

# Management of contacts of multidrug-resistant tuberculosis

**Guideline**

**Version 2.0 April 2017**

## Management of contacts of multidrug-resistant tuberculosis

Contacts of individuals with multidrug-resistant tuberculosis (MDR-TB) should be assessed using protocols similar to those of drug-susceptible tuberculosis (TB). The diagnosis of latent TB (LTB) is made using the same diagnostic criteria and contacts should be assessed based on their risk of exposure (the probability of being infected based on the duration and closeness of contact), along with the risk of progression to active disease (for example, children under five years of age and those with compromised immunity are at increased risk).

It is essential that active TB is thoroughly excluded before commencing any preventative therapy regimen. This is particularly the case with MDR-TB where inadvertent treatment of active TB with a preventative regimen may result in the progression to even more highly resistant and difficult to treat TB. When the diagnosis of LTB is established, there are two options for the management of contacts with exposure to MDR-TB:

- (a) education of the patient and/or care giver, with observation over at least two years, with the aim of detecting active TB at the earliest possible stage
- (b) preventative drug therapy to decrease the likelihood of progression to active TB.

There is strong evidence that isoniazid prophylaxis for LTB decreases the risk of progression to active TB for drug-susceptible disease<sup>1</sup>. However, there is little evidence available for guiding decisions on the use of fluoroquinolones or other drugs for the treatment of LTB due to MDR-TB<sup>2</sup>.

Fluoroquinolones are the agents most commonly recommended for prophylactic therapy in this setting, although this recommendation is not universally endorsed. The World Health Organisation currently does not recommend giving preventative drug therapy to people with LTB where the source case has MDR-TB. In contrast, European and US guidelines include the option of preventative therapy with a quinolone, usually moxifloxacin<sup>3,4</sup>. Although there are no randomised trials, the few small observational studies performed seem to support the use of preventative therapy<sup>5,6</sup>.

Although quinolones have been used as monotherapy for preventative therapy, combinations of a quinolone with another agent have been trialled<sup>7,8</sup>. Given concerns of side effects and the lack of evidence to support combination therapy fluoroquinolone monotherapy is acceptable unless the drug sensitivity profile from the index case suggests fluoroquinolone resistance. Some guidelines also allow for combination of a quinolone with another drug based on susceptibility profiles.

A concern with the use of long-term fluoroquinolone is the possibility of resistance to these agents, should people with LTB progress to active disease. Modelling studies taking this into account have, however, suggested that universal moxifloxacin prophylaxis for MDR LTBI is cost effective and leads to lower overall drug resistance through a decreased incidence of active MDR-TB<sup>9</sup>.

Decisions to offer or withhold prophylactic therapy for the treatment of LTB will be based upon three main considerations<sup>3</sup>:

- (c) **Host risk factors for progression to active TB.**
  - In children under the age of five years and those who are immunocompromised (for example, HIV or biological agents for rheumatoid arthritis), it is more likely that preventative therapy is beneficial.
- (d) **Drug susceptibility pattern** of the source case of infection will guide options for preventative therapy.
- (e) **The possibility of adverse reactions** will differ between patients and the drug regimen chosen. Variables will include patient age, medical co-morbidities and the possibility of drug interactions with quinolones.

## Recommended approach to contacts of multidrug-resistant tuberculosis with latent tuberculosis

All clinical cases of MDR-TB are required to be discussed with the TB Expert Advisory Group (TEAG). Similarly a decision to provide chemoprophylaxis to contacts of MDR-TB cases must be endorsed by TEAG in all cases.

Appropriate regimens would include: a fluoroquinolone alone (either moxifloxacin or levofloxacin) or a fluoroquinolone in combination with another agent to which the organism from the source case has been documented to be susceptible (e.g. ethambutol or prothionamide). The combination of a fluoroquinolone and pyrazinamide has been shown to be associated with more frequent adverse events and should be avoided. The length of therapy should be for at least six months.

Given the risk of prolonged QTc with quinolones we recommend a baseline ECG repeated at 4 weeks for all patients receiving moxifloxacin.

Given the consequences of non-adherence are greater than with drug susceptible TB, we recommend directly observed therapy (DOT) for preventative therapy for MDR-TB, as well as close monitoring for adverse reactions.

Regardless of whether preventative therapy is offered for adults we suggest follow up with 6 monthly CXR and review for 2 years and then annual CXR for a further 3 years (5 years follow up total). For children follow up is for two years with six-monthly assessment/CXR (children don't necessarily need 6 monthly CXR; but one CXR at a year post contact/LTB diagnosis advisable). For all MDR TB contacts sputum culture if productive is required, as is standard practice with follow up of all LTB.

## Extensively drug-resistant tuberculosis

The lack of tolerable drugs means that preventative therapy is not feasible for extensively drug-resistant tuberculosis (XDR-TB) and careful follow up over at least two years for children and five years for adults is the only option<sup>3</sup>.

## Definitions

Term	Definition	Source
MDR-TB (Multidrug-resistant tuberculosis)	MDR-TB is TB resistant to at least isoniazid and rifampicin (and possibly other drugs). MDR-TB treatment is based on susceptibility results and should only be treated by clinicians experienced in managing TB.	Centers for Disease Control & Prevention (CDC)
XDR-TB (Extensively drug-resistant tuberculosis)	XDR-TB is a type of MDR-TB that is resistant to isoniazid and rifampicin, plus any fluoroquinolone, and at least one of three injectable second-line drugs.	Centers for Disease Control & Prevention (CDC)
LTB (Latent tuberculosis)	LTB is a state of persistent immune response to prior-acquired Mycobacterium tuberculosis antigens, without evidence of clinically manifested active TB.	World Health Organization <a href="http://www.who.int/tb/publications/latent-tuberculosis-infection/en/">Guidelines on the management of latent tuberculosis infection</a> <a href="http://www.who.int/tb/publications/latent-tuberculosis-infection/en/">http://www.who.int/tb/publications/latent-tuberculosis-infection/en/</a>

## References

1. Getahun H., Matteelli A., Chaisson R., Raviglione M. Latent Mycobacterium tuberculosis Infection. *NEJM* 2015; 372:2127–35.
2. Van der Werf, M., Langendam, M., Sandgren, A., Manissero, D. Lack of evidence to support policy development for management of contacts of multidrug-resistant tuberculosis patients: two systematic reviews *Int J Tuberc Lung Dis* 2012 16,(3): 288–296.
3. European Centre for Disease Prevention and Control. Management of contacts of MDR TB and XDR TB patients. Stockholm ECDC 2012.  
[www.ecdc.europa.eu/en/publications/Publications/201203-Guidance-MDR-TB-contacts.pdf](http://www.ecdc.europa.eu/en/publications/Publications/201203-Guidance-MDR-TB-contacts.pdf).
4. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. *MMWR Recomm Rep*. 2000; 49(RR-6): 1–51.
5. Bamrah S., Brostrom R., Dorina F., et al. Treatment for LTBI in contacts of MDR-TB patients, Federated States of Micronesia, 2009-2012. *Int J Tuberc Lung Dis* 18(8):912–918.
6. Seddon J., Hesselning A., Finlayson H., et al. Preventive Therapy for Child Contacts of Multidrug-Resistant Tuberculosis: A Prospective Cohort Study. *Clin Inf Dis* 2013; 57(12):1676–84.
7. Adler-Shohet F., Low J., Carson, et al. Management of Latent Tuberculosis Infection in Child Contacts of Multidrug resistant Tuberculosis. *Ped Inf Dis J* 2014; 33 (6): 664–666.
8. Trieu L., Proops D., Ahuja S. Moxifloxacin Prophylaxis against MDR TB, New York, New York, USA. *Emerg Inf Dis* 2015; 21 (3): 500–503.
9. Fox G., Oxlade O., Menzies D. Fluoroquinolone therapy for the prevention of multi-drug resistant tuberculosis in contacts: a cost-effectiveness analysis. *AJRCCM* 2015 article in press.

## Revision history

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## Document custodian

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Tuberculosis Expert Advisory Group