Drug Resistance and Concentration Testing for *Mycobacterium Tuberculosis* Complex

Purpose

The purpose of this document is to define drug resistance for the *Mycobacterium tuberculosis* complex and specify the concentrations of first and second line antituberculous drugs tested at DSHS laboratories.

Testing Standards and Process

The DSHS Laboratory will perform antimycobacterial susceptibility testing for the *Mycobacterium tuberculosis* complex as specified by national standards (see References). These standards specify that laboratories test antituberculous drugs at a single critical concentration of the drug. The result of testing at the critical concentration defines whether the organism is considered resistant or susceptible. For isoniazid, laboratories will also test an additional higher concentration of that drug. However, isoniazid resistance is defined as resistance at the critical concentration.

Critical concentrations of three first-line antituberculous drugs tested by the Middlebrook 7H10 agar method of proportion are:

- Isoniazid: 0.2 microgram per milliliter
- Rifampin: 1.0 microgram per milliliter
- Ethambutol: 5.0 micrograms per milliliter

Laboratories may also test first-line antituberculous drugs by a U.S. FDA-cleared commercial rapid broth system at critical concentrations that are equivalent to those established for the Middlebrook 7H10 agar method of proportion.

For isoniazid, laboratories will test an additional higher concentration of 1.0 microgram per milliliter for the Middlebrook 7H10 agar method of proportion, or equivalent concentration with a U.S. FDA-cleared commercial rapid broth system.

Laboratories cannot accurately test Pyrazinamide, another first-line antituberculous drug, by the Middlebrook 7H10 agar method of proportion. Pyrazinamide is tested by either the BACTEC MGIT 960 TB system or the VersaTrek Pyrazinamide Susceptibility test system. Both systems are FDA-cleared and test Pyrazinamide at a concentration equivalent to a concentration of 100 micrograms per milliliter as tested in the "gold standard" BACTEC 460TB system. The vendor discontinued the BACTEC 460TB test system due to its use of radioisotopes.

Critical concentrations of second line antituberculous drugs tested by the Middlebrook 7H10 agar method of proportion are:

- Capreomycin: 10.0 micrograms per milliliter

- Ethionamide: 5.0 micrograms per milliliter
- Kanamycin: 5.0 micrograms per milliliter
- Rifabutin: 2.0 micrograms per milliliter
- Ofloxacin: 2.0 micrograms per milliliter
- Streptomycin: 2.0 micrograms per milliliter

Laboratories may also test second line antituberculous drugs by other methods validated to meet U.S. laboratory licensure requirements.

People Affected

- Employees of the DSHS Laboratory
- Employees of other laboratories in Texas performing drug susceptibility testing on isolates of *Mycobacterium tuberculosis* complex
- Employees of DSHS regional and local health departments
- Licensed health care providers, physicians and nurses involved in the delivery of TB services
- Employees of U.S. Centers for Disease Control and Prevention

Responsibilities

Employees of laboratories will report resistance according to the critical concentrations noted under definitions.

Employees of DSHS regional and local health departments and physicians and nurses involved in the delivery of TB services will follow national guidelines in providing care for people with TB disease that is resistant to antituberculous drugs. This includes obtaining expert consultation as described in the Texas Tuberculosis Work Plan.

References

1. Clinical and Laboratory Standards Institute (CLSI). *Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes*; Approved Standard, 3rd Edition. November 2018. CLSI document M24.
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Susceptibility Testing of Mycobacteria, Nocardia spp., and Other Aerobic Actinomycetes, 1st Edition*. November 2018. CLSI document M62.

3. American Thoracic Society, U.S. Centers for Disease Control and Prevention, Infectious Diseases Society of America. *Treatment of Tuberculosis*. American Journal of Respiratory Critical Care and Medicine, Vol 167. pp 603–662, 2003.

4. American Thoracic Society, U.S. Centers for Disease Control and Prevention and Infectious Diseases Society of America. *Diagnostic Standards and Classification of Tuberculosis in Adults and Children*. American Journal of Respiratory Critical Care and Medicine, Vol 161. pp 1376–1395, 2000.

5. *Treatment of Drug-Resistant Tuberculosis,* American Journal of Respiratory and Critical Care Medicine, 2019.

Definitions

Resistance — diminished susceptibility of a strain that differs from wild-type strains from patients who have not been treated with the drug, so that the strain is unlikely to show clinical responsiveness to the drug.

Critical Concentration — the lowest concentration that inhibits 95 percent of "wild strains" of *Mycobacterium tuberculosis* that have never been exposed to the drug, while at the same time does not inhibit strains of *Mycobacterium tuberculosis* considered resistant that are isolated from patients who are not responding to therapy.

Multidrug-Resistant Tuberculosis (MDR-TB) — the occurrence of tuberculosis in people whose isolates are resistant to isoniazid and rifampin.

Pre-Extensively Drug-Resistant Tuberculosis (Pre XDR-TB) — the occurrence of TB in people whose *Mycobacterium tuberculosis* isolates are resistant to isoniazid and rifampin plus resistant to either a fluoroquinolone or at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

Extensively Drug-Resistant Tuberculosis (XDR-TB) — the occurrence of TB in people whose *Mycobacterium tuberculosis* isolates are resistant to isoniazid and rifampin plus resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).