

CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

# Therapeutic Substitution of Drug Treatment for Multi- Drug Resistant Tuberculosis: Guidelines

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## Research Questions

1. What are the evidence-based guidelines regarding the therapeutic substitution of different drugs for the treatment of multi-drug resistant tuberculosis when there is a shortage of, or limited access to, the first line treatment?
2. What are the evidence-based guidelines regarding the therapeutic substitution of different drugs for the treatment of multi-drug resistant tuberculosis when there is an intolerance to the first line treatment?

## Key Findings

Three evidence-based guidelines were identified regarding the therapeutic substitution of different drugs for the treatment of multi-drug resistant tuberculosis when there is a shortage or intolerance of the first line treatment.

## Methods

A limited literature search was conducted by an information specialist on key resources including Medline via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine’s MeSH (Medical Subject Headings), and keywords. The main search concepts were tuberculosis and second-line therapy. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, and guidelines. The search was also limited to English language documents published between January 1, 2015 and June 18, 2020. Internet links were provided, where available.

This report is a component of a larger CADTH Condition Level Review on tuberculosis. A condition level review is an assessment that incorporates all aspects of a condition, from prevention, detection, treatment, and management. For more information on CADTH’s Condition Level Review of tuberculosis, please visit the project page (<https://www.cadth.ca/tuberculosis>).

## Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

**Table 1: Selection Criteria**

<b>Population</b>	People receiving drug treatment for active MDR-TB
<b>Intervention</b>	First-line drug treatments for MDR-TB
<b>Comparators</b>	Second-line or substituted drug treatments for MDR-TB
<b>Outcomes</b>	Recommendation (e.g., which drug(s) can be substituted for each other in MDR-TB regimens in the case of shortage or intolerance)
<b>Study Designs</b>	Health technology assessments, systematic reviews, evidence-based guidelines

MDR-TB = multi-drug resistant tuberculosis

## Results

Three evidence-based guidelines<sup>1-3</sup> were identified regarding the therapeutic substitution of different drugs for the treatment of multi-drug resistant tuberculosis when there is a shortage or intolerance of the first line treatment. No relevant health technology assessments or systematic reviews of guidelines were identified.

References of potential interest that did not meet the inclusion criteria are provided in the appendix.

## Overall Summary of Findings

Three evidence-based guidelines<sup>1-3</sup> were identified regarding the therapeutic substitution of different drugs for the treatment of multi-drug resistant tuberculosis when there is a shortage or intolerance of the first line treatment. A summary of relevant recommendations is presented in Table 2. As part of the condition level review, the guidelines in this report were previously included in a CADTH report<sup>4</sup> on guidelines for drug-resistant tuberculosis. The detailed critical appraisal of these guidelines can be found in that report.<sup>4</sup>

**Table 2: Summary of Relevant Recommendations**

Summary of Recommendations	
American Thoracic Society, 2019 <sup>1</sup>	
<ul style="list-style-type: none"> <li>The recommended treatment regimen for MDR-TB includes bedaquiline, and either levofloxacin or moxifloxacin (page e97). <b>(strong recommendation, very low certainty in the evidence)</b></li> <li>A variety of other drugs are suggested to complete the regimen so that there are five drugs in the intensive phase of treatment and four drugs in the continuation phase of treatment (page e97). <b>(conditional recommendation, very low certainty in the evidence)</b></li> </ul>	
World Health Organization, 2019 <sup>2</sup>	
<ul style="list-style-type: none"> <li>The treatment regimen for MDR-TB should include all three Group A drugs (levofloxacin/moxifloxacin, bedaquiline, and linezolid), one or both Group B drugs (clofazimine and cycloserine/terizidone), and as many Group C drugs as necessary to complete the regimen if Group A or B drugs cannot be used (page 9; page 24). <b>(conditional recommendation, very low certainty in the estimates of effect)</b></li> </ul>	
Public Health Agency of Canada, 2014 <sup>3</sup>	
<ul style="list-style-type: none"> <li>The recommended treatment regimen for patients with MDR-TB consists of a combination of the following drugs and/or drug classes: aminoglycosides (streptomycin, amikacin, kanamycin), polypeptides (capreomycin), fluoroquinolones, ethionamide, cycloserine, para-aminosalicylic acid (page 17).</li> </ul>	

MDR-TB = multi-drug resistant tuberculosis

## References Summarized

### Health Technology Assessments

No literature identified.

### Systematic Reviews and Meta-Analyses

No literature identified.

## Guidelines and Recommendations

1. Treatment of Drug-Resistant Tuberculosis: An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. New York (NY): American Thoracic Society; 2019.  
<https://www.atsjournals.org/doi/pdf/10.1164/rccm.201909-1874ST>  
*See: Figure 1, page e97*
2. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva (CH): World Health Organization; 2019.  
<https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf?ua=1>  
*See: Current policy recommendations on treatment and care for DR-TB, The composition of longer MDR-TB regimens, page 9; Table 2.1 Grouping of medicines recommended for use in longer MDR=TB regimens, page 24*
3. Canadian Tuberculosis Standards, Chapter 8: Drug-Resistant Tuberculosis. Ottawa (ON): Public Health Agency of Canada; 2014.  
<https://www.canada.ca/content/dam/phac-aspc/migration/phac-aspc/tbpc-latb/pubs/tb-canada-7/assets/pdf/tb-standards-tb-normes-ch8-eng.pdf>  
*See: Management of Drug-Resistant TB, MDR AND XDR TB, page 17*

## Appendix — Further Information

### Previous CADTH Reports

4. Drug-Resistant Tuberculosis: A Review of the Guidelines. (*CADTH Rapid response report: summary with critical appraisal*). Ottawa (ON): CADTH; 2020.  
<https://cadth.ca/drug-resistant-tuberculosis-review-guidelines>
5. Treatment of Tuberculosis: A Review of Guidelines. (*CADTH Rapid response report: summary with critical appraisal*). Ottawa (ON): CADTH; 2020.  
<https://www.cadth.ca/treatment-tuberculosis-review-guidelines>

### Clinical Practice Guidelines – Unclear Methodology

6. Caminero JA, Garcia-Garcia JM, Cayla JA, Garcia-Perez FJ, Palacios JJ, Ruiz-Manzano J. Update of SEPAR guideline <<Diagnosis and Treatment of Drug-Resistant Tuberculosis>>. *Arch Bronconeumol*. 2020 May 20;20:20.  
[PubMed: PM32446667](https://pubmed.ncbi.nlm.nih.gov/32446667/)
7. National Clinical Advisory Committee. Interim clinical guidance for the implementation of injectable-free regimens for rifampicin-resistant tuberculosis in adults, adolescents and children. Pretoria (ZA): Health Department, Republic of South Africa; 2018.  
[http://www.tbonline.info/media/uploads/documents/dr\\_tb\\_clinical\\_guidelines\\_for\\_rsa\\_september\\_2018.pdf](http://www.tbonline.info/media/uploads/documents/dr_tb_clinical_guidelines_for_rsa_september_2018.pdf)
8. Clinical Guidelines & Standard Operating Procedure for the Implementation of the Short & Long DR-TB regimens for Adults, Adolescents and Children. Cape Town (ZA): Western Cape Government; 2018.  
[https://www.westerncape.gov.za/assets/departments/health/tuberculosis\\_-\\_dr\\_tb\\_clinical\\_guidelines\\_2018.pdf](https://www.westerncape.gov.za/assets/departments/health/tuberculosis_-_dr_tb_clinical_guidelines_2018.pdf)  
*See: Section 3: Overview of Long Treatment Regimens for RR/MDR TB, page 15*
9. British Thoracic Society. The management of multidrug-resistant tuberculosis (MDRTB); 2016.  
<https://www.brit-thoracic.org.uk/document-library/clinical-statements/mdrtb/bts-clinical-statement-on-the-management-of-multidrug-resistant-tuberculosis-mdrtb/>  
*See: Specific Advice for Using the Short-Course Regimen for MDRTB, Statements #5 and #6, page 2*
10. Galli L, Lancella L, Garazzino S, et al. Recommendations for treating children with drug-resistant tuberculosis. *Pharmacol Res*. 2016 Mar;105:176-182.  
[PubMed: PM26821118](https://pubmed.ncbi.nlm.nih.gov/26821118/)
11. Daley CL. Treatment. Drug-resistant tuberculosis: a survival guide for clinicians, 3rd ed. San Francisco (CA): Curry International Tuberculosis Center; 2016  
[https://www.currytbcenter.ucsf.edu/sites/default/files/tb\\_sg3\\_chap4\\_treatment.pdf](https://www.currytbcenter.ucsf.edu/sites/default/files/tb_sg3_chap4_treatment.pdf)  
*See: Figure 2: Building a Treatment Regimen for MDR-TB, page 74*

### Review Articles

12. Park M, Satta G, Kon OM. An update on multidrug-resistant tuberculosis. *Clin Med*. 2019;19(2):135-9. <https://www.rcpjournals.org/content/clinmedicine/19/2/135>

13. Pranger AD, van der Werf TS, Kosterink JGW, et al. The Role of Fluoroquinolones in the Treatment of Tuberculosis in 2019. *Drugs*. 2019;79:161–171.  
<https://link.springer.com/article/10.1007/s40265-018-1043-y>