TEXAS Department of State Health Services **Drug Resistance**	Policy Number	**TB-4002**
	Effective Date *(original issue)*	6/26/2008
	Revision Date *(most recent)*	
	Subject Matter Expert *(title)*	Manager, Infectious Disease Intervention and Control Branch
	Approval Authority *(title)*	Manager, Infectious Disease Control Unit
	Signed by *(signature for hard copy; name for online)* Susan C. Penfield, M.D. Denise Dunbar Susan Neill, Ph.D., M.B.A.	

1.0 Purpose

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

2.0 Policy

The DSHS laboratory will perform antimycobacterial susceptibility testing for *Mycobacterium tuberculosis* complex as specified by national standards (7.1, 7.2, 7.3). These standards specify that antituberculous drugs be tested 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, an additional higher concentration of that drug will also be tested. However, isoniazid resistance is defined as resistance at the critical concentration.

3.0 Definitions

3.1 Resistance is defined as 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.

3.2 Critical Concentration: The lowest concentration that inhibits 95% 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.

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

- 3.3.1 Isoniazid: 0.2 micrograms per milliliter
- 3.3.2 Rifampin: 1.0 micrograms per milliliter
- 3.3.3 Ethambutol: 5.0 micrograms per milliliter

3.4 First-line antituberculous drugs may also be tested by an 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.

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

3.6 Pyrazinamide, another first-line antituberculous drug, cannot be accurately tested by the Middlebrook 7H10 agar method of proportion. Pyrazinamide is tested by the BACTEC 460TB system at a critical concentration of 100 micrograms per milliliter. Pyrazinamide may also be tested by an U.S. FDA-cleared commercial rapid broth system at a critical concentration that is equivalent to that established for the BACTEC 460TB system.

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

- 3.7.1 Capreomycin: 10.0 micrograms per milliliter
- 3.7.2 Ethionamide: 5.0 micrograms per milliliter
- 3.7.3 Kanamycin: 5.0 micrograms per milliliter

3.7.4 Rifabutin: 0.5 micrograms per milliliter
3.7.5 Ofoxacin: 2.0 micrograms per milliliter
3.7.6 Streptomycin: 2.0 micrograms per milliliter

3.8 Second-line antituberculous drugs may also be tested by an 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.

3.9 Multidrug resistant tuberculosis (MDR-TB) is defined as the occurrence of tuberculosis in persons whose isolates are resistant to isoniazid and rifampin.

3.10 Extensively drug-resistant tuberculosis (XDR-TB) is defined as the occurrence of TB in persons 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).

4.0 Persons Affected

Employees of DSHS Laboratories
Employees of DSHS Infectious Disease Control and Prevention
Employees of other laboratories in Texas performing drug susceptibility testing on isolates of *Mycobacterium tuberculosis* complex.
Employees of DSHS and local health departments
Local and regional health department managers
Physicians and nurses involved in the delivery of TB services
Employees of U.S. Centers for Disease Control and Prevention

5.0 Responsibilities

Employees of laboratories will report resistance according to the critical concentrations noted under definitions.
Employees of DSHS and local health departments and physicians and nurses involved in the delivery of TB services will follow national guidelines in providing care for persons with TB disease that is resistant to antituberculous drugs including obtaining expert consultation as described in DSHS policy TB-4001.

6.0 Procedures

7.0 References

7.1 Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes; Approved Standard. 2003. Clinical and Laboratory Standards Institute (CLSI) document M24-A.

7.2 Treatment of Tuberculosis. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America. Am J Respir Crit Care Med Vol 167. pp 603–662, 2003.

7.3 Diagnostic Standards and Classification of Tuberculosis in Adults and Children. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America. Am J Respir Crit Care Med Vol 161. pp 1376–1395, 2000.

8.0 Revision History

Date	Action	Section
6/26/2008	New	

***Mycobacterium tuberculosis* complex Drug Susceptibility Testing (DST) Methods and Critical Concentrations**

(Critical Concentration values from Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes; Approved Standard. 2003. Clinical and Laboratory Standards Institute, document M24-A, unless otherwise noted.)

Drug Group	**Drug**	**DST method available**	**DST Critical concentrations (µg/ml)**				
			Middlebrook 7H10 agar	Middlebrook 7H11 agar	BACTEC460 liquid system[1]	BACTEC MGIT 960 liquid system[1]	VersaTREK liquid system[1]
First-line oral anti-TB drugs	Isoniazid	Agar, Liquid	0.2	0.2	0.1	0.1	0.1
	Rifampin	Agar, Liquid	1.0	1.0	2.0	1.0	1.0
	Ethambutol	Agar, Liquid	5.0	7.5	2.5	5.0	5.0
	Pyrazinamide	Liquid	-	-	100.0	100.0	300.0
Injectable second-line anti-TB drugs	Streptomycin	Agar, Liquid	2.0	2.0	2.0	1.0	-
	Kanamycin[2]	Agar, Liquid	5.0	6.0	5.0	-	-
	Amikacin[3]	Agar, Liquid	4.0	-	1.0	1.0	-
	Capreomycin	Agar, Liquid	10.0	10.0	1.25	2.5	-
Fluoroquinolones	Ciprofloxacin[4]	Solid, Liquid	2.0	2.0	2.0	1.0	-
	Ofloxacin[5]	Solid, Liquid	2.0	2.0	2.0	2.0	-
	Levofloxacin[3]	Solid, Liquid	2.0	-	2.0	2.0	-
	Moxifloxacin[4]	Liquid	-	-	0.5	0.25	-
Oral second-line anti-TB drugs	Ethionamide	Agar, Liquid	5.0	10.0	1.25	5.0	-
	P-aminosalicylic acid	Agar, Liquid	2.0	8.0	-	-	-
Rifamycin alternative	Rifabutin	Agar, Liquid	0.5	-	0.5	-	-

- not available or not recommended

[1] Rapid commercial liquid systems that have been U.S. FDA-cleared as of June 2, 2008 for testing first-line oral anti-TB drugs.

[2] Kanamycin is the class representative for Amikacin; critical concentration value for BACTEC 460 system from multi-center studies

[3] Values from proposed Clinical Laboratory Standards Institute M24-A2 standard (December 2007 draft)

[4] Values from proposed World Health Organization Policy Guidance on Drug Susceptibility Testing (DST) of Second-line Anti-Tuberculosis Drugs (December 2007 draft)

[5] Ofloxacin is the class representative for fluoroquinolones