South African National Essential Medicine List
Primary Healthcare Medication Review process
Component: Respiratory conditions

EVIDENCE REVIEW

Title: To determine whether fluoroquinolones are safe and effective as MDR TB prophylaxis for household contacts exposed to an index case.

Date: 30 November 2021

Key findings

- We conducted a search for systematic reviews of randomised controlled trials, or individual randomized control trials, to determine whether fluoroquinolones are safe and effective as MDR TB prophylaxis for household contacts exposed to an index case.
- No systematic reviews or randomized controlled trials were identified. Therefore an AGREE assessment was performed on the World Health Organization's 2020 Tuberculosis Prevention Therapy (TPT) guidelines, which were based on observational data.
- WHO's TPT guidelines recommended fluoroquinolones could be considered for high risk individuals (e.g. children, immunocompromised people, including people living with HIV) on the basis of several small observational studies that were assessed as being of "very low" quality. However, the guideline suggested a careful individualised risk assessment that included the intensity of exposure, certainty of the source case, and reliable information on the drug resistance pattern of the index case and potential adverse events. If further noted that confirmation of latent TB status (e.g. by tuberculin skin test) would be required.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: Based on this evidence review, the PHC/Adult Hospital Level Committee suggests not to use fluoroquinolones as prophylaxis for high risk contacts of cases of active MDR TB (conditional recommendation).
Rationale: Very low quality evidence based on small observational studies with substantial methodological problems. In addition the need to establish latent TB status by tuberculin skin testing was felt not to be feasible; and side-effect profile of longterm fluoroquinolone use and its possible impact on the development of drug resistance were concerns
Level of Evidence: Low certainty evidence
Review indicator: Randomised controlled trial evidence showing benefit.

NEMLC RECOMMENDATION (9 DECEMBER 2021): The NEMLC accepted the review and the proposed recommendation made by the PHC-AH ERC. The Committee added its concerns regarding the side-effect profile of longterm fluoroquinolone use and the possible inpact on the development of drug resistance.

Monitoring and evaluation considerations

Research priorities

1. Executive Summary

Date: 21 October 2021
Medicine (INN): fluoroquinolones
Medicine (ATC): J01MA
Indication (ICD10 code): Z29.2
Patient population: Adults and paediatrics
Prevalence: 6700 cases of MDR TB diagnosed in 2020 in South Africa [WHO Global TB Report 2021].
Level of Care: Primary healthcare
Prescriber Level: Nurse prescriber
Current standard of Care: n/a
Efficacy estimates: n/a
Motivator/reviewer name(s): Trudy Leong, Jeremy Nel
PTC affiliation: Jeremy Nel - Helen Joseph Hospital PTC

2. Authors, affiliation and conflict of interest details:

1) Trudy D Leong, Essential Drugs Programme, National Department of Health
2) Jeremy Nel, Helen Joseph Hospital, University of the Witwatersrand

TDL and JN have no interests related to DR-prophylaxis therapy.

Acknowledgements:

- Tamara Kredo (Cochrane-SA) assisted with the literature search and screening of the retrieved records.
- Millicent Reddy (BHPSA) assisted with the AGREE 2 assessment Module 1: Tuberculosis preventive treatment, 2020 of the World Health Organization Consolidated guidelines on tuberculosis.

3. Introduction/ Background

Latent tuberculosis infection (LTBI) is the "state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest active TB".[1] The 2019 Global TB report[2] listed South Africa amongst the top high burden TB countries (520 per 100,000 population) for both drug sensitive (DS) TB and multi-drug resistant (MDR) TB. The most prominent risk factor was HIV-infection. Of note, was that the national HIV prevalence survey of TB in 2018[3] reported a higher rate of 737 per 100,000 population (highest amongst men, those aged 35-44 years and the elderly, ≥ 65 years of age).

To achieve the United Nations End TB Strategy targets,[4, 5] preventive actions have been recommended by the World Health Organization ranging from screening for active TB, infection control, prevention and care of HIV and other co-morbidities and health risks, access to universal health care, social protection and poverty alleviation, as well as TB preventive treatment (TPT).[1]

The National Department of Health's (NDoH's) TB Programme had tabled a draft national TPT Guideline for review and ratification by the National Essential Medicines List Committee (NEMLC), at a meeting that was convened on 30 January 2020.[6] The NEMC raised concerns and provided recommendations for a way forward. Related to drug-resistant (DR) TB, the NEMLC recommended that the evidence of efficacy and safety of fluoroquinolones for MDR-TB prophylaxis be provided.

Thus, an evidence review was conducted.

4. Purpose/Objective:

To determine whether fluoroquinolones are safe and effective as MDR TB prophylaxis for household contacts exposed to an index case.

PICO eligibility criteria:

Population	Household contacts of patient with MDR tuberculosis. No restriction on age.
Intervention	Fluoroquinolone administered alone or in combination with a second drug (e.g. isoniazid, ethambutol)
Comparator	placebo or active comparator e.g. isoniazid
Outcome	Active tuberculosis Drug resistance Adverse events and adverse reactions
Studies	Systematic reviews of randomised controlled trials, followed by randomised controlled trials if systematic reviews could not be sourced.

5. Methods:

Cochrane-SA (TK) assisted with a literature search for systematic reviews in 2 databases, conducted on 27 October 2020.

a. **Data sources** : Epistemonikos and PUBMED was searched.
b. **Search strategy :** See appendix I.
c. **Search yield:** 74 articles were screened, of which none were eligible and all were excluded. Excluded PUBMED records are listed below.
d. **Excluded studies:** See table 1, below.

Table 1: Excluded studies

Study		Reason for exclusion
1	Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017, Ahmad N, et al. Lancet. 2018 Sep 8;392(10150):821-834. doi: 10.1016/S0140-6736(18)31644-1.	PICO criteria not met (treatment of MDR-TB)
2	Marks SM, et al. Clin Infect Dis. 2017 Jun 15;64(12):1670-1677. doi: 10.1093/cid/cix208. Erratum in: Clin Infect Dis. 2017 Oct 15;65(8):1433-1434.	Trials were not RCTs, only 2 comparative trails conducted in endemic TB regions
3	Schaaf HS, et al.. Pediatrics. 2002 May;109(5):765-71. doi: 10.1542/peds.109.5.765. PMID: 11986434.	Observational study
4	Fregonese F, et al.. Lancet Respir Med. 2018 Apr;6(4):265-275. doi: 10.1016/S2213-2600(18)30078-X. Erratum in: Lancet Respir Med. 2018 Apr 18;:	IPD analysis of very low quality – "the quality of the evidence was very low. These results support the conduct of randomised trials to identify the optimum regimen for this important and common form of drug-resistant tuberculosis."
5	Goyal V, et al.. BMC Public Health. 2017 Oct 17;17(1):817. doi: 10.1186/s12889-017-4779-5.	PICO criteria not met (prevalence study)
6	Isaakidis P, et al.. Int J Tuberc Lung Dis. 2015 Aug;19(8):969-78. doi: 10.5588/ijtld.15.0123. PMID: 26162364.	PICO criteria not met (treatment of MDR-TB)
7	Lan Z, et al; Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment 2017.. Lancet Respir Med. 2020 Apr;8(4):383-394. doi: 10.1016/S2213-2600(20)30047-3.	PICO criteria not met (treatment of MDR-TB)
8	Kwak M, et al. J Microbiol Methods. 2017 Oct;141:1-9. doi: 10.1016/j.mimet.2017.07.001.	PICO criteria not met (diagnostic study)
9	Mao X, et al. Ann Clin Lab Sci. 2015 Fall;45(5):533-44. Erratum in: Ann Clin Lab Sci. 2015 Fall;45(6):720.	PICO criteria not met (diagnostic study)
10	Falzon D, et al; Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB. Eur Respir J. 2013 Jul;42(1):156-68. doi: 10.1183/09031936.00134712.	PICO criteria not met (treatment of MDR-TB)
11	Ziganshina LE, et al. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD004795. doi: 10.1002/14651858.CD004795.pub3. Update in: Cochrane Database Syst Rev. 2013;6:CD004795.	PICO criteria not met (treatment of MDR-TB)
12	Ahmad Khan F et al.. Eur Respir J. 2017 Jul 27;50(1):1700061. doi: 10.1183/13993003.00061-2017.	PICO criteria not met (treatment of MDR-TB)
13	Fox GJ, et al; Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB.. PLoS One. 2016 Mar 29;11(3):e0151724. doi: 10.1371/journal.pone.0151724.	PICO criteria not met (treatment of MDR-TB)
14	Chang KC, et al.. J Antimicrob Chemother. 2010 Aug;65(8):1551-61. doi: 10.1093/jac/dkq202.	PICO criteria not met (diagnostic study)
15	Jacobson KR,et al.. Clin Infect Dis. 2010 Jul 1;51(1):6-14. doi: 10.1086/653115.	PICO criteria not met (treatment of XDR-TB)
16	Chang KC, et al.. Antimicrob Agents Chemother. 2013 Sep;57(9):4097-104. doi: 10.1128/AAC.00120-13.	PICO criteria not met (treatment of MDR-TB)
17	Mori T, et al. Kekkaku. 2012 Sep;87(9):565-75.	PICO criteria not met(Japanese epidemiology study)
18	Chen TC, et al.. Int J Infect Dis. 2011 Mar;15(3):e211-6. doi: 10.1016/j.ijid.2010.11.008. Epub 2010 Dec 30.	PICO criteria not met (treatment of MDR-TB)
19	Ziganshina LE, et al. Cochrane Database Syst Rev. 2013 Jun 6;2013(6):CD004795. doi: 10.1002/14651858.CD004795.pub4.	PICO criteria not met (treatment of MDR-TB) & update of #10
20	Theron G, et al. Cochrane Database Syst Rev. 2016 Sep 8;9(9):CD010705. doi: 10.1002/14651858.CD010705.pub3.	PICO criteria not met (diagnostic study) & update of # 29
21	Guan Y, et al.2020 Jun 19;99(25):e20648. doi: 10.1097/MD.0000000000020648.	PICO criteria not met (treatment of MDR-TB)
22	Bastos ML, et al; Collaborative Group for Meta-analysis of Individual Patient Data in MDR-TB. Clin Infect Dis. 2014 Nov 15;59(10):1364-74. doi: 10.1093/cid/ciu619.	PICO criteria not met (treatment of MDR-TB)
23	Chisompola NK, et al. BMC Infect Dis. 2020 May 13;20(1):344. doi: 10.1186/s12879-020-05031-5.	PICO criteria not met (genomic study)

24	Ahuja SD, et al., Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB. PLoS Med. 2012;9(8):e1001300. doi: 10.1371/journal.pmed.1001300.	PICO criteria not met (treatment of MDR-TB)
25	Feng Y, et al. PLoS One. 2013;8(2):e55292. doi: 10.1371/journal.pone.0055292.	PICO criteria not met (diagnostic study)
26	Chang KC, et al. Int J Tuberc Lung Dis. 2015 Dec;19(12):1417-27. doi: 10.5588/ijtld.15.0216.	PICO criteria not met (treatment of MDR-TB)
27	Langendam MW, et al.. PLoS One. 2013;8(1):e53599. doi: 10.1371/journal.pone.0053599.	PICO criteria not met (comparative study of various fluoroquinolones)
28	Johnston JC et al.. PLoS One. 2009 Sep 9;4(9):e6914. doi: 10.1371/journal.pone.0006914.	PICO criteria not met (treatment of MDR-TB)
29	Theron G,et al.. Cochrane Database Syst Rev. 2014 Oct 29;(10):CD010705. doi: 10.1002/14651858.CD010705.pub2.	PICO criteria not met (diagnostic study)
30	Ziganshina LE, et al. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD004795. doi: 10.1002/14651858.CD004795.pub2.	PICO criteria not met (treatment of MDR-TB) & review updated
31	Bisson GP, et al. Lancet. 2020 Aug 8;396(10248):402-411. doi: 10.1016/S0140-6736(20)31316-7. Erratum in: Lancet. 2020 Sep 26;396(10255):886.	PICO criteria not met (treatment of MDR-TB in HIV patients)

e. Evidence synthesis

As no systematic reviews of RCTs could be retrieved, the recent 2020 WHO guidelines[1] for TPT was appraised using the AGREE2 instrument.[7] Refer to the table below for the AGREE2 assessment conducted by TL and MR.

Guidance relevant to this review are provided in Table 2. The recommended targeted treatment options apply to children, adolescents and adults of all ages who are considered high-risk and are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines".

Table 2: WHO Guidelines 2020 recommendations for preventive treatment for contacts of patients with multidrug- or rifampicin-resistant TB

Citation (date published)	Recommendation (pg)	AGREE II appraisal
WHO consolidated guidelines on tuberculosis. Module 1: prevention - tuberculosis preventive treatment. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.	Pg 20. In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification. ***(Conditional recommendation, very low certainty in the estimates of effect)*** Examples of high risk-groups were defined as: • children, • people on immunosuppressive therapy • PLHIV Confirmation of infection by LTBI testing is usually required before treatment is initiated.	**6/7**

Remarks: The preventive treatment should be individualized after a careful assessment of the intensity of exposure, the certainty of the source case, reliable information on the drug resistance pattern of the source case and potential adverse events. The preventive treatment should be given only to household contacts at high risk (e.g. children, people receiving immunosuppressive therapy and people living with HIV). The drugs should be selected according to the drug susceptibility profile of the source case. Confirmation of infection with LTBI tests is required. This recommendation must not affect on-going placebo-controlled clinical trials of MDR-TB contacts on ethical grounds. The results of such clinical trials are crucial for updating this recommendation. Strict clinical observation and close monitoring for the development of active TB disease for at least 2 years are required, regardless of the provision of preventive treatment.

Rationale: Overall, the Guideline Development Group (GDG) judged that the potential benefits of targeted preventive treatment for MDR-TB contacts based on individual risk assessments outweigh the harm but acknowledged uncertainty about the efficacy of the intervention due to the lack of RCTs. It also noted that provision of preventive treatment for MDR-TB contacts would be acceptable, particularly to patients and health care workers. The GDG stressed that treatment should be given to selected individuals after a careful risk assessment, including intensity of exposure, certainty of the source case, reliable information on the drug resistance pattern of the index case and potential adverse events. It should be given only to household contacts at high risk (e.g. children, people on immunosuppressive therapy and people living with HIV). Confirmation of infection by LTBI testing is required before individualized treatment is initiated.

Table 2: GRADE evidence tables from the WHO Guidelines, 2020 for PICO 10: Should preventive treatment be recommended for contacts of patients with multidrug-resistant or rifampicin-resistant TB?

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preventive treatment	No treatment	Relative (95% CI)	Absolute (95% CI)		
INCIDENCE OF ACTIVE TB DISEASE (BOTH DRUG-SUSCEPTIBLE AND DRUG-RESISTANT TB)												
4 *(66-69)*	Observational	Very serious[1]	Not serious	Not serious	Very serious[3]	None	2/41 (4.9%)	13/64 (20.3%)	0.20 (0.04;0.94)[4]	154 fewer per 1000 (273 fewer to 36 fewer)	⊕◯◯◯ Very low	Critical
							0/93 (0%)	3/15 (20%)	0.02 (0.00;0.39)[5]	200 fewer per 1000 (403 fewer to 3 more)		
							0/21 (0%)	0/10 (0%)	-[6]	0 more per 1000 (138 fewer to 138 more)		
							0/30 (0%)	0/166 (0%)	-[7]	0 more per 1000 (45 fewer to 45 more)		
INCIDENCE OF MDR-TB												
3[2] *(66, 67, 69)*	Observational	Very serious[1]	Not serious	Not serious	Very serious[3]	None	0/93 (0%)	3/15 (20%)	0.02 (0.00;0.39)[5]	200 fewer per 1000 (403 fewer to 3 more)	⊕◯◯◯ Very low	Critical
							0/21 (0%)	0/10 (0%)	-[6]	0 more per 1000 (138 fewer to 138 more)		
							0/30 (0%)	0/166 (0%)	-[7]	0 more per 1000 (45 fewer to 45 more)		
MORTALITY												
0	No evidence								Cannot be estimated		-	Important

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preventive treatment	No treatment	Relative (95% CI)	Absolute (95% CI)		
ADVERSE EVENTS												
0	No evidence								Cannot be estimated		-	Critical
DEVELOPMENT OF DRUG RESISTANCE												
0	No evidence											Important

[1] Risk of bias in selection of the control group, and none of the studies adjusted for confounders. Downgraded by two levels.
[2] The study by Shaaf et al. was excluded, as the incidence of MDR-TB was not reported.
[3] Small sample sizes and wide 95% CIs. Downgraded by two levels.
[4] Reference (68)
[5] Reference (66)
[6] Reference (67)
[7] Reference (69)

Overall quality: very low

Five studies that included fewer than 20 participants who completed preventive TB treatment were excluded. In addition, the study by Kritski [8] was excluded as only isoniazid monotherapy was given.

The updated review comprised 10 studies comparing participants who received preventive treatment for MDR-TB and those who did not. However, clinical heterogeneity among the studies prevented the conducting of a meta-analysis. One study was excluded because only isoniazid monotherapy was used, and five studies were excluded as less than 20 participants completed preventive TB treatment. Therefore, the quality of the evidence was based on only four studies. No active TB was reported in either the intervention or the control group in one study, while one person with active TB due to a drug-susceptible strain that was different from the presumed source was reported in another study. The remaining two studies addressed the efficacy of preventive treatment - In one cohort of 119 contacts, 104 with LTBI initiated fluoroquinolone-based preventive treatment, of whom 93 (89%) completed treatment, and none developed active TB; while 3 of 15 (20%) contacts who refused treatment developed MDR-TB (OR 0.02, 95% CI 0.00; 0.39). In the other study, confirmed or probable TB developed in 2 of 41 (4.9%) children receiving tailored preventive treatment and in 13 of 64 (20.3%) children who did not receive proper preventive treatment (OR 0.2, 95% CI 0.04; 0.94)

Conclusion

Targeted MDR-TB preventive treatment of high-risk groups exposed to an index case of MDR-TB or rifampicin-resistant TB is recommended in the 2020 WHO consolidated guidelines on TPT. However, this is based on very low-quality evidence, the guidelines recommends that "clients must be given detailed information about the benefits and harms of the preventive treatment and asked for explicit informed consent. In view of the uncertainty about the balance of benefit to harm, informed consent, preferably in writing, is required, based on the local context and practice in similar situations".

Appendix 1 – Search strategy

Database: **PubMed**
Date: **27 October 2020**

Search	Query	Results
#5	Search: (#1 AND #2) NOT (animals[mh] NOT humans[mh]) Filters: Systematic Review, Meta-Analysis	31
#3	Search: (#1 AND #2) NOT (animals[mh] NOT humans[mh])	1,201
#2	Search: Fluoroquinolones[mh] OR Fluoroquinolone[tiab] OR Fluoroquinolones[tiab] OR Fluroquinolone[tiab] OR Fluroquinolones[tiab] OR Ciprofloxacin[tiab] OR Fleroxacin[tiab] OR Enoxacin[tiab] OR Enrofloxacin[tiab] OR Gatifloxacin[tiab] OR Gemifloxacin[tiab] OR Moxifloxacin[tiab] OR Norfloxacin[tiab] OR Ofloxacin[tiab] OR Levofloxacin[tiab] OR Pefloxacin[tiab]	60,169
#1	Search: Tuberculosis, Multidrug-Resistant[mh] OR Multidrug-Resistant Tuberculosis[tiab] OR MDR Tuberculosis[tiab] OR Multi-Drug Resistant Tuberculosis[tiab] OR Drug-Resistant Tuberculosis[tiab]	10,814

Database: **Epistemonikos**
Date: **27 October 2020**

#	Query	Records
4	#3 filtered by systematic reviews	25
3	(title:(Fluoroquinolone OR Fluoroquinolones OR Fluroquinolone OR Fluroquinolones OR Ciprofloxacin OR Fleroxacin OR Enoxacin OR Enrofloxacin OR Gatifloxacin OR Gemifloxacin OR Moxifloxacin OR Norfloxacin OR Ofloxacin OR Levofloxacin OR Pefloxacin) OR abstract:(Fluoroquinolone OR Fluoroquinolones OR Fluroquinolone OR Fluroquinolones OR Ciprofloxacin OR Fleroxacin OR Enoxacin OR Enrofloxacin OR Gatifloxacin OR Gemifloxacin OR Moxifloxacin OR Norfloxacin OR Ofloxacin OR Levofloxacin OR Pefloxacin)) AND (title:("Multidrug-Resistant Tuberculosis" OR "MDR Tuberculosis" OR "Multi-Drug Resistant Tuberculosis" OR "Drug-Resistant Tuberculosis") OR abstract:("Multidrug-Resistant Tuberculosis" OR "MDR Tuberculosis" OR "Multi-Drug Resistant Tuberculosis" OR "Drug-Resistant Tuberculosis"))	77
2	(title:(Fluoroquinolone OR Fluoroquinolones OR Fluroquinolone OR Fluroquinolones OR Ciprofloxacin OR Fleroxacin OR Enoxacin OR Enrofloxacin OR Gatifloxacin OR Gemifloxacin OR Moxifloxacin OR Norfloxacin OR Ofloxacin OR Levofloxacin OR Pefloxacin) OR abstract:(Fluoroquinolone OR Fluoroquinolones OR Fluroquinolone OR Fluroquinolones OR Ciprofloxacin OR Fleroxacin OR Enoxacin OR Enrofloxacin OR Gatifloxacin OR Gemifloxacin OR Moxifloxacin OR Norfloxacin OR Ofloxacin OR Levofloxacin OR Pefloxacin))	2011
1	(title:("Multidrug-Resistant Tuberculosis" OR "MDR Tuberculosis" OR "Multi-Drug Resistant Tuberculosis" OR "Drug-Resistant Tuberculosis") OR abstract:("Multidrug-Resistant Tuberculosis" OR "MDR Tuberculosis" OR "Multi-Drug Resistant Tuberculosis" OR "Drug-Resistant Tuberculosis"))	519

Appendix 2: Adaptation of the WHO 2020 TPT Guidelines Evidence to decision framework

(Note: Where judgements differed, both WHO and PHC/Adult Hospital Level's assessments have been described)

Problem: Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ No **x Yes** ○ Varies ○ Don't know	Rationale as per WHO guideline panel: "Drug-resistant TB continues to threaten global TB control, remains a major public health concern and poses a global health security risk. An estimated 580 000 people developed MDR or rifampicin-resistant TB in 2015, and 250 000 people died as a result (WHO Global report, 2016). Prevention of MDR-TB would reduce the global burden and also address demands from individuals to be protected against development of MDR-TB[9 10 11 12]". **South Africa.** Over 6700 patients developed MDR or rifampicin-resistant TB in South Africa in 2020.**Error! Reference source not found.**	
Balance of effects: Do the benefits outweigh the harms?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
X Yes ○ No ○ Equal ○ Uncertain	We conducted a systematic review of the effectiveness of preventive treatment for contacts of patients with MDR or rifampicin-resistant TB. The review covered 10 studies with control groups, of which five found no TB case in either group. The table above (table 2) summarizes the results after exclusion of studies with <20 participants who completed preventive TB treatment and those on isoniazid monotherapy. Common adverse events included gastrointestinal symptoms, muscle or joint pain, headache, dizziness and hepatitis. In four studies, ≥ 50% of participants experienced at least one adverse event. Bamrah et al. (74) reported no serious adverse events, defined as hospitalization or irreversible morbidity, attributable to fluoroquinolone-based preventive treatment. The median proportion of participants who discontinued treatment because of adverse events in all studies was 5.1% (IQR 1.9–30.2%). No study reported preventive treatment for contacts of rifampicin-resistant TB.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ Yes ○ No ○ Equal **x Uncertain**	Very low quality evidence, based on small observational studies with significant methodological deficiencies [8-11]. There are rare but serious safety concerns associated with use of fluoroquinolones: • *Musculoskeletal:* tendonitis, tendon rupture, myalgia, muscle weakness, arthralgia, joint swelling; • *Nervous system:* peripheral neuropathy, psychosis, anxiety, insomnia, depression, hallucinations, suicidal thoughts, confusion, impairment of vision, hearing, smell and taste; • *Cardiac:* aortic aneurysm and dissection; endocrine: hypoglycaemic coma. (SAHPRA media statement, December 2018; FDA safety signal reports for fluoroquinolones; EMA safety signal report for fluoroquinolones)	

Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
X Very low o Low o Moderate o High o No included studies	As per WHO Guideline panel: "The overall quality of the evidence was very low because of very serious risks of bias and imprecision. In the study by Trieu et al.[9], active TB was ascertained during follow-up by checking cases identified in the TB registry. A meta-analysis was not conducted because of the heterogeneity of the drugs used".	
Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
o Important uncertainty or variability o No important uncertainty or variability **x Minimal uncertainty**	As per WHO Guideline panel: "We conducted an online survey to solicit the values and preferences of individuals affected by the recommendations (https://apps.who.int/iris/bitstream/handle/10665/260235/WHO-CDS-TB-2018.9-eng.pdf). Data were available from 142 respondents. More than 80% of the respondents reported that they would strongly or somewhat prefer to receive preventive treatment or give it to their children if they were exposed to someone with MDR-TB disease in the household. The reasons for not preferring preventive treatment included: limited evidence on preventive treatment for MDR-TB and concern about side-effects and development of drug resistance".	
Resources required: How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
x Greater resource requirements with intervention o Less resource requirements with the intervention o Neither greater nor less o Varies o Don't know	Judgement as per WHO Guideline panel, no rationale provided	
Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies		Providing preventive treatment could be cost–effective by preventing MDR-TB cases in settings with low transmission of MDR-TB. In settings with high risk of MDR-TB transmission, the potential benefit may wane and the cost–effectiveness becomes uncertain. The need for drug susceptibility testing, regimens used, risk of re-infection and adverse events could also affect cost–effectiveness.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Not applicable.	
Equity: What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased **X Increased** ○ Varies ○ Don't know		
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Not applicable.	
Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		

○ No ○ Probably no ○ Probably yes **X Yes** ○ Varies ○ Don't know	As per WHO Guideline panel: "Some national or clinical guidelines already recommend preventive treatment for contacts of MDR-TB"[13] [14] [15] South African National Department of Health's TB program recommends fluoroquinolones for DR-TB prophylaxis, in the draft TPT Guidelines.	Preventive treatment could be acceptable, particularly to patients and health care workers. The intervention may not be acceptable in some settings, particularly to programme managers for fear of development of XDR-TB and little experience in using TB preventive treatment for drug susceptible TB.
Feasibility: Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINES, 2020**		
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know		
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
X No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	The product is registered in South Africa with the South African Health Products Regulatory Authority, and is procured in the public sector. However, as per the WHO recommendation below, targeted treatment with individual risk assessment and the need to establish latent TB status by tuberculin skin testing was considered not to be feasible. WHO Guidelines, 2020 recommendation: *"In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification.* ***(Conditional recommendation, very low certainty in the estimates of effect)****…. Confirmation of infection by LTBI testing is usually required before treatment is initiated".*	

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	30 November 2021	TL, JN	Fluoroquinolones not to be used as prophylaxis for high risk contacts of cases of active MDR TB; very low quality evidence based on small observational studies. Targeted treatment needs individualized risk assessment and tuberculin skin testing.

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