Treatment of Drug-Resistant Tuberculosis: An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline

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ONLINE DATA SUPPLEMENT

APPENDIX A: METHODOLOGY

Panel composition and meetings

We followed the procedures and methodology of the Guideline Development Checklist (available at: http://cebgrade.mcmaster.ca/guidelinechecklistonline.html) and the Guideline Development Tool (GDT), available at: http://www.gradepro.org/, to assemble a team of experts including specialists in pulmonary medicine, infectious disease, pharmacokinetics, pediatrics, primary care, and public health. The panel also included a member from the Treatment Action Group, providing patient advocacy and community engagement input. Methodologists helped in conducting systematic reviews, summarizing the evidence, formulating recommendations, and assessing the certainty in the evidence (also known as the quality of evidence) and rating the strength of the recommendations using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach (1, 2). Face-to-face meetings were held in May 2016 and May 2017 coinciding with ATS International Conferences. During the meetings, the guideline panel discussed specific questions, the existing research evidence, and drafted recommendations. In addition, videoconferencing calls were held on a near monthly basis for continued discussion of the evidence and recommendations.

Disclosure of potential conflicts of interest

Guideline panel members disclosed all potential conflicts of interest according to the American Thoracic Society (ATS) policies (see Financial Disclosures). The chairs and co-chairs (P. Nahid, S. Mase, T. Chorba, GB. Migliori, G. Sotgui and B. Seaworth) and the ATS reviewed and managed all potential conflicts of interest of panel members. During all deliberations, panel members with potential conflicts of interest abstained from decisions about specific questions being asked and recommendations related to their potential conflict of interest. The ATS provided meeting facilities during its conference and financial support to perform systematic reviews to support recommendations. The views and interests of the ATS, as well as of any commercial entity that provided external funding for ATS, had no influence on the final recommendations.

Formulating specific clinical questions and determining outcomes of interest

We used the GDT and electronic questionnaires to brainstorm and subsequently prioritize questions related to the treatment of various forms of tuberculosis.

The following questions were prioritized and addressed in this document:

1. Should patients with MDR-TB be prescribed 5 effective drugs versus more or fewer agents during the intensive and continuation phases of treatment.
2. Should patients with MDR-TB undergoing intensive phase treatment be treated for ≥6 months after culture conversion or <6 months after culture conversion?
3. Should patients with MDR-TB undergoing continuation phase treatment be treated for ≥18 months after culture conversion or <18 months after culture conversion?
4. In patients with MDR-TB, are outcomes safely improved when regimens include amoxicillin/clavulanate as compared to regimens that do not include amoxicillin/clavulanate?
5. In patients with MDR-TB, are outcomes safely improved when regimens include bedaquiline as compared to regimens that do not include bedaquiline?
6. In patients with MDR-TB, are outcomes safely improved when regimens include carbapenems with clavulanic acid as compared to regimens that do not include them?
7. In patients with MDR-TB, are outcomes safely improved when regimens include clofazimine as compared to regimens that do not include clofazimine?
8. In patients with MDR-TB, are outcomes safely improved when regimens include cycloserine as compared to regimens that do not include cycloserine?

9. In patients with MDR-TB, are outcomes safely improved when regimens include delamanid as compared to regimens that do not include delamanid?
10. In patients with MDR-TB, are outcomes safely improved when regimens include ethambutol as compared to regimens that do not include ethambutol?
11. In patients with MDR-TB, are outcomes safely improved when regimens include ethionamide/prothionamide as compared to regimens that do not include ethionamide/prothionamide?
12. In patients with MDR-TB, are outcomes safely improved when regimens include fluoroquinolones as compared to regimens that do not include fluoroquinolones?
13. In patients with MDR-TB, are outcomes safely improved when regimens include an injectable as compared to regimens that do not include injectable?
14. In patients with MDR-TB, are outcomes safely improved when regimens include linezolid as compared to regimens that do not include linezolid?
15. In patients with MDR-TB, are outcomes safely improved when regimens include macrolides as compared to regimens that do not include macrolides?
16. In patients with MDR-TB, are outcomes safely improved when regimens include *p*-aminosalicylic acid as compared to regimens that do not include *p*-aminosalicylic acid?
17. In patients with MDR-TB, are outcomes safely improved when regimens include pyrazinamide as compared to regimens that do not include pyrazinamide?
18. In patients with MDR-TB, does treatment with a standardized MDR-TB regimen for ≤12 months lead to better outcomes than treatment with an MDR TB regimen for 18–24 months?
19. Treatment of isoniazid-resistant TB:
    a. Should patients with isoniazid-resistant TB be treated with a regimen comprised of a fluoroquinolone, rifampin, ethambutol, and pyrazinamide for 6 months as compared to rifampin, ethambutol, pyrazinamide (without a fluoroquinolone) for 6 months?
    b. Should patients with isoniazid-resistant TB be treated with a regimen comprised of fluoroquinolone, rifampin, ethambutol for 6 months and pyrazinamide for the first 2 months as compared to regimen comprised of a fluoroquinolone, rifampin, ethambutol, and pyrazinamide for 6 months?
20. Among patients with M/XDR TB receiving antimicrobial therapy, does lung resection surgery (i.e. lobectomy or pneumonectomy) lead to better outcomes than no surgery?
21. Should contacts exposed to an infectious MDR-TB patient be offered LTBI treatment versus followed with observation alone?

The writing committee selected outcomes of interest for each question following the approach suggested by the GRADE Working Group (http://www.gradeworkinggroup.org). All outcomes were identified a priori and the panel explicitly rated their relative importance for decision-making. Ranking outcomes by their relative importance can help to focus attention on those outcomes that are considered the most important and help to manage or clarify potential disagreements.

Literature search and selection of evidence

The GRADE and systematic review methodologists (D. Menzies, F. Fregonese, Z. Lan, F. Khan, P. Nahid, G. Sotgui and J. Brozek) prepared/reviewed evidence profiles (**See Appendix B**) for each question following the GRADE approach and using the GDT. The chairs and co-chairs (P. Nahid, S. Mase, T. Chorba, GB. Migliori, G. Sotgui and B. Seaworth), and all guideline panel members, reviewed the summaries of evidence and made corrections when appropriate. The evidence profiles were based on an individual-patient level meta-analysis, now published in Lancet, performed specifically for these guidelines (3).

Methodologies used for the individual-patient level meta-analysis have been published (3). Additional details are as follows:

Data sources

The full study protocol is available upon request from the authors. This study was approved by an ethics committee of the McGill University Health Centre Research Institute (14-274-BMB) and by local ethical review boards when necessary.

Eligible studies were identified by a systematic review of studies published between Jan 1, 2009, and Sept 15, 2015 (updated in April, 2017), on treatment of multidrug-resistant tuberculosis (MDR-TB - including extensively drug-resistant), and the reference lists from all systematic reviews of treatment of MDR-TB published since 2009. The search used MEDLINE, Embase, and the Cochrane library. Studies were eligible if they reported original results on treatment outcome for 25 or more adults with bacteriologically confirmed pulmonary MDR-TB. Investigators of potentially eligible studies, and investigators who participated in an earlier meta-analysis of multidrug-resistant tuberculosis , were invited to contribute data. Investigators provided de-identified clinical, diagnostic, treatment and outcomes individual-level patient data and center-level information (outcome definitions, drug doses, directly observed therapy, hospital admission, and laboratory methods).

For the isoniazid monoresistant TB analyses, eligible studies, published from 1990 onwards, were identified in a systematic review of INH-R TB that was completed in May 2015 and published in 2016, or included in a review of INH-R TB in children . Additional studies were identified with an updated search up to February 10th 2016, using the same search terms and databases as the original review. In addition: five of the contacted authors provided unpublished datasets (three have since been published) and three regional or national surveillance datasets were provided by those responding to an invitation to all participants at a WHO European regional Resistant TB surveillance meeting.

Studies were included in the IPD if authors agreed to share their data and signed formal data-sharing agreements, the regimens and outcomes were known for individual patients, and at least 20 subjects were treated for INH-R TB if a cohort study (randomized trials were eligible regardless of the number of patients).

Authors provided de-identified patient level information (demographic data, clinical characteristics, pre-treatment DST, treatment information) and center-level information (diagnostic laboratory methods, usual treatment doses and supervision, and treatment outcome definitions).

Whereas the the last search for cohort selection for these ATS/CDC/ERS/IDSA guidelines was conducted in April 2017 and published in 2018 (3), the WHO expansion of our IPDMA was completed in the Fall of 2018 and with additional cohorts the WHO reached similar conclusions and provided similar recommendations.

Quality of studies

Quality of included studies was assessed with a checklist of seven indicators, adapted from the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for non-randomized studies and Cochrane Collaboration's risk of bias tool for randomized studies (4-7). Two of these indicators were considered essential (population selection using a census or random selection approach, and availability of drug susceptibility tests results to at least one fluoroquinolone and one second-line injectable medication). Of the remainder, quality was judged to be adequate if the participation rate exceeded 80%, loss to follow-up was less than 20%, treatment outcomes were defined according to published guidelines, and more than 90% of patient records had information about HIV infection, previous tuberculosis treatment, and age. Studies of high quality met both essential criteria and at least four of the other six. Studies of moderate quality met one of the two essential parameters and at least five in total. Remaining studies were considered of low quality.

Outcomes

Outcomes were end of treatment success (defined as cure or completion), compared with failure or relapse; and death from any cause during tuberculosis treatment, compared with success or failure or relapse. For the analysis of each drug, patients were included if they received at least 1 month of the drug, and the association with success or death was stratified by drug susceptibility testing (DST) – if the isolates were susceptible, or resistant to that drug. For most drugs, if DST results were missing, susceptibility was assumed only if more than 90% of isolates from other patients at the same centre were confirmed susceptible to that drug. Ethambutol, pyrazinamide, all injectable drugs and fluoroquinolones, ethionamide and protionamide, cycloserine and terizidone, and p-aminosalicylic acid, were considered possibly effective drugs if DST confirmed susceptibility to

those drugs. Clofazimine, linezolid, carbapenems, bedaquiline, and delamanid were considered possibly effective if the isolate was susceptible, or there was no DST result. Patients who died or were lost to follow-up during treatment were excluded from analyses of optimum treatment duration. Start of MDR-TB treatment was defined as the date on which one or more second-line tuberculosis drugs were started; duration of the initial phase was defined as the duration of injectable drugs. Sputum culture conversion was defined as two consecutive negative sputum cultures, at least 30 days apart.

Data analysis

Propensity score analysis is a versatile statistical method used mainly in observational studies for improving treatment comparison by adjusting for potentially confounding covariates, thereby helping reduce effects of confounding (8). A propensity score is the probability of treatment assignment conditional on observed baseline characteristics. Propensity score matching entails forming matched sets of treated and untreated subjects who share a similar value of the propensity score (9). We used propensity score matching (caliper method with difference of 0.02 allowed, 1:1 matching with replacement) based on individual-level covariates of age, sex, HIV co-infection, acid-fast bacilli smear results, cavitation on chest radiographs, history of tuberculosis treatment with first-line or second-line tuberculosis drugs, and number of possibly effective drugs in the initial phase. For the analysis of individual drugs we also adjusted for resistance to fluoroquinolones or second-line injectable drugs, unless the drugs of interest were the fluoroquinolones or second-line injectable drugs themselves, or the analysis was restricted to the subgroup with extensive drug resistance. We used a random-effects (random intercept and random slope for matched pairs) generalized logistic mixed effects model (PROC GLIMMIX in SAS) to estimate adjusted odds ratios (ORs) and 95% CIs of success (versus failure or relapse, but not death) or death (versus success) during treatment associated with use of specific drugs, or with number of drugs, or duration of treatment. We calculated adjusted risk differences and 95% CIs with fixed effects generalized linear models with identity link, adjusted for the propensity score, because the random effects models did not converge. For propensity score matching only, we imputed missing patient characteristics from the mean values of other patients at the same center. We estimated I^2 for the adjusted ORs using a generalized linear mixed model with a simulation-based approach, whenever possible. We did sensitivity analyses stratified by country income level, and for extensive drug resistance. All analyses were performed using SAS (version 9.4).

Appraisal of the guideline panel's "certainty in the evidence" for all recommendations

We followed the methods of the Cochrane Collaboration (http://handbook.cochrane.org) and assessed the risk of bias at the outcome level using the Cochrane Collaboration's risk of bias tool (6). Subsequently, we assessed the certainty in the evidence (i.e., confidence that the estimated effects are true) for each of the outcomes of interest following the GRADE approach based on the following criteria: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publications bias, presence of dose–effect relationship, and an assessment of the effect of residual, opposing confounding. Certainty in the evidence was categorized into 4 levels ranging from very low to high. We prepared the evidence-to-decision tables based on the estimates of the health effects, values and preferences and resource use.

All recommendations in these guidelines are based on very low certainty in the evidence. The writing committee selected death, treatment success, and serious adverse effects as the endpoints of critical importance, on which to generate recommendations. The PS-matched IPDMA attempted to adjust for baseline imbalance of various prognostic factors in observational studies. However, the risk of bias remained serious, because the average loss to follow-up across included studies was 10% to 20%. In addition, despite the efforts, there was a large residual imbalance in background regimens used in experimental and control groups.

Formulation of clinical recommendations

We prepared evidence profiles that described the summary of findings and quality of evidence assessment for each outcome, as well as evidence-to-decision tables that described the estimates of the health effects, values and preferences, and resource use. The guideline panel used the evidence summaries and the evidence-to-decision tables to formulate its recommendations.

For each recommendation, the guideline panel considered and agreed on the following: The quality of the evidence, the balance of desirable and undesirable consequences of compared management options and the assumptions about the values and preferences associated with the decision. The guideline panel also explicitly took into account possible extent of resource use associated with alternative management options. Recommendations were decided by consensus and no recommendation required voting. The panel agreed on the final wording of recommendations and remarks with further qualifications for each recommendation. The final recommendations were reviewed and approved by all members of the guideline panel.

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are its integral parts and serve to facilitate more accurate interpretation; they should never be omitted when quoting or translating recommendations from these guidelines.

Rating and implications of the strength of the recommendations

We rated the recommendations as either "strong" or "weak/conditional" according to the GRADE approach. We used the words "the panel members recommend" for strong recommendations and "the panel members suggest" for weak/conditional recommendations. Understanding the interpretation of these two grades of strength of recommendations is essential for health care decision-making and has explicit implications as follows:

Strong recommendation

- For patients: Most individuals in this situation would want the recommended course of action, and only a small proportion would not.
- For clinicians: Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
- For policy makers: The recommendation can be adopted as policy in most situations.

Conditional recommendation

- For patients: The majority of individuals in this situation would want the suggested course of action, but many would not.
- For clinicians: Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
- For policy makers: Policy-making will require substantial debate and involvement of various stakeholders.

Peer review

A final draft of the guidelines was reviewed and approved by each member of the guideline panel. It was subsequently peer reviewed by multiple content experts from each organization and several methodologists, then further reviewed and approved by the leadership of each organization society. The document was also presented for public input through the Advisory Committee for the Elimination of Tuberculosis, and reviewed by the Centers for Disease Control and Prevention. The document was revised to incorporate the comments suggested by the peer reviewers. Once the peer reviewers were satisfied with the guidelines, the document was further reviewed and edited by the co-sponsoring societies (American Thoracic Society, Infectious Diseases Society of America, European Respiratory Society and the Centers for Disease Control and Prevention, as well as by patient representatives from the Community Research Advisors Group (CRAG) of the Treatment Action Group (http://www.treatmentactiongroup.org/tb/community-engagement/crag). Once all of the co-sponsoring societies and the Centers for Disease Control and Prevention were satisfied with the quality of the document, it was formally submitted for publication.

Updates to the guidelines

Per American Thoracic Society protocol, this guideline will be reviewed and the need for updating will be determined three years after publication.

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Official ATS/CDC/ERS/IDSA Clinical Practice Guidelines: Treatment of Drug-Resistant Tuberculosis (AJRCCM 2019)
APPENDIX B: GRADE Evidence Profiles

NOTE: Relative measures of an effect are reported as adjusted odds ratios (aOR) whenever they have been estimated in the individual participant data meta-analysis (IPD-MA). The corresponding risk ratios (RR) are reported in footnotes to facilitate interpretation. For all other analyses we present RR as the most intuitive for interpretation by health care practitioners. Whenever data came from one study only and the authors calculated hazard ratios (HR) we did not convert HR to RR as the HR likely represents the better estimate of the effect taking into account the timing of outcome occurrence.

Date: 2017-11-28
Question: Should **amikacin** added to a background MDR TB regimen, compared to background MDR TB regimen without an injectable agent, be used in adults with MDR TB?
Setting: low and high resource settings, within hospital or ambulatory models of care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	amikacin added to a background MDR TB regimen	background MDR TB regimen alone	Relative (95% CI)	Absolute (95% CI)		
Death												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	not serious [c]	none	250/1644 (15.2%)	78/533 (14.6%) [m]	**aOR 1.0** (0.8 to 1.2)[e,d]	**0 fewer per 100** (from 2 more to 3 fewer) [f]	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	not serious [c]	none	1302/1394 (93.4%)	406/455 (89.2%) [m]	**aOR 2.0** (1.5 to 2.6)[e,k]	**6 more per 100** (from 4 more to 8 more) [f]	⊕◯◯◯ VERY LOW	CRITICAL
Culture conversion (follow up: 6 months)												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	not serious [g]	none	740/863 (85.7%)	4146/4583 (90.5%) [m]	**aOR 1.2** (0.9 to 1.6)[e,l]	**2 more per 100** (from 1 fewer to 5 more) [f]	⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse effect												
19 [2]	observational studies	not serious	not serious [b]	very serious [h]	serious [i]	none	184/2538 (7.2%) [j]	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Discontinuation of treatment owing to adverse effect - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Acquisition of drug resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations

a. Data from experimental and observational studies pooled in propensity score matched IPDMA. 13% to 15% were lost to follow-up. Fewer patients in amikacin group received linezolid (13%) compared to those not receiving any injectable agent (33%).
b. Updated systematic review with IPDMA performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB did not report study-level analyses so it was not possible to assess heterogeneity, however, previous meta-analysis of study-level data performed for the 2016 update of WHO guidelines did not show serious heterogeneity.
c. We did not downgrade the certainty of evidence owing to imprecision because the overall certainty is very low regardless, however, the number of events most likely does not meet the optimal information size.
d. **corresponding RR 1.00; 95% CI: 0.82 to 1.17** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
e. Effect adjusted for Age, Sex, HIV, AFB smear, Cavities on CXR, Prior treatment with first and second line TB drugs, and resistance to Fluoroquinolones or SLI, and Number of Possibly effective drugs in Initial Phase.
f. Adjusted risk difference was estimated directly in the IPD risk difference meta-analysis performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.
g. We did not reduce the certainty of evidence owing to imprecision, however, if one would consider 36 more culture conversions as clinically important, then the CI would not exclude a possibility of a benefit or no difference.
h. Data for all injectable agents pooled together; preferential inclusion of capreomycin in the individualized regimens of patients with more advanced resistance patterns or disease.
i. Only 184 events for all injectable agents; we assumed that the optimal information size would not be met for individual agents.
j. Combined proportion 95% CI: 6.2% to 8.4%
k. **corresponding RR 1.06, 95% CI: 1.04 to 1.07** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
l. **corresponding RR 1.02, 95% CI: 0.99 to 1.04** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
m. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

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Date: 2017-11-28
Question: Should **capreomycin** added to a background MDR TB regimen, compared to background MDR TB regimen without an injectable agent, in adults with MDR TB?
Setting: low and high resource settings, within hospital or ambulatory models of care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	capreomycin added to a background MDR TB regimen	background MDR TB regimen alone	Relative (95% CI)	Absolute (95% CI)		
Death												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	not serious [c]	none	176/1114 (15.8%)	78/533 (14.6%) [k]	**aOR 1.4** [d] (1.1 to 1.7)	**4 more per 100** (from 1 more to 7 more) [e]	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	not serious [c]	none	821/938 (87.5%)	406/455 (89.2%) [k]	**aOR 0.8** [i] (0.6 to 1.1)	**3 fewer per 100** (from 0 fewer to 6 fewer) [e]	⊕◯◯◯ VERY LOW	CRITICAL
Culture conversion (follow up: 6 months)												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	not serious	none	570/628 (90.8%)	4345/4818 (90.2%) [k]	**aOR 0.7** [j] (0.4 to 1.0)	**1 more per 100** (from 4 fewer to 4 more)	⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse effect												
19 [2]	observational studies	not serious	not serious	very serious [f]	serious [g]	none	184/2538 (7.2%) [h]	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Discontinuation of treatment owing to adverse effect - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Acquisition of drug resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations
a. Data from experimental and observational studies pooled in propensity score matched IPDMA. 13% to 18% were lost to follow-up. Fewer patients in capreomycin group received linezolid (12%) compared to those not receiving any injectable agent (33%).
b. Updated systematic review with IPDMA performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB did not report study-level analyses so it was not possible to assess heterogeneity, however, previous meta-analysis of study-level data performed for the 2016 update of WHO guidelines did not show serious heterogeneity.
c. We did not downgrade the certainty of evidence owing to imprecision because the overall certainty is very low regardless, however, the number of events most likely does not meet the optimal information size.
d. corresponding **RR 1.32, 95% CI: 1.08 to 1.54** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
e. Based on IPD risk difference meta-analysis performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.
f. Data for all injectable agents pooled together; preferential inclusion of capreomycin in the individualized regimens of patients with more advanced resistance patterns or disease.
g. Only 184 events for all injectable agents; we assumed that the optimal information size would not be met for individual agents.
h. Combined proportion 95% CI: 6.2% to 8.4%
i. corresponding **RR 0.97, 95% CI: 0.93 to 1.01** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
j. corresponding **RR 0.96, 95% CI: 0.87 to 1.00** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
k. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References
1. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392: 821–34
2. Menzies R, Bastos M,Lan Z. WHO treatment guidelines for drug resistant tuberculosis, 2016 Update. World Health Organization; (11 November 2015).

Date: 2017-11-28
Question: Should **kanamycin** added to a background MDR TB regimen, compared to background MDR TB regimen without an injectable agent, be used in adults with MDR TB?
Setting: low and high resource settings, within hospital or ambulatory models of care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**kanamycin added to a background MDR TB regimen**	**background MDR TB regimen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Death												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	serious [c]	none	435/2958 (14.7%)	78/533 (14.6%) [k]	**aOR 1.1** [d] (0.9 to 1.2)	**1 more per 100** (from 1 fewer to 2 more) [e]	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	not serious [f]	none	2192/2523 (86.9%)	406/455 (89.2%) [k]	**aOR 0.5** [j] (0.4 to 0.6)	**7 fewer per 100** (from 5 fewer to 8 fewer) [e]	⊕◯◯◯ VERY LOW	CRITICAL
Culture conversion (follow up: 6 months)												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	not serious	none	1393/1480 (94.1%)	3522/3966 (88.8%) [k]	**aOR 1.5** (1.1 to 2.0)	**3 more per 100** (from 2 more to 5 more)	⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse effect												
19 [2]	observational studies	not serious	not serious [b]	very serious [g]	serious [h]	none	184/2538 (7.2%) [i]	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Discontinuation of treatment owing to adverse effect - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Acquisition of drug resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations

a. Data from experimental and observational studies pooled in propensity score matched IPDMA. 13% to 16% were lost to follow-up. Fewer patients in kanamycin group received linezolid (3%) compared to those not receiving any injectable agent (33%) and later generation fluoroquinolone (39% vs. 73%).
b. Updated systematic review with IPDMA performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB did not report study-level analyses so it was not possible to assess heterogeneity, however, previous meta-analysis of study-level data performed for the 2016 update of WHO guidelines did not show serious heterogeneity.
c. CI does not exclude an appreciable harm (45 more patients dying per 1000) or no difference.
d. **corresponding RR 1.08, 95% CI: 0.91 to 1.17** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
e. Based on IPD risk difference meta-analysis performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.
f. We did not reduce the certainty of evidence owing to imprecision, however, if one would consider treatment success in 27 more patients per 1000 as important, then the CI would not exclude an appreciable benefit or no difference.
g. Data for all injectable agents pooled together; preferential inclusion of capreomycin in the individualized regimens of patients with more advanced resistance patterns or disease.
h. Only 184 events for all injectable agents; we assumed that the optimal information size would not be met for individual agents.
i. Combined proportion 95% CI: 6.2% to 8.4%
j. **corresponding RR 0.90, 95% CI: 0.86 to 0.93** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
k. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone
l. **corresponding RR 1.04, 95% CI: 1.01 to 1.06** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).

References

1. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392: 821–34
2. Menzies R, Bastos M,Lan Z. WHO treatment guidelines for drug resistant tuberculosis, 2016 Update. World Health Organization; (11 November 2015).

Date: 2017-11-28
Question: Should **streptomycin** added to a background MDR TB regimen, compared to background MDR TB regimen without an injectable agent, be used in adults with MDR TB?
Setting: low and high resource settings, within hospital or ambulatory models of care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**streptomycin added to a background MDR TB regimen**	**background MDR TB regimen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Death												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	serious [c]	none	104/1121 (9.3%)	78/533 (14.6%) [l]	**aOR 0.8** [d] (0.6 to 1.1)	**2 fewer per 100** (from 4 fewer to 1 more) [e]	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	not serious [f]	none	959/1017 (94.3%)	406/455 (89.2%) [l]	**aOR 1.5** [j] (1.1 to 2.1)	**2 more per 100** (from 0 fewer to 4 more) [e]	⊕◯◯◯ VERY LOW	CRITICAL
Culture conversion (follow up: 6 months)												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	not serious	none	750/860 (87.2%)	4165/4586 (90.8%) [l]	**aOR 0.8** [k] (0.6 to 1.1)	**0 fewer per 100** (from 4 fewer to 2 more)	⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse effect												
19 [2]	observational studies	not serious	not serious [b]	very serious [g]	serious [h]	none	184/2538 (7.2%) [i]	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Discontinuation of treatment owing to adverse effect - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Acquisition of drug resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations

a. Data from experimental and observational studies pooled in propensity score matched IPDMA. 13% to 17% were lost to follow-up. Fewer patients in streptomycin group received linezolid (3%) compared to those not receiving any injectable agent (33%).
b. Updated systematic review with IPDMA performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB did not report study-level analyses so it was not possible to assess heterogeneity, however, previous meta-analysis of study-level data performed for the 2016 update of WHO guidelines did not show serious heterogeneity.
c. Confidence interval does not exclude an appreciable benefit or no difference.
d. **corresponding RR 0.82, 95% CI: 0.64 to 1.08** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
e. Based on IPD risk difference meta-analysis performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.
f. We did not downgrade the certainty of evidence owing to imprecision because the overall certainty is very low regardless, however, the number of events most likely does not meet the optimal information size.
g. Data for all injectable agents pooled together; preferential inclusion of capreomycin in the individualized regimens of patients with more advanced resistance patterns or disease.
h. Only 184 events for all injectable agents; we assumed that the optimal information size would not be met for individual agents.
i. Combined proportion 95% CI: 6.2% to 8.4%
j. **corresponding RR 1.04, 95% CI: 1.01 to 1.06** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
k. **corresponding RR 1.00, 95% CI: 0.96 to 1.02** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
l. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References

1. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392: 821–34
2. Menzies R, Bastos M,Lan Z. WHO treatment guidelines for drug resistant tuberculosis, 2016 Update. World Health Organization; (11 November 2015).

Date: 2017-11-28
Question: Should **ethambutol** added to a background MDR TB regimen, compared to background MDR TB regimen alone, be used in adults with MDR TB?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ethambutol added to a background MDR TB regimen**	**background MDR TB regimen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Death												
50 [1]	observational studies	serious [a]	not serious [b]	not serious [c]	serious [d]	none	397/3002 (13.2%) [e]	95/762 (12.5%) [k]	**aOR 1.0** [f] (0.9 to 1.2)	**0 fewer per 100** (from 2 fewer to 2 more) [g]	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
50 [1]	observational studies	serious [a]	not serious [b]	not serious [c]	serious [h]	none	2374/2605 (91.1%)	588/667 (88.2%) [k]	**aOR 0.9** [i] (0.7 to 1.1)	**1 fewer per 100** (from 0 fewer to 3 fewer) [g]	⨁◯◯◯ VERY LOW	CRITICAL
Culture conversion - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Discontinuation of treatment owing to adverse effect - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Serious adverse effect												
16 [2]	observational studies	serious [a]	not serious	not serious	serious [j]	none	6/1325 (0.5%)	-	-	-	⨁◯◯◯ VERY LOW	CRITICAL
Acquisition of drug resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations

a. Data from experimental and observational studies pooled in propensity score-matched IPDMA. Most original studies were observational without an independent control group. On average 16% of patients were lost to follow-up.
b. Updated systematic review with IPDMA performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB did not report study-level analyses so it was not possible to assess heterogeneity, however, the certainty of evidence was already very low so we did not lower the certainty for inconsistency.
c. In most studies ethambutol was used in a dose of 25 mg/kg.
d. Confidence interval does not exclude an appreciable benefit or an appreciable harm, if one assumes that 2% more patients dying would be clinically important. However, most likely there is no difference, thus we downgraded only by one level.
e. All patients were infected with strains susceptible to EMB
f. **corresponding RR 1.00, 95% CI: 0.91 to 1.17** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
g. Based on IPD risk difference meta-analysis performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.
h. Confidence interval does not exclude an appreciable harm or no difference.
i. **corresponding RR 0.99, 95% CI: 0.95 to 1.01** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
j. It was not possible to assess precision as there were only 6 events and no information about the control group.
k. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References

1. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392: 821–34
2. Menzies R, Bastos M,Lan Z. WHO treatment guidelines for drug resistant tuberculosis, 2016 Update. World Health Organization; (11 November 2015).

Date: 2017-11-29
Question: Should **pyrazinamide** added to a background MDR TB regimen, compared to background MDR TB regimen alone, be used in adults with MDR TB?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	pyrazinamide added to a background MDR TB regimen	background MDR TB regimen alone	Relative (95% CI)	Absolute (95% CI)		
Death												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	serious [c]	none	168/1986 (8.5%)	39/307 (12.7%) [h]	**aOR 0.7** [d] (0.6 to 0.8)	**3 fewer per 100** (from 1 fewer to 5 fewer) [e]	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	not serious	none	1683/1818 (92.6%)	249/268 (92.9%) [h]	**aOR 0.7** [f] (0.5 to 0.9)	**3 fewer per 100** (from 1 fewer to 4 fewer) [e]	⊕◯◯◯ VERY LOW	CRITICAL
Culture conversion - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Discontinuation of treatment owing to adverse effect - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Serious adverse effects												
19 [2]	observational studies	serious [a]	not serious	not serious	serious [g]	none	56/2023 (2.8%)	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Acquisition of drug resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations

a. Data from experimental and observational studies pooled in propensity score-matched IPDMA. Most original studies were observational without an independent control group. On average 16% of patients were lost to follow-up. Fewer patients in PZA group received linezolid (4% vs. 25%) and later generation fluoroquinolone (53% vs 71%) but more kanamycin (44% vs. 33%) compared with controls.
b. Updated systematic review with IPDMA performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB did not report study-level analyses so it was not possible to assess heterogeneity, however, previous meta-analysis of study-level data performed for the 2016 update of WHO guidelines did not show serious heterogeneity.
c. CI does not exclude an appreciable benefit or a benefit that some may consider negligible; number of events most likely does not meet optimal information size.
d. **corresponding RR 0.73, 95% CI: 0.63 to 0.82** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
e. Based on IPD risk difference meta-analysis performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.
f. **corresponding RR 0.97, 95% CI: 0.93 to 0.99** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
g. It was not possible to assess precision as there were only 56 events and no information about the control group.
h. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References

1. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392: 821–34
2. Menzies R, Bastos M,Lan Z. WHO treatment guidelines for drug resistant tuberculosis, 2016 Update. World Health Organization; (11 November 2015).

Date: 2017-11-28
Question: Should **ethionamide**[a] added to a background MDR TB regimen, compared to background MDR TB regimen alone, be used in adults with MDR TB?
Setting: low and high resource settings, within hospital or ambulatory models of care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ethionamide added to a background MDR TB regimen**	**background MDR TB regimen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Death												
50 [1]	observational studies	serious [b]	not serious [c]	serious [d]	serious [e]	none	628/4063 (15.5%)	55/394 (14.0%) [l]	**aOR 0.9** [f] (0.8 to 1.0)	**0 fewer per 100** (from 2 fewer to 1 more) [g]	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
50 [1]	observational studies	serious [b]	not serious [c]	serious [d]	not serious [h]	none	3027/3435 (88.1%)	306/339 (90.3%) [l]	**aOR 0.8** [k] (0.7 to 0.9)	**2 fewer per 100** (from 4 fewer to 1 fewer) [g]	⊕◯◯◯ VERY LOW	CRITICAL
Culture conversion - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Serious adverse effect - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Discontinuation of treatment owing to adverse effects												
4 [2]	observational studies	serious [i]	not serious	not serious	serious [j]	none	Adverse effects leading to discontinuation of treatment were equally frequent with ethionamide (11.3%; range 6% to 42%) and protionamide (11.9%; range 6% to 40%). No study compared a regimen containing these drugs to the regimen that does not; all studies were done in 1968-1969. Adverse effects, when reported, included: abnormal liver function tests and gastrointestinal intolerance.				⊕◯◯◯ VERY LOW	CRITICAL
Acquisition of drug resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations
a. ethionamide or protionamide
b. Data from experimental and observational studies pooled in propensity score matched IPDMA. 16% were lost to follow-up.
c. Updated systematic review with IPDMA performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB did not report study-level analyses so it was not possible to assess heterogeneity; we did not downgrade for inconsistency as the evidence was already of very low certainty.
d. Fewer patients in ETO/PTO group, compared with controls, received newer generation fluoroquinolone (50% vs. 75%), amikacin (17% vs. 35%), and linezolid (5% vs. 18%), but more received kanamycin (51% vs. 12%) and capreomycin (27% vs. 15%).
e. CI does not exclude an appreciable benefit or no difference.
f. **corresponding RR 0.91, 95% CI: 0.82 to 1.00** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
g. Based on IPD risk difference meta-analysis performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.
h. We did not downgrade the certainty as it has already been low but CI does not exclude an appreciable benefit or almost no difference
i. case series
j. Given no information about control groups it was not possible to assess precision of the estimates but there were only 62 events in ethionamide and protionamide groups together which would most likely not meet the optimal information size.
k. **corresponding RR 0.98, 95% CI: 0.96 to 0.99** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
l. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References
1. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392: 821–34
2. Scardigli A, Caminero JA,Sotgiu G,Centis R,D'Ambrosio L,Migliori GB.. Efficacy and tolerability of ethionamide versus protionamide: a systematic review. Eur Respir J; 2016.

Date: 2017-11-28
Question: Should **cycloserine**[a] added to a background MDR TB regimen, compared to background MDR TB regimen alone, be used in adults with MDR TB?
Setting: low and high resource settings, within hospital or ambulatory models of care

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**cycloserine added to a background MDR TB regimen**	**background MDR TB regimen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Death												
50 [1]	observational studies	serious [b]	not serious [c]	not serious	not serious	none	1065/6749 (15.8%)	415/1575 (26.3%) [k]	**aOR 0.6** [d] (0.5 to 0.6)	**9 fewer per 100** (from 7 fewer to 10 fewer) [e]	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
50 [1]	observational studies	serious [b]	not serious [c]	not serious	not serious	none	5017/5684 (88.3%)	984/1160 (84.8%) [k]	**aOR 1.5** [i] (1.4 to 1.7)	**5 more per 100** (from 3 more to 6 more) [e]	⊕◯◯◯ VERY LOW	CRITICAL
Culture conversion - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Serious adverse effect - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Discontinuation of treatment owing to adverse effects												
27 [2]	observational studies	serious [f]	serious [g]	not serious	not serious [h]	none	There were altogether 201 events among 2164 patients across all studies. An average weighted proportion of patients receiving cycloserine who discontinued treatment owing to adverse effect pooled across the studies was 9.1% (6.4% to 11.7%). Psychiatric adverse effects were observed in 5.7% (95% CI: 3.7 to 7.6)				⊕◯◯◯ VERY LOW	CRITICAL
Acquisition of drug resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations
a. cycloserine and terizidone
b. Data from experimental and observational studies pooled in propensity score matched IPDMA. 16% were lost to follow-up.
c. Updated systematic review with IPDMA performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB did not report study-level analyses so it was not possible to assess heterogeneity; we did not downgrade for inconsistency as the evidence was already of very low certainty.
d. **corresponding RR 0.67, 95% CI: 0.58 to 0.67** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
e. Based on IPD risk difference meta-analysis performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.
f. case series
g. Visual inspection showed confidence intervals for many studies not overlapping, the proportion of patients who discontinued treatment owing to adverse effects ranged from 0% to 76%, and I^2 was 83%.
h. Despite it was not possible to assess it owing to lack of information about control group, we did not downgrade the certainty of the evidence for imprecision because it has already been very low.
i. **corresponding RR 1.05, 95% CI: 1.05 to 1.07** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
k. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References
1. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392: 821–34
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. International Journal of Tuberculosis and Lung Disease; 2013.

Question: Should **para-aminosalicylic acid (PAS)** added to a background MDR TB regimen, compared to background MDR TB regimen without PAS, be used in adults with MDR TB?
Setting: low and high resource settings, within hospital or ambulatory models of care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PAS added to a background MDR TB regimen	background MDR TB regimen without PAS	Relative (95% CI)	Absolute (95% CI)		
Death												
50 [1]	observational studies	serious [a]	not serious [b]	serious [c]	not serious [d]	none	702/3307 (21.2%)	678/3950 (17.2%) [k]	**aOR 1.2** [e] (1.1 to 1.4)	**2 more per 100** (from 1 more to 4 more) [f]	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
50 [1]	observational studies	serious [a]	not serious [b]	serious [c]	serious [g]	none	2230/2605 (85.6%)	2865/3272 (87.6%) [k]	**aOR 0.8** [j] (0.7 to 1.0)	**1 fewer per 100** (from 3 fewer to 1 more) [f]	⊕◯◯◯ VERY LOW	CRITICAL
Culture conversion - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Serious adverse effect												
16 [2]	observational studies	serious [h]	not serious	not serious	not serious	none	208/1706 (12.2%) [i]	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Discontinuation of treatment owing to adverse effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Acquisition of drug resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations

a. Data from experimental and observational studies pooled in propensity score matched IPDMA. 14 to 17% were lost to follow-up.
b. Updated systematic review with IPDMA performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB did not report study-level analyses so it was not possible to assess heterogeneity; we did not downgrade for inconsistency as the evidence was already of very low certainty.
c. More patients in PAS group, compared with controls, received newer generation fluoroquinolone (69% vs. 47%) and capreomycin (45% vs. 9%), but fewer received amikacin (10% vs. 31%). Average number of effective drugs in initial phase also seemed higher in PAS group (3.8 vs. 3.2).
d. CI does not exclude an appreciable benefit or no difference.
e. **corresponding RR 1.16, 95% CI: 1.08 to 1.31** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
f. Based on IPD risk difference meta-analysis performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.
g. CI does not exclude an appreciable harm or no difference
h. case series
i. Pooled proportion 95%CI: 10.6% to 13.9%.
j. **corresponding RR 0.97, 95% CI: 0.95 to 1.00** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA).
k. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References

1. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392: 821–34
2. Menzies R, Bastos M,Lan Z. WHO treatment guidelines for drug resistant tuberculosis, 2016 Update. World Health Organization; (11 November 2015).

Date: 2017-11-28
Question: Should **levofloxacin** added to a background MDR TB regimen, compared to background MDR TB regimen alone, be used in adults with MDR TB?
Setting: low and high resource settings, within hospital or ambulatory models of care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	levofloxacin added to a background MDR TB regimen	background MDR TB regimen alone	Relative (95% CI)	Absolute (95% CI)		
Death												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	not serious	none	182/1632 (11.2%)	292/647 (45.1%) [r]	**aOR 0.6** [c] (0.5 to 0.7)	**6 fewer per 100** (from 4 fewer to 9 fewer) [g]	⊕◯◯◯ VERY LOW	CRITICAL
								16.9% [d]	**RR 0.64** (0.55 to 0.74) [e]	**6 fewer per 100** (from 4 fewer to 8 fewer) [h]		
Treatment success (assessed with: as opposed to treatment failure or relapse)												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	not serious	none	1361/1450 (93.9%)	258/355 (72.7%) [r]	**aOR 4.2** [f] (3.3 to 5.4)	**15 more per 100** (from 13 more to 18 more) [g]	⊕◯◯◯ VERY LOW	CRITICAL
								88.4% [d]	**RR 1.10** (1.09 to 1.10)	**9 more per 100** (from 8 more to 9 more) [h]		
Culture conversion (follow up: 2 months)												
1 [2]	randomised trials	serious [l]	not serious	not serious [m]	serious [n]	none	49/53 (92.5%)	72/79 (91.1%)	**RR 1.01** (0.91 to 1.12)	**1 more per 100** (from 8 fewer to 11 more)	⊕⊕◯◯ LOW	CRITICAL
Serious adverse effect												
1 [2]	randomised trials	serious [l]	not serious	not serious [m]	serious [o]	none	11/87 (12.6%) [p]	13/87 (14.9%)	**RR 0.85** (0.40 to 1.78)	**2 fewer per 100** (from 9 fewer to 12 more)	⊕⊕◯◯ LOW	CRITICAL
Discontinuation of treatment owing to adverse effect												
1 [2]	randomised trials	serious [l]	not serious	not serious [m]	serious [q]	none	7/87 (8.0%)	10/87 (11.5%)	**RR 0.70** (0.28 to 1.75)	**3 fewer per 100** (from 8 fewer to 9 more)	⊕⊕◯◯ LOW	CRITICAL
Acquisition of drug resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations

a. Data from experimental and observational studies pooled in propensity score matched IPDMA. 12% to 15% patients were lost to follow-up. Fewer patients in levofloxacin group, compared with controls, received linezolid (6% vs. 15%) and capreomycin (18% vs. 66%), but more received amikacin (29% vs. 7%) and kanamycin (26% vs. 13%). On average, they also received more effective drugs (4 vs. 2).
b. Updated systematic review with IPDMA performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB did not report study-level analyses so it was not possible to assess heterogeneity, however, previous meta-analysis of study-level data performed for the 2016 update of WHO guidelines did not show serious heterogeneity.
c. **corresponding RR 0.73, 95% CI: 0.65 to 0.81** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
d. Average event rate among controls across all 50 studies included in IPD MA performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.
e. mortality in this sample was high in control groups – RR based on aOR and a median of average baseline mortality risks in control groups in all comparisons in IPDMA (16.9%).
f. **corresponding RR 1.26, 95% CI: 1.24 to 1.29** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
g. Based on IPD risk difference meta-analysis performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.
h. Based on aOR and assumed baseline risk.
l. Allocation concealment not reported, 73/174 (42%) excluded from analysis at 8 weeks.
m. Adults with and without HIV infection in New York; only 20% had MDR-TB but we assumed that the adverse effects would be similar.
n. CI does not exclude a possibility of an appreciable benefit or an appreciable harm.
o. Only 24 events; CI does not exclude a possibility of an appreciable benefit or an appreciable harm.
p. A systematic review of observational studies performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB found 13 studies in which the rate of serious adverse events (Grade 3 or 4, or drugs stopped due to adverse events) in patients receiving any later-generation fluoroquinolone was 10/827 (1.2%; 95% CI: 0.6 to 2.4)
q. Only 17 events; CI does not exclude a possibility of an appreciable benefit or an appreciable harm.
r. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References

1. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392: 821–34
2. El-Sadr W.M. et al. Evaluation of an Intensive Intermittent-Induction Regimen and Duration of Short-Course Treatment for Human Immunodeficiency Virus–Related Pulmonary Tuberculosis. Clinical Infectious Diseases; 1998.

Date: 2017-11-28
Question: Should **moxifloxacin** added to a background MDR TB regimen, compared to background MDR TB regimen without a fluoroquinolone, be used in adults with MDR TB?
Setting: low and high resource settings, within hospital or ambulatory models of care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	moxifloxacin and background MDR TB regimen	background MDR TB regimen alone	Relative (95% CI)	Absolute (95% CI)		
Death												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	not serious	none	114/1145 (10.0%)	292/647 (45.1%) [s]	**aOR 0.5** [f] (0.4 to 0.6)	**7 fewer per 100** (from 4 fewer to 10 fewer) [h]	⊕◯◯◯ VERY LOW	CRITICAL
								16.9% [d]	**RR 0.55** (0.45 to 0.64) [e]	**8 fewer per 100** (from 6 fewer to 9 fewer) [i]		
Treatment success (assessed with: as opposed to treatment failure or relapse)												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	not serious	none	974/1031 (94.5%)	258/355 (72.7%) [s]	**aOR 3.8** [g] (2.8 to 5.2)	**11 more per 100** (from 8 more to 14 more) [h]	⊕◯◯◯ VERY LOW	CRITICAL
								88.4% [d]	**RR 1.09** (1.08 to 1.10) [k]	**8 more per 100** (from 7 more to 9 more) [i]		
Culture conversion (follow up: 2 months)												
2 [2,3]	randomised trials	not serious [l]	not serious	not serious	very serious [m]	none	40/46 (87.0%) [n]	27/47 (57.4%) [n]	**RR 2.70** (0.82 to 8.84)	**98 more per 100** (from 10 fewer to 100 more)	⊕⊕◯◯ LOW	CRITICAL
								90.0% [d]		**100 more per 100** (from 16 fewer to 100 more)		
Serious adverse effect												
4 [4,o]	randomised trials	serious [o,p]	not serious	serious [q]	serious [r]	none	29/526 (5.5%)	24/484 (5.0%)	**RR 1.06** (0.63 to 1.80)	**0 fewer per 100** (from 2 fewer to 4 more)	⊕◯◯◯ VERY LOW	CRITICAL
Discontinuation of treatment owing to adverse effect - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Acquisition of drug resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations

a. Data from experimental and observational studies pooled in propensity score matched IPDMA. 12% of patients were lost to follow-up. Fewer patients in moxifloxacin group, compared with controls, received capreomycin (34% vs. 66%), but more received amikacin (17% vs. 7%), kanamycin (32% vs. 13%), and linezolid (23% vs. 15%). On average, they also received more effective drugs (4 vs. 2).
b. Updated systematic review did not report study-level analyses, so it was not possible to assess heterogeneity, however, previous meta-analysis of study-level data performed for the 2016 update of WHO guidelines did not show serious heterogeneity.
d. Average event rate among controls across all 50 studies included in IPD MA performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.
e. RR based on a pooled adjusted OR and a median of average assumed risks in control groups in all comparisons in IPDMA (16.9%)
f. **corresponding RR 0.65, 95% CI: 0.55 to 0.73** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
g. **corresponding RR 1.25, 95% CI: 1.21 to 1.28** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
h. Based on IPD risk difference meta-analysis performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.
i. Based on aOR and assumed baseline risk.
k. RR based on a pooled adjusted OR and a median of average assumed risks in control groups in all comparisons in IPDMA (88.4%)
l. One study was not blinded
m. Confidence interval does not exclude an appreciable benefit or an appreciable harm.
n. Numbers from one study (Wang 2010). Number of events and total number in the group was not reported in another study in which there were 74 patients altogether (Chen 2013).
o. One additional study measured the effects of moxifloxacin added to standard regimen but adverse effects were reported for both groups together without specifying their severity (Velayutham 2014).
p. All five trials were at high risk of bias due to dropout (>15%), differential dropout between groups, or participants missing from the primary analysis who could not be accounted for; none of the trials included all of the randomized participants in the final analysis.
q. Studies did not compare moxifloxacin as an addition to standard regimen but rather as a replacement for ethambutol or isoniazid.
r. Only 53 events and CI does not exclude the possibility of an appreciable harm.
s. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References

1. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392: 821–34
2. Chen Y. Effects of moxifloxacin combined with regimenin the treatment of patients with drug-resistant pulmonary tuberculosis. J Clin Pulm Med. 2013;18(2):309–10 (Chinese).
3. Wang JF et al. Treatment effect of regimen which contains the moxifloxacin on multi-drug resistant pulmonary tuberculosis. Chin. J. Clin. Pharm. 2010;19(1): 33-35 (Chinese).
4. Ziganshina LE, Titarenko AF,Davies GR.. Fluoroquinolones for treating tuberculosis (presumed drug-sensitive).. Cochrane Database of Systematic Reviews; 2013.

Date: 2017-11-28
Question: Should regimens including **levofloxacin** rather than **moxifloxacin** be used in adults with MDR TB?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	levofloxacin	moxifloxacin	Relative (95% CI)	Absolute (95% CI)		
Death												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	serious [c]	none	182/1632 (11.2%)	114/1145 (10.0%) [p]	**aOR 0.9** (0.8 to 1.2) [d]	**0 fewer per 100** (from 2 fewer to 2 more)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	serious [g]	none	1361/1450 (93.9%)	974/1031 (94.5%) [p]	**aOR 0.7** (0.5 to 0.9) [h]	**2 fewer per 100** (from 1 fewer to 4 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Culture conversion												
11 [2-11]	randomised trials	not serious [j]	not serious	serious [k]	not serious	none	427/553 (77.2%)	503/556 (90.5%)	**RR 0.84** (0.77 to 0.92)	**14 fewer per 100** (from 7 fewer to 21 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse effect												
1 [11]	randomised trials	serious [l]	not serious	not serious	serious [m,n]	none	6/78 (7.7%)	4/77 (5.2%)	**RR 1.48** (0.43 to 5.04)	**2 more per 100** (from 3 fewer to 21 more)	⊕⊕◯◯ LOW	CRITICAL
Discontinuation of treatment owing to adverse effect - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Acquisition of drug resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Any AE												
11 [2-11]	randomised trials	not serious [j]	not serious	serious [o]	serious [m]	none	186/576 (32.3%)	154/585 (26.3%)	**RR 1.20** (1.02 to 1.41)	**5 more per 100** (from 1 more to 11 more)	⊕⊕◯◯ LOW	IMPORTANT
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations

a. Data from experimental and observational studies pooled in propensity score matched IPDMA. 12% to 15% patients were lost to follow-up.
b. Updated systematic review did not report study-level analyses so it was not possible to assess heterogeneity, however, previous meta-analysis of study-level data performed for the 2016 update of WHO guidelines did not show serious heterogeneity.
c. CI does not exclude a small benefit with either moxifloxacin or levofloxacin.
d. **corresponding RR 0.91, 95% CI: 0.72 to 1.09** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
g. CI does not exclude a small benefit with levofloxacin or no difference.
h. **corresponding RR 0.99, 95% CI: 0.96 to 1.01** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
j. Authors of the systematic review (Liu 2012) judged most studies as low risk of bias.
k. Dosing of medications was uncertain in these studies.
l. Only one study reported this outcome (Koh 2013); we did not extract data from other individual studies but based on overall suboptimal reporting of SAE in MDR-TB trials we assumed that many would not report them adequately.
m. CI does not exclude an appreciable benefit with moxifloxacin or no difference.
n. Very few events.
o. Many different AEs were put together of which some may be more important to patients than the others.
p. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References

1. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392: 821–34
2. Liang LL et al. Effects of anti-Tuberculosis containing with moxifloxacin or levofloxacin on multidrug resistant pulmonary tuberculosis. Chin. Gener. Pract. 2011; 14(5): 1451-1454 (Chinese).
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10. Chen Y, Zhang X, Zhang HM. Comparison of moxifloxacin and levofloxacin in treating widely multi-drug resistant pulmonary tuberculosis. Clin. Med. 2009; 29(5): 49-50 (Chinese).
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Date: 2017-11-28
Question: Should **linezolid** added to a background MDR TB regimen, compared to background MDR TB regimen alone, be used in adults with MDR TB?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**linezolid added to a background MDR TB regimen**	**background MDR TB regimen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Death[1]												
50 [1]	observational studies	serious [a]	serious [b]	not serious [c]	not serious	strong association [d]	84/883 (9.5%)	1456/7320 (19.9%) [n]	**aOR 0.3** [e] (0.2 to 0.3)	**20 fewer per 100** (from 16 fewer to 23 fewer) [f]	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
50 [1]	observational studies	serious [a]	serious [b]	not serious [c]	not serious	none	722/799 (90.4%)	5066/5864 (86.4%) [n]	**aOR 3.4** [l] (2.6 to 4.5)	**15 more per 100** (from 11 more to 18 more) [f]	⊕◯◯◯ VERY LOW	CRITICAL
Culture conversion (follow up: 6 months)												
50 [1]	observational studies	serious [a]	serious [g]	not serious [c]	serious [h]	none	521/609 (85.6%)	4394/4837 (90.8%) [n]	**aOR 0.7** [m] (0.5 to 1.0)	**4 fewer per 100** (from 0 fewer to 8 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse effect and/or discontinuation of treatment owing to adverse effect												
4 [i]	observational studies	serious	not serious	not serious	serious [j]	none	11/49 (22.4%) [k]	112/1305 (8.6%)	–	**14 more per 100** (from 2 more to 26 more) [i]	⊕◯◯◯ VERY LOW	CRITICAL
Acquisition of drug resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations

a. Data from experimental and observational studies pooled in propensity score matched IPDMA. 11% to 15% of patients were lost to follow-up.
b. Systematic review did not report study-level analyses so it was not possible to assess heterogeneity, however, previous meta-analysis of study-level data performed for the 2016 update of WHO guidelines showed serious heterogeneity among observational studies.
c. There is some uncertainty about doses used and their timing.
d. The effect was large that would justify upgrading the certainty of evidence if it was not already downgraded for risk of bias and other potential limitations.
e. **corresponding RR 0.35, 95% CI: 0.24 to 0.35** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
f. Based on IPD risk difference meta-analysis performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.
g. Systematic review did not report study-level analyses so it was not possible to assess heterogeneity, however, previous meta-analysis of study-level data performed for the 2016 update of WHO guidelines found heterogeneity both in the estimates of death and treatment success, therefore, we assumed that the results for culture conversion would also be inconsistent among studies.
h. CI does not exclude an appreciable harm or no difference.
i. Data from the "WHO treatment guidelines for drug resistant tuberculosis, 2016 update" Annexes 4, 5 and 6 (Menzies R, Bastos M, Lan Z; 11 November 2015)
j. Only 123 events which makes the results fragile; estimates of frequency of events in the linezolid groups were lower in case series.
k. A systematic review of safety of linezolid in MDR TB (Agyeman 2016) found 21 studies (mostly case series) that reported discontinuation of treatment by patients receiving linezolid (pooled proportion 15.8% (95% CI: 9.7 to 23.1)
l. **corresponding RR 1.11, 95% CI: 1.09 to 1.12** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
m. **corresponding RR 0.96, 95% CI: 0.92 to 1.00** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
n. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References

1. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392: 821–34
2. Agyeman AA, Ofori-Asenso R.. Efficacy and safety profile of linezolid in the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis: a systematic review and meta-analysis.. Ann Clin Microbiol Antimicrob.; 2016.
3. Menzies R, Bastos M,Lan Z. WHO treatment guidelines for drug resistant tuberculosis, 2016 Update. World Health Organization; (11 November 2015).

Date: 2017-11-28
Question: Should **clofazimine** added to a background MDR TB regimen, compared to background MDR TB regimen alone, be used in adults with 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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**clofazimine added to a background MDR TB regimen**	**background MDR TB regimen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Death												
50 [4]	observational studies	serious [a]	not serious	serious [b]	serious [c]	none	115/679 (16.9%)	1292/7398 (17.5%) [o]	**aOR 0.8** [d] (0.6 to 1.0)	**4 fewer per 100** ethio [e]	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
50 [4]	observational studies	serious [a]	serious [f]	serious [b]	not serious	none	485/564 (86.0%)	5321/6106 (87.1%) [o]	**aOR 1.5** [m] (1.1 to 2.1)	**6 more per 100** (from 1 more to 10 more) [e]	⊕◯◯◯ VERY LOW	CRITICAL
Culture conversion (follow up: 6 months)												
50 [4]	observational studies	serious [a]	serious [f]	serious [b]	serious [c]	none	269/300 (89.7%)	4646/5146 (90.3%) [o]	**aOR 1.1** [n] (0.6 to 1.8)	**1 more per 100** (from 5 fewer to 6 more)	⊕◯◯◯ VERY LOW	CRITICAL
Discontinuation of treatment owing to an adverse effect												
5 [1,2,3,g]	observational studies	very serious [h]	not serious	not serious	not serious	none	2/81 (2.5%) [i]	281/658 (42.7%)	–		⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse effects												
6 [3]	observational studies	serious [j]	serious [k]	serious [l]	serious	none	One systematic review of 12 studies (Dey 2013) found that 6 of them did not report adverse effects at all and the remaining 6 reported only adverse effects among patients receiving clofazimine; altogether there were 513 patients and studies reported: liver dysfunction (4), neuropathy/neurological symptoms (16), anemia (4), myelosuppression (1), gastrointestinal symptoms (193), skin discoloration – however those were not measured systematically within and among studies.				⊕◯◯◯ VERY LOW	CRITICAL
Acquisition of drug resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Transmission of infection - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations

a. Data from experimental and observational studies pooled in propensity score matched IPDMA. 14% to 17% were lost to follow-up.
b. More patients in clofazimine group received also linezolid (46% vs. 16%) and bedaquiline (around 28% vs. 12%). On average, they also received more effective drugs (4 vs. 3).
c. CI does not exclude an appreciable benefit or no difference.
d. **corresponding RR 0.83, 95% CI: 0.65 to 1.00** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
e. Based on IPD risk difference meta-analysis performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.
f. Systematic review performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB did not report study-level analyses so it was not possible to assess heterogeneity, however, previous meta-analysis of study-level data performed for the 2016 update of WHO guidelines found heterogeneity in the estimates of treatment success, therefore, we assumed that the results for culture conversion would also be inconsistent among studies.
g. Data from the "WHO treatment guidelines for drug resistant tuberculosis, 2016 update" Annexes 4, 5 and 6 (Menzies R, Bastos M, Lan Z; 11 November 2015)
h. 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.
i. A systematic review performed for the 2016 update of WHO guidelines also found the rate of adverse effects requiring treatment discontinuation in 3.3% to 12.8% of NTM patients receiving clofazimine. A systematic review of 5 studies reported the pooled proportion of adverse effects requiring discontinuation or withdrawal of clofazimine in 0.1% of patients (95% CI: 0 to 0.6%) (Hwang 2014). Previous systematic review found similar results (Gopal 2013). Howevernone has reported the nature of those events.
j. Adverse effects were reported only for patients receiving clofazimine; they were assessed by authors who were unblinded and used non-standardized methods to define, ascertain and report adverse effects.
k. Studies reported adverse effects selectively and their frequency ranged from 12% to 89%.
l. Studies did not report how adverse effects were assessed and their severity; it is very likely that some studies reported all adverse effects (mild and severe) and some only the severe ones, thus, it is uncertain to what extent all those were important for patients.
m. **corresponding RR 1.04, 95% CI: 1.01 to 1.07** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
n. **corresponding RR 1.01, 95% CI: 0.94 to 1.05** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
o. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References

1. Hwang TJ, et al.. Safety and availability of clofazimine in the treatment of multidrug and extensively drug-resistant tuberculosis: analysis of published guidance and meta-analysis of cohort studies. BMJ Open; 2014.
2. Gopal M, et al.. Systematic review of clofazimine for the treatment of drug-resistant tuberculosis. INT J TUBERC LUNG DIS; 2013.

3. Dey T, et al.. Outcomes of clofazimine for the treatment of drug-resistant tuberculosis: a systematic review and meta-analysis. J Antimicrob Chemother; 2013.
4. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392: 821–34

Date: 2017-11-28
Question: Should **amoxicillin with clavulanic acid** added to a background MDR TB regimen, compared to background MDR TB regimen alone, be used in adults with MDR TB?
Setting: low and high resource settings, within hospital or ambulatory models of care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**amoxicillin with clavulanic acid and background MDR TB regimen**	**background MDR TB regimen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Death												
50 [1]	observational studies	serious [a]	not serious [b]	not serious	not serious	none	234/1206 (19.4%)	717/4660 (15.4%) [i]	**aOR 1.7** [c] (1.3 to 2.1)	**6 more per 100** (from 4 more to 9 more) [d]	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
50 [1]	observational studies	serious [a]	not serious	not serious	not serious	none	768/972 (79.0%)	3443/3943 (87.3%) [i]	**aOR 0.6** [h] (0.5 to 0.8)	**7 fewer per 100** (from 3 fewer to 10 fewer) [d]	⊕◯◯◯ VERY LOW	CRITICAL
Culture conversion - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Serious adverse effect												
3 [2]	observational studies	serious [e]	serious [f]	not serious	serious [g]	none	Proportion of patients receiving amoxicillin who experienced SAE was reported in 3 series of cases (77 patients with MDR-TB not HIV-infected) and ranged from 4% to 60% -- pooled estimate 12% (95% CI: 0–28).				⊕◯◯◯ VERY LOW	CRITICAL
Discontinuation of treatment owing to adverse effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Acquisition of drug resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations
a. Data from experimental and observational studies pooled in propensity score matched IPDMA. Around 15% of patients were lost to follow-up. More patients in amoxicillin group received capreomycin and linezolid compared to controls (58% vs. 32% and 25% vs. 8%, respectively).
b. Updated systematic review with IPDMA performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB did not report study-level analyses so it was not possible to assess heterogeneity; we did not downgrade for inconsistency as the evidence was already of very low certainty.
c. **corresponding RR 1.53, 95% CI: 1.24 to 1.80** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
d. Based on IPD risk difference meta-analysis performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.
e. case series
f. risk of SAE ranged from 4 to 60% in those studies
g. Only 77 patients
h. **corresponding RR 0.92, 95% CI: 0.89 to 0.97** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
i. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References
1. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392: 821–34
2. 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.

Date: 2017-12-07
Question: Should a **macrolide** added to a background MDR TB regimen, compared to background MDR TB regimen without a macrolide, be used in adults with MDR TB?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**macrolide added to a background MDR TB regimen**	**background MDR TB regimen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Death												
50 [1]	observational studies	serious [a]	not serious	not serious	not serious	none	185/908 (20.4%)	562/3655 (15.4%) [r]	**aOR 1.6** [b] (1.2 to 2.0)	**6 more per 100** (from 2 more to 9 more) [c]	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
50 [1]	observational studies	serious [a]	not serious	not serious	not serious	none	560/723 (77.5%)	2628/3039 (86.5%) [r]	**aOR 0.6** [q] (0.5 to 0.8)	**8 fewer per 100** (from 3 fewer to 12 fewer) [c]	⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse effects; azithromycin used for treatment / prevention of non-tuberculous mycobacteria (NTM) in HIV-positive patients[n]												
7 [4]	randomised trials	not serious	not serious	serious [d,n]	not serious	none	113/1215 (9.3%)	57/1196 (4.8%)	**RR 1.94** (1.29 to 2.91)	**4 more per 100** (from 1 more to 9 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse effects rate with azithromycin used for treatment of non-tuberculous mycobacteria (NTM) in HIV-negative patients[p] (assessed with: as defined by the study authors)												
5 [4]	observational studies	serious [e]	not serious	serious [d,p]	serious [f]	none	7/197 (3.6%) [g]	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse effects; clarithromycin												
1	observational studies	serious [e]	not serious	not serious	very serious [h]	none	0/39 (0.0%)	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse effects; clarithromycin used for treatment / prevention of non-tuberculous mycobacteria (NTM) in HIV-positive patients[n] (assessed with: as defined by study authors)												
8 [4]	randomised trials	not serious	not serious	serious [d,n]	serious [i]	none	108/1088 (9.9%)	118/1111 (10.6%)	**RR 0.93** (0.72 to 1.18)	**1 fewer per 100** (from 2 more to 3 fewer)	⊕⊕◯◯ LOW	CRITICAL
Serious adverse effects rate with clarithromycin used for treatment/prevention of non-tuberculous mycobacteria (NTM) in HIV-positive patients[n] (assessed with: as defined by study authors)												
6 [4]	observational studies	serious [e]	not serious	serious [d,n]	not serious	none	122/584 (20.9%) [j]	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse effects; clarithromycin used for treatment of non-tuberculous mycobacteria (NTM) in HIV-negative patients[p] (assessed with: as defined by study authors)												
3 [4]	randomised trials	not serious	not serious	serious [d,p]	very serious [k]	none	31/174 (17.8%)	26/175 (14.9%)	**RR 1.24** (0.79 to 1.95)	**4 more per 100** (from 3 fewer to 14 more)	⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse effects with clarithromycin used for treatment of non-tuberculous mycobacteria (NTM)[p] in HIV-negative patients (assessed with: as defined by study authors)												
15 [4]	observational studies	serious [e]	not serious	serious [d,p]	serious [l]	none	41/615 (6.7%) [m]	-	-	-	⊕◯◯◯ VERY LOW	CRITICAL
Culture conversion - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Acquisition of drug resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations

a. Data from experimental and observational studies pooled in propensity score matched IPDMA. 15% of patients were lost to follow-up.
b. **corresponding RR 1.46, 95% CI: 1.16 to 1.73** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
c. Based on IPD risk difference meta-analysis performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.
d. All studies were done in patients with non-tuberculous mycobacterial (NTM) infections, but we assumed that the adverse effects would be similar.
e. Series of cases
f. Only 7 events
g. Pooled weighted proportion was 3% (95% CI: 0 to 8)
h. Only 39 patients
i. CI does not exclude an appreciable benefit or an appreciable harm with macrolides
j. Pooled weighted proportion was 20% (12 to 27)
k. Only 57 events; CI does not exclude an appreciable benefit or an appreciable harm with macrolides
l. Only 41 events
m. Pooled weighted proportion was 4% (2 to 7)

n. Studies of treatment/prevention of NTM infections/disease in HIV infected patients – macrolide was used alone for prevention or as part of multi-drug regimen for treatment (adverse events were those attributed to macrolide by care providers).
p. Studies of treatment of NTM pulmonary disease in HIV uninfected patients – macrolide was used as part of a multi-drug regimen (adverse events were those attributed to macrolide by care providers).
q. **corresponding RR 0.92, 95% CI: 0.88 to 0.97** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
r. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References

1. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392: 821–34
2. Agyeman AA, Ofori-Asenso R.. Efficacy and safety profile of linezolid in the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis: a systematic review and meta-analysis.. Ann Clin Microbiol Antimicrob.; 2016.
3. Menzies R, Bastos M,Lan Z. WHO treatment guidelines for drug resistant tuberculosis, 2016 Update. World Health Organization; (11 November 2015).
4. 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.

Date: 2017-11-28
Question: Should **bedaquiline** added to a background MDR TB regimen, compared to background MDR TB regimen alone, be used in adults with MDR TB?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	bedaquiline and background MDR TB regimen	background MDR TB regimen alone	Relative (95% CI)	Absolute (95% CI)		
Death												
50 [4]	observational studies	serious [a,b]	not serious [c]	serious [d]	not serious	strong association [e]	59/550 (10.7%)	1569/8789 (17.9%) [p]	**aOR 0.4** [f,g] (0.3 to 0.5)	**14 fewer per 100** (from 10 fewer to 19 fewer) [h]	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
50 [4]	observational studies	serious [a,b]	not serious [c]	serious [d]	not serious	none	431/491 (87.8%)	6312/7220 (87.4%) [p]	**aOR 2.0** [f,n] (1.4 to 2.9)	**10 more per 100** (from 5 more to 14 more) [h]	⊕◯◯◯ VERY LOW	CRITICAL
Culture conversion (follow up: 6 months)												
50 [4]	observational studies	serious [a,b]	not serious [c]	serious [d]	not serious	none	340/372 (91.4%)	4575/5074 (90.2%) [p]	**aOR 2.1** [f,o] (1.3 to 3.4)	**7 more per 100** (from 2 more to 12 more)	⊕◯◯◯ VERY LOW	CRITICAL
Discontinuation of treatment owing to adverse effect												
2 [1,2,3]	randomised trials	not serious	not serious	not serious	very serious [i,j]	none	4/102 (3.9%)	5/105 (4.8%)	**RR 0.82** (0.23 to 2.94)	**1 fewer per 100** (from 4 fewer to 9 more)	⊕⊕◯◯ LOW	CRITICAL
Serious adverse effect												
2 [1,2,3]	randomised trials	not serious	not serious	not serious	very serious [i,k]	none	19/102 (18.6%)	16/105 (15.2%)	**RR 1.22** (0.67 to 2.22)	**3 more per 100** (from 5 fewer to 19 more)	⊕⊕◯◯ LOW	CRITICAL
Acquisition of new resistance to at least one anti-TB drug												
2 [1,2,3]	randomised trials	not serious	not serious	not serious	serious [l]	strong association [m]	3/102 (2.9%)	21/105 (20.0%)	**RR 0.15** (0.05 to 0.49)	**17 fewer per 100** (from 10 fewer to 19 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Any adverse effect												
2 [1,2,3]	randomised trials	not serious	not serious	not serious	very serious [i]	none	98/102 (96.1%)	99/105 (94.3%)	**RR 1.01** (0.97 to 1.06)	**1 more per 100** (from 3 fewer to 6 more)	⊕⊕◯◯ LOW	IMPORTANT
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations

a. Data from experimental and observational studies pooled in propensity score matched IPDMA. 15% of patients were lost to follow-up.
b. More patients in bedaquiline group received also linezolid (around 64% vs. 4%) and clofazimine (around 48% vs. 4%). On average, they also received more of the effective drugs (4 effective drugs vs. 3 effective drugs).
c. Systematic review performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB did not report study-level analyses so it was not possible to assess heterogeneity; we did not downgrade the certainty of evidence for inconsistency because the overall certainty is already very low owing to other limitations.
d. Patients were not tested for resistance to BDQ; all were assumed to be sensitive in the analyses.
e. There was a strong association between treatment and the effect. However, it did not increase our confidence in the estimated effect because of the serious risk of bias.
f. Adjusted for Age, Sex, HIV, AFB smear, Cavities on CXR, Prior treatment with First and Second line TB drugs, resistance to Fluoroquinolones and SLI, AND Number of possibly effective drugs in the initial phase
g. **corresponding RR 0.45, 95% CI: 0.34 to 0.55** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
h. Based on IPD risk difference meta-analysis performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.
i. CI does not exclude an appreciable benefit or harm.
j. Only 9 events
k. Only 35 events
l. Despite relatively narrow CI there were only 24 events making this result fragile.
m. There was a strong association between treatment and the effect. However, it did not increase our confidence in the estimated effect because of small number of events and the fragility of the result.
n. **corresponding RR 1.07, 95% CI: 1.04 to 1.09** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
o. **corresponding RR 1.05, 95% CI: 1.02 to 1.07** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
p. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References

1. Deacon AH, et al.. Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline. N Engl J Med; 2014.
2. Deacon AH, et al.. Randomized Pilot Trial of Eight Weeks of Bedaquiline (TMC207) Treatment for Multidrug-Resistant Tuberculosis: Long-Term Outcome, Tolerability, and Effect on Emergence of Drug Resistance. Antimicrobial Agents and Chemotherapy; 2012.
3. Deacon AH, et al.. The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis. N Engl J Med; 2009.
4. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392: 821–34

Author(s): jlb
Date: 2017-11-28
Question: Should **carbapenem**[a] with clavulanic acid added to a background MDR TB regimen, compared to background MDR TB regimen alone, be used in adults with MDR TB?
Setting: low and high resource settings, within hospital or ambulatory models of care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**carbapenem[a] with clavulanic acid added to background MDR TB regimen**	**background MDR TB regimen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Death												
50 [1]	observational studies	serious [b]	not serious [c]	serious [d]	serious [e]	none	30/169 (17.8%)	1674/9535 (17.6%) [o]	**aOR 1.0** [f] (0.5 to 1.7)	**0 fewer per 100** (from 9 fewer to 8 more) [g]	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
50 [1]	observational studies	serious [b]	not serious [c]	serious [d]	not serious	none	130/139 (93.5%)	6871/7861 (87.4%) [o]	**aOR 4.0** [m] (1.7 to 9.1)	**14 more per 100** (from 6 more to 21 more) [g]	⨁◯◯◯ VERY LOW	CRITICAL
Culture conversion (follow up: 6 months)												
50 [1]	observational studies	serious [b]	not serious [c]	serious [d]	not serious	none	130/135 (96.3%)	4785/5311 (90.1%) [o]	**aOR 2.3** [n] (0.8 to 6.9)	**4 more per 100** (from 1 fewer to 10 more)	⨁◯◯◯ VERY LOW	CRITICAL
Discontinuation of treatment owing to adverse effect												
1 [2,h]	observational studies	serious [i]	not serious	not serious	serious [j]	none	19/183 (10.4%) [h]	11/57 (19.3%)	**RR 0.44** (0.11 to 1.03)	**11 fewer per 100** (from 1 more to 17 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse effect												
3 [2]	observational studies	serious [k]	not serious	not serious	serious [l]	none	4/33 (12.1%)	-	-	-	⨁◯◯◯ VERY LOW	CRITICAL
Acquisition of drug resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations
a. imipenem or meropenem
b. Data from experimental and observational studies pooled in propensity score matched IPDMA. 8% to 16% were lost to follow-up.
c. Updated systematic review with IPDMA performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB did not report study-level analyses so it was not possible to assess heterogeneity; we did not downgrade for inconsistency as the evidence was already of very low certainty.
d. All patients in carbapenem group received amoxicillin + clavulanate as well. More patients in carbapenem group received also linezolid (around 88% vs. 7%) and bedaquiline (around 31% vs. 5%). On average, they also received more effective drugs (4 vs. 3).
e. CI does not exclude an appreciable benefit or an appreciable harm
f. **corresponding RR 1.00, 95% CI: 0.55 to 1.51** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
g. Based on IPD risk difference meta-analysis performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.
h. 6 studies reported the rate of adverse effects in an experimental group only: weighted mean 9.1% (95% CI: 4.9 to 13.3)
i. Only 1 out of 8 studies properly reported this obvious to measure outcome.
j. Only 30 events; CI does not exclude an appreciable benefit or no difference
k. Only 3 out of 8 studies reported this outcome in experimental group; no study reported number of SAE in controls.
l. Only 4 events
m. **corresponding RR 1.10, 95% CI: 1.05 to 1.13** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
n. **corresponding RR 1.06, 95% CI: 0.98 to 1.09** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
o. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References
1. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392: 821–34
2. Sotgiu G, et al.. Carbapenems to Treat Multidrug and Extensively Drug-Resistant Tuberculosis: A Systematic Review. International Journal of Molecular Sciences; 2016.

Date: 2018-01-26
Question: Should a **shorter total duration of treatment**, compared to a standard total duration of treatment (17 to 24 months), be used in adults with MDR TB
Setting: low and high resource settings, within hospital or ambulatory models of care

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	shorter duration of treatment	standard duration of treatment	Relative (95% CI)	Absolute (95% CI)		
Death (data from IPD-MA)												
33 [1,a]	observational studies [b]	serious [c]	not serious [d]	not serious	serious [e]	none	34/532 (6.4%)	100/1469 (6.8%) [t]	**aOR 1.7** [f] (0.6 to 4.6)	**1 more per 100** (from 3 fewer to 5 more) [g,h]	⊕◯◯◯ VERY LOW	CRITICAL
Death (preliminary unpublished results from STREAM Stage 1 RCT; mean follow up: 2.5 years)												
1 [2,i]	randomised trials	serious [r]	not serious	not serious	very serious [e,j]	none	24/282 (8.5%)	9/141 (6.4%) [t]	**RR 1.33** (0.64 to 2.79)	**2 more per 100** (from 2 fewer to 11 more)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse in IPDMA)												
33 [1,a]	observational studies	serious [k]	not serious [d]	not serious	serious [e]	none	477/498 (95.8%)	1311/1369 (95.8%) [t]	**aOR 0.5** [s] (0.02 to 13.0)	**1 more per 100** (from 2 fewer to 3 more) [g,h]	⊕◯◯◯ VERY LOW	CRITICAL
Favorable outcome (preliminary unpublished results from STREAM Stage 1 RCT; mean follow up: 2.5 years)[l]												
1 [2,i]	randomised trials	serious [m,r]	not serious	not serious	very serious [e]	none	164/210 (78.1%)	87/108 (80.6%)	**RR 0.97** (0.86 to 1.09)	**2 fewer per 100** (from 7 more to 11 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Culture conversion (preliminary unpublished results from STREAM Stage 1 RCT; mean follow up: 2.5 years)												
1 [2,i]	randomised trials	serious [r]	not serious	not serious	very serious [e]	none	– /273	– /139 90.0% [n]	**HR 1.14** (0.93 to 1.40)	**–** **3 more per 100** (from 2 fewer to 6 more)	⊕◯◯◯ VERY LOW	CRITICAL
Any adverse effects (grade 3-4) (data from IPD-MA)												
4 [3]	observational studies	serious [o]	not serious	serious	serious [p]	none	Any AE grade 3-4 (4 studies): 55 out of 303 participants (18.1%). Hearing loss grade 3-4 (3 studies): 37 events (14% to 23%)				⊕◯◯◯ VERY LOW	CRITICAL
Serious adverse effects (preliminary unpublished results from STREAM Stage 1 RCT; mean follow up: 2.5 years)												
1 [2,i]	randomised trials	serious [r]	not serious	not serious	very serious [e]	none	91/282 (32.3%)	53/141 (37.6%)	**RR 0.86** (0.65 to 1.13)	**5 fewer per 100** (from 5 more to 13 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Any adverse effect (grade 3-5) (preliminary unpublished results from STREAM Stage 1 RCT; mean follow up: 2.5 years)												
1 [2,i]	randomised trials	serious [r]	not serious	not serious	very serious [e]	none	129/282 (45.7%)	63/141 (44.7%)	**RR 1.02** (0.82 to 1.28)	**1 more per 100** (from 8 fewer to 13 more)	⊕◯◯◯ VERY LOW	IMPORTANT
Acquisition of drug resistance (data from IPD-MA)												
3 [3]	observational studies	serious [o]	not serious	not serious	very serious [q]	none	There were 4 out of 21 participants who failed or relapsed that acquired drug resistance (Swaziland, Bangladesh and Uzbekistan).				⊕◯◯◯ VERY LOW	CRITICAL
Discontinuation of treatment owing to adverse effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

aOR: adjusted odds ratio; **CI:** Confidence interval; **HR:** Hazard ratio; **RR:** Risk ratio

Explanations

a. 3 studies investigated a short-course treatment and 30 studies – standard treatment duration.

b. Median duration of treatment in standard duration studies was 21 months (IQR: 18.5 to 24) and in shorter duration regimens 9 months (IQR: 9 to 9.5).

c. Data from experimental and observational studies pooled in propensity score matched IPDMA. 12.7% were lost to follow-up.

d. Updated systematic review with IPDMA performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB did not report study-level analyses so it was not possible to assess heterogeneity; we did not downgrade for inconsistency as the evidence was already of very low certainty.

e. CI does not exclude an appreciable benefit or an appreciable harm

f. **corresponding RR 1.62, 95% CI: 0.62 to 3.69** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)

g. Based on IPD risk difference meta-analysis performed by Dr. R. Menzies and colleagues in 2017 for the ATS/CDC/IDSA guidelines on treatment of MDR-TB.

h. 99% confidence interval

i. In STREAM stage 1 of the trial, 424 participants with MDR-TB were randomly assigned to receive the standardised 20–24 month regimen or a 9 month regimen comprising moxifloxacin, clofazimine, ethambutol, and pyrazinamide (supplemented by kanamycin, isoniazid, and protionamide in the first 4 months). All patients were infected with strains sensitive to fluoroquinolones and injectable agents.

j. Only 33 events

k. Data from experimental and observational studies pooled in propensity score matched IPDMA. Median loss to follow-up across studies was 13.6%

l. Favorable outcome was defined as: 1) did not change the regimen or started not more than 1 additional drug, 2) did not extend treatment beyond permitted duration, 3) survived at least 132 weeks post-randomisation, 4) negative culture result at 132 weeks, and 5) did not drop out before 76 weeks

m. 25% excluded from analysis

n. Culture conversion over 6 months observed across all observational studies in IPD-MA

o. Data from observational studies with 5% to 23% patients lost to follow-up.
p. Only 55 events in total
q. Only 4 events
r. The trial was not blinded and
s. **corresponding RR 0.96, 95% CI: 0.33 to 1.04** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
t. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References

1. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet 2018; 392: 821–34
2. Meredith S., Nunn AJ,Rusen ID,Van Deun A,Torrea G,Phillips PPJ,Chiang CY,Squire SB,Madan J. STREAM Stage 1 trial (preliminary data). unpublished; 2017.
3. Ahmad Khan F, et al.,. Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses.. Eur Respir J; 2017.

Date: 2018-03-22
Question: Should a **fluoroquinolone plus rifampin/ethambutol/pyrazinamide for 6 months**, compared to rifampin/ethambutol/pyrazinamide for 6 months without a fluoroquinolone, be used in adults with **isoniazid-resistant tuberculosis**?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**FQ plus (H)REZ for 6 months**	**(H)REZ for 6 months**	**Relative (95% CI)**	**Absolute (95% CI)**		
Death												
15 [1]	observational studies	serious [a]	not serious	not serious	serious [b]	none	25/524 (4.8%)	97/2174 (4.5%) [o]	**aOR 0.7** [c] (0.4 to 1.1)	**2 fewer per 100** (from 0 fewer to 5 fewer) [d]	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
15 [1]	observational studies	serious [a]	not serious	not serious	serious [b]	none	245/251 (97.6%)	1253/1350 (92.8%) [o]	**aOR 2.8** [m] (1.1 to 7.3)	**5 more per 100** (from 0 fewer to 9 more) [d]	⊕◯◯◯ VERY LOW	CRITICAL
Acquisition of rifampin resistance												
10 [1]	observational studies	serious [a]	not serious	not serious	serious [b]	none	1/221 (0.5%)	44/1160 (3.8%) [o]	**aOR 0.1** [n] (0.0 to 1.2)	**3 fewer per 100** (from 0 fewer to 6 fewer) [d]	⊕◯◯◯ VERY LOW	CRITICAL
Culture conversion - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Serious adverse effect (levofloxacin)												
1 [2]	randomised trials	serious [e]	not serious	not serious [f]	serious [g]	none	11/87 (12.6%)	13/87 (14.9%)	**RR 0.85** (0.40 to 1.78)	**2 fewer per 100** (from 9 fewer to 12 more)	⊕⊕◯◯ LOW	CRITICAL
Serious adverse effect (moxifloxacin)												
4 [3,h]	randomised trials	serious [h,i]	not serious	serious [j]	serious [k]	none	29/526 (5.5%)	24/484 (5.0%)	**RR 1.06** (0.63 to 1.80)	**0 fewer per 100** (from 2 fewer to 4 more)	⊕◯◯◯ VERY LOW	CRITICAL
Discontinuation of treatment owing to adverse effect (levofloxacin)												
1 [2]	randomised trials	serious [e]	not serious	not serious	serious [l]	none	7/87 (8.0%)	10/87 (11.5%)	**RR 0.70** (0.28 to 1.75)	**3 fewer per 100** (from 8 fewer to 9 more)	⊕⊕◯◯ LOW	CRITICAL
Discontinuation of treatment owing to adverse effect (moxifloxacin) - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations
a. Data from experimental and observational studies pooled in propensity score matched IPDMA. Loss to follow up not available but based on other analyses of IPD we assumed more than 10% of patients lost to follow-up.
b. CI does not exclude an appreciable benefit or no difference.
c. **corresponding RR 0.71, 95% CI: 0.41 to 1.10** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
d. Based on IPD risk difference meta-analysis (Fregonese 2018).
e. Allocation concealment not reported, 73/174 (42%) excluded from analysis at 8 weeks.
f. Adults with and without HIV infection in New York; only 20% had MDR-TB but we assumed that the adverse effects would be similar.
g. Only 24 events; CI does not exclude a possibility of an appreciable benefit or an appreciable harm.
h. One additional study measured the effects of moxifloxacin added to standard regimen but adverse effects were reported for both groups together without specifying their severity (Velayutham 2014).
i. All five trials were at high risk of bias due to dropout (>15%), differential dropout between groups, or participants missing from the primary analysis who could not be accounted for; none of the trials included all of the randomized participants in the final analysis.
j. Studies did not compare moxifloxacin as an addition to standard regimen but rather as a replacement for ethambutol or isoniazid.
k. Only 53 events and CI does not exclude the possibility of an appreciable harm.
l. Only 17 events; CI does not exclude a possibility of an appreciable benefit or an appreciable harm.
m. **corresponding RR 1.05, 95% CI: 1.01 to 1.07** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
n. **corresponding RR 0.10, 95% CI: 0.00 to 1.19** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
o. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References
1. Fregonese, F. et al.. Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis. Lancet Respir Med; 2018.
2. El-Sadr,W.M.,et. al. Evaluation of an Intensive Intermittent-Induction Regimen and Duration of Short-Course Treatment for Human Immunodeficiency Virus–Related Pulmonary Tuberculosis. Clinical Infectious Diseases; 1998.
3. Ziganshina LE, Titarenko AF,Davies GR.. Fluoroquinolones for treating tuberculosis (presumed drug-sensitive).. Cochrane Database of Systematic Reviews; 2013.

Date: 2018-03-22
Question: Should **fluoroquinolone/rifampin/ethambutol for 6 months and pyrazinamide for first 2 months only**, compared to fluoroquinolone/rifampin/ethambutol/pyrazinamide for 6 months, be used in adults with **isoniazid-resistant tuberculosis**?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**FQ + (H)RE for 6 months and pyrazinamide for first 2 months only**	**FQ + (H)REZ for 6 months**	**Relative (95% CI)**	**Absolute (95% CI)**		
Death - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
15 [1]	observational studies	serious [a]	not serious	not serious	very serious [b]	none	117/118 (99.2%) [c]	245/251 (97.6%) [f]	**aOR 1.0** [d] (0.1 to 16.8)	**1 fewer per 100** (from 23 fewer to 21 more) [e]	⨁◯◯◯ VERY LOW	CRITICAL
Culture conversion - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Acquisition of drug resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Serious adverse effect - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations
a. Data from experimental and observational studies pooled in propensity score matched IPDMA. a mean 10% of patients were lost to follow-up across included studies.
b. CI does not exclude an appreciable benefit or an appreciable harm.
c. Of the 118 patients 82 received isoniazid for one month or more and 36 did not receive isoniazid
d. **corresponding RR 1.00, 95% CI: 0.82 to 1.02** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
e. Based on IPD risk difference meta-analysis (Fregonese 2018).
f. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References
1. Fregonese, F. et al.. Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis. Lancet Respir Med; 2018.

Date: 2018-03-22
Question: Should **fluoroquinolone/rifampin/ethambutol for 6 months and pyrazinamide for first 2 months only**, compared to rifampin/ethambutol/pyrazinamide for 6 months, be used in adults with **isoniazid-resistant tuberc**ulosis?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**FQ + (H)RE for 6 months and pyrazinamide for first 2 months only**	**(H)REZ for 6 months**	**Relative (95% CI)**	**Absolute (95% CI)**		
Death - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
15 [1]	observational studies	serious [a]	not serious	not serious	very serious [b]	none	117/118 (99.2%) [c]	1253/1350 (92.8%) [f]	**aOR 5.2** [d] (0.6 to 46.7)	**4 more per 100** (from 2 fewer to 9 more) [e]	⨁◯◯◯ VERY LOW	CRITICAL
Culture conversion - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Acquisition of drug resistance - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Transmission of infection - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Quality of life - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Serious adverse effect - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

aOR: adjusted odds ratio; **CI:** Confidence interval; **RR:** Risk ratio

Explanations
a. Data from experimental and observational studies pooled in propensity score matched IPDMA. a mean 10% of patients were lost to follow-up across included studies.
b. CI does not exclude an appreciable benefit or an appreciable harm.
c. Of the 118 patients 82 received isoniazid for one month or more and 36 did not receive isoniazid
d. **corresponding RR 1.06, 95% CI: 0.95 to 1.08** (calculated based on a pooled adjusted OR from IPD MA and assumed risk in control groups estimated as a mean among patients included in IPD MA)
e. Based on IPD risk difference meta-analysis (Fregonese 2018).
f. Assumed baseline risk of an outcome was estimated among propensity score matched patients who received background MDR-TB regimen alone

References
1. Fregonese, F. et al.. Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis. Lancet Respir Med; 2018.

Date: 2019-04-10
Question: Partial lung resection compared to medical treatment alone for adults with MDR-TB

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	partial lung resection	medical treatment alone	Relative (95% CI)	Absolute (95% CI)		
Death												
26 [1,a]	observational studies	serious [b]	not serious [c]	serious [d]	very serious [e]	none	10/214 (4.7%)	304/1702 (17.9%)	**aOR 0.6** (0.2 to 2.2) [f]	**6 fewer per 100** (from 14 fewer to 14 more)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
26 [1,a]	observational studies	serious [b]	not serious [c]	serious [d]	very serious [e]	none	185/204 (90.7%)	1134/1702 (66.6%)	**aOR 2.4** (0.4 to 15.6) [f]	**16 more per 100** (from 22 fewer to 30 more)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure, relapse, or death)[g]												
18 [1]	observational studies	serious [h]	not serious [i]	not serious [j]	not serious	none	185/214 (86.4%)	1842/2608 (70.6%)	**aOR 3.0** (1.5 to 5.9) [f]	**17 more per 100** (from 8 more to 23 more)	⊕◯◯◯ VERY LOW	CRITICAL
Adverse effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations
a. Includes unpublished data presented in Web Annex 4 for the WHO treatment guidelines for drug-resistant tuberculosis, 2016 update.
b. Analysis included only 26 out of 67 eligible studies: 35 were excluded because no individual patient data could be obtained, 5 (2851 patients) - because surgical status was not available. The average loss to follow-up in the included studies was 5% in surgical groups and 22% in medical treatment groups. Surgical patients had more extensive disease, a longer duration of therapy, and received more effective antibiotics in the intensive phase of treatment than nonsurgical patients.
c. There was large unexplained heterogeneity in treatment effects among medical treatment groups across studies (I2 was 74%). However, the sensitivity analysis assuming the lower and upper 95% confidence limits for baseline risk of mortality (8% to 18%) and treatment success (54% to 73%) did not show an important change in absolute effects of partial lung resection on those outcomes.
d. Analysis compared patients treated with partial lung resection in health care settings where surgical treatment was available with patients who received medical treatment in different health care settings in which surgery was not available. Patients with extrapulmonary tuberculosis and those living with HIV were excluded.
e. Confidence interval around the estimated absolute effect does not exclude an appreciable benefit or an appreciable harm.
f. Adjusted estimate obtained using propensity score matching IPD MA.
g. Note that the definition of "treatment success" includes death. In other analyses supporting the guidelines death was not included in the definition of treatment success. we were not able to obtain the adjusted estimates of the outcome defined as for other analyses.
h. Analysis included only 18 out of 67 eligible studies: 35 were excluded because no individual patient data could be obtained, 5 (2851 patients) - because surgical status was not available. 8 studies (2193 patients) did not directly compare surgery to medical treatment but reported the results of medical treatment alone ("non-surgical" studies). The average loss to follow-up in the included studies was 5% in surgical groups and 22% in medical treatment groups.
i. There was large unexplained heterogeneity in treatment effects among medical treatment groups across studies (I2 was 92-94%). However, the sensitivity analysis assuming the lower and upper 95% confidence limits for baseline risk of mortality (8% to 19%) and for treatment success (71% to 84%) did not show an important change in absolute effects of partial lung resection on those outcomes.
j. Analysis compared patients who received one or the other treatment in the same health care setting. Patients with extrapulmonary tuberculosis and those living with HIV were excluded.

References
1. Fox G.J. et al., . Surgery as an Adjunctive Treatment for Multidrug- Resistant Tuberculosis: An Individual Patient Data Meta-analysis. Clinical Infectious Diseases; 2016.

Date: April 10, 2019
Question: Pneumonectomy compared to medical treatment alone for adults with MDR-TB

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**pneumonectomy**	**medical treatment alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Death												
26 [1,a]	observational studies	serious [b]	not serious [c]	serious [d]	very serious [e]	none	14/105 (13.3%)	304/1702 (17.9%)	**aOR 1.8** (0.6 to 5.1) [f]	**10 more per 100** (from 6 fewer to 35 more)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success (assessed with: as opposed to treatment failure or relapse)												
26 [1,a]	observational studies	serious [b]	not serious [c]	serious [d]	very serious [e]	none	72/91 (79.1%)	1134/1398 (81.1%)	**aOR 0.8** (0.1 to 6.0) [f,g]	**4 fewer per 100** (from 51 fewer to 15 more)	⊕◯◯◯ VERY LOW	CRITICAL
Adverse effects - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: Confidence interval; **OR:** Odds ratio

Explanations
a. Includes unpublished data presented in Web Annex 4 for the WHO treatment guidelines for drug-resistant tuberculosis, 2016 update.
b. Analysis included only 26 out of 67 eligible studies: 35 were excluded because no individual patient data could be obtained, 5 (2851 patients) - because surgical status was not available. The average loss to follow-up in the included studies was 11% in surgical groups and 22% in medical treatment groups. Surgical patients had more extensive disease, a longer duration of therapy, and received more effective antibiotics in the intensive phase of treatment than nonsurgical patients.
c. There was large unexplained heterogeneity in treatment effects among medical treatment groups across studies (I2 was 74%). However, the sensitivity analysis assuming the lower and upper 95% confidence limits for baseline risk of mortality (8% to 18%) and treatment success (54% to 73%) did not show an important change in absolute effects of partial lung resection on those outcomes.
d. Analysis compared patients treated with partial lung resection in health care settings where surgical treatment was available with patients who received medical treatment in different health care settings in which surgery was not available. Patients with extrapulmonary tuberculosis and those living with HIV were excluded.
e. Confidence interval around the estimated absolute effect does not exclude an appreciable benefit or an appreciable harm.
f. Adjusted estimate obtained using propensity score matching IPD MA.
g. Sensitivity analysis comparing patients who received one or the other treatment in the same health care setting (thus, increasing the risk of bias owing to indication) or defining the treatment success as opposed to treatment failure, relapse, or death, showed similar results and any differences did not influence conclusions.

References
1. Fox G.J. et al., . Surgery as an Adjunctive Treatment for Multidrug- Resistant Tuberculosis: An Individual Patient Data Meta-analysis. Clinical Infectious Diseases; 2016.

Date: 2019-01-23
Question: Treatment for MDR LTBI compared to no treatment for persons having contact with infectious MDR-TB

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**treatment for MDR LTBI**	**no treatment**	**Relative (95% CI)**	**Absolute (95% CI)**		
Development of active MDR-TB (follow up: 2 to 5 years)												
5 [1]	observational studies	serious [a]	not serious [b,c]	not serious [d]	serious [e]	none	2/190 (1.1%) [f]	18/116 (15.5%)	**RR 0.15** (0.03 to 0.65)	**13 fewer per 100** (from 15 fewer to 5 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
								5.0% [g]		**4 fewer per 100** (from 5 fewer to 2 fewer)		
								38.0% [h]		**32 fewer per 100** (from 37 fewer to 13 fewer)		
Discontinuation of treatment owing to adverse effects (follow up: 2 to 5 years)												
12	observational studies	serious [i]	not serious	not serious	not serious	none	Adverse effects resulted in treatment discontinuation in 19% (106/558) of individuals (12 studies). Fewer children aged 15 years or less discontinued treatment (5%, 13/277; 4 studies), compared with 33% of adults (93/281; 8 studies). Regimens containing PZA had the highest proportion of adverse effects resulting in discontinuation of MDR LTBI treatment (51%).				⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval; **RR:** Risk ratio

Explanations
a. All results were not adjusted in the analysis.
b. Baseline risk of developing TB was not consistent ranging from 0% to 28%. Also the effect of treatment was not consistent ranging from RR 0.02 to 0.65.
c. We did not lower the certainty of evidence because of inconsistency as it already is very low, because of other limitations of the available body of evidence.
d. Three of the 5 studies included only children.
e. Results are very fragile as there were only 20 events among 306 persons in total.
f. There were additional 2 series of cases of contacts with LTBI who received treatment and 5 series of cases who did not receive treatment. Weighted mean incidence of incidence of TB was 3% (95% CI: 0.7 to 5.3) in those who did receive treatment and 4.2% (95% CI: 1.1 to 7.3) in those who did not.
g. presumed MDR LTBI among contacts in Australia
h. children less than 5 years of age who had household contact to infectious MDR-TB in South Africa
i. series of cases

References
1. Suzanne M. Marks, Sundari R. Mase,and Sapna Bamrah Morris. Systematic Review, Meta-analysis, and Cost-effectiveness of Treatment of Latent Tuberculosis to Reduce Progression to Multidrug-Resistant Tuberculosis. Clinical Infectious Diseases; 2017.