III. 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Bibliography: Refer to Appendix 6, paper 3 for a summary of this unpublished study (Harausz E, Garcia-Prats AJ, Schaaf S, Law S, Furin J, Kredo T, et al., for The Collaborative Group for Meta-Analysis of Paediatric Individual Patient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 Appendix 6, paper 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 Appendix 6, paper 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 Appendix 6, paper 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 Appendix 6, paper 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 Appendix 6, paper 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 Appendix 6, paper 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 Appendix 6, paper 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 Appendix 6, paper 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).