

# Screening and Treatment Recommendations for People Exposed to Multidrug Resistant TB

All people at increased risk of tuberculosis (TB) infection should be screened for TB infection per United States Preventive Services Task Force [1] and Centers for Disease Control and Prevention guidelines [2]. This document provides specific guidance for screening and post-screening management of all people who have been identified through public health investigations as having been exposed to multidrug resistant tuberculosis (MDR TB). Recommendations for symptomatic contacts, children less than 5 years of age and those who are highly immunocompromised (see step **1B**) are different from other groups.

## Step 1: Initial Screening

### A. Assess contacts for symptoms of active TB disease

- Cough lasting 3 weeks or longer
  - Contacts reporting cough of less than 3 weeks duration at the time of screening should have follow-up to determine if the cough has resolved. If they have a persistent cough for greater than or equal to 3 weeks, further evaluation is indicated.
- Hemoptysis (coughing up blood)
- Chest pain
- Night sweats
- Fevers or chills
- Unintentional weight loss
- Loss of appetite
- Fatigue

### B. Obtain a medical history including prior TB screening and TB treatment information

- Contacts with prior positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA) results (documentation of previous testing is recommended) do not need a new TST or IGRA performed; they should be considered to have a positive TB screening test. In the event a person with a past positive TST or IGRA has a new TST or IGRA performed and it is negative, the significance of the new screening test is uncertain. Please contact MDH (651-201-5414) to discuss these discrepant results with a physician or nurse in the TB Program.

- Identify contacts less than 5 years of age and those who are highly immunocompromised as screening and management recommendations differ for these groups. For the purposes of TB screening, the following conditions are considered highly immunocompromising:
  - HIV infection
  - Stem cell or solid organ transplant recipients receiving immunosuppressive medications
  - Daily treatment with moderate or high dose corticosteroid (equivalent to prednisone  $\geq 15$  mg for 1 month or longer)
  - Treatment with a TNF-alpha antagonist

**C. Obtain a TB screening test (i.e., IGRA or TST) if the contact has no prior positive IGRA or TST (documentation of previous testing is recommended)**

- An IGRA (QuantiFERON<sup>®</sup>-TB Gold [QFT-G], QuantiFERON<sup>®</sup>-TB Gold Plus [QFT-Plus] or T-SPOT<sup>®</sup> TB test [T-Spot]) is the preferred test for contacts who originate from areas where they likely received BCG vaccine or are unlikely to return for TST reading.
- A TST result of  $\geq 5$  mm of induration is considered positive for people exposed to infectious TB.
- A TST should be performed for children less than 2 years of age. A negative TST result in a child less than 6 months of age is unreliable. A negative TST obtained in a child 6 months of age and older is considered valid.
- If the T-Spot test result is borderline, consult a TB expert.
- If the QFT-G or QFT-Plus is indeterminate, repeat QFT-G or QFT-Plus as soon as possible. If the repeat test remains indeterminate, call MDH to consult with a TB expert.

**D. Contacts with an initial negative TB screening test who are 5 years of age or older and not highly immunocompromised should be tested again 8–10 weeks after their last exposure to TB (aka “post-exposure screening”).**

- Contacts with an initial negative TB screening test who are less than 5 years of age or highly immunocompromised need additional management; see steps 1F, 2A, 2F, and 2G.
- Obtain a chest x-ray for contacts that meet any of the following criteria:
  - Pediatric contacts less than 5 years of age
  - Highly immunocompromised people (see step 1B)
  - People reporting any TB symptoms listed in step 1A
  - People with a new positive TB screening test

- All contacts who have a previously positive IGRA or TST (documentation of previous testing is recommended), or a history of latent TB infection (LTBI) or active TB disease, regardless of treatment history
- Exposure in settings determined to be very high risk for MDR TB transmission by MDH or local public health. If uncertain if a contact falls into this category, contact MDH (651-201-5414) or your local public health department.

## Step 2: Rule out Active TB Disease

### A. Determine if a provider visit is needed

The following contacts should be directly evaluated by a provider as soon as possible to rule out active TB disease:

- Pediatric contacts less than 5 years of age
- Highly immunocompromised people (see step 1B)
- People reporting any TB symptoms listed in step 1A
- People with a new positive TB screening test
- All contacts who have a previously positive IGRA or TST (documentation of previous testing is recommended), or a history of LTBI or active TB disease, regardless of treatment history
- Abnormal chest x-ray concerning for active TB disease

### B. Physical exam and testing to evaluate for active TB disease

- For contacts that require a provider visit, perform a thorough review of systems and physical exam to assess for abnormalities including extrapulmonary sites of infection.
- The following contacts must be tested for active pulmonary TB disease (see step 2C):
  - **Symptomatic contacts** (defined as cough lasting  $\geq 3$  weeks, or hemoptysis, or  $\geq 2$  of the other symptoms listed in step 1A) regardless of medical history or TB screening test result.
  - **Contacts with chest x-ray abnormalities** that could be consistent with active pulmonary TB disease, regardless of medical history or TB screening test result.
  - Any other contacts for whom the provider has reason to suspect active TB disease.

### C. Test for active pulmonary TB disease

- Obtain 3 sputum samples for AFB smear and AFB culture, and, for at least 1 of the 3 samples, *Mycobacterium tuberculosis* PCR.
- Gastric aspirate samples may be substituted for sputum samples in pediatric patients. Please consult with the MDH TB Program to coordinate specimen collection.
- Notify MDH (651-201-5414) whenever ordering sputum samples for TB testing.

- Contacts should stay in home isolation while waiting for smear and PCR results assuming they reside in a low-risk setting. Call MDH if the contact lives in a high-risk setting (see **Appendix B**).
- Continued avoidance of public settings will be made on a case-by-case basis while awaiting culture results.

#### **D. Negative sputum testing does not necessarily rule out active TB disease**

If a contact has symptoms or radiological findings concerning for TB, consult with a TB expert before fully ruling out active TB disease. Additional testing may be required to rule out active TB disease, including, but not limited to, chest CT or other imaging, bronchoscopy, or further assessment for extrapulmonary TB.

#### **E. Determine next steps**

- If active TB disease is diagnosed, refer contact to a TB expert for treatment.
- If active TB disease has been ruled out, and contact is 5 years of age or older and not highly immunocompromised, proceed to step **3**.
- For contacts less than 5 years see step **2F**.
- For highly immunocompromised contacts see step **2G**.

#### **F. Contacts less than 5 years of age with an initial negative screening test** should receive window prophylaxis (i.e., treatment for presumptive LTBI while awaiting post-exposure screening) after active TB disease has been ruled out.

- A negative TST result in a child less than 6 months of age is unreliable. A negative TST obtained in a child 6 months of age and older is considered valid.
- Contacts less than 6 months at the time of post-exposure screening should continue window prophylaxis until TST is performed after 6 months of age.
- If the post-exposure screening test is positive, the child should continue treatment for LTBI and also be re-evaluated for active TB disease. This includes obtaining a repeat chest x-ray and provider visit. Consultation with a TB expert is advised.

#### **G. Contacts with highly immunocompromising conditions (see step 1B)** Who have an initial negative screening test should receive window prophylaxis for LTBI after active TB disease has been ruled out. Similar to other groups, these contacts should have a post-exposure TB screening test 8–10 weeks after their last exposure. However, a negative post-exposure screening does not mean treatment should be stopped. The decision to administer a complete treatment course, versus window prophylaxis only, should be made in consultation with a TB expert.

## **Step 3: Determine Diagnosis**

After active TB disease has been ruled out, place contact into one of the following six categories and follow the management guidance listed.

### Category 1. History of inadequate treatment for LTBI or active TB disease

- Encourage treatment with LTBI regimen as outlined in steps **4A** and **4B**

### Category 2. Newly detected LTBI (i.e., new positive TB screening test)

- Encourage treatment with LTBI regimen as outlined in steps **4A** and **4B**.

### Category 3. History of adequate treatment for LTBI or active TB disease

- See step **4D**.

### Category 4. No evidence of LTBI (i.e. negative TB screening test) and not highly immunocompromised

- If most recent TB screening test and symptom screen were obtained at least 8 weeks after last known TB exposure **AND** the contact is not highly immunocompromised: no further follow-up needed.
- If most recent TB screening test and symptom screen were obtained less than 8 weeks after last known TB exposure, repeat TB screening test and symptom screen 8–10 weeks after last exposure.

### Category 5. TB screening test indeterminate

- Repeat TB screening test as soon as possible after receiving indeterminate result. If repeat TB screening test remains indeterminate, call MDH to consult with a TB expert.

### Category 6. Highly immunocompromised with no evidence of LTBI or active TB disease

- See step **2G**.
- Call MDH to talk with a TB expert.

## Step 4: LTBI Management

Before starting a patient on treatment for multidrug resistant LTBI (MDR LTBI), ensure active TB disease has been ruled out as described in step **2**.

### A. Administer 9 months of treatment for presumed MDR LTBI

- For people  $\geq 15$  years old: Moxifloxacin 400 mg by mouth daily, if unable to tolerate Moxifloxacin see step **4B**.
- For people  $< 15$  years old: Levofloxacin 15–20 mg/kg by mouth daily (not to exceed 750 mg daily), if unable to tolerate Levofloxacin, see step **4C**.

## B. If patient unable to tolerate Moxifloxacin due to side effects

(e.g., headache, dizziness, nausea, vomiting, diarrhea, abdominal pain, tendonitis, peripheral neuropathy, arthralgias, etc.)

- Switch to Levofloxacin
- For people  $\geq 18$  years old: Levofloxacin 500 mg by mouth daily if  $\leq 45.5$ kg; 750 mg by mouth daily if  $>45.5$ kg
- For people  $<18$  years old: Levofloxacin 15–20 mg/kg by mouth daily (not to exceed 750 mg daily)
- Renal failure/dialysis: Levofloxacin 750–1000 mg/dose 3 times weekly for creatinine clearance  $<30$  mL/min
- If unable to tolerate both Moxifloxacin and Levofloxacin: discontinue treatment and monitor for 2 years as outlined in step **4C**.

## C. If patient is unable to take fluoroquinolones due to a medical reason or after multiple attempts refuses treatment

Monitor patient for at least 2 years after last exposure to MDR TB. Patients may require monitoring for more than 2 years if they were re-exposed to MDR TB after the start of monitoring. If a patient is re-exposed to MDR TB during monitoring, the monitoring period is extended so that a patient is monitored for 2 years from the last date of MDR TB exposure.

- Baseline provider visit and chest x-ray should occur as soon as possible after last exposure to MDR TB.
- Following the baseline provider visit, the following monitoring is recommended:
  - 3 months after last exposure: Provider visit with symptom screen and physical exam. (If the baseline provider visit occurs more than 3 months after last exposure, the 3-month follow-up visit is not needed.)
  - 6, 12, 18, and 24 months after last exposure: Chest x-ray and provider visit including symptom screen and physical exam.
- At each encounter:
  - Educate patient about the need to notify their medical provider if the patient becomes symptomatic at any time during or after the monitoring period.
  - Initiate evaluation for active TB disease immediately if symptoms or chest x-ray abnormalities develop during the monitoring period.

## D. For those who have previously completed treatment for either drug resistant or pan-susceptible LTBI or active TB disease.

The need for treatment of MDR LTBI should be made on an individual basis. In general:

- For highly immunocompromised patients (see step **1B**) or patients with other comorbidities associated with increased risk of TB reactivation (i.e., diabetes mellitus,

status post gastrectomy or jejunioileal bypass, silicosis, underweight for height, or currently receiving chemotherapy), **and/or** patients with history of completed treatment for either active TB disease or LTBI 10 years ago or longer:

- Encourage treatment with MDR LTBI regimen as outlined in steps **4A** and **4B**.
- If after multiple attempts to start patient on treatment patient continues to refuse treatment or is unable to take fluoroquinolones due to other medical reasons, perform active monitoring for at least 2 years as outlined in step **4C**.
- If **not** highly immunocompromised and **no** comorbidities associated with increased risk of TB reactivation, **and** active TB disease treatment or LTBI treatment (i.e., isoniazid [INH] x 6–9 months, rifampin x 4 months, or INH + rifapentine x 3 months) was completed <10 years ago:
  - Treatment for MDR LTBI is likely unnecessary.
  - Perform active monitoring for at least 2 years as outlined in step **4C**.

## Step 5: Screening for Adverse Events related to MDR LTBI treatment

- Evaluate patients monthly using the MDH MDR LTBI Treatment Monitoring Flow Sheet to ensure adequate screening for side effects at each monthly medical visit.
- Fluoroquinolones can lower blood glucose, cause tendinitis, peripheral neuropathy, and prolong the QTc interval which, rarely, can lead to life-threatening arrhythmias.
- Screen patients for medical conditions and for potential medication interactions that could increase the risk of adverse events associated with Moxifloxacin and Levofloxacin before starting MDR LTBI treatment.
- People with congenital prolonged QT syndromes should not be offered a fluoroquinolone; they should be monitored for 2 years.
- For people with electrolyte abnormalities, bradycardia, ischemic heart disease, intracranial disease, HIV infection, hepatic impairment, connective tissue diseases with anti-Ro/SSA antibodies, and people who are taking a medication known to prolong the QTc interval, obtain a baseline ECG before starting MDR LTBI treatment and a repeat ECG 1–2 weeks after starting treatment. For a list of QTc prolonging medications go to the [Credible Meds website \(https://www.crediblemeds.org/\)](https://www.crediblemeds.org/).
- Take a complete history of all patients' medications at each monthly clinic visit. If the patient reports a new QTc prolonging medication, continue the fluoroquinolone and obtain an ECG at time of first report of the new medication and then again in 1–2 weeks.
- If the QTc is longer than normal (i.e.,  $\geq 0.44$  seconds among children 1–15 years old,  $\geq 0.43$  seconds among males >15 years, or  $\geq 0.45$  seconds among females >15 years, or

if the QTc increases by >25% during the course of treatment), consider consultation with a cardiologist before starting or continuing MDR LTBI treatment.

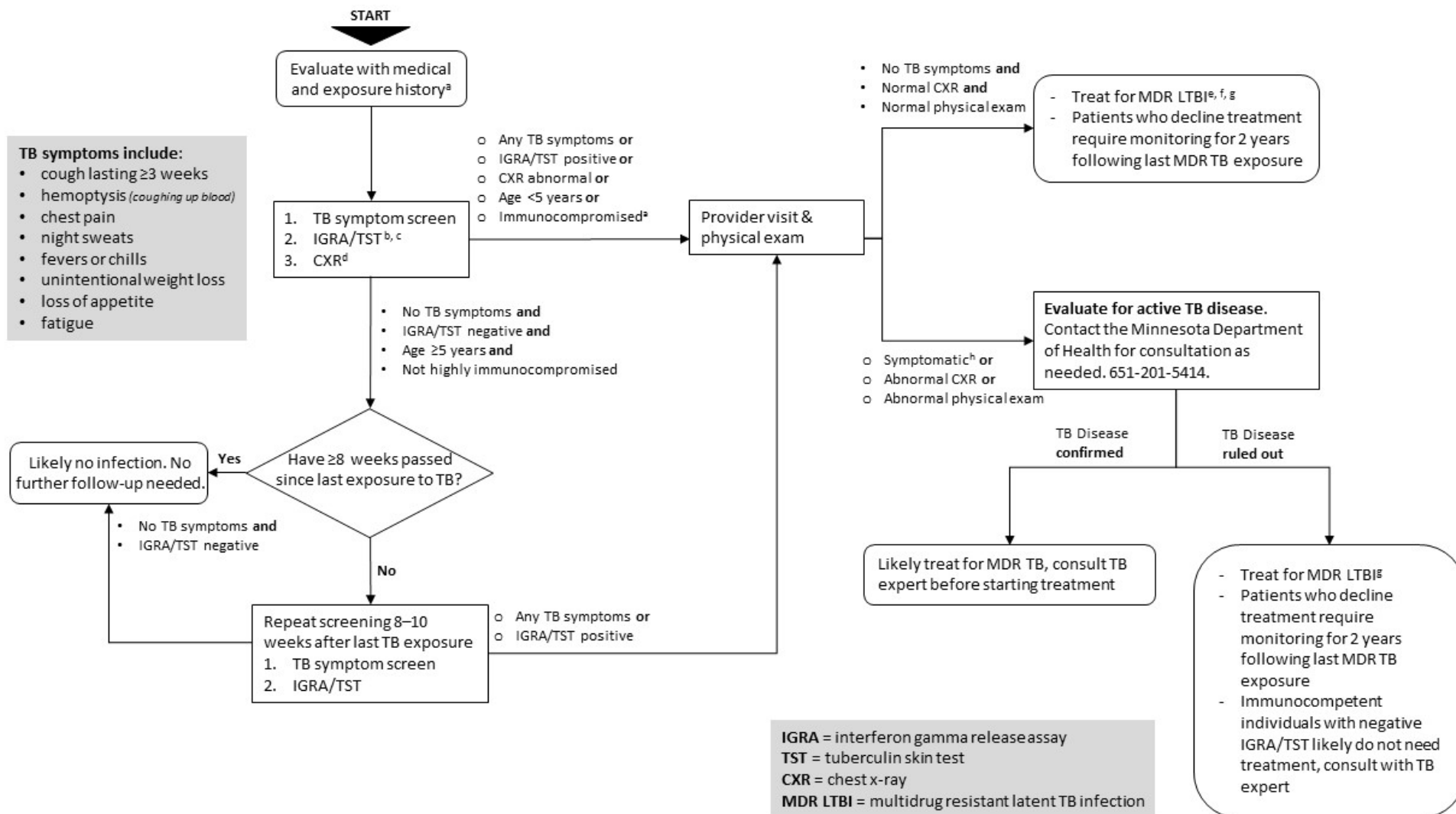
- While taking MDR LTBI treatment, patients should be instructed to promptly report any new palpitations or fainting which may be signs of QTc prolongation.
- Patients should be educated on the small risk of tendinitis related to fluoroquinolone use and that the concomitant use of corticosteroids with fluoroquinolones may increase the risk for tendinopathy. The risk of tendinitis may also be increased among patients with kidney failure and rheumatoid arthritis
- Patients taking medications to lower blood glucose, especially oral hypoglycemic agents, should be notified to check their blood sugar closely while taking a fluoroquinolone and to contact their primary care provider immediately if blood glucose levels are measuring lower than normal so oral hypoglycemic dosage(s) can be adjusted.
- Moxifloxacin and levofloxacin may worsen muscle weakness among patients with myasthenia gravis.
- People with renal insufficiency require dosing adjustment for levofloxacin (see step **4B**), but not for Moxifloxacin.
- Although the risk of liver damage with fluoroquinolones is low, all patients should be notified to stop taking the fluoroquinolone if they develop jaundice.

## References

1. Kahwati LC, Feltner C, Halpern M, et al. Primary Care Screening and Treatment for Latent Tuberculosis Infection in Adults Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2016; 316(9):970–983. doi:10.1001/jama.2016.10357
2. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clinical Infectious Diseases, Volume 64, Issue 2, 15 January 2017, Pages 111–115, <https://doi.org/10.1093/cid/ciw778>



## Appendix A: TB Screening Flow Diagram for Contacts of Infectious MDR TB Disease



## Footnotes

<sup>a</sup> Medical history includes prior TB screening and treatment. Identify children younger than 5 years, and those who are highly immunocompromised (i.e., HIV infection, stem cell or solid organ transplant recipients, daily treatment with moderate or high dose corticosteroid [i.e., equivalent to prednisone  $\geq 15$  mg for 1 month or longer], treatment with TNF-alpha antagonist) as follow-up recommendations differ for these groups.

<sup>b</sup> Contacts with previous positive IGRA/TST do not need a repeat IGRA/TST, they should be considered IGRA/TST positive (documentation of previous testing is recommended).

<sup>c</sup> IGRAs are the preferred test for people who originate from areas where they likely have received BCG vaccine. TST is recommended for children younger than 2 years.

<sup>d</sup> Obtain a chest x-ray for contacts that meet any of the following criteria: 1) Pediatric patients younger than 5 years; 2) highly immunocompromised people (see footnote “a”); 3) person with any TB symptoms; 4) positive TB screening test, either previously documented or newly positive; 5) history of LTBI or active TB disease, regardless of treatment history; 6) exposure in setting determined to be very high risk for TB transmission.

<sup>e</sup> Contacts less than 5 years of age with an initial negative TB screening test should receive window prophylaxis (i.e., treatment for presumptive MDR LTBI while awaiting post-exposure screening) after active TB disease has been ruled out. If repeat IGRA/TST screening 8–10 weeks after last TB exposure is negative and contact is 6 months of age or older, treatment can likely be discontinued. Consultation with a TB expert is advised.

<sup>f</sup> Contacts with highly immunocompromising conditions (see footnote “a”) should be started on treatment for MDR LTBI. The decision to administer a complete treatment course versus window prophylaxis should be made in consultation with a TB expert.

<sup>g</sup> Contacts who are not highly immunocompromised and do not have other comorbidities associated with increased risk of TB activation and completed treatment for active TB disease or drug susceptible LTBI (isoniazid [INH] x 6–9 months, rifampin x 4 months, or INH + rifapentine x 3 months) within the past 10 years likely do not require MDR LTBI treatment. Perform active monitoring for 2 years following last known MDR TB exposure.

<sup>h</sup> Symptomatic = cough lasting  $\geq 3$  weeks, or hemoptysis, or  $\geq 2$  of the other listed TB symptoms.

## Appendix B: Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, Third Edition [page 230]\*.

TABLE 4.

### Criteria for Release from Isolation to High and Lower Risk Settings\*

Patient Category	Setting	Criteria
TB case (or suspect on treatment for TB) at increased risk for MDR-TB	High or Lower risk	<ul style="list-style-type: none"> <li>Obtain direct NAAT, if available, for RIF and/or INH resistance.</li> <li>If direct NAAT not available, while phenotypic DST for RIF is pending, at the discretion of the local TB controller, either criteria for patients with known MDR-TB or criteria for patients not at increased risk of MDR-TB may be applied.</li> </ul>
Known MDR-TB case	High risk	<ul style="list-style-type: none"> <li>Three consecutive respiratory specimens collected on separate days, including at least one early AM or induced sputum, or BAL, are AFB smear negative, and no subsequent sputum specimen is AFB smear positive;</li> <li>At least 14 daily doses of treatment for MDR-TB taken and tolerated by DOT;</li> <li>Clinical improvement; and</li> <li>At least 2 consecutive negative sputum cultures without a subsequent positive culture.</li> </ul>
	Lower risk**	<ul style="list-style-type: none"> <li>Three consecutive sputum specimens collected on separate days are AFB smear negative;</li> <li>At least 14 daily doses of treatment for MDR-TB taken and tolerated by DOT; and</li> <li>Clinical improvement.</li> </ul>

### Definitions:

#### High Risk Setting

- A housing or work setting in which others will share air with the TB patient and which is characterized by 1 or more of the following factors:
  - A large number or high density of persons.
  - The presence of persons at high risk of progression to active TB disease (e.g., children < 5, persons with HIV infection)
  - The presence of persons who have not been previously exposed to the TB patient.

#### Lower Risk Setting

- A **residential** setting not characterized as high risk, and:
  - No other persons will share the air with the TB patient; OR
  - Other persons who will share the air with the TB patient are not at increased risk for progression to TB disease if infected; OR
  - All persons at increased risk of progression to TB disease if infected, including all children under the age of 5 years, who will share the air with the TB patient, have been previously exposed to the TB patient, have had a complete medical evaluation and have been started on therapy, including window period treatment for presumed LTBI (TB1), as appropriate.
- A **work** setting not characterized as high risk, and in which no contacts are known or reasonably expected to be at increased risk of progression to TB disease if infected

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