB strain needs to be tested for susceptibility to medicines planned for inclusion in the regimen. The availability of reliable tests for susceptibility to fluoroquinolones and to the second-line injectable drugs (which would give results within a few days) is valuable to ensure that longer MDR-TB regimens are strengthened as necessary (reference is made to the recommendations on the use of line probe assay for second-line drugs – the MTBDRsl assay).

Where reliable DST is not an option, proof of the effectiveness of a medicine needs to be based on a careful clinical history of the patient's previous exposure to the medicine, of significant contact with another rifampicin-resistant TB/MDR-TB patient whose antibiogramme is documented, and from knowledge of the prevalent resistance patterns centred on representative drug-resistance surveillance. Both the DST and the individual clinical history should be considered when constructing a treatment regimen. The only reliable laboratory tests for TB drug susceptibility (or resistance) that are widely used today are those for isoniazid, rifampicin, fluoroquinolones and second-line injectable agents.

A. Fluoroquinolones

Both levofloxacin and moxifloxacin are commonly used to treat MDR-TB. Levofloxacin is more widely available than moxifloxacin, which is more expensive although a reduction in its price is expected in the coming years.

Gatifloxacin was an affordable drug and had been commonly used by TB treatment programmes until the concerns about its dysglycaemic effects led to a global shortage in this medicine. If manufacture of quality-assured formulations of the drug restarts, it could substantially lower the costs of regimens by substituting more expensive options in fluoroquinolones.

Moxifloxacin is relatively easy to administer to older children. However, the tablet must be split to accommodate dosing in younger children and it is highly unpalatable once split or crushed. Levofloxacin is available as a suspension.

B. Second-line injectable agents

These agents present problems to administer parenterally on a daily basis for several months, often necessitating hospitalization. Giving injections to children and underweight adults is particularly painful and unwelcome.

C. Other agents

Ethionamide and prothionamide are inexpensive, readily available worldwide and easily administered.

Cycloserine has been one of the standard drugs for the treatment of MDR-TB for several years and therefore experience in its use is widespread. It is inexpensive.

Terizidone is less widely used but is available on the GDF Products List.

Clofazimine is inexpensive but it can be difficult to procure.

The implementation of these guidelines at national level needs to ensure that sufficient quantities of these medicines are available to meet the demand and that no stock-outs occur. Moreover, given that there are no good paediatric formulations the capsule contents need to be expressed manually and divided into smaller doses, with risks of incorrect dosing in children.

When linezolid is used, there needs to be close monitoring for side effects, particularly anaemia, thrombocytopenia, lactic acidosis, peripheral neuropathy and optic neuropathy, as these can be severe and life threatening. Historically linezolid has been very expensive, however, it has recently come off patent and the availability of generic products has reduced its market price substantially and it may decrease even further.

	D. Add-on agents Pyrazinamide is inexpensive, readily available and easy to administer. Isoniazid is inexpensive. It is important to consider the epidemiology of high-level versus low-level isoniazid mutations in a population before standard treatment regimens including high-dose isoniazid are recommended. Ethambutol is inexpensive and readily available. PAS may be difficult to obtain although it is available through the GDF. Otherwise it is relatively inexpensive and easy to administer. Amoxacillin-clavulanate is inexpensive and easily obtainable. However, the carbapenems are expensive and are difficult to administer as they must be given two or three times per day via an intravenous line. Thioacetezone is inexpensive but it has limited availability and it is not currently available through the GDF. The current revision of the guidelines did not re-analyse the optimal duration of treatment (intensive and continuation phases). The recommendations from the 2011 guidelines that were based on the aIPD meta-analysis, thus continue to apply. The 2011 guidelines conditionally recommended an intensive phase of eight months for most MDR-TB patients and total treatment duration of 20 months in patients who had not been previously treated. The duration may need to be modified according to the patient's response to therapy. The association between treatment success and the total length of treatment was less clear in patients who had been previously-treated compared with those who had not, although the likelihood of treatment success appeared to peak between 27.6 and 30.5 months. The number of observations was also far fewer than for those who had no previous MDR-TB treatment. As a result no recommendation on total duration was made in the 2011 revision for previously treated patients. Many of the rifampicin-resistant TB/MDR-TB patients who will be ineligible for the shorter MDR-TB regimen and referred for treatment with longer regimens would have been treated with second-line medication in the past; in these patients uncertainties will remain on the optimal duration of treatment and therefore the length of therapy would need to be guided primarily by the response to therapy.
Monitoring and evaluation	Patients on longer MDR-TB treatment regimens need to be monitored for response to treatment and for safety using reasonable schedules of relevant clinical and laboratory testing. Frameworks for the surveillance of bacteriological status, drug resistance and outcomes have been fairly standardized over the past decade. The systematic monitoring of adverse events during and after the end of treatment is a more recent introduction in TB programmes and experience in their implementation is still developing in many countries. Its rationale is largely defined by more frequent use of new and re-purposed medications in MDR-TB treatment regimens in the world, at times in combinations for which there has been very limited experience of use.
Research priorities	▪ A need for more randomized control studies, especially involving the new drugs and regimens. ▪ Inclusion and separate reporting of outcomes for key subgroups in such studies, especially children and HIV-positive individuals on treatment. ▪ More complete recording of adverse events and standardized data recording on organ class, seriousness, severity, and certainty of association, to allow reliable comparison of the association between adverse events and exposure to different medicines. ▪ Identification of factors that determine the optimal duration of treatment (e.g. previous treatment history, baseline resistance patterns, site of disease, child/adult). ▪ Determination of the minimum number of drugs and treatment duration (especially in patients previously treated for MDR-TB). ▪ Conditions under which injectable-sparing regimens can be used in both children and adults (e.g. surrogates for severity / extent of disease, alternative medication). ▪ Pharmacokinetic studies to determine optimal drug dosing and safety (especially in pregnancy). ▪ Improved diagnostics and drug-susceptibility testing methods (e.g. which test for pyrazinamide). ▪ Palliative and end-of-life care in patients with very advanced resistance patterns.

3. Elective partial lung resection versus no surgery for patients on treatment for MDR-TB

Population:	Patients on treatment for MDR-TB
Intervention:	Elective partial lung resection
Comparison:	No surgery
Main outcomes:	Success versus treatment failure or relapse; success versus treatment failure or relapse or death; success versus treatment failure or relapse or death or loss to follow-up; death versus treatment failure or relapse or success.
Setting:	Which types of surgery encompassed (lobectomy, segmentectomy, wedge resection); definition of non-response and adverse outcome of surgery; definition of extensive disease; how specialized were the centres/practitioners which provided surgery (external validity); under which conditions to indicate resection surgery and when to contraindicate; before or after culture conversion.
Perspective:	Defining better the role of surgery; decision when to operate and type of intervention; and its impact in patients on treatment for MDR-TB or XDR-TB.

Background: Surgery has been used to treat TB patients since before the advent of chemotherapy. With the challenging prospect of inadequate regimens to treat MDR/XDR-TB and the risk for serious sequelae, the role of pulmonary surgery is being re-evaluated as a means to "debulk" intractable pathology in the lung and to reduce bacterial load and thus improve prognosis.

The review for this question is based upon an individual, patient-level meta-analysis to evaluate the effectiveness of different forms of elective surgery as an adjunct to combination medical therapy for MDR-TB (supplemented by a literature review). Demographic, clinical, bacteriological, surgical and outcome data on MDR-TB patients on treatment were obtained from the authors of 26 cohort studies, identified from three systematic reviews of MDR-TB treatment.

The analyses summarized in the GRADE tables consist of three strata comparing treatment success (cure and completion) with different combinations of treatment failure, relapse, death and loss to follow-up. Two sets of such tables were prepared for: (i) partial pulmonary resection and (ii) pneumonectomy. Partial pulmonary resection was significantly associated with treatment success when compared with all other outcomes put together (treatment failure or relapse or death or loss to follow-up) ($P<0.05$). Prognosis appeared to be better when surgery was performed after culture conversion. No effect was observed in pneumonectomy.

Despite a number of potential biases and limitations which could not be adjusted for, partial lung resection surgery after culture conversion may help improve outcomes in selected patients who do not respond to appropriate medication.

Reference: Fox GJ, Mitnick CD, Benedetti A, Chan ED, Becerra M, Chiang C-Y, et al. Surgery as an adjunctive treatment for multidrug-resistant tuberculosis: An individual patient data metaanalysis. Clin Infect Dis. 2016;62(7):887–95.

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ◉ Moderate ○ Large ○ Varies ○ Don't know	In the surgical meta-analysis that examined all forms of surgery together, there was a statistically significant improvement in cure and successful treatment outcomes among patients who received surgery. However, when the individual patient data meta-analysis examined patients that underwent partial lung resection and those that underwent pneumonectomy, versus patients that did not undergo surgery, those that underwent partial lung resection had statistically significant higher rates of treatment success. Those that underwent pneumonectomy did not have better outcomes than those who did not undergo surgery. There are several caveats to this data. Selection bias may be an issue, as patients who were determined to be healthy enough to undergo surgery were the only people who underwent surgery. People living with HIV were excluded from the IPD. Additionally, although there is likely quite a bit of confounding, patients with XDR-TB were found to have significantly worse outcomes when they underwent surgery. Rates of death did not differ significantly between those who underwent surgery versus those who received medical treatment only. There was not enough data on adverse events or surgical complications to do an analysis. Reference: Fox GJ, Mitnick CD, Benedetti A, Chan ED, Becerra M, Chiang C-Y, et al. Surgery as an adjunctive treatment for multidrug-resistant tuberculosis: An individual patient data metaanalysis. Clin Infect Dis. 2016; 62(7):887–95.	Effect expected to be moderate in the average patient considered appropriate for surgery.
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ◉ Don't know		Uncertainty about perioperative or post-operative complications.
CERTAINTY OF EVIDENCE	**What is the overall certainty of the evidence of effects?** ○ Very low ◉ Low ○ Moderate ○ High ○ No included studies	No research evidence was identified.	Substantial heterogeneity expected in a number of parameters including the criteria used to select candidates for surgery, the type/quality of intervention, the effectiveness of concomitant chemotherapy and other supportive measures, and the rigour and length of time during which effects (beneficial or adverse) were monitored.

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favour the intervention or the comparison?** ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ◉ Varies ○ Don't know	No research evidence was identified.	Long term sequelae, some of which may be ultimately fatal, may be unknown. The benefits vary depending on the population selection; however, overall the effects of surgery appear to be beneficial as long as patients are selected carefully for surgery. Despite the unknown magnitude of perioperative complications the panel assumed that overall there is a net benefit from surgery.
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ○ Probably yes ○ Yes ◉ Varies ○ Don't know	No research evidence was identified.	Surgery is used extensively in many countries but the quality varies. If programmes invest in surgery in preference to other components there are opportunity costs. Equity issues: there is an issue of access to high quality surgery so equity is "probably reduced" and inequity is a possibility. Acceptability to stakeholders and patients: "varies" depending on the stakeholder.

Conclusions

ELECTIVE PARTIAL LUNG RESECTION VERSUS NO SURGERY FOR PATIENTS ON TREATMENT FOR MDR-TB

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	◉	○
	Voting results of the GDG for conditional recommendation on elective partial surgery: 15 in favour; 1 against; 1 abstention; 2 no recommendation; 2 not available				
Recommendation	In patients with rifampicin-resistant TB or MDR- TB, the WHO Guideline Development Group suggests that elective partial lung resection (lobectomy or wedge resection) may be used alongside an approved MDR-TB regimen (conditional recommendation, very low certainty in the evidence).				

Justification	In the surgical meta-analysis that examined all forms of surgery together, there was a statistically significant improvement in cure and successful treatment outcomes among patients who received surgery. However, when the individual patient data meta-analysis examined patients that underwent partial lung resection and those that underwent pneumonectomy versus patients that did not undergo surgery, those that underwent partial lung resection had statistically significant higher rates of treatment success. Those who underwent pneumonectomy did not have better outcomes than those who did not undergo surgery. There are several caveats to these data. Selection bias may be an issue, as patients who were determined to be healthy enough to undergo surgery were the only people who underwent surgery. People living with HIV were excluded from the IPD. Additionally, although there is possibly quite a bit of confounding, patients with XDR-TB were found to have significantly worse outcomes when they underwent surgery. Rates of death did not differ significantly between those who underwent surgery versus those who received medical treatment only. There was not enough data on adverse events or surgical complications to do an analysis.
Subgroup considerations	The data show that XDR patients who underwent surgery did worse than other patients (aOR 0.4, 0.2–0.9) and therefore the recommendation does not apply to XDR-TB patients
Implementation considerations	The recommendation is limited to partial resection, conducted as an elective intervention. Minimal surgical interventions such as drainage of abscesses were not included. More radical pneumonectomy is not included. Partial lung resection for patients with MDR-TB is recommended only under conditions of good surgical facilities, trained and experienced surgeons and with careful selection of appropriate surgical candidates.
Monitoring and evaluation	▪ Definition of extensive disease ▪ Definition of the parameters for monitoring response, non-response, adverse outcome and sequelae of surgery ▪ Monitoring for the optimal timing after culture conversion to undertake surgery
Research priorities	▪ Which conditions indicate resection surgery and when to contraindicate (selection of patients and type of disease)

ANNEX 6

Summaries of unpublished data used for the recommendations

1. Short MDR-TB regimens: meta-analyses of data from published and unpublished studies

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Background

For the treatment of multidrug-resistant tuberculosis (MDR-TB), the World Health Organization (WHO) recommends an intensive phase of at eight months, and total treatment duration of at least 20 months. Shortening the treatment duration without compromising efficacy would substantially reduce the burden that prolonged therapy places on patients and programmes. To inform updated policy recommendations, we synthesized data from published and unpublished studies of MDR-TB patients treated with standardized regimens based on the 9-month "Bangladesh regimen" initially described by Van Deun and co-workers in 2010 *(1)*.

Methods

An expert committee identified published and ongoing studies of MDR-TB patients treated with standardized regimens of up to 12 months in duration ("short MDR-TB regimens") that were based on the Bangladesh regimen. We sought to: (i) estimate the probability of treatment success (cure or treatment completion) versus an unfavourable outcome (failure/relapse, death, or default); (ii) identify baseline characteristics associated with these outcomes; and (iii) compare outcomes to those reported in patients treated with regimens of conventional duration (at least 18 months). Patients were included if they had MDR-TB confirmed by culture or molecular drug-susceptibility testing (DST). We also included patients with rifampicin-resistant TB in whom isoniazid DST had not been performed. Aggregate (study-level) meta-analyses were performed to estimate pooled proportions using data from all studies. To identify patient characteristics associated with outcomes, we conducted individual patient data meta-analyses stratified by characteristics of interest. Lastly, we compared outcomes with short MDR-TB regimens to those with longer duration regimens. To do so, we used data from MDR-TB patients treated with regimens of at least 18 months ("longer regimens") taken from a previous individual patient meta-analysis. Hence, the comparison group included many different regimens, some of which were individualized, and not all

of which met existing WHO recommendations for MDR-TB treatment. Meta-analyses used random effects models with the exact binomial likelihood method.

Results

Six studies were identified. Three are ongoing and shared interim data for this analysis. One published and two ongoing studies provided individual patient data. The description of the studies and patients is reported in Table A6.1.1.

Exclusion criteria

Five studies excluded patients that had previously been treated with second-line anti-TB medications. The following exclusion criteria were used in some of the studies: pregnancy, age <14 years, severe liver or renal co-morbidity, baseline XDR-TB, baseline resistance to moxifloxacin, baseline resistance to ofloxacin, resistance to at least two second-line injectables, severe clinical condition, baseline QT prolongation and extrapulmonary TB.

Regimens

In all six studies, the minimum duration of the intensive phase was four months. The intensive phase could be extended by two months – exceptionally up to four months in the Swaziland series – in the absence of conversion. The duration of the continuation phase was five months in four studies, and eight months in two studies. The intensive phase regimens typically consisted of kanamycin, moxifloxacin (usual dose) or gatifloxacin (high or usual dose), high-dose isoniazid, prothionamide, clofazimine, pyrazinamide and ethambutol. In all studies, the continuation phase regimen included the same fluoroquinolone (moxifloxacin or gatifloxacin), clofazimine, pyrazinamide and ethambutol; prothionamide was also continued in three studies. All treatment was under direct observation, and in most studies either some or all patients were hospitalized for a portion of the treatment.

Outcome definitions

Outcomes of cure, treatment completion, failure, death and default were reported in all studies. Relapse was defined as a positive culture, post treatment completion. Because this outcome was rare and only reported in the three published studies, the few relapse cases were counted as failures.

Aggregate meta-analyses

Rates of successful and unsuccessful treatment are reported in Table A6.1.2. The proportion of those successfully treated was higher with standardized short regimens. When death and "loss to follow-up" were included as unsuccessful outcomes along with failure/relapse, the percentage success was significantly higher in patients on the shorter regimens compared with those on the longer regimen (confidence limits not overlapping).

Individual patient data meta-analyses

When stratified by baseline susceptibility to fluoroquinolone and pyrazinamide, the proportion of patients successfully treated remained consistently greater with standardized short MDR-TB regimens; however, the confidence limits overlapped. There was a trend towards worsening treatment outcomes in

both the short regimens group, and the longer regimen group, in patients with fluoroquinolone- and/or pyrazinamide-resistant MDR-TB.

Conclusion

Short MDR-TB regimens based on the "Bangladesh regimen" have shown promising results in patients that have never been treated with second-line drugs and with baseline susceptibility to fluoroquinolones and pyrazinamide. There is a paucity of data on relapse; however, the available evidence suggests relapse is rare.

Table A6.1.1. Description of studies and patients

	BANGLADESH 2005–2011	NIGER 2008–2010	CAMEROON 2008–2011	UZBEKISTAN 2013–2015	MULTIPLE 2013–2015	SWAZILAND 2014–2015
Status	Published	Published	Published	Ongoing	Ongoing	Ongoing
Data available for meta-analysis	Individual patient	Aggregate	Aggregate	Individual patient	Aggregate	Individual patient
Data available on relapse at 2 years post-end of treatment	Yes	Yes	No	No	No	No
Patients eligible for initiation of MDR treatment	640	124	323	NR	1169	114
Patients with MDR-TB or rifampicin-resistant TB confirmed	527†	97†	237†	117*	1169**	76*
Excluded from analysis, n (%)	34 (6.4%)	32 (33.0%)	87 (36.7%)	52 (44.4%)Ω	761 (65.1%)***	52 (68.4%) Ω
Included, n (%)	493 (93.5%)	65 (67.0%)	150 (63.3%)	65 (55.6%)	408 (34.9%)	24 (31.5%)
Age (± standard deviation, or IQR)	33.6 (±12.9)	31 (27–38)	35.1	34.1 (±14.3)	35.1	35.2 (±14.4)
Female, n (%)	150/493 (30.4%)	12/65 (18.5%)	73/150 (48.7%)	35/65 (53.8%)	152/408 (37.3%)	13/24 (54.2%)
Primary MDR, n (%)	4/493 (0.8%)	1/65 (1.5%)	1/150 (0.1%)	47/61 (77.0%)	59/407 (14.5%)	20/24 (83.3%)
HIV, n (%)	0	1/58 (1.7%)	30/150 (20%)	0/44	91/407 (22.4%)	16/24 (66.7%)
Smear positive, n (%)	475/493 (96.3%)	54/65 (83.1%)	150/150 (100%)	28/62 (45.2%)	354/406 (87.2%)	12/23 (52.2%)
Chest radiograph cavities, n (%)	99/493 (20.1%)	23/65 (35.4%)	NR	26/61 (42.6%)	NR	NR
Pyrazinamide resistance, n (%)	99/240 (41.3%)	NR	NR	33/39 (84.6%)	80/150 (51.3%)	10/14 (71.4%)
Ethambutol resistance, n (%)	321/493 (65.1%)	45/65 (69.2%)	NR	31/44 (70.5%)	NR	12/17 (70.6%)

MDR: multidrug-resistant; TB: tuberculosis; NR: not reported

Multiple: Benin, Burkina Faso, Burundi, Cameroon, Central Africa Republic, Democratic Republic of Congo, Niger.

† Isoniazid and rifampicin resistance confirmed in all participants.

* Includes participants with rifampicin-resistant TB in whom DST to isoniazid was not performed (Uzbekistan, n=7; Swaziland, n=6).

** Includes participants with rifampicin-resistant TB in whom DST to isoniazid was not performed (n=137) or with DST-confirmed susceptibility to isoniazid (n=22).

*** 409/761 never initiated the short MDR-TB regimen: 65 with prior exposure to second-line drugs; 1 with XDR-TB; 112 lost prior to initiation; 34 died prior to initiation; 197 other (pregnancy, children, medical/social contra-indications, refusals, non-residents).

Ω Majority of exclusions were accounted for by participants in whom short MDR-TB treatment was ongoing, or had ended recently: Uzbekistan, 39/52; Swaziland, 47/52.

Table A6.1.2. Pooled treatment outcomes from aggregate data meta-analyses

OUTCOME	STANDARDIZED SHORT MDR-TB REGIMENS, 6 STUDIES		LONGER REGIMENS, 31 STUDIES	
	SUCCESS/N	WEIGHTED PROPORTION (95% CL)	SUCCESS/N	WEIGHTED PROPORTION (95% CL)
Success versus failure or relapse	1008/1033	97.5% (92.4%–99.2%)	4033/4639	91.2% (86.1%–94.6%)
Success versus failure, relapse or death	1008/1116	**90.3% (87.8%–92.4%)**	4033/5850	78.3% (71.2%–84.0%)
Success versus failure, relapse, death, or loss to follow up	1008/1205	**83.7% (79.2%–87.4%)**	4033/7665	61.7% (53.1%–69.6%)

CL: Confidence limits
Meta-analyses used random-effects models.
In the shorter regimens, data on relapse were only available in the three published studies.
Bold indicates that 95% CL does not overlap with the longer regimens group.

Reference

1. Van Deun A, Maug AKJ, Salim MAH, Das PK, Sarker MR, Daru P, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 2010;182(5):684–692.

2. An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis

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Introduction

Treatment for MDR-TB or XDR-TB requires lengthy use of second-line TB drugs, although the regimens used vary widely. The WHO 2011 guidelines recommended that MDR-TB treatment include as a minimum pyrazinamide, one second-line injectable (kanamycin, amikacin or capreomycin), one later generation fluoroquinolone (levofloxacin or moxifloxacin), and at least two Group 4 drugs (ethionamide/prothionamide, cycloserine/terizidone or *p*-aminosalicylic acid). We performed a systematic review to update the evidence for MDR-TB treatment to inform the WHO Guideline Development Group.

Methods

Literature search and study selection

The PICO (Patients, Intervention, Comparator and Outcomes) questions were developed by the WHO Guideline Development Group in 2014–2015 to assist evidence reviews to inform its 2016 update of the guidance on MDR-TB treatment. The main focus of this review was the efficacy and safety of available drugs for the treatment of MDR-TB patients. The following groups of drugs were analyzed: first-line drugs (pyrazinamide, ethambutol, and high dose isoniazid), injectable drugs (streptomycin, kanamycin, amikacin, and capreomycin), fluoroquinolones (ofloxacin, levofloxacin and moxifloxacin), drugs from Group 4 (ethionamide/prothionamide, cycloserine /terizidone and *p*-aminosalicylic acid (PAS)), and the new drug bedaquiline. Drugs from Group 5 were not included in our review since at least four independent systematic reviews were recently conducted for these drugs.

Three major databases were used for our search: MEDLINE (through OVID), EMBASE (through OVID) and The Cochrane Library. The search strategy used a combination of Medical Subject Heading (MeSH) terms and free-text words in titles, abstracts and key words. Terms related to MDR-TB and XDR-TB, drugs of interest and treatment outcomes were included. Since this is an update from previous reviews which included studies published up to December 2008 our search was limited to the period from January 2009 to August 2015. The detailed search strategy is available in the supplemental material.

Two independent reviewers screened titles, abstracts and full texts, with consensus in each stage. A third reviewer was consulted to resolve possible disagreements. We included studies published in English, French, Chinese, Portuguese and Spanish. All studies that met the following inclusion criteria were selected: (i) MDR-TB confirmed by phenotypic tests (*GeneXpert*® was not adequate unless confirmed); (ii) pulmonary TB (studies that had more than 10% extrapulmonary patients and did not report the outcomes separately were excluded); (iii) cohorts or RCTs with a minimum of 25 MDR-TB (or XDR-TB) patients treated; (iv) a clear regimen specifying the drugs received; and (v) at least reported one of the following outcomes: end-of-treatment outcomes, six-month culture conversion, adverse events due to MDR-TB treatment. Studies that evaluated short regimens (<18 months) were excluded.

Data abstraction

Data from eligible studies were abstracted using a standardized data abstraction form (see supplemental material). We recorded information of age, sex, HIV (and use of antiretroviral treatment), acid-fast bacillus smear results, chest radiograph cavitation, prior TB treatment (with first-line drugs or second-line drugs), drug susceptibility test results, number of patients that received each drug, duration of treatment, and whether the regimen was standardized or individualized. Outcomes abstracted included: end of treatment outcomes defined according to published criteria, six-month sputum culture conversion and serious adverse events (SAEs; defined as Grade 3–4 events, or defined operationally as drugs discontinued permanently). For SAEs, we recorded the study definition of severity and the drug responsible for the event, if identified.

Data synthesis and statistical analysis

For end of treatment outcomes, we compared success (defined as cured or treatment completed) to: (i) failure or relapse; or (ii) failure or relapse or death. We examined the relationship between end of treatment outcomes and six-month culture conversion; the number of patients receiving each specific drug, average number of drugs used, and duration of treatment; as well as the average value for each cohort of major clinical and demographic characteristics of the patients. If HIV information or age were missing, values were estimated using information from other studies in this review from the same country, and if no such study was available, from data published by the World Bank or WHO. Variables were categorized according to the distribution observed (i.e. in median, terciles or quartiles).

Occurrence of adverse events was pooled if the study identified the drug responsible for the event and if the event was classified as Grade 3 to 4 severity, or the drug of interest was permanently stopped.

All statistical analyses were performed using SAS (version 9.2 Institute, Cary, NC, USA). Linear mixed models were used to pool the proportion with events (NLIMIXED procedure in SAS). For pooling the proportions of adverse events, we used generalized linear mixed model (GLIMMIX procedure in SAS).

Results

A total of 2336 titles were identified, and after eliminating duplicates and non-relevant publications based on review of titles and abstracts, 250 were selected for full text review, of which 74 met the review inclusion criteria. 19 studies reported adverse events that were classified as Grade 3 or 4, or required permanent discontinuation of the drug, and identified the drug responsible.

Pooled treatment success rate was 26% (CI 95%, 23%–30%) in XDR-TB patients, compared to 60% in all cohorts of MDR-TB patients (with or without additional second-line resistance). The occurrence of SAE ranged from 0.5% to 12.2% (Table A6.2.1). Less than 3% of patients receiving fluoroquinolones or pyrazinamide experienced an SAE, compared to more than 5% of patients receiving second-line injectables or a thiamide (ethionamide or prothionamide).

Conclusion

This review identified 74 studies, with 84 distinct cohorts, published since January 2009 that reported treatment regimens and outcomes in 17 494 MDR-TB and XDR-TB patients. These studies reported

adverse events, six-month culture conversion and end of treatment outcomes. Treatment outcomes were substantially worse in patients with XDR-TB, and somewhat worse in patients who received standardized regimens for MDR-TB. However, despite the large number of studies and patients, no other treatment parameter, including number or duration of drugs, and individual drugs were associated with improved six-month culture conversion, or end of treatment outcomes. This may reflect the limitations and difficulties of pooling this data rather than true lack of differences in efficacy of regimens or individual drugs. This review highlights the need for more standardized reporting as well as evidence from well-designed randomized trials, or from meta-analysis of pooled individual patient data set from multiple observational studies.

Table A6.2.1. Occurrence of serious adverse events (SAEs), attributed to specific drugs in treatment of MDR-TB or XDR-TB

(Results from 19 studies (20 cohorts) that reported Grade 3–4 adverse events, or drugs permanently stopped due to adverse events, and identified the drug responsible for the adverse events.)

			SERIOUS ADVERSE EVENTS DUE TO DRUG	
DRUG	ARMS/COHORTS REPORTING SAE AND USED THE DRUG	N PATIENTS RECEIVED THE DRUG	N PATIENTS WITH SAE RELATED TO THE DRUG	POOLED ESTIMATE[1] (CI 95%)
Pyrazinamide	19	2023	56	2.8% (2.1%-3.7%)
Ethambutol	16	1325	6	0.5% (0.2%-1.1%)
Injectable	19	2538	184	7.3% (6.2%-8.4%)
Later gen. FQN	13	827	10	1.2% (0.6%-2.4%)
Ofx/Cfx	9	1408	40	2.8% (1.9%-4.1%)
Thiamide	17	2106	173	8.2% (7.0%-9.6%)
Cycloserine	16	2140	96	4.5% (3.6%-5.5%)
PAS	16	1706	208	12.2% (10.6%-13.9%)

Later gen. FQN: Later generation fluoroquinolone (includes gatifloxacin /levofloxacin /moxifloxacin), Ofx/Cfx: ofloxacin/ciprofloxacin, PAS: *p*-aminosalicylic acid

[1] Pooled using Proc Glimmix in SAS – fixed effects meta-analysis.

3. A systematic review and individual patient data meta-analysis of treatment and outcomes among children with multidrug-resistant tuberculosis

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Introduction

Multidrug-resistant tuberculosis (MDR-TB) in children is under-recognized, under-diagnosed and under-reported. Despite approximately 32 000 children developing MDR-TB each year *(1)* and historical studies showing mortality rates from TB of 40%, 16% and 5% for infants, toddlers and young children, respectively *(2)*, very little is known about optimal treatment for children with MDR-TB. Treatment of MDR-TB is difficult, requiring use of toxic medications for at least 18 months with formulations and regimens not suited to children. However, individual studies have reported successful treatment outcomes in at least 80% of children treated for MDR-TB *(3)*. A more rigorous evidence base is needed to help inform the management of MDR-TB treatment in children. A systemic review in 2012 sought to better quantify treatment outcomes in children, however, many questions remain on how to optimize successful treatment outcomes and minimize adverse events *(3)*.

In order to address key questions regarding the treatment of MDR-TB and to inform paediatric-specific guidelines, we undertook a systematic review and individual patient data meta-analysis (IPD) of children with MDR-TB. The objective was to provide information on the management of children with MDR-TB by analysing determinants of key treatment outcomes among children treated for MDR-TB, and addressing questions specifically relevant to the paediatric population with MDR-TB (Table A6.3.1).

Methods

Eligibility criteria

Data sets were eligible if they included a minimum of three children (aged <15 years) within a defined treatment cohort who were treated for clinically diagnosed or bacteriologically confirmed pulmonary or extrapulmonary MDR-TB, and for whom treatment outcomes were reported, using standard World Health Organization (WHO) TB case definitions *(4,5)*. Eligibility criteria were applied at the individual level, so that studies reporting on both adults and children could be considered eligible if they otherwise met the specified criteria. Both published and unpublished data were included, without date restriction. Eligible study designs included controlled and non-controlled retrospective and prospective studies and

case series. All cohorts containing children included in a previous systematic review and individual patient data meta-analysis of MDR-TB were considered eligible *(6)*. Only reports written in Dutch, English, French, Russian and Spanish were included. We excluded studies that utilized only combinations of rifampicin, isoniazid (INH), pyrazinamide (PZA), ethambutol (EMB) or streptomycin to treat MDR-TB, as this is now considered inadequate therapy.

Identifying primary reports

To identify eligible reports, including conference abstracts, we searched PubMed, LILACS, Embase, The Cochrane Library, PsychINFO, and BioMedCentral databases up to 30 September 2014, with a search strategy, using a combination of the search terms, viz. "tuberculosis", "multidrug resistance", "MDR-TB", "multidrug-resistant", and "children", both as exploded MESH headings and free-text terms, and without language restriction. The specific search strategies for Pubmed and Embase are presented in Appendix 6A. We also reviewed conference abstracts from the annual meeting of the International Union Against Tuberculosis and Lung Diseases.

To identify additional published and unpublished data we contacted experts in the field of paediatric MDR-TB. We also requested additional data through multiple routes, such as at national and international conferences and training events, and through international and in-country organizations working in paediatric MDR-TB, including the Sentinel Project on Pediatric Drug-Resistant Tuberculosis, the WHO Childhood TB sub-Group, Médecins Sans Frontières (MSF), the United States and European CDC, International Union Against Tuberculosis and Lung Disease (UNION), National Institutes of Health (NIH) and others.

Report selection and review

All abstracts were screened by EH and a researcher with the South African Cochrane Centre to select full text reports to review. All full text reports were reviewed independently by two reviewers (EH, AGP, HSS, JF, ACH) to assess for eligibility, except reports in Dutch, French, Russian and Spanish, which were reviewed by a single reviewer (from among AT, EH, ACH and JF). A third reviewer resolved any disagreements about study selection. If report eligibility was unclear, two attempts were made to contact the authors of the primary report; and if we could not make contact after two unsuccessful attempts, these reports were excluded.

Individual patient data abstraction

The authors of all eligible studies were contacted to access individual patient data. Individual patient data were used following a written agreement with the study team by the original authors, which included confirmation of ethical approval according to local guidelines.

Data were collected on multiple factors which could influence treatment decision and outcome, including: demographic characteristics, nutritional status, HIV status and antiretroviral usage, adult MDR-TB source case information, culture confirmed versus clinical diagnosis, information on disease location (pulmonary or extrapulmonary) and severity (using a standard approach), drug susceptibility test results, the use of individual drugs, and the duration of drug use within the treatment regimen. Data were collected on acid-fast bacillus (smear) microscopy and culture conversion, adverse effects, as well as WHO-defined treatment

outcomes including cure, treatment completion, culture conversion by six months, treatment failure, relapse, loss to follow-up and mortality. Severity of disease on chest radiograph, based on a standardized disease severity classification developed for an international paediatric TB randomized control trial (Palmer M, personal communication), was graded independently by two reviewers (EH, ACH) as either severe or non-severe; disagreements were arbitrated by a third reviewer (HSS). The primary authors of all included reports were contacted as needed to resolve any queries.

In order to contextualize the clinical data, information was also requested from each primary author on site-level characteristics, including but not limited to methods for TB diagnosis, availability and type of drug-susceptibility testing performed, how treatment outcomes were defined, and how adverse effects were assessed.

A database was created, and primary data from each study were entered into the database.

Analysis

The analysis was planned to address PICO question 1, as per Table A6.3.1. Primary analyses focused on success versus failure/relapse/death in children with confirmed MDR-TB only. There were no paediatric data available to address the section in PICO question 1 regarding rifampicin mono-resistant TB.

Table A6.3.1. WHO-defined PICO question 1, in HIV-infected and uninfected children aged 0–14 years with MDR-TB; and which individual drugs in the regimens are likely to lead to the outcomes listed below?

POPULATION	INTERVENTION	COMPARATOR	OUTCOMES
MDR-TB **without** resistance to the second-line drugs	A second-line regimen[a] which includes:		▪ Cured/completed by end of treatment ▪ Failure ▪ Relapse ▪ Survival (or death) ▪ Adverse reactions from TB drugs (severity, type, organ class)
	– pyrazinamide	– no pyrazinamide	
	– injectable agents (Km/Am/Cm)	– no injectable agents (Km/Am/Cm)	
	– prothionamide/ethionamide	– no prothionamide/ethionamide	
	– cycloserine or terizidone	– no cycloserine or terizidone	
	– PAS	– no PAS	
	– later-generation fluoroquinolone[2]	– no later-generation fluoroquinolone[b]	
	– high-dose isoniazid	– no high-dose isoniazid	
	– clofazimine	– no clofazimine	
	– linezolid	– no linezolid	
	– other individual Group 5 drugs	– no other individual Group 5 drugs	

[a] Data from regimens lasting up to 12 months were not included in this question.
[b] Moxifloxacin or gatifloxacin; any use of standard or high-dose levofloxacin was included as levofloxacin use.

For all analyses, treatment outcomes were dichotomized as either successful or unsuccessful. Successful outcome was defined as when cure was achieved or treatment was completed, and unsuccessful outcome was defined as failure, relapse or death. There were inadequate numbers of events to support analysis of

failure/relapse. The primary analyses estimated the odds of treatment success (versus fail/relapse/death) associated with the use of each drug among patients with bacteriologically confirmed MDR-TB but without confirmed XDR-TB. To assess the effect of fluoroquinolones, the use of any later generation fluoroquinolone was compared to a regimen excluding the use of a later generation fluoroquinolone.

All analyses were repeated on patients with clinically diagnosed MDR-TB (i.e. not bacteriologically confirmed MDR-TB), where the data supported analyses. Children with confirmed XDR-TB were excluded from the primary analysis.

For all adjusted analyses, we fitted random-effects logistic regressions (random intercept and random slopes, when possible, and only random intercept when not) by maximum likelihood with quadrature approximation, using PROC GLIMMIX in SAS software (version 9.4, SAS Institute, Cary, North Carolina). Patients were considered to be clustered within studies, and intercepts and slopes of the main exposure variables were allowed to vary across studies. This was to account for unmeasured differences between patient populations across studies, as well as site-specific differences in data ascertainment, measurement and other factors. Estimates were adjusted for four covariates: age (dichotomized as under five years old and 5–15 years old), sex, HIV infection and severe TB disease (defined as being underweight or malnourished, having oedema, having low weight for age, having severe extrapulmonary disease, or having severe disease on chest radiograph). In order to improve data modelling, given some missing data on HIV status, children from countries with very low HIV prevalence who did not have an HIV test done were assumed to be HIV negative, following consultation with the study investigators. For the main analyses, single imputation (as opposed to multiple imputation) was performed where missing values for the four covariates used in multivariable analyses were substituted with the mean value from the other participants of the same study to which the individual belonged. In sensitivity analyses, multiple imputation using chained equations was used for missing values. All statistical analyses were performed using SAS 9.4.

Data on adverse events were sparse, and therefore we chose to provide descriptive analysis only for key toxicities in studies consistently reporting adverse events; in particular the incidence of ototoxicity (descriptive analysis only) because it is a frequent and serious side effect of aminoglycosides, which are a cornerstone of treatment, and of particular interest to health care providers and patients with MDR-TB.

Assessment of overall quality of evidence

The quality of studies was described using a modified Newcastle-Ottawa tool (Appendix 6B) adapted for use in paediatric MDR-TB. We assessed the quality of evidence across the studies with Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology *(7)* defining the quality of evidence for each outcome as "the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest" *(8)*. The quality rating across studies has four levels: high, moderate, low or very low. Randomized controlled trials are initially categorized as providing high quality evidence, but the quality can be downgraded. Similarly, other types of controlled trials and observational studies are categorized as providing low quality evidence but the quality can be upgraded if justified. Factors that decrease the quality of evidence include limitations in design, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results or high probability of publication bias. Factors that can increase the quality level of a body of evidence include studies with a large magnitude of effect, and studies in which all plausible confounding would lead to an underestimation of effect.

Ethics

The Health Research Ethics Committee of the Faculty of Medicine and Health Sciences and Stellenbosch University provided ethical approval for this study.

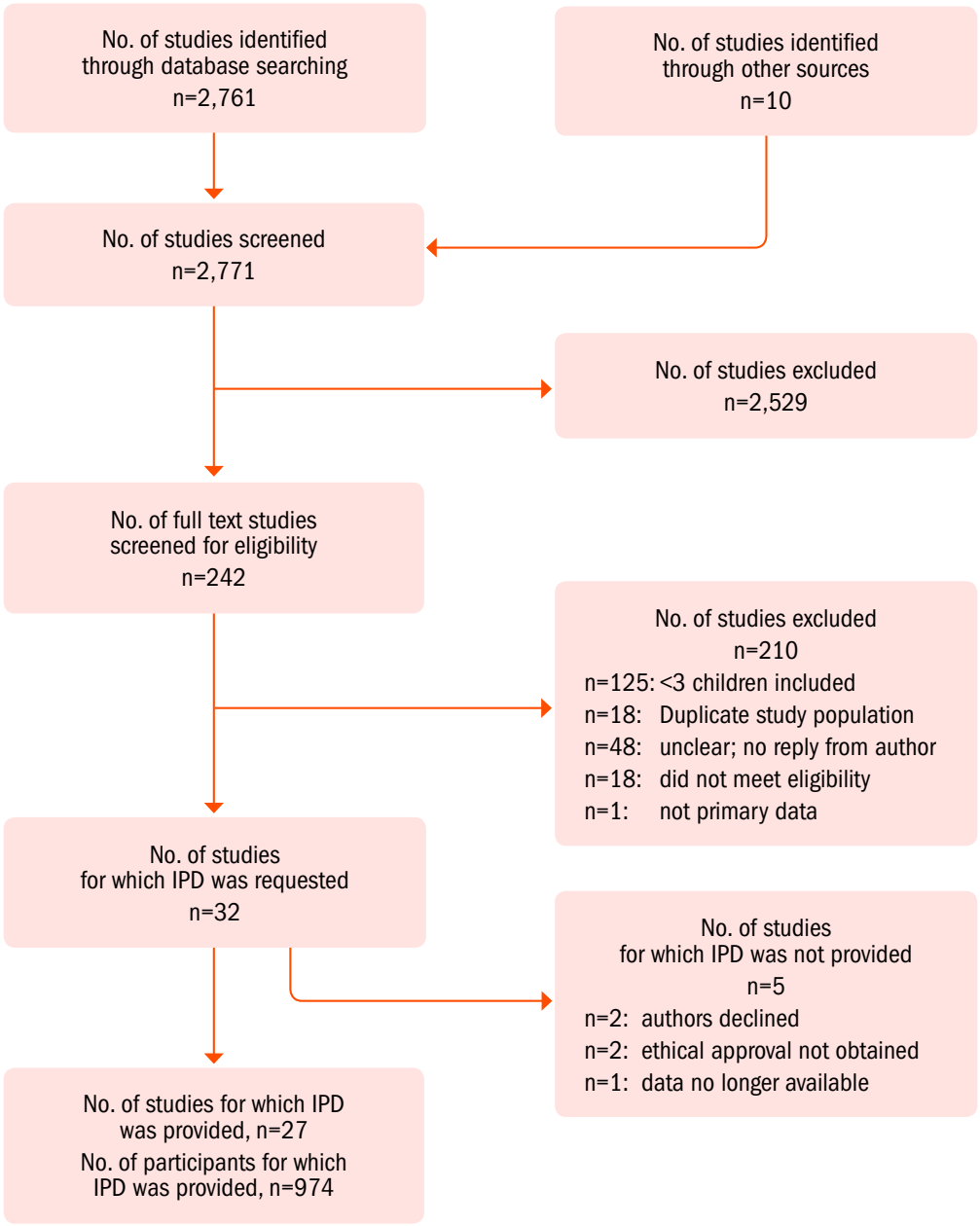
Results

Search results and report selection

Figure A6.3.1 presents a summary of the search results and report selection. Results from searching the database and other sources yielded 2771 search results, which were narrowed down to 242 results, after screening of abstracts (Figure A6.3.1). Of these 242 papers reviewed and 210 were excluded. Included in these excluded studies were 89 studies in which the authors were contacted when eligibility criteria were unclear; of those authors, 48 never replied, 18 confirmed that their study did not meet inclusion criteria and 1 study was rejected as it did not include primary data (a systematic review). It's important to note that the vast majority of these queries were for studies that were primarily adult studies but may have possibly contained a small number of children, however the precise number was often not specified. It is therefore unlikely that a large number of children were missed from these excluded studies.

Twenty-seven studies (from 32 studies requested) provided individual patient data (9–26) that included data from 974 patients. Two authors declined to share data, two authors could not get Internal Review Board permission in time to share their data and one author no longer had access to the primary data (Figure A6.3.1).

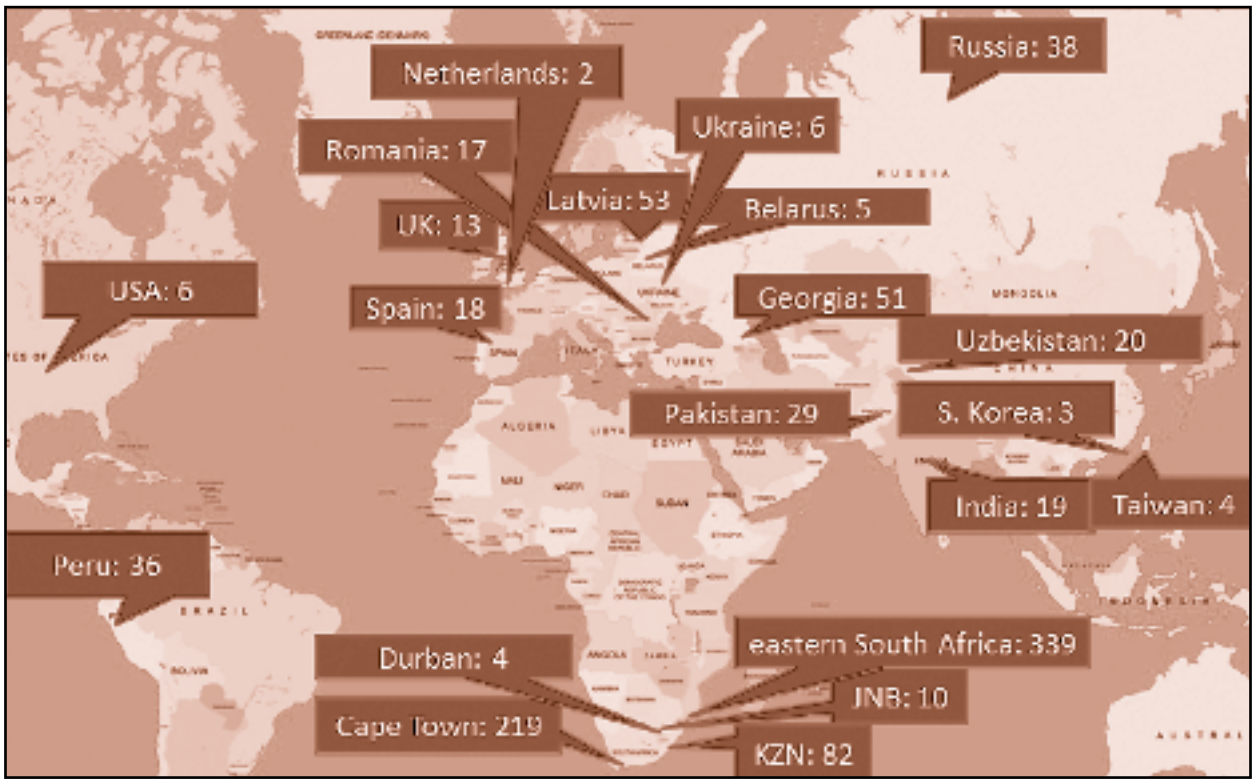
Figure A6.3.1. Flow diagram of study selection for systematic review and individual patient meta-analysis of children with multidrug-resistant tuberculosis



Report characteristics

Geographic distribution of the data received from sites from 18 countries is shown in Figure A6.3.2. Patients from six continents were included; the majority were from Africa. Four countries (India, Pakistan, Russia and South Africa) are among the 30 high-burden TB countries. Details of the included studies are presented in Appendix 6B.

Figure A6.3.2. Details of geographic locations of patients included in the individual patient data meta-analysis (the number indicates the number of participants included at each location)



Summary patient data and outcomes

Data from 974 children that were included in the analysis showed median age of 7.1 years and 44% males. The HIV status was known in 822 children, of whom 44% had HIV infection. Two-hundred thirty seven children had clinically diagnosed MDR-TB, and 737 children had bacteriologically confirmed MDR-TB. Of those with a confirmed diagnosis, 35 had MDR-TB with additional resistance to a fluoroquinolone, 28 had MDR-TB with additional second-line injectable resistance and 36 had XDR-TB (i.e. resistance to both a fluoroquinolone and a second-line injectable). Children with XDR-TB were not included in the primary analysis and data from children with additional resistance to a fluoroquinolone or a second-line injectable agent were combined with MDR-TB (see methods). Key clinical and demographic characteristics, stratified by clinically diagnosed versus bacteriologically confirmed MDR-TB are shown in Table A6.3.2. Treatment outcomes summarized for the entire data set are shown in Table A6.3.3. Some children were listed as "cured", because they were bacteriologically diagnosed with TB disease, but their MDR-TB was not confirmed by drug-susceptibility testing.

Table A6.3.2. Key demographic and clinical characteristics among children with clinically diagnosed or bacteriologically confirmed multidrug-resistant tuberculosis

	CLINICALLY DIAGNOSED MDR-TB N = 237 (%)	BACTERIOLOGICALLY CONFIRMED MDR OR PRE-XDR N = 701 (%)
Age		
▪ Under 5 years	156 (66)	231 (33)
▪ 5 to 15 years	81 (34)	470 (67)
Malnourished*		
▪ Yes	47 (19.8)	274 (39.1)
▪ No	67 (28.3)	366 (52.2)
▪ Unknown	123 (51.9)	61 (8.7)
Severe Disease on chest radiograph**		
▪ Yes	68 (28.7)	519 (74.0)
▪ No	126 (53.2)	163 (23.3)
▪ Unknown	43 (18.1)	19 (2.7)
Severe Extrapulmonary Disease***	24 (10.1)	103 (14.7)
HIV status		
▪ HIV-infected	36 (15.2)	318 (45.4)
▪ HIV-uninfected	141 (59.5)	300 (42.8)
▪ HIV status unknown	60 (25.3)	83 (11.8)

A combined variable of "severe disease: included the presence of malnutrition* or severe disease on chest radiograph** or severe extrapulmonary disease***, given missing data on these three variables, individually.

Table A6.3.3. Summary of treatment outcomes for children with multidrug-resistant tuberculosis

	CLINICALLY DIAGNOSED MDR-TB N = 237	CONFIRMED MDR-TB WITHOUT CONFIRMED XDR-TB N = 701	CONFIRMED XDR-TB N = 36
Cured	46 (19.3%)	327 (46.6%)	23 (64%)
Completed treatment	166 (69.7%)	209 (29.8%)	7 (19%)
Fail or relapse	0	14 (1.9%)	1 (3%)
Death	7 (2.9%)	73 (10.4%)	3 (8%)
Lost to follow-up	18 (8%)	77 (11%)	2 (6%)

The results for primary outcome analysis of treatment benefit for individual drugs are presented in GRADE tables (see Annex 4). Note that although numbers are small, children who did not receive a second-line injectable, but who had clinically diagnosed/unconfirmed disease (and in general had less severe disease, Table A6.3.2) did well (93.5% successful outcomes, see GRADE table for second-line injectables). Children who did not receive a second-line injectable tended to have less severe TB disease overall, and have lower rates of malnutrition, severe disease (on chest radiograph) and severe extrapulmonary TB disease (see Table A6.3.4).

Adverse events were in general poorly reported. Only nine datasets consistently reported toxicities, and these data are presented in Table A6.3.5.

Table A6.3.4. Characteristics of children who received a second-line injectable (SLI) versus those who did not

	TREATED WITH SLI		NOT TREATED WITH SLI	
	N	%	N	%
Severe disease	296	91%	30	9%
Malnourished	239	93%	18	7%
Severe pulmonary disease on chest radiograph	479	92%	40	8%
Severe extrapulmonary disease	85	83%	18	17%

Table A6.3.5. Frequency of specific toxicities in studies that reported adverse events (N=306 subjects in 9 datasets where adverse events were consistently reported)

SIDE EFFECT	NUMBER OF CHILDREN	DENOMINATOR	% EVENTS
Hearing loss	39	383	10.1%
Peripheral neuropathy	2	383	0.5%
Optic neuropathy	11	383	2.9%
Thyroid dysfunction	50	383	13.1%
Liver toxicity	16	383	4.2%
Arthropathy	20	383	5.2%
Nephrotoxicity	2	383	0.5%

Note: Secondary analyses are planned in the future, including analyses of outcomes in children with shorter durations of injectable treatment, stratified by severe and non-severe TB disease, and by bacteriological status.

Discussion

This first ever systematic review and IPD of paediatric MDR-TB, which included a large number of children, shows overall good treatment outcome with 76.4% of children with bacteriologically confirmed MDR-TB, and 89% of children with unconfirmed MDR-TB, having successful treatment outcomes. More than two-thirds of children had bacteriologically confirmed MDR-TB, which strengthens the quality of data from this review, given the fact that TB in children is typically paucibacillary in nature. The overall mortality was low (10.4% in children with confirmed disease, and 2.9% in the unconfirmed group). Children with confirmed XDR-TB although a small number (n=36) had favourable treatment outcomes in 83% of cases.

Most children (77%) received injectable drugs. There was a high prevalence of HIV infection, with 45% of children in the confirmed and 15% in the unconfirmed MDR-TB group, being HIV-infected; HIV testing was relatively complete. A high proportion of children had chest radiographic or features of

extrapulmonary disease compatible with severe TB, as well as malnutrition. The overall good treatment outcomes should therefore be seen in the context of HIV co-infection and more severe disease, indicating that good outcomes are achievable in children with MDR-TB.

There are a number of notable findings from the analysis of the impact of individual second-line drugs. The use of second-line injectable drugs significantly predicted the treatment success versus failure/relapse/death (OR: 3.32; 95% CI: 1.53–7.21) in children with confirmed MDR-TB. This has to be seen in the context of high toxicity with hearing loss reported in 10.1% of the studies that reported on safety outcomes. However, children with clinically (unconfirmed) diagnosed MD-TB (who tended to have less severe disease) had good outcomes when not treated with a second-line injectable. These data are supportive of the practice of using injectable sparing regimens in children with less severe disease in order to spare children from SAEs associated with second-line injectables, without an adverse impact on treatment outcomes.

High-dose isoniazid (used in approximately 25% of subjects, at a dose of 15–20 mg/kg), predicted treatment success (versus failure/relapse/death; OR: 6.97; 95% CI: 2.11–23.03), even after adjusting for site in the analysis (high-dose isoniazid was most frequently used in South African sites). Another consideration to this finding is that high-dose isoniazid is also typically used in combination with ethionamide/prothionamide.

Later-generation fluoroquinolones (primarily moxifloxacin; since there was virtually no reported use of gatifloxacin) did not appear to offer a treatment benefit. However, only 10% of cases in the dataset received later-generation fluoroquinolones, which may have masked any benefit associated with their use.

In general, these findings of individual drug effects should be taken in the context of the use of multiple drugs as part of MDR-TB treatment regimens.

Limitations

This individual patient data (IPD) is limited by the overall low quality of studies; most studies included were retrospective or prospective observational cohort studies and there were no trials that could be included. The overall sample size was modest compared to adult IPD datasets, and estimates were frequently imprecise while some associations were not estimated due to limited data (e.g. relapse/failure). There were no data available yet on the novel drugs, delamanid and bedaquiline, for inclusion in this IPD. We also had a very small sample of children with confirmed XDR-TB. Toxicity was frequently poorly assessed while missing data regarding HIV status was handled by imputation. Missing data on individual variables of nutritional status and disease severity were handled using a composite disease severity variable.

In summary, this first paediatric specific IPD has provided data for guideline development of high clinical and programmatic relevance. Overall, the proportion of children with favourable treatment outcome, even with severe TB and with HIV co-infection, was good. Data regarding the use of novel drugs, bedaquiline and delamanid in children, are urgently needed. Future questions should focus on the use of shorter (<18 months) regimens and injectable-sparing regimens in children. Paediatric-specific treatment evidence is important to allow for inclusion of children in evidence-based MDR-TB treatment guidelines.

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APPENDIX 6A

Search strategies

DATABASE: PUBMED; SEARCH DATE: 01 OCTOBER 2014

SEARCH	QUERY	ITEMS FOUND
#25	Search ((#22 AND #23) NOT (animals[mh] NOT humans[mh]))	1653
#24	Search (#22 AND #23)	1653
#23	Search (infant[mh] OR infant[tiab] OR infants[tiab] OR infancy[tiab] OR toddler*[tiab] OR preterm*[tiab] OR prematur*[tiab] OR postmatur*[tiab] OR baby[tiab] OR babies[tiab] OR neonat*[tiab] OR newborn[tiab] OR preschool*[tiab] OR pre-school*[tiab] OR child[mh] OR child*[tiab] OR kindergar*[tiab] OR pupil*[tiab] OR schoolchild*[tiab] OR teen*[tiab] OR youth[tiab] OR youths[tiab] OR youngster*[tiab] OR young person*[tiab] OR young people[tiab] OR minors[mh] OR minors[tiab] OR puberty[mh] OR puberty[tiab] OR pubescen*[tiab] OR prepubescen*[tiab] OR paediatric*[tiab] OR pediatric*[tiab] OR peadiatric*[tiab] OR schools[mh:noexp] OR school*[tiab] OR kid[tiab] OR kids[tiab] OR boy*[tiab] OR girl*[tiab] OR creche*[tiab] OR highschool*[tiab] OR juvenil*[tiab] OR adolescent[mh] OR adolescen*[tiab] OR under ag*[tiab] OR underag*[tiab])	3521601
#22	Search (tuberculosis, multidrug-resistant[mh] OR multidrug resistant tuberculosis[tiab] OR drug resistant tuberculosis[tiab] OR multiple drug resistant tuberculosis[tiab] OR MDR tuberculosis[tiab] OR MDR TB[tiab] OR MDRTB[tiab] OR ((drug resistance[tiab] OR multidrug resistance[tiab] OR multiple drug resistance[tiab] OR multiresistant[tiab] OR multi resistant[tiab]) AND (tuberculosis[tiab] OR TB[tiab]))	8600

DATABASE: EMBASE; SEARCH DATE: 01 OCTOBER 2014

NO.	QUERY	RESULTS
#8	**#3** NOT **#7**	1837
#7	**#4** NOT **#6**	5002895
#6	**#4** AND **#5**	1303481
#5	**'human'**/de OR **'normal human'**/de OR **'human cell'**/de	15207023
#4	**'animal'**/de OR **'animal experiment'**/de OR **'invertebrate'**/de OR **'animal tissue'**/de OR **'animal cell'**/de OR **'nonhuman'**/de	6306376
#3	**#1** AND **#2**	1889
#2	**'infant'**/exp OR **infant**:ab,ti OR **infants**:ab,ti OR **infancy**:ab,ti OR **toddler***:ab,ti OR **preterm***:ab,ti OR **prematur***:ab,ti OR **postmatur***:ab,ti OR **baby**:ab,ti OR **babies**:ab,ti OR **neonat***:ab,ti OR **newborn**:ab,ti OR **preschool***:ab,ti OR **pre+school***:ab,ti OR **'child'**/exp OR **child***:ab,ti OR **kindergar***:ab,ti OR **pupil***:ab,ti OR **schoolchild***:ab,ti OR **teen***:ab,ti OR **youth**:ab,ti OR **youths**:ab,ti OR **youngster***:ab,ti OR **'young person'**:ab,ti OR **'young persons'**:ab,ti OR **'young people'**:ab,ti OR **'minors'**/exp OR **minors**:ab,ti OR **'puberty'**/exp OR **puberty**:ab,ti OR **pubescen***:ab,ti OR **prepubescen***:ab,ti OR **paediatric***:ab,ti OR **pediatric***:ab,ti OR **peadiatric***:ab,ti OR **'schools'**/exp OR **school***:ab,ti OR **kid**:ab,ti OR **kids**:ab,ti OR **boy***:ab,ti OR **girl***:ab,ti OR **creche***:ab,ti OR **highschool***:ab,ti OR **'juvenile'**/exp OR **juvenil***:ab,ti OR **'adolescent'**/exp OR **adolescen***:ab,ti OR (**under** NEXT/1 **ag***):ab,ti OR **underag***:ab,ti	4649411
#1	**'multidrug resistant tuberculosis'**/exp OR **'multidrug resistant tuberculosis'**:ab,ti OR **'drug resistant tuberculosis'**:ab,ti OR **'multiple drug resistant tuberculosis'**:ab,ti OR **'mdr tuberculosis'**:ab,ti OR **'mdr tb'**:ab,ti OR (**'drug resistance'**:ab,ti OR **'multidrug resistance'**:ab,ti OR **'multiple drug resistance'**:ab,ti OR **multiresistant**:ab,ti AND (**tuberculosis**:ab,ti OR **tb**:ab,ti))	9249

APPENDIX 6B

Table of included studies

SITE/AUTHOR	COUNTRY	NUMBER	PREVIOUS IPD INCLUSION	NUMBER OF SUBJECTS	PUBLICATION STATUS	TITLE OF PAPER	STUDY DESIGN	STUDY POPULATION
Achar	Uzbekistan	1	No	20	Unpublished	N/A	Retrospective cohort	Bacteriologically confirmed and clinically diagnosed
Amanullah	Pakistan	2	No	29	Unpublished	N/A	Retrospective cohort	Bacteriologically confirmed
Banerjee	USA	9	Menzies IPD 2012	3	Published	Extensively drug-resistant tuberculosis in California, 1993–2006	Retrospective cohort	Bacteriologically confirmed
Chan	Taiwan	4	No	4	Unpublished	N/A	Retrospective cohort	Bacteriologically confirmed
Chan	USA	5	Menzies IPD 2012	3	Published	Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis	Retrospective cohort	Bacteriologically confirmed
Chiotan	Romania	16	No	17	Unpublished	N/A	Retrospective cohort	Bacteriologically confirmed
Datta	India	12	No	3	Published	Multidrug-resistant and extensively drug resistant tuberculosis in Kashmir, India	Prospective cohort	Bacteriologically confirmed
Drobac	Peru	6	No	36	Published	Community-based therapy for children with multidrug-resistant tuberculosis	Retrospective cohort	Bacteriologically confirmed and clinically diagnosed
Fairlie	South Africa	7	No	10	Published	High prevalence of childhood multi-drug resistant tuberculosis in Johannesburg, South Africa: a cross sectional study	Retrospective cohort	Bacteriologically confirmed

SITE/AUTHOR	COUNTRY	NUMBER	PREVIOUS IPD INCLUSION	NUMBER OF SUBJECTS	PUBLICATION STATUS	TITLE OF PAPER	STUDY DESIGN	STUDY POPULATION
Gegia	Georgia	8	No	55	Published	Outcomes of children treated for tuberculosis with second-line medications in Georgia, 2009–2011	Retrospective cohort	Bacteriologically confirmed and clinically diagnosed
Hicks	South Africa	22	No	82	Published	Malnutrition associated with unfavourable outcomes and death among South African MDR-TB and HIV co-infected children	Retrospective cohort	Bacteriologically confirmed
Isaakidis	India	11	No	8	Published	Poor outcomes in a cohort of HIV-infected adolescents undergoing treatment for multidrug-resistant tuberculosis in Mumbai, India	Retrospective cohort	Bacteriologically confirmed
Maryandyshev	Russia	17	No	38	Unpublished	N/A	Retrospective cohort	Bacteriologically confirmed and clinically diagnosed
Mendez-Echevarria	Spain	13	No	8	Published	Multidrug-resistant tuberculosis in the pediatric age group	Retrospective cohort	Bacteriologically confirmed and clinically diagnosed
Moore	South Africa	14	No	339	Published	Epidemiology of drug-resistant tuberculosis among children and adolescents in South Africa, 2005–2010	Retrospective cohort	Bacteriologically confirmed and clinically diagnosed
Ozere/ Kuksa	Latvia	15	No	53	Some published	Multi and extensively drug-resistant tuberculosis in Latvia: trends, characteristics and treatment outcomes.	Retrospective cohort	Bacteriologically confirmed and clinically diagnosed
Rybak	Ukraine	18	No	6	Unpublished	N/A	Retrospective cohort	Bacteriologically confirmed and clinically diagnosed
Santiago	Spain	19	No	10	Some published	Pediatric drug-resistant tuberculosis in Madrid: family matters	Retrospective cohort	Bacteriologically confirmed and clinically diagnosed

SITE/AUTHOR	COUNTRY	NUMBER	PREVIOUS IPD INCLUSION	NUMBER OF SUBJECTS	PUBLICATION STATUS	TITLE OF PAPER	STUDY DESIGN	STUDY POPULATION
Seddon (1)	South Africa	20	No	88	Published	Culture confirmed multidrug resistant tuberculosis in children: clinical features, treatment and outcome	Retrospective cohort	Bacteriologically confirmed
Seddon (2)	South Africa	21	No	131	Published	High treatment success in children treated for multidrug resistant tuberculosis: an observational cohort study	Prospective cohort	Bacteriologically confirmed and clinically diagnosed
Sharma	India	23	No	8	Unpublished	N/A	Retrospective cohort	Bacteriologically confirmed
Shim/Kim	Korea	24	Menzies IPD 2014	2	Published	Treatment outcomes and long-term survival in patients with extensively drug-resistant tuberculosis	Retrospective cohort	Bacteriologically confirmed
Skrahina	Belarus	25	No	5	Unpublished	N/A		Bacteriologically confirmed and clinically diagnosed
Van Der Werf/ Geerlings	Netherlands	26	Menzies IPD 2014	2	Published	Multidrug-resistant tuberculosis: long-term treatment outcome in the Netherlands	Retrospective cohort	Bacteriologically confirmed
Williams	United Kingdom	3	No		Published	Multidrug-resistant tuberculosis in UK children: presentation, management and outcome	Retrospective cohort	Bacteriologically confirmed
Yim/ Kim	Korea	27	Menzies IPD 2014	1	Published	Impact of extensive drug resistance on treatment outcomes in non-HIV-infected patients with multidrug-resistant tuberculosis	Retrospective cohort	Bacteriologically confirmed