

Appendices

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Appendix 1: List of Expert Resources for Drug-Resistant TB

In 2005, the Centers for Disease Control and Prevention's Division of Tuberculosis Elimination funded four TB Regional Training and Medical Consultation Centers (RTMCCs). The RTMCCs are regionally assigned to cover all 50 states and the U.S. territories. Information about the RTMCC system can be found at: www.cdc.gov/tb/rtmcc.htm.

Contact information for the RTMCCs and other regional and national resources can be found in this appendix.

California Department of Public Health TB Control Branch, Division of Communicable Disease Control MDR-TB Service

CONTACT Lisa True, RN, MS, Coordinator

TELEPHONE 510-620-3054

E-MAIL lisa.true@cdph.ca.gov

ADDRESS 850 Marina Bay Parkway, Richmond, CA 94804-6403

- **Types of consultation:** Telephone and e-mail (for callers within California or other state agencies within the United States)
 - Can provide on-site presentations related to MDR-TB
 - Can provide ongoing consultation during drug-resistant treatment
-

Centers for Disease Control and Prevention (CDC) Coordinating Center for Infectious Diseases National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention Division of Tuberculosis Elimination (DTBE)

CONTACT CDC INFO Contact Center

TELEPHONE 1-800-CDC-INFO

E-MAIL cdcinfo@cdc.gov

INTERNET www.cdc.gov/tb/

ADDRESS Mailstop E-10, 1600 Clifton Road, NE, Atlanta, GA 30333

- **Types of consultation:** Telephone and e-mail
- In general, CDC/DTBE does not provide medical consultation for management of individual patients. CDC/DTBE does provide information on current guidelines and their interpretation. CDC/DTBE also is available for programmatic consultation to local and state health departments including onsite assistance for outbreaks.

Chicago Department of Public Health TB Control Program

CONTACT William Clapp, MD
TELEPHONE 312-746-6003
E-MAIL clapp_william@cdph.org
ADDRESS 2160 W. Ogden Ave., Chicago, IL 60612

- **Types of consultation:** Telephone, e-mail, and in-person.
- Can provide advice for patients not in jurisdiction.
- Patients can be sent to our facility.
- **Comments:** Insurance not needed for initial evaluation, further services available depending on needs and resources; TB medications available at no cost only to patients living in the City of Chicago.
- Can provide ongoing consultation during drug-resistant treatment.

Most of our MDR work is collaborative, utilizing the collective wisdom of recognized authorities (listed below).

ADULT

University of Illinois Hospitals and Clinics
Dr. Dean Schraufnagel
Department of Medicine
312-996-8039
Division of Pulmonary and Critical Care Medicine

ADULT

University of Illinois Hospitals and Clinics
Dr. James Cook
Department of Medicine
312-996-6732
Division of Infectious Diseases

PEDIATRICS

Rush-Presbyterian St. Lukes Hospital
Dr. James McAuley
Department of Pediatrics
312-942-6396
Division of Infectious Diseases

Francis J. Curry National Tuberculosis Center—TB Warmline

CONTACT Warmline Coordinator
TELEPHONE 877-390-6682 (toll-free) or 415-502-4700
E-MAIL tbcenter@nationaltbcenter.ucsf.edu
INTERNET www.nationaltbcenter.ucsf.edu
ADDRESS 3180 18th Street, Suite 101, San Francisco, CA 94110

- **Types of consultation:** Telephone, email, and bimonthly MDR-TB Expert Network case conferences
- As the Western Regional TB Training and Medical Consultation Center, can provide medical consultation to providers in Alaska, California, Colorado, Hawaii, Idaho, Montana, Nevada, Oregon, Utah, Washington, Wyoming, and the U.S. Pacific Island Territories
- Patients can be sent to our facility—see San Francisco Department of Public Health
- Can provide ongoing consultation during drug-resistant treatment

Heartland National TB Center and Texas Center for Infectious Disease

CONTACT Barbara J. Seaworth, MD
TELEPHONE 210-534-8857, ext. 2489
E-MAIL Barbara.Seaworth@dshs.state.tx.us
INTERNET www.heartlandntbc.org
ADDRESS 23023 SE Military Drive, San Antonio, TX 78218

- **Types of consultation:** Telephone, e-mail, and in-person (clinic)
- Can provide ongoing consultation during drug-resistant treatment
- Provides consultations for all Texas cases of drug-resistant TB, contacts of drug-resistant TB, and use of fluoroquinolones, or other non-formulary drugs (linezolid)
- Provides any needed consultation for the Heartland region and works to support other regions as requested by them
- **Comments:** Enabling legislation has been passed to allow states to contract for the care of patients from other states at the Texas Center for Infectious Disease. There is a fair amount of administrative effort to resolve prior to the first patient.
- We like to use a case management approach for all cases to make sure treatment not only begins correctly but also continues on course, and that problems leading to toxicity and treatment failure are identified and corrected early.

Los Angeles County TB Control Program

CONTACT Jaimin Kim, PHN, MDR-TB Unit
TELEPHONE 213-744-6180
ADDRESS 2615 S. Grand Avenue, Room 507, Los Angeles, CA 90007

- **Types of consultation:** Nursing and medical consultation for Los Angeles County cases

National Jewish Mycobacterial Diseases Consult Line

CONTACT Bessie Mishra, RN
TELEPHONE 800-423-8891, ext 1279 or 303-398-1279
E-MAIL mycoconsults@njc.org
INTERNET www.nationaljewish.org
ADDRESS National Jewish Medical and Research Center
1400 Jackson Street, Denver, CO 80206

- **Types of consultation:** Telephone, e-mail, and in-person
- Can provide advice for patients not in jurisdiction
- Patients can be sent to our facility
- **Comments:** Contact Bessie Mishra, RN, to discuss referral process or to ask for a clinical consultation (consultations provided by Michael Iseman, MD; Gwen Huitt, MD; Charles Daley, MD; Leonid Heifets, MD; and Charles Peloquin, PharmD).
- Our service provides comprehensive evaluation and treatment programs, including consideration of surgery. If indicated, surgery is performed at our sister institution, the University of Colorado Health Science Center.

New Jersey Medical School Global Tuberculosis Institute Northeastern Regional Training and Medical Consultation Center

CONTACT Reynard J. McDonald, MD or Alfred Lardizabal, MD
TELEPHONE 800-4TB-DOCS or 973-972-3270
INTERNET <http://www.umdnj.edu/globaltb>
ADDRESS 225 Warren Street, 2nd Floor, East Wing, Newark, NJ 07103

- **Types of consultation:** Telephone, e-mail, and in-person.
- Consultants to the New Jersey DHSS for TB problems, including all cases of MDR-TB.
- Center provides comprehensive diagnostic, treatment, and consultation services for TB patients in the state of New Jersey.
- Can provide advice and consultation for patients not in jurisdiction.
- MDR-TB work is collaborative, utilizing the collective wisdom of the following recognized authorities at the New Jersey Medical School Global Tuberculosis Institute:

ADULTS

Dr. Lee B. Reichman
Dr. Reynard J. McDonald
Dr. Bonita Mangura
Dr. Alfred Lardizabal
Dr. Kevin Fennelly

CHILDREN

Dr. George McSherry
Dr. Helen Aguilla

New York City Department of Health and Mental Hygiene

CONTACT Diana Nilsen, MD
TELEPHONE 212-442-9737
E-MAIL dnilsen@health.nyc.gov
ADDRESS 225 Broadway, 22nd Floor, New York, NY 10007

- **Type of consultation:** Telephone, e-mail, and in-person
- Can provide advice for patients not in jurisdiction
- Patients can be sent to our facility
- **Comments:** Free evaluation and treatment, including CXR, sputa, DOT, and meds in outpatient facilities
- Can provide ongoing consultation during drug-resistant treatment

Partners In Health

TELEPHONE 617-432-5256
E-MAIL info@pih.org
INTERNET www.pih.org
ADDRESS 641 Huntington Ave., Boston, MA 02115

- **Type of consultation:** Telephone, e-mail, and in-person
- Can provide advice for patients not in jurisdiction
- **Comments:** We are a non-profit organization with more than 10 years of experience treating MDR-TB in resource-poor settings
- Can provide ongoing consultation during drug-resistant treatment

San Francisco Department of Public Health—TB Control Section

CONTACT Masae Kawamura, MD
TELEPHONE 415-206-3387
E-MAIL masae.kawamura@sfdph.org
ADDRESS TB Clinic, San Francisco General Hospital, 1001 Potrero Ave., San Francisco, CA 94110

- **Types of consultation:** Telephone (in-person consultation for San Francisco patients only)
- Can provide advice for patients not in jurisdiction
- Can provide ongoing consultation during drug-resistant treatment

Southeastern National Tuberculosis Center / A.G. Holley Hospital TB Hotline

CONTACT Southeastern National TB Center
TELEPHONE 800-4TB-INFO (800-482-4636)
E-MAIL sntc@medicine.ufl.edu
INTERNET <http://sntc.medicine.ufl.edu>
ADDRESS 1329 SW 16th Street, Room 5174, Gainesville, FL 32608

- **Types of consultation:** Telephone, e-mail, web-based and in-person on all aspects related to TB control and patient care
- Expert medical consultation available 24 hours a day, seven days a week for the 11 southeastern states (Alabama, Arkansas, Florida, Georgia, Kentucky, Mississippi, New Orleans, North Carolina, South Carolina, Tennessee, Virginia) and Puerto Rico and the Virgin Islands. Focus is on providing medical consultation and support to health care providers within the southeast region, supporting the existing resources within each state and working in close partnership with the state TB Control Program.
- Patients requiring complex inpatient support can be sent to our state facility (AG Holley Hospital) on a case-by-case decision once determined appropriate and upon final agreement between the two state programs.
- Provide ongoing medical consultation for drug-resistant TB cases and other complex and challenging TB cases, including use of collaborative case conferences involving multiple providers across the southeast connected by web-based conferencing system.
- Can provide medical consultation for patients not in jurisdiction

Appendix 2: Contact Information for Selected Organizations Working to Control and Prevent TB in the International Arena

CureTB: Binational TB Referral Program

www.curetb.org
619-542-4013

Foundation for Innovative New Diagnostics (FIND)

www.finddiagnostics.org
+ 41-22-710-0590

Global Alliance for TB Drug Development

www.tballiance.org
212-227-7540

Green Light Committee

www.who.int/tb/challenges/mdr/greenlightcommittee/en
+ 41-22-791-2708 or 3224

International Union Against Tuberculosis and Lung Disease (IUATLD)

www.iuatld.org
+33-1-44-32-0360

KNCV Tuberculosis Foundation

www.tuberculose.nl
+31-70-416-7222

Médecins Sans Frontières (Doctors Without Borders)

International headquarters: Geneva, Switzerland
www.msf.org
+41-22-849-8400
United States headquarters: New York
www.doctorswithoutborders.org
212-679-6800

Pan American Health Organization (PAHO)

www.paho.org/english/ad/dpc/cd/tuberculosis.htm
202-974-3000

Partners In Health

www.pih.org
617-432-5256

Program for Appropriate Technology in Health (PATH)

www.path.org
206-285-3500

Stop TB Partnership

(housed by the World Health Organization)
www.stoptb.org
+ 41-22-791-4650

TBNet (Migrant Clinicians Network)

www.migrantclinician.org/network/tbnet
800-825-8205

World Health Organization

www.who.int/en
+ 41-22-791-2111

Appendix 3: International Resources for TB Treatment and Policies

The following websites are potential sources of information about the various TB protocols practiced in countries with high rates of immigration to the United States:

Global

The World Health Organization (WHO) Report on Global TB Control compiles data from 200 countries each year, monitoring the scale and direction of TB epidemics, implementation and impact of the Stop TB Strategy, and progress towards the Millennium Development Goals:

www.who.int/tb/publications/global_report/en/index.html

The fourth report by the WHO/International Union Against TB and Lung Disease Global Project on Anti-Tuberculosis Drug Resistance Surveillance presents data from 93 settings or countries:

www.who.int/tb/publications/2008/drs_report4_26feb08.pdf

The WHO website provides links to, and contact information for TB programs located throughout the world:

www.who.int/topics/tuberculosis/en/

The CDC Division of Global Migration and Quarantine is another source of information:

www.cdc.gov/ncidod/dq/ E-mail: dqweb@cdc.gov

The *International Standards for Tuberculosis Care (ISTC)* (in English, French, and Spanish); the *Patients' Charter for Tuberculosis Care* (in English and Spanish); and a comprehensive list of guidelines, statements, and standards on tuberculosis from agencies around the world are available at:

www.nationaltbcenter.ucsf.edu/international/index.cfm

China

www.wpro.who.int/china/sites/stb/

India

www.tbcindia.org
www.whoindia.org/EN/Section3/Section123.htm

Mexico

www.salud.gob.mx
www.who.int/countries/mex/en/

Philippines

www.doh.gov.ph/programs/tbcontrol
www.wpro.who.int/countries/2007/phl.htm
www.usaid.gov/our_work/global_health/id/tuberculosis/countries/ane/philippines_profile.html

Russian Federation

www.mednet.ru/main/
www.eurotb.org/index.htm
www.who.int/countries/rus/en/

Vietnam

www.moh.gov.vn
www.who.int/countries/vnm/en/

Appendix 4: Laboratory Resources

The laboratory is the cornerstone of diagnosis and management of drug-resistant tuberculosis (TB) in the United States and other industrialized countries. While initial treatment regimens are designed empirically based on risk of resistance and prior use of antimicrobials, definitive regimens rely on accurate and timely susceptibility results.

There are several types of laboratories that culture mycobacteria:

- **Hospital-based laboratories**
- **Local public health laboratories**
- **State public health laboratories**
- **Commercial laboratories**

Each laboratory performs different services: different types of smears, culture methods, identification methods, rapid tests for early identification (i.e., nucleic acid amplification) or species identification, and susceptibility testing with different panels of drugs for susceptibility testing. Services and protocols may vary based on the source of the specimen (e.g. private provider vs. hospitalized patient), type of specimen (e.g. sputum vs. cerebrospinal fluid [CSF] vs. other specimen type), and third-party payor source.

Case managers and treating physicians should have an in-depth understanding of the laboratory practices of the facilities processing their patients' specimens.

Specific Elements to Know:

Will the laboratory perform nucleic acid amplification tests upon request? On any sputum requested or only smear-positive sputum?

Nucleic acid amplification tests (NAATs) enable rapid detection of DNA of *M. tuberculosis* complex directly on clinical specimens. They are usually used to diagnose TB in sputum from smear-positive patients in order to guide empiric treatment and guide infection control measures. They can be performed on smear-negative specimens as well, but negative results in such a case have a lower predictive value (higher probability of false-negative results) compared to smear-positive specimens. The test can be useful with various biopsy and autopsy specimens and various body fluids, especially with CSF when TB meningitis is suspected (these uses are less well studied). Contact the individual laboratory regarding their policies and protocols for using the NAAT tests.

How and when will smear, nucleic acid amplification, and culture results be reported to me?

Positive acid-fast bacilli (AFB) smear results should be reported to the local public health jurisdiction and the ordering physician or referring laboratory within 24 hours after the arrival of the specimen to the laboratory. Consult with your laboratory on how frequently they perform NAAT testing and when to expect results. Once mycobacterial growth from primary isolation media is confirmed, a DNA probe technique may be used to determine whether the organism is a member of the *M. tuberculosis* complex (in the United States, *M. tuberculosis* and *M. bovis* are the two clinically important species in the complex) or a nontuberculous mycobacterium (NTM). Commercial probes are available for *M. tuberculosis* complex, *M. avium* complex, *M. kansasii* and *M. goodii*. Identification of *M. tuberculosis* complex should be available in less than 1 week after the culture becomes positive. The positive culture result can be available as early as 14 days from specimen collection on a new patient and is reported to the local public health jurisdiction and the ordering physician or referring laboratory. Communication with the laboratory will ensure that the results are reported to the correct individuals immediately.

How can I keep track of serial cultures being performed at different laboratories?

It is advisable to submit serial cultures to the same laboratory, usually the state or local public health laboratory. Many

public health departments and case managers can access their public health laboratories' computerized results directly, making smear, culture, identification, and susceptibility status available as rapidly as possible. Additionally, most public health laboratories will automatically repeat susceptibilities for patients whose cultures remain positive after 3 months. Having all follow-up cultures at the same laboratory provides the greatest efficiency and optimal communication.

How can I ensure that adequate specimens are being submitted?

It is not possible to be sure of specimen adequacy. It is prudent to submit 2-3 specimens (minimum volume 5-10 ml) biweekly until the sputum is smear-negative. Two specimens should be collected at least monthly until the patient is consistently culture-negative. If there is any concern about the quality of the specimen, arrange sputum induction for the patient, and always submit 2 specimens 8 to 24 hours apart.

Will drug susceptibility tests be performed immediately?

Some mycobacteriology laboratories require an additional request from the ordering physician in order to perform susceptibility tests. Contact your laboratory to expedite this testing.

If the laboratory does not perform susceptibility tests on-site, where will the isolate be sent? Will it be sent automatically? How will that laboratory share results with me?

Contracts between payors and individual hospitals and laboratories determine where susceptibility testing is performed. The reference laboratory reports results to the referring laboratory.

What is the panel of drugs studied initially?

It is fairly routine for laboratories to test for at least isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB). If a laboratory intends not to test routinely for these drugs, it should seek approval from TB Control. Some laboratories may include streptomycin in the primary drug panel, and some may not test for PZA susceptibility. Request molecular assays, where available, for rapid testing from a sputum sediment or a broth culture if drug-resistance is suspected.

Can I request that second-line susceptibility tests be performed as soon as growth is detected?

In the event of suspected drug-resistance, the laboratory should be informed at the time of specimen submission, in order to set-up second-line drugs simultaneously with first-line drug assays. Request molecular assays, where available, for rapid testing from a sputum sediment or a culture.

How can I arrange to receive results as soon as they are available?

Some laboratories perform confirmatory tests before releasing results. It is valuable to know that an AFB is growing even before identification is performed. It is essential to know if the mycobacteria is *M. tuberculosis* complex (frequently this is the extent of the speciation), even if the laboratory intends to fully speciate the isolate. The laboratory should know that you want to be informed of drug resistance detected by broth methods before confirmation by a reference laboratory or by an alternate method.

How can I arrange for a broader panel of drug susceptibility tests to be performed?

Many laboratories have a regional reference laboratory under contract to perform confirmatory tests or more extensive testing. In the case of many commercial laboratories and some public health laboratories, the list of second-line drugs tested may be quite limited. In the case of extensive drug resistance, many second- and third-line drugs may need to be tested in order to design a curative regimen for your patient. While unnecessary expense should be avoided, expeditious appropriate testing should be performed. Very comprehensive second- and third-line testing is only performed at a few reference laboratories.

An open dialogue with the laboratorian facilitates the prompt communication of results and the most efficient and comprehensive laboratory evaluation of the patient's isolate.

Contact your state/local public health, hospital-based or commercial laboratory for more information.

STATE PUBLIC HEALTH LABORATORIES				
Laboratory	Tests performed	Requirements	Cost	Contact information
California Department of Public Health Microbial Disease Laboratory (MDL)	Indirect susceptibility testing: first-line drugs: INH, RIF, PZA, EMB ; second-line (if resistant to RIF or 2 first-line drugs, or by request): SM, capreomycin, ethionamide, amikacin and levofloxacin	Isolates from solid or broth media	None Full services available only to CA residents	<p>Edward P. Desmond, PhD, 510-412-3781 Ed.Desmond@cdph.ca.gov Chief of Mycobacteriology & Mycology Section</p> <p>Molecular beacons: 510-412-3929 Grace.lin@cdph.ca.gov Genotyping: 510-412-3928 or 3926 Culture identification: 510-412-3924 FAX: 510-412-3927</p> <p>Microbial Diseases Laboratory c/o Specimen Receiving California Department of Public Health 850 Marina Bay Parkway Richmond, CA 94804</p> <p>Most specimens come from county public health laboratories</p> <p>ALL laboratories must submit all MDR-TB isolates from any CA resident</p>
	Molecular drug resistance assay for INH (<i>katG</i> , <i>inhA</i>) or RIF (<i>rpoB</i>) by molecular beacons: by request only – contact Dr. Desmond or Grace Lin	At least 1+ smear- positive, NALC-NaOH processed sediments Isolates from solid or broth media		
	TB strain typing	Isolates from solid or broth media		
	Identification of mycobacterial species by HPLC or AccuProbes	Isolates from solid or broth media		

EMB ethambutol INH isoniazid PAS para-aminosalicylate PZA pyrazinamide RIF rifampin SM streptomycin

STATE PUBLIC HEALTH LABORATORIES continued

Laboratory	Tests performed	Requirements	Cost	Contact information
<p>Florida Department of Health Bureau of Laboratories, Jacksonville Mycobacteriology Section</p>	<p>AFB smear microscopy and growth detection; species ID; nucleic acid amplification of <i>M. tuberculosis</i> complex in diagnostic respiratory specimens</p> <hr/> <p>Indirect susceptibility testing; first-line: INH, RIF, PZA, EMB, SM; second-line (automatically performed if resistant to 2 first-line drugs, or by request): kanamycin, clofazimine, capreomycin, rifabutin, ofloxacin, ethionamide</p> <hr/> <p>Molecular drug resistance assays for INH (<i>katG</i>, <i>inhA</i>), RIF (<i>rpoB</i>)</p>	<p>Clinical specimens Broth aliquots LJ/Middlebrook agar slants</p> <hr/> <p>Broth aliquots LJ/Middlebrook agar slants pure culture required.</p> <hr/> <p>Clinical specimens Broth aliquots LJ/Middlebrook agar slants</p>	<p>Full services available only to FL residents</p> <p>For non-FL inquiries, contact David Ashkin, MD, at 1-800-4TB-INFO 1-800-482-4636</p>	<p>Susan Dean Medical Laboratory Scientist IV susan_dean@doh.state.fl.us 904-791-1630 FAX: 904-791-1633</p> <p>1217 Pearl St Jacksonville, FL 32202</p> <p>For detailed information see: www.doh.state.fl.us/Lab/index.html</p>

EMB ethambutol INH isoniazid PAS para-aminosalicylate PZA pyrazinamide RIF rifampin SM streptomycin

STATE PUBLIC HEALTH LABORATORIES continued

Laboratory	Tests performed	Requirements	Cost	Contact information
<p>New York State Department of Health Wadsworth Center</p>	<p>Smear and primary culture; species ID using AccuProbe, deletion analysis (final ID within <i>M. tuberculosis</i> complex), DNA sequencing for NTM; real-time PCR for NYS FAST TRACK specimens (if suspicion for MDR-TB, molecular assays are performed on strongly smear-positive specimens or upon growth in broth medium), other specimens by request. Several susceptibility testing methods available.</p>	<p>Clinical specimens: can be sent as part of the NYS Fast Track program (eligibility: newly diagnosed, AFB smear-positive, or high likelihood of TB and/or suspicion for drug resistance) Broth samples (at least 3 ml preferred) LJ Slants</p>	<p>Service free for all New York residents</p>	<p>Vincent E. Escuyer, PhD Director, Laboratory of Clinical Mycobacteriology 518-474-2196 FAX: 518-408-2264 vee01@health.state.ny.us P.O. Box 509 Albany, NY 12201 Street address: 120 New Scotland Avenue Albany, NY 12208 Laboratory supervisor Phyllis Cunningham: 518-474-7043 www.wadsworth.org</p>
	<p>Indirect susceptibility testing; first-line drugs: INH, RIF, PZA, EMB, SM; second-line drugs susceptibility by agar proportion automatically upon detection of any first-line resistance: INH, RIF, EMB, SM, capreomycin, cycloserine, ethionamide, kanamycin, PAS, amikacin, ofloxacin, rifabutin, cycloserine</p>	<p>Broth samples (at least 3 ml preferred) LJ Slants</p>		
<p>TB strain typing</p>	<p>Molecular drug resistance assays for INH (<i>katG</i>), RIF (<i>rpoB</i>), PZA (<i>pnxA</i>), EMB (<i>embB</i>)</p>	<p>Clinical specimens Broth samples (at least 3 ml preferred) LJ Slants</p>		

STATE PUBLIC HEALTH LABORATORIES continued

Laboratory	Tests performed	Requirements	Cost	Contact information
<p>Texas Department of State Health Services Mycobacteriology/ Mycology Group</p>	<p>Smear and primary culture; species ID; HPLC for smear-positive specimens (MTB and common NTMs in smear positive specimens); nucleic acid amplification performed weekly on HPLC inconclusive smear positive specimens and upon request</p> <hr/> <p>HPLC identification for referred isolates. For <i>M. tuberculosis</i> complex: indirect susceptibility testing: First-line INH, RIF, EMB. Second-line drugs upon detection of resistance or upon request: SM, PZA, ofloxacin, capreomycin, kanamycin, ethionamide, rifabutin</p>	<p>Clinical specimens</p> <hr/> <p>LJ slants or Middlebrook agar slants Broth cultures</p>	<p>Free for clients of the Texas TB Elimination program; other patients and hospitals will be billed</p>	<p>Denise Dunbar Mycobacteriology/Mycology Group Manager 512-458-7342 FAX 512-458-7167 Denise.dunbar@dshs.state.tx.us</p> <p>For overnight shipping to physical address: Denise Dunbar, Mycobacteriology Mycology Laboratory Laboratory Services Section MC 1947 Texas Department of State Health Services 1100 West 49th Street Austin TX 78756-3199</p> <p>For USPS mailing address: Denise Dunbar Laboratory Services Section MC 1947 Texas Department of State Health Services PO Box 149347 Austin, TX 78714-9347</p> <p>www.dshs.state.tx.us/lab</p>

EMB ethambutol INH isoniazid PAS para-aminosalicylate PZA pyrazinamide RIF rifampin SM streptomycin

LOCAL PUBLIC HEALTH LABORATORIES

Laboratory	Tests performed	Requirements	Cost	Contact information
<p>Los Angeles County Public Health Laboratory</p>	<p>Smear and primary culture; species ID by AccuProbes, HPLC, and biochemicals. Amplified <i>M. tuberculosis</i> direct tests for first-time smear-positive patients and by request.</p> <p>Indirect susceptibility testing: INH, RIF, PZA, EMB, SM; second-line susceptibilities performed automatically: if RIF, INH/SM; or INH/EMB resistance detected; or by request of TB control. Second-line drugs: ciprofloxacin, ofloxacin, capreomycin, kanamycin, ethionamide, cycloserine, PAS, rifabutin, amikacin, azithromycin and clarithromycin</p> <p>TB strain typing</p> <p>Molecular beacons for RIF- and INH-resistance mutation</p> <p>Therapeutic drug concentrations are sent to a commercial laboratory after approval by TB Control</p>	<p>Clinical specimens LJ Slants</p> <p>LJ Slants MGIT broth (slants preferred)</p> <p>LJ Slants MGIT broth (slants preferred)</p> <p>Sputum sediment; at least 0.5 ml with (+) AFB smear (1+ or greater)</p> <p>Frozen serum</p>	<p>Free for LA County patients</p>	<p>Lorna Eusebio / Elena Ortiz / Hector Rivas Mycobacteriology Section Supervisors</p> <p>S.F. Sabet, PhD, Dipl (ABMM) Director, Public Health Laboratory</p> <p>562-658-1380 FAX: 562-401-5992</p> <p>12750 Erickson Avenue Downey, CA 90242</p> <p>www.lapublichealth.org/lab/labtb.htm www.lapublichealth.org/lab/tb-1.htm</p>

EMB ethambutol **INH** isoniazid **PAS** para-aminosalicylate **PZA** pyrazinamide **RIF** rifampin **SM** streptomycin

LOCAL PUBLIC HEALTH LABORATORIES continued

Laboratory	Tests performed	Requirements	Cost	Contact information
New York City Department of Health TB Laboratory	Smear and primary culture; species ID by HPLC; nucleic acid amplification for direct specimens for new smear-positive patients and by request First-line drug indirect susceptibility testing by MGIT: INH, RIF, PZA, EMB, SM ; second-line drug susceptibility testing by agar proportion automatically if drug resistance detected: ethionamide, ciprofloxacin, PAS, capreomycin, kanamycin, cycloserine and rifabutin	Clinical specimens LJ Slants Broth samples LJ Slants Broth samples	MTD and drug susceptibilities free for New York City and 5 boroughs residents	Jafar H. Razeq, PhD Interim Chief, Mycobacteriology Laboratory 212-447-5155 jrazeq@health.nyc.gov Main laboratory: 212-447-6745 FAX: 212-447-8283 455 1st Avenue New York, New York 10016
	Therapeutic drug monitoring is processed by the NYC DOH laboratory and performed at a commercial laboratory	Frozen serum		

NATIONAL PUBLIC HEALTH LABORATORY

Laboratory	Tests performed	Requirements	Cost	Contact information
Centers for Disease Control and Prevention	Indirect susceptibility testing: INH, RIF, PZA, EMB, SM, ofloxacin, capreomycin, amikacin, kanamycin, ethionamide, PAS, rifabutin Other services available upon consultation with laboratory director	LJ Slants preferred Will accept plates or broth	None	Beverly Metchock, DrPH, D(ABMM) 404-639-2455 All specimens must come from state public health department laboratories

EMB ethambutol **INH** isoniazid **PAS** para-aminosalicylate **PZA** pyrazinamide **RIF** rifampin **SM** streptomycin

COMMERCIAL LABORATORIES

Laboratory	Tests performed	Requirements	Cost	Contact information
Focus Diagnostics, Inc.	<p>Smear and primary culture isolation; ID by HPLC or nucleic acid probe of isolate; nucleic acid amplification of <i>M. tuberculosis</i> in raw specimens</p> <p>Direct and indirect susceptibility testing: INH, RIF, PZA, EMB, SM, rifabutin, ciprofloxacin, capreomycin, amikacin, ethionamide, PAS, cycloserine</p> <p>Therapeutic drug concentrations: ciprofloxacin, capreomycin, kanamycin, ethionamide, cycloserine, INH, RIF, PZA, SM, rifabutin, ofloxacin</p> <p>Rifampin mutation analysis</p> <p>AMPLICOR™ PCR on clinical specimens</p>	<p>Clinical specimens LJ Slants Broth samples Plates if safely packaged</p> <p>LJ Slants Broth samples Plates if safely packaged</p> <p>Frozen serum (See website for methodologies and sample requirements)</p> <p>Frozen smear-positive respiratory secretions OR pure culture growth</p> <p>Frozen clinical specimens (sputum/CSF/tissue, etc.)</p>	<p>Contracted with each institution – see catalog for base price</p>	<p>Scientific Director of Microbiology 800-445-0185 FAX: 714-484-1296 5785 Corporate Ave. Cypress, CA 90630 www.focusdx.com</p>

EMB ethambutol **INH** isoniazid **PAS** para-aminosalicylate **PZA** pyrazinamide **RIF** rifampin **SM** streptomycin

COMMERCIAL LABORATORIES continued

Laboratory	Tests performed	Requirements	Cost	Contact information
National Jewish Medical and Research Center	Smear and primary culture isolation; species ID; nucleic acid amplification of <i>M. tuberculosis</i> complex in raw specimens; direct and indirect susceptibility testing; several susceptibility testing methods available; TB and NTM genotyping (fingerprinting)	Clinical specimens LJ Slants Broth samples LJ Slants Broth samples Frozen serum	For cost, download requisition from website National Jewish will bill CO Medicaid, the patient's credit card or the facility from which the specimen came	Leonid Heifets MD, PhD, Director Mycobacteriology Reference Laboratory 303-398-1953 FAX: 303-398-1953 www.njc.org/research/clinical-labs Charles Peloquin, PharmD, Director Infectious Diseases Pharmacokinetics Laboratory (IDPL) 303-398-1427 main: 303-398-1422 FAX: 303-270-2124 peloquinlab@njc.org www.njc.org/research/clinical-labs click on the IDPL link to access information and to download a requisition for therapeutic drug concentrations Customer service: 303-398-1422 1400 Jackson St. Denver, CO 80206

EMB ethambutol INH isoniazid PAS para-aminosalicylate PZA pyrazinamide RIF rifampin SM streptomycin

The following websites give details for packaging, labeling, and shipping specimens and cultures:

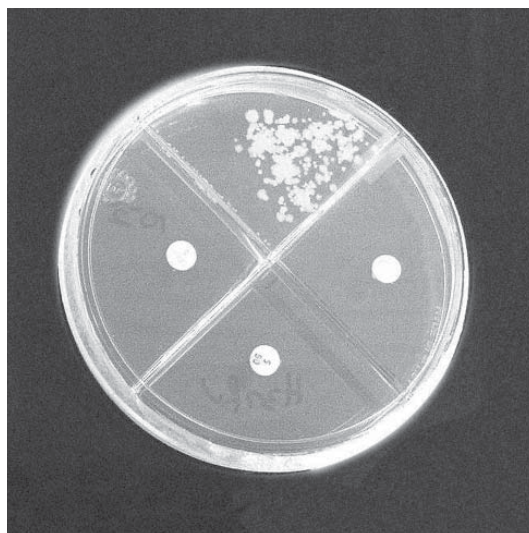
- www.cdc.gov/od/ohs/biosfty/shipdir.htm
- www.njc.org/pdf/2005%20shipping%20instructions.doc
- www.saftpak.com

Appendix 5: Direct Method

Note: Given the rapidity of broth methods, this test is very rarely performed in the United States.

- The clinical specimen (usually acid-fast bacilli [AFB] smear-positive sputum) is digested, decontaminated, and diluted. The processed specimen is plated onto agar containing critical concentrations of anti-tuberculosis drugs and a control containing no drugs.
- Results are interpretable if appropriate growth (at least 50 to 150 colonies, identified as *M. tuberculosis*) is found on control agar (no drug). The number of colonies that grow on each drug-containing agar plate (or quadrant) is reported as a percent of the colonies that grow on the control plate. The isolate is resistant if more than 1% of the number of colonies on control agar grow on a given drug agar plate.
- The direct method takes 3 to 5 days longer than indirect method (from the time of plating).
- The direct method is problematic when specimen contains nontuberculous mycobacteria either in pure or mixed culture. The colonies should be scrutinized for the possibility of growth with nontuberculous mycobacteria.
- Currently, only agar methods are well studied; broth methods should not be used.
- Results from the direct method are usually confirmed using the indirect method, especially if the isolate is found to be drug-resistant.
- The direct method may more accurately represent the patient's population of tuberculosis (TB) bacilli. Plates should be read each week for 3 weeks, giving time for slow-growing resistant colonies to be recognized.
- The direct method may be requested if drug-resistant TB is **strongly** suspected, molecular assays are not available, and the sputum is AFB smear-positive.

Figure 1. Quad plate – Sputum containing AFB smear-positive organisms is plated onto each of the 4 quadrants. The top quadrant contains no antibiotic and has allowed growth of *M. tuberculosis* colonies. The other 3 quadrants contain antibiotic-containing discs. The antibiotic has diffused into the agar and suppressed growth of the *M. tuberculosis* in the 3 quadrants. This is a pan-susceptible TB isolate.



Appendix 6: Critical Concentrations

of Antimycobacterial Agents to Test Against
M. tuberculosis by Broth or Agar Proportion Methods

Antimicrobial Agent	Typical MIC (µg/ml) for susceptible strains	Concentration in serum (µg/ml)	Medium and concentration (µg/ml)				
			7H10 low/high	BACTEC 460TB 12B low/high	MGIT 960 low/high	VersaTREK low/high	MB/BacT ALERT 3D
Primary Agents							
• INH	0.05-0.2	7	0.2/1	0.1/0.4	0.1/0.4	0.1/0.4	1
• RIF	0.5	10	1	2	1	1.0	1
• PZA	20	45	NR*	100	100	300	200
• EMB	1-5	2-5	5/10	2.5/7.5	5	5.0/8.0	2
Secondary Agents							
• SM	8	25-50	2/10	2/6	1/4	8.0	1
• Capreomycin	1-50	30	10	1.25			
• Kanamycin	5	14-29	5	5			
• Cycloserine	5-20	20-40	NR*	NR*			
• Ethionamide	0.6-2.5	2-20	5	1.25			
• PAS	1	7.5	2	4			
Alternative Agents							
• Rifabutin	0.06-8	0.2-0.5	0.5-1	0.5			
• Amikacin	1	16-38	4	1			
• Ofloxacin	0.5-2.5	3-11	2	2			

The critical concentration is the level of drug that inhibits a wild-type TB strain (a strain which has not been exposed to TB drugs), but does not appreciably suppress the growth of a resistant strain.

* NR: no recommendation.

Adapted, by permission, from Inderlied CB, Pfyffer BE. Antimicrobial Agents and Susceptibility Test Methods: Susceptibility Test Methods: Mycobacteria. In: Murray PR, Baron EJ, Jorgensen JH, Pfaller MA, Yolden RH, American Society for Microbiology. Manual for Clinical Microbiology. 8th edition. Washington, DC: ASM Press; 2003:1158.

Modified from Francis J. Curry National Tuberculosis Center and California Department of Public Health, 2004: *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians*, [234].

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Appendix 7: Molecular Method

- Molecular methods are based on detection of specific mutations associated with drug resistance.
- Ideal targets are genes whose mutations account for the vast majority of drug resistance; i.e., *rpoB* for rifampin (RIF) resistance and *pncA* for pyrazinamide (PZA) resistance. Several mutations that cause isoniazid (INH) resistance have been detected; however, 15 to 25% of INH-resistant isolates tested conventionally do not contain known mutations.
- In the laboratory, DNA is released from the mycobacterial cells—either from clinical specimens (if sufficient mycobacteria are present) or from growth on solid medium or in broth.
- Amplified products (amplicons) are detected by:

DNA sequencing

Line-probe assays that use PCR and reverse hybridization methods

Gel analysis (traditional PCR)

Enzyme-linked immunosorbent assay (ELISA)-based methods

Fluorescent hybridization with probes or molecular beacons

Other methods

- Over 96% of resistance to RIF is associated with known mutations within an 81bp region of the *rpoB* gene. Therefore, molecular testing of RIF resistance is highly reliable. Additionally, since RIF monoresistance is rare, detection of RIF resistance is usually diagnostic of MDR-TB.
- A few reference laboratories are routinely using molecular methods to rapidly diagnose drug resistance, and others are studying the practicality of these methods. The methods require specialized instrumentation and expertise, but may become more practical as more applications are found for molecular methods and their use becomes more widespread.
- Line-probe assays are a family of novel DNA strip-based tests that use PCR and reverse hybridization methods for the rapid detection of mutations associated with rifampin and/or rifampin and isoniazid drug resistance. These kits are not currently FDA-approved for use in the United States. Line-probe assays are designed to identify *M. tuberculosis* complex and simultaneously detect mutations associated with drug resistance.
- Advantages of molecular methods include rapid turnaround times and the benefit of knowing the exact location of the point mutation.
- Disadvantages of molecular assays include low sensitivity for some compounds, the potential for false-positive results due to amplicon contamination, and lack of standardization of the assays.

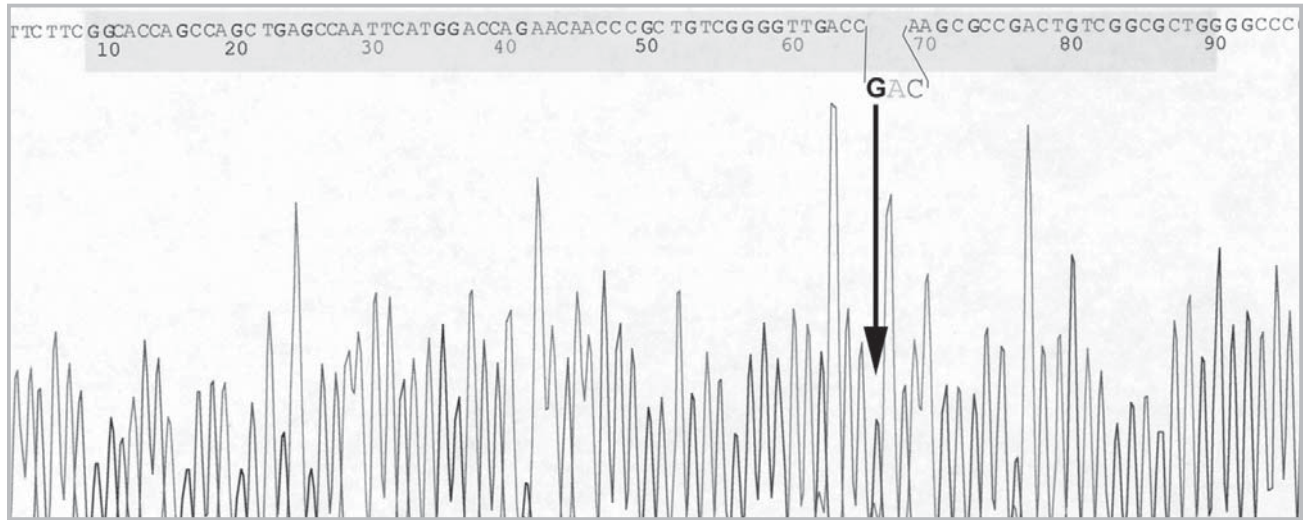


Figure 1. Mutations found in the 81bp of *M. tuberculosis* *rpoB* gene that are associated with rifampin resistance are located between codons 507 through 533 (highlighted in gray).

This sequence example shows a common mutation seen in rifampin-resistant isolates. Codon 526 (CAC), which encodes amino acid histidine in susceptible isolates, is replaced with amino acid aspartate (GAC, see arrow) in this resistant TB strain.

Appendix 8: Proportion Method

- Method of susceptibility testing using agar plates inoculated with either clinical specimen (direct method) or a suspension of mycobacterial growth (indirect method). See Appendix 9, “Indirect Method.”
- The proportion method is the gold standard method of drug susceptibility testing in the United States (Middlebrook 7H10 agar medium).
- Anti-tuberculosis drugs are added to the agar media in the form of stock solutions made from reference powders or drug-impregnated discs in order to achieve the critical concentration. Plates are either produced in-house or commercially purchased.
- The isolate is resistant if more than 1% of the number of colonies on the control agar plate.
- Pyrazinamide is difficult to study using solid medium due to the requirements of achieving an acidic environment; therefore, the BACTEC 460TB is considered the gold standard.

Figure 1. Quad plate – Inoculum of *M. tuberculosis* growth from broth has been plated into each of the 4 quadrants with the following results:

Control quadrant:

90 colonies

Isoniazid (INH) quad:

30 colonies

Rifampin (R) quad:

23 colonies

Streptomycin (S) quad:

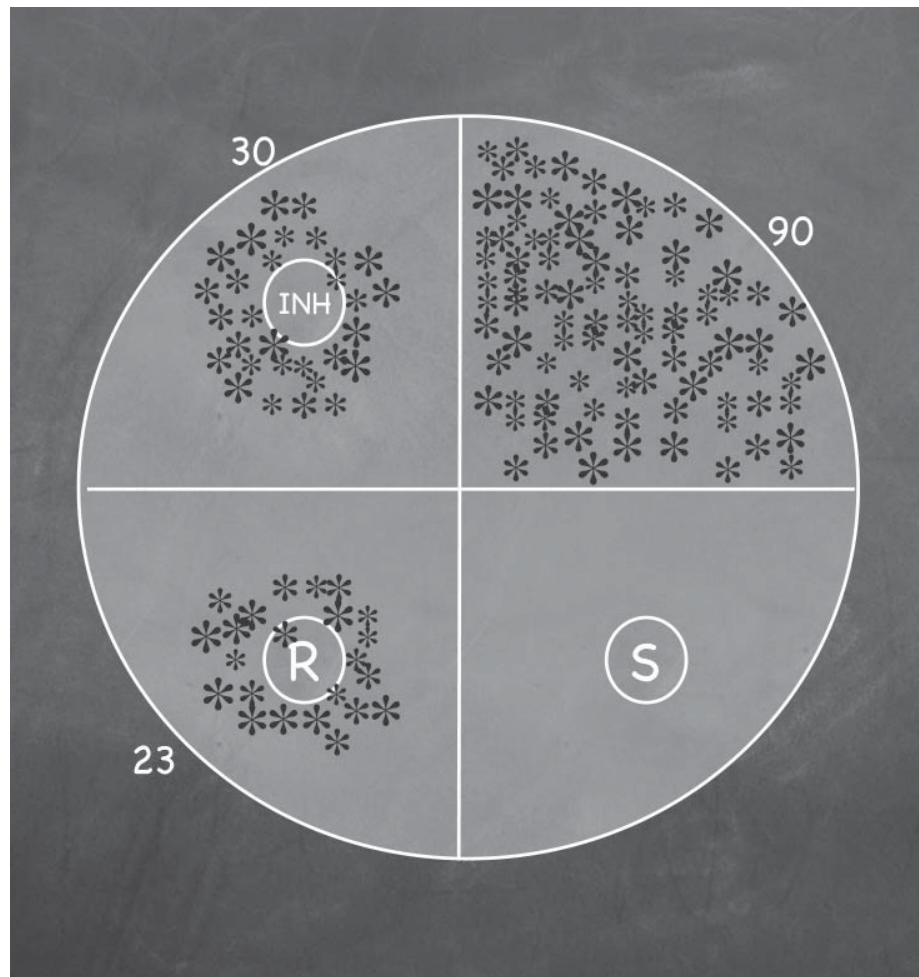
0 colonies

Isoniazid 30/90 = 33% resistant

Rifampin 23/90 = 25% resistant

Streptomycin 0/90 = susceptible

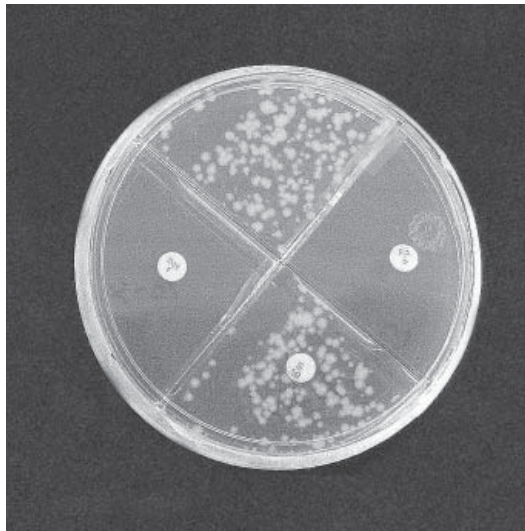
This is an MDR-TB isolate.



Appendix 9: Indirect Method

- The inoculum for indirect susceptibility testing is a suspension of mycobacteria that has already been cultivated on agar or an aliquot from the broth medium, rather than the clinical specimen itself, as for the direct testing.
- Results are interpretable if appropriate growth (at least 50-150 colonies, identified as *M. tuberculosis*) is found on control agar (no drug). The number of colonies that grow on each drug-containing agar plate (or quadrant) is reported as a percent of the colonies that grow on the control plate. The isolate is resistant if more than 1% of number of colonies on control agar grow on a given drug agar plate.
- Several colonies are picked from the solid medium in order to avoid a bias in testing.
- Chocolate plates should be used to ensure that a pure strain is being studied rather than a mixture of different organisms. This is especially important if the source of the inoculum is from a broth system rather than from colonies on a solid medium.
- Egg-based media, such as Löwenstein-Jensen, are not usually used in North America. The preferred agar is Middlebrook 7H10 agar media. If the drug-resistant strain does not grow sufficiently well on this media, 7H11 is sometimes successful (with adjusted critical concentrations of drugs).
- Broth media are used routinely for first-line TB drugs and occasionally for second-line TB drugs.

Figure 1. Quad plate – Inoculum of *M. tuberculosis* growth from broth has been plated into each of the 4 quadrants. The organism grows well in the control quadrant (top) and in the quadrant containing streptomycin (diffused into agar from the disc). The other 2 quadrants contain INH and PAS, and the organism has not grown in these quadrants. The isolate is resistant to streptomycin and susceptible to INH and PAS.



Appendix 10: BACTEC 460TB Method

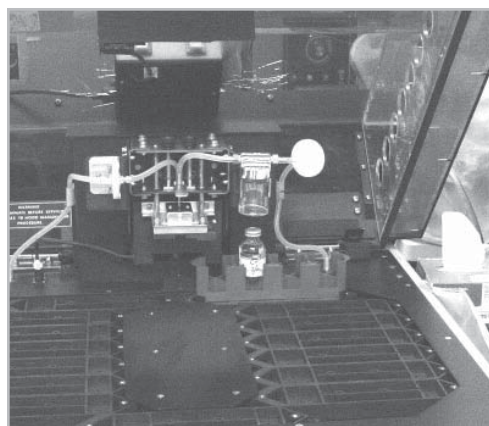
This method utilizes a broth system containing ^{14}C -labeled palmitic acid to grow the mycobacteria. If the organism grows in the broth, $^{14}\text{CO}_2$ is released into the headspace in the vial and the machine detects the $^{14}\text{CO}_2$, indicating growth.

- Drug-containing vials receive 100-fold more inoculum than the drug-free control vials for each strain (corresponding to the 1% resistance rate considered to be clinically significant).
- The method is faster than the proportion method using solid medium, but does not provide an estimate of percentage of resistant bacilli.
- Kits are available for testing the SIRE drugs (streptomycin, isoniazid, rifampin, and ethambutol), and pyrazinamide.
- Second-line drugs can be tested by adding stock solutions from reference powders of individual anti-tuberculosis drugs to the broth vial.
- Resistant strains should be confirmed by the agar proportion method or molecular assays.
- The results are interpreted based on the change in “growth index” in the drug-containing vials compared to the control vial (without drug). If the daily change in the control growth index exceeds that of the drug-containing vial, the isolate is susceptible.

Figure 1. BACTEC bottles containing Middlebrook 7H12 media prior to inoculation.



Figure 2. BACTEC machine.



Appendix 11: Newer Broth Methods

- Newer broth methods are replacing the radiometric (^{14}C) system (in order to avoid use and disposal of radioactive materials) and, in addition, are fully automated.
- These systems can detect and monitor growth for culture and can also be used to determine susceptibility to isoniazid, rifampin, ethambutol, pyrazinamide, and streptomycin.
- *M. tuberculosis* is grown in vials/tubes of broth containing either the critical concentration of an anti-tuberculosis drug or no drug (control). The growth of the bacteria in the drug-containing bottles is compared to the growth in the control vial/tube.
- The VersaTREK system detects pressure changes due to gas production or consumption due to mycobacterial growth.
- The BACTEC MGIT 960 system (mycobacterial growth indicator tube) uses a fluorescence quenching-based oxygen sensor to detect mycobacterial growth. If mycobacteria are growing in the system, they consume oxygen and fluorescence is increased and detected by the system.
- The MB/BacT ALERT 3D system colorimetrically detects CO_2 production in order to indicate mycobacterial growth.

Figure 1. BACTEC MGIT (mycobacterial growth indicator tube) system – MGIT machine; upper right inset, MGIT tubes; lower right inset, antibiotics solutions for performing susceptibility testing in MGIT.



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Appendix 12: Therapeutic Drug Monitoring

Therapeutic drug monitoring is routinely used for several circumstances:

- Aminoglycoside/capreomycin serum concentrations in patients with renal impairment
- Cycloserine concentrations in order to minimize risk of CNS toxicity and to safely use optimal dose
- Ethambutol concentrations in patients with significant renal impairment
- Known or suspected malabsorption

Many drug-resistant TB experts routinely monitor certain TB drug concentrations in anticipation of toxicity and to escalate a drug dose when possible.

Most hospital laboratories perform amikacin concentrations. Only a few laboratories perform drug concentrations for other TB drugs (National Jewish Medical Center and Focus Labs performing the most).

Table 1 details the time for blood collection after an injectable drug dose.

Drug name	Blood draw times after completion of IV infusion	Hours after IM dose to “peak”
Amikacin Capreomycin Kanamycin* Streptomycin	1.5 – 2 hours and 6 hours	2 hours

* Kanamycin is determined using a bioassay. **All** other antibiotics must be stopped at least 24 hours prior to sample collection for kanamycin.

To calculate a true peak after an intravenous dose, a level is drawn 90 to 120 minutes and again 6 hours after the infusion is complete. It is important to allow enough time for the dose to be completely distributed before drawing the first level. The exact times of the dose infusion and blood draws must be recorded. The pharmacist can then extrapolate or calculate a peak using a linear regression feature on a computer program or semi-logarithmic graph paper. A trough before the next dose is sometimes necessary for patients with renal failure.

Table 2 details the time for blood collection after an oral drug dose.

Drug name	Hours after oral dose to “peak”	Time after dose for additional concentration if desired *
Azithromycin	2-3 hours	
Ciprofloxacin	2 hours	
Clarithromycin	2-3 hours	
Clofazimine	2-3 hours	
Cycloserine	2-3 hours	6-7 hours
Ethambutol	2-3 hours	6-7 hours
Ethionamide	2 hours	
Isoniazid	1-2 hours	6 hours
Levofloxacin	2 hours	6 hours
Linezolid	2 hours	6 hours
Moxifloxacin	2 hours	
Ofloxacin	2 hours	6 hours
PAS	6 hours	
Pyrazinamide	2 hours	6 hours
Rifabutin	3-4 hours	7 hours
Rifampin	2 hours	6 hours

*An additional concentration may be obtained to evaluate for delayed absorption or to calculate a half-life in order to more accurately prescribe a drug dose and interval.

Collecting and Processing Samples for Therapeutic Drug Monitoring

One milliliter of serum (about 2 ml of blood) is required per test. It is advisable to provide some excess serum in case there are technical problems.

- The patient should come to clinic with his/her medications.
- No doses of the medication to be tested should have been taken/given since the previously scheduled doses (12 to 24 hours prior).
- Observe the taking or injection of the medications and record the exact time and date.
- Collect the blood by direct venipuncture (timing as described by Tables 1 and 2) and record the exact time of the blood collection.
 - For streptomycin, note if the patient is also receiving ampicillin.
 - Kanamycin is measured using a bioassay. Stop all other antibiotics for at least 24 hours prior to sampling.
- After the blood clots, centrifuge the samples, harvest the serum into labeled polypropylene (or polyethylene) tubes (allow room for expansion of sample inside tube), label, and freeze (-70°C is preferable, if available).
- Label the tubes with the patient's name, date and time of collection, and the drug(s) to be assayed.
- The samples can be stored frozen until ready for shipping.
- Place the samples in a ziplock plastic bag and pack upright in a Styrofoam box (about 10 cubic inches in size) with 3 pounds of dry ice. Fill the empty air space with paper or Styrofoam "peanuts."
- Complete the requisition and provide billing information. Place the requisition and billing page in a plastic bag and tape to the outside of the lid. The foam box is placed inside a cardboard box to prevent damage.
- Ship samples Monday through Wednesday by an overnight delivery service that accepts dry ice packages.

Information excerpted from National Jewish Medical Center website (www.njc.org) and literature.

Appendix 13: Multicultural Resources

General Cultural Information Sites

Cross Cultural Health Care Program

www.xculture.org/

Cultural Clues

<http://depts.washington.edu/pfes/cultureclues.html>

EthnoMed

<http://ethnomed.org/>

National Center for Cultural Competence (NCCC)

www11.georgetown.edu/research/gucchd/nccc/index.html

**University of Michigan Program for Multicultural Health:
Cultural Competency Division**

www.med.umich.edu/multicultural/ccp/

Translated Patient Education TB Resources

Canadian Lung Association

www.lung.ca/tb/notenglish/

EthnoMed

http://ethnomed.org/ethnomed/patient_ed/index.html#tuberculosis

Minnesota Department of Health

www.health.state.mn.us/divs/idepc/diseases/tb/brochures.html

National Prevention Information Network (NPIN) Educational Materials Database

www.cdcnpin.org/scripts/search/matSearch.aspx

New South Wales Health

www.mhcs.health.nsw.gov.au

TB Education and Training Resources

www.findtbresources.org/scripts/index.cfm

General Interpreter Resources

CyraCom (customer service number: 800-481-3293)

www.cyacom.net

Appendix 14: Frequently Asked Questions (FAQs)

General

1. What is the optimal drug regimen for multidrug-resistant tuberculosis (MDR-TB)?

See Chapter 3, “Treatment.”

The optimal drug regimen depends on the susceptibility pattern of the patient’s tuberculosis (TB) isolate, the patient’s previous TB treatment regimen, underlying health conditions, and other medications the patient currently takes. The patient should generally be initially treated with 4 to 6 drugs to which the isolate is susceptible. Depending on the susceptibility pattern of the isolate, the regimen should include all available first-line drugs, a fluoroquinolone, an aminoglycoside, and appropriate second-line oral drugs.

In general, avoid:

- Drugs the patient has taken previously (associated with a failing regimen)
- Drugs that cause that individual undue toxicity
- Drugs that cause unnecessary drug interactions

2. How many drugs are necessary?

See Chapter 3, “Treatment.”

The patient needs to complete therapy with at least 3 drugs to which the isolate is susceptible. In practice, this requires that the patient be initially treated with 4 to 6 drugs that he/she has not previously received. Using this strategy, the injectable drugs can be discontinued after a number of months if appropriate and other drugs that were very poorly tolerated can be trimmed away.

3. How long post-culture conversion should a patient be treated—18 months or 24 months?

See Chapter 3, “Treatment.”

There are no randomized controlled studies that have determined optimal length of MDR-TB treatment. The American Thoracic Society (ATS) recommends 18 to 24 months of treatment for MDR-TB. Many experts prefer to choose the duration of therapy based on the time from culture conversion (sputa are consistently culture-negative). In general, the longer regimens are used for patients with more extensive disease and more extensive drug resistance pattern. Shorter regimens might be used for patients with more localized disease who responded promptly to therapy and whose resistance pattern allowed use of more bactericidal drugs in the regimen.

4. The patient’s isolate is resistant to all first-line drugs and most second-line drugs. What options exist for treatment?

See Chapter 3, “Treatment.”

Use as many/all drugs to which the organism is susceptible. This may include “third-line agents” such as linezolid, gamma-interferon, and β -lactam drugs (imipenem, amoxicillin/clavulanate). Consider use of higher doses of individual drugs (as tolerated by the patient and using therapeutic drug monitoring as appropriate). Consider prolonged use of an injectable drug if tolerated by the patient. Consider surgical intervention if the patient is an appropriate candidate.

5. Can a patient take split doses by self-administered therapy (SAT)?

See Chapter 8, “Case Management.”

Some drugs (cycloserine, ethionamide, and para-aminosalicylate [PAS] in particular) may not be tolerated in once-daily doses and must be given more than once a day (split doses). Ideally, all drug-resistant TB treatment will be given fully by directly observed therapy (DOT), even split doses. Patients who have difficulty taking their medications as once-daily doses (amenable to DOT) sometimes are well served by being hospitalized during the initial phase of treatment until they tolerate the regimen well enough at home.

6. Can weekend doses be given by self-administered therapy (SAT)?

See Chapter 8, “Case Management.”

Ideally, all drug-resistant TB treatment will be given fully by DOT. Again, hospitalization in the early phase of treatment is sometimes necessary. After documented clinical and microbiologic improvement, some jurisdictions will treat patients with 5-days-per-week therapy by DOT or give SAT on the weekends when local resources do not permit monitored weekend administration.

Use of Specific Drugs

FLUOROQUINOLONES

1. Can I use fluoroquinolones in children? For TB disease? For contacts to MDR-TB?

See Chapter 5, “Special Situations – Pediatrics.”

Fluoroquinolones are among the most important agents in MDR-TB treatment when the isolate is susceptible. Most experts feel that fluoroquinolones are indicated in children exposed to or infected with MDR-TB resistant to other first-line drugs.

Fluoroquinolones have been avoided in children because puppy models have suffered irreversible arthropathy. Irreversible joint destruction has not been seen in children who have received fluoroquinolones. Ciprofloxacin has been licensed for use in older children for treatment of complicated urinary tract infection. Levofloxacin and gatifloxacin have been studied for use in children. However, few children have received the very long courses of fluoroquinolones required for TB treatment. If a fluoroquinolone drug is very important for the treatment of an individual child, it can be employed after discussing risks and benefits with the parents and in consultation with a pediatric TB expert. The parents have to be aware of the potential risks and report to the provider and public health workers any signs or symptoms of joint problems (decreased mobility, pain, decreased range of motion, joint swelling, etc.). Additionally, all providers involved in the case should be actively screening for these processes. Finally, many experts avoid these drugs in children too young to show signs and symptoms of musculoskeletal complaints (children too young to sit up, crawl, etc.).

2. What is the optimal dose of levofloxacin for TB disease? For latent tuberculosis infection (LTBI)?

See Chapter 3, “Treatment.”

A common strategy for levofloxacin is to initiate therapy at 500 mg daily. If tolerated, the dose can be elevated to 750 mg or even 1000 mg daily (sometimes in divided doses). If the patient weighs more than 100 pounds, a dose of at least 750 mg should be attempted. Fluoroquinolones should not be dosed in close proximity to milk-based products, antacids, or other divalent cations. Currently studied doses of the newer fluoroquinolones (gatifloxacin and moxifloxacin) are limited. At this time, doses should be limited to 400 mg daily to avoid the possibility of more drug-related toxicities (unless serum concentrations are monitored). In the case of patients who are too sick to take enteral doses, the fluoroquinolones are available in IV forms.

AMINOGLYCOSIDES

1. What is the dose when one changes to 2- or 3-times weekly?

See Chapter 4, “Medication Fact Sheets.”

When aminoglycoside drugs are administered 2- or 3-times-weekly, the drugs are usually administered at the same dose as daily therapy for that individual (customized based on age, renal function, and sometimes drug concentrations). Some experts use higher doses and monitor concentrations closely.

2. What is the target blood concentration with intermittent dosing?

See Chapter 4, “Medication Fact Sheets.”

The target blood concentration depends on dose and planned duration of use.

3. How long do I need to use an aminoglycoside?

See Chapter 3, “Treatment.”

Expert opinions vary, as there are no firm data to support a specific length of treatment. At a minimum, use the aminoglycosides for at least 6 months (longer if extensive disease, delayed culture conversion, or limited alternative medications). Some experts continue the aminoglycoside or capreomycin as long as absolutely possible (barring limiting side effects) and use doses to achieve somewhat lower peak concentrations to avoid toxicity.

4. What aminoglycoside is most frequently used?

See Chapter 4, “Medication Fact Sheets.”

The injectable drug chosen depends on several factors: susceptibility of the isolate, cost, route of administration, availability of therapeutic drug monitoring tests, and side effects. Many drug-resistant isolates are resistant to streptomycin; amikacin and kanamycin have cross-reactivity and therefore nearly identical resistance. Kanamycin and streptomycin are least expensive; amikacin concentrations are most readily available; streptomycin is less painful if used intramuscularly, but is associated with more vestibular toxicity.

5. A patient on aminoglycoside complains of slight tinnitus. How is this side effect monitored?

See Chapter 7, “Adverse Reactions.”

Patients receiving injectable agents should be monitored with hearing tests as well as vestibular monitoring. Patients who suffer tinnitus should be evaluated for the possibility that something other than the injectable agent is causing the problem. Sometimes patients who have isolated tinnitus can be monitored prospectively without change. If change is required, changing to intermittent therapy or lowering the dose of the injectable drug (while remaining in the appropriate therapeutic range) can sometimes lessen the symptoms. If the patient suffers unsteadiness or other vestibular signs or symptoms, the drug should be stopped. Vestibular toxicity is usually irreversible and is generally a contraindication to further use of these drugs.

Use of BCG

1. Is bacille Calmette-Guérin (BCG) indicated for a newborn exposed to a mother with a highly resistant strain of MDR-TB?

See Chapter 5, “Special Situations – Pregnancy.”

BCG should be administered to infants and young children who cannot be separated from drug-resistant TB cases and for whom no practical prophylactic regimen is available. There are usually a number of other options before considering BCG use.

Side Effects

1. What do I do when a patient is nauseated but intolerant to compazine?

See Chapter 7, “Adverse Reactions.”

Other drug options include phenergen, metoclopramide, lorazepam, and ondansetron. Other options include dosing the drug with a snack, giving at a time of day away from other drugs, splitting the dose, etc.

2. A patient on cycloserine had a high depression score this week. What does this mean?

See Chapter 7, “Adverse Reactions.”

Extreme care should be exercised with patients receiving cycloserine and suffering mental health symptoms. Monitoring for suicidal ideation is crucial, and the patient should be evaluated for the need for an antidepressant medication. A cycloserine therapeutic drug concentration should be collected and the dose held until toxicity can be ruled out as a cause.

3. What should be done for a teenage patient on fluoroquinolone with bilateral wrist pain?

See Chapter 7, “Adverse Reactions.”

For achiness without significant tendon inflammation, therapy can be continued with use of analgesics and rest. If significant tendon inflammation is present, the fluoroquinolone should be held and measures to reduce inflammation should be undertaken. The patient should not undertake unusual exertion to the area.

Infection Control

1. Can I return a case patient to the home setting if other household members (non-immunocompromised) are tuberculin skin test (TST)-negative after several months of exposure to case?

See Chapter 8, “Case Management.”

MDR-TB patients should be considered potentially infectious until they have 3 consecutive culture-negative sputum specimens. Decisions about management at home, and return to school and work, should be undertaken with local health officers and drug-resistant TB experts after considering many factors regarding the patient’s disease, treatment, and the household situation.

2. A patient no longer has a productive cough. Are monthly induced sputa necessary?

See Chapter 6, “Monitoring Patients.”

National guidelines suggest monthly sputum monitoring. Some experts collect 2 monthly sputa 8 to 24 hours apart to lessen the likelihood of false-negative results. If necessary, sputum induction is indicated both during and after treatment. MDR-TB patients have a higher risk of relapse and delayed sputum sterilization. Persistently positive cultures may be an early indicator for increasing drug resistance and may assist in determining length of treatment.

Payment

See Chapter 8, “Case Management.”

1. How can I pay for expensive drugs when a patient is uninsured?

Social workers and financial counselors should work with the family to investigate any third-party payer possible. If the patient is uninsurable, patient assistance programs (PAPs) sponsored by pharmaceutical companies can be explored. Some states and large jurisdictions have programs available to pay for drugs for all TB patients.

2. How can I pay for hospitalization when a patient is uninsured?

Social workers and financial counselors should work with the family to investigate any third-party payer possible. Some states and large jurisdictions have programs available to pay for TB care or have specific TB inpatient facilities. Barring these options, the local “safety net” hospital that is funded to provide indigent care will have to admit the patient.

3. Is an IV injectable agent more costly than IM preparation?

IV therapy is more expensive because, in addition to drug costs, maintenance of the IV requires a home health agency, etc.

Press Release

1. We are doing a highly visible contact investigation at a school. Do we need a press release?

A press release can be very helpful to update the media on results of testing and to educate the public. Some jurisdictions manage the contact investigation successfully without involving the media.

2. Should we reveal in the press release that exposure was to an MDR strain? (If we did, it might create public angst and increase our workload.)

If the media is involved, it is better to be upfront about the nature of the isolate, but also state that medications are available for LTBI treatment. If this is not disclosed upfront, criticism is likely to follow.

Laboratory

1. When do I draw serum drug concentrations?

See Chapter 6, “Monitoring Patients,” and Appendix 12, “Therapeutic Drug Monitoring.”

Draw cycloserine concentrations before increasing the dose from the initial regimen; draw aminoglycoside concentrations if appropriate after approximately 2 weeks of therapy.

2. To which laboratory do I send samples for serum drug concentrations?

See Appendix 4, “Laboratory Resources.”

In many cases, the patient’s insurance will mandate which lab will perform the therapeutic drug concentrations. Most large hospital labs will perform amikacin concentrations, and only a few reference labs perform many of the other TB drug concentrations.

3. Are serum drug concentrations (therapeutic drug monitoring [TDM]) useful? Necessary?

See Chapter 6, “Monitoring Patients.”

Despite the fact that there are few data proving improved outcomes with TDM, many drug-resistant TB experts monitor drug concentrations routinely. In several circumstances, therapeutic drug monitoring is common: aminoglycoside concentrations in patients who have known renal dysfunction; cycloserine concentrations can help the provider predict and minimize central nervous system (CNS) adverse reactions and prevent seizure activity; and ethambutol (EMB) concentrations may be useful for patients with reduced renal function. Other therapeutic drug monitoring is used depending on the patient’s other health issues, concomitant medications, number of drugs in the regimen, preference of the provider, etc.

4. How do I interpret discordant susceptibility results?

See Chapter 2, “Diagnosis.”

Discuss results with the laboratorian, repeat the susceptibilities on a second sample, and send a sample to a reference laboratory for confirmation.

5. How do I clarify to my lab that we need a cycloserine blood serum concentration, not a cyclosporine?

Talk to the lab in advance, type or write the request very clearly, and if necessary, write in parentheses: (NOT CYCLOSPORINE). Note: Very few laboratories in the country perform cycloserine concentrations, while most large hospital labs perform cyclosporine concentrations. This may help you discuss this “send-out” test with your lab.

6. Molecular methods: How quick and accurate are the results?

As an example, the “molecular beacon” assay, performed by the California Department of Public Health Microbial Disease Laboratory, uses real-time polymerase chain reaction (real-time PCR) technology with molecular probes for rapid detection of mutations associated with isoniazid (INH) or rifampin (RIF) resistance. Acceptable specimen types are smear-positive (at least 1+) concentrated sediments or growth from solid or broth media. The average turnaround time for results is 1 to 3 days of specimen receipt. The sensitivity of the test is 83% for INH and 97% for RIF. Discuss the results with the laboratory and a drug-resistant TB expert before implementing management plans based on the results.

7. How do I ship/package specimens to send to National Jewish since it’s out of state?

See Appendix 4, “Laboratory Resources,” www.njc.org and www.saftpak.com.

8. What type of courier do I use to send specimens out of state?

See Appendix 4, “Laboratory Resources,” www.njc.org/research/clinical-labs and www.saftpak.com.

9. When sending specimens to the State of California Microbial Diseases Laboratory (MDL) for isolate identification, are susceptibilities automatically performed or is an additional request necessary?

Specific requests are necessary. Susceptibility testing is not automatically performed. Of note: at the time of printing, MDL is performing first-line and second-line drug susceptibility testing by MGIT only, and the second-line drug panel includes levofloxacin, amikacin, capreomycin, and ethionamide. Check with the laboratory (contact information in Appendix 4, “Laboratory Resources”) for current testing capabilities.

When dealing with any laboratory performing TB culture, identification, and susceptibilities, you should determine whether susceptibilities will automatically be performed and under which circumstances second-line susceptibilities will be performed. Many commercial laboratories have contracts defining these details for individual clients and third-party payers. Lengthy delays will occur if these details are not defined early on. Sometimes the physician who ordered the initial culture will need to order first- and second-line susceptibility tests.

10. Why does pyrazinamide (PZA) susceptibility testing take longer? Is there a quicker method?

PZA susceptibilities are technically difficult in agar because of the low pH required. Many laboratories do not perform them at all. Testing PZA with the BACTEC TB 460 system is considered the gold standard. However, many laboratories have replaced BACTEC TB 460 with the BACTEC MGIT 960 non-radiometric system. The average turnaround time for PZA testing with the BACTEC MGIT 960 system is 7 to 10 days.

Treatment and Evaluation of Contacts

1. How do I treat contacts?

See Chapter 10, “Managing Contacts.”

Each contact is managed on an individual basis. Determinants include extent and intimacy of contact with the source case, susceptibility pattern of the source case isolate, evidence of transmission from the source case, prior TST results, risks for progression to TB, etc. If treatment of drug-resistant LTBI is desired, the regimen is generally based on the susceptibility pattern of the source case.

2. For contacts to an MDR case with positive TST and who refuse treatment, how often should a symptom review or chest radiograph be done?

See Chapter 10, “Managing Contacts.”

Untreated contacts should be monitored every 3 to 6 months for at least 2 years.

3. Can a single drug be used to treat MDR-TB infection?

See Chapter 10, “Managing Contacts.”

Lower-risk contacts are sometimes treated with fluoroquinolone monotherapy based on *in vitro* drug activity data. No controlled data are available regarding treatment of drug-resistant TB contacts, and current national guidelines recommend 2-drug MDR-LTBI treatment.

4. When should LTBI treatment with levofloxacin/moxifloxacin be discontinued for ambiguous side effects?

See Chapter 7, “Adverse Reactions.”

Every effort should be made to safely continue the patient on therapy, including use of rest and analgesics. Significant inflammation of the tendon should be treated with at least temporary cessation of the fluoroquinolone.

5. Can moxifloxacin be used to treat MDR-LTBI?

While programs have less experience with moxifloxacin use, it has excellent *in vitro* activity against many drug-resistant TB strains and has been used in some patients with good success.

Appendix 15: Case Examples

CASE EXAMPLE 1

Robert is a 53-year-old Vietnam veteran who is a musician and living in a single-room occupancy hotel in a tough part of town.

11/18/05 Robert is admitted to his local Veterans Administration (VA) hospital with cough and hemoptysis. A chest radiograph shows extensive infiltrates in the right upper lobe, left upper and lower lobes, and cavities in both apices. Acid-fast bacilli (AFB) sputum smears are 4+ positive, and he is started on a regimen of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB). He slowly begins to clinically improve. He is discharged after 2 weeks to ongoing care through the local health department.

This is an older, American-born man with no previous history of tuberculosis (TB) treatment. A 4-drug regimen such as the one prescribed for him would be a standard treatment.

1/15/06 Because the VA sends all specimens to a central laboratory for AFB cultures, there was a significant delay before the health department received the results of drug susceptibility testing. On 1/15/06, the report arrives and shows that the isolate is resistant to INH, streptomycin (SM), and EMB, and susceptible to RIF and PZA. Two new drugs, capreomycin and moxifloxacin are begun, and INH and EMB are stopped. Additional sputum is collected and sent for smear, culture, and repeat susceptibility testing. The sputum AFB smear is still positive.

Robert had been effectively on RIF and PZA alone for about 2 months. PZA is not considered a good companion drug for RIF, as it does not prevent the emergence of acquired drug resistance. At this point, there was a reasonable chance that resistance to RIF and/or PZA may have developed, especially in a patient with a large bacillary load (cavitary disease and strongly smear positive). Two drugs are not adequate for multidrug-resistant (MDR) TB treatment, and at least 1 additional drug should have been added at this time. Appropriately, repeat susceptibility testing was ordered.

3/4/06 Repeat susceptibility testing show that the isolate is still PZA-susceptible, but that it has now acquired RIF resistance. Robert now has MDR-TB. Second-line susceptibility testing shows sensitivity to ethionamide, capreomycin, and levofloxacin, but resistance to kanamycin. Sputum smears convert to negative by early March, and Robert clinically improves. RIF is discontinued and capreomycin, PZA, and moxifloxacin are continued.

A 3-drug regimen is not optimal for MDR-TB; 4 to 6 drugs are recommended. Because of the slow growth characteristics of M. tuberculosis, there is a significant delay between obtaining a specimen and finding out the results of the culture. The treating providers believed that the sputum cultures were likely to be negative given the smear-negative results.

CASE EXAMPLE 1 continued

6/8/06 Of 6 sputum specimens obtained between 3/4/06 and 6/8/06, 2 are culture-positive. Second-line susceptibility testing done on 1 of these specimens now shows resistance to levofloxacin. Robert is now diagnosed with extremely drug-resistant (XDR) TB.

The regimen should have been strengthened in March, pending the results of cultures as well as smears. Robert was still culture-positive, and 3 drugs were not enough to prevent additional resistance from developing.

6/18/06 A full evaluation is now repeated with 3 sputum examinations and a chest radiograph. The chest radiograph is improved, but still shows a residual left apical cavity and right apical fibrosis. A follow-up chest CT confirms that the principle site of disease activity is the left apex. Surgery is discussed with Robert, but he adamantly refuses to consider it. A new regimen of linezolid, amikacin, ethionamide, cycloserine, and para-aminosalicylate (PAS) is now begun.

This is a classic situation in which resectional surgery should be considered. Robert has XDR-TB and a residual cavity, which makes the likelihood of treatment failure or relapse much higher. He has predominantly unilateral disease, which increases the potential benefit of surgery. Regardless, he needs the strongest regimen still available to him, and the use of linezolid, which has good in vitro activity against M. tuberculosis but substantial potential for toxicity, is warranted. Ethionamide, cycloserine, and PAS have overlapping gastrointestinal (GI) toxicities, but there are few other options for this patient.

12/18/06 Robert is unable to tolerate cycloserine, complaining of severe depression and mood swings, even at relatively low serum concentrations, and it is stopped. The 2 sputa collected each month are now smear- and culture-negative since mid-July 2006. The serum creatinine increases from 1.4 to 1.8 mg/dli. His amikacin, which had been decreased to 3 times a week in October, is now decreased to twice weekly.

Cycloserine has significant central nervous system (CNS) effects and can cause depression and even delusional states. It has been associated with suicide. The drug was appropriately stopped. Because of the Robert's extensive resistance, the goal is to continue the injectable agent for 12 months post-culture, if at all possible, so decreasing the frequency to twice weekly is reasonable..

7/18/07 Robert is now 12 months post-culture conversion and is doing well. The amikacin is stopped and a further 12 months of the remaining oral drugs are planned, to complete 24 months total treatment post culture conversion.

Lessons Learned

- If there is a possibility that MDR-TB has developed, a patient should have a minimum regimen of 3 new drugs, planning on a total of between 4 to 6 drugs to which the isolate is likely to be susceptible. PZA is a poor “companion” drug to prevent the emergence of acquired drug resistance in a functional 2-drug regimen.
- Surgery should be considered if there is extensive resistance, residual cavities, and predominantly unilateral disease. In the California experience, only about half of XDR-TB patients have been cured. Surgery may improve those odds if the patient is a good candidate.
- Once the fluoroquinolones are lost because of resistance, therapy becomes more difficult. Linezolid, despite its cost and potential toxicity, becomes an important mainstay of treatment. Patients must be carefully monitored for bone marrow suppression and peripheral neuropathy.
- Cycloserine has been associated with suicide and severe depression as well as delusional states. Monitoring a patient’s mental status is crucial. Vitamin B6 (pyridoxine) is used to prevent seizures, but it does not appear to protect against mood disturbances.
- In the treatment of XDR-TB, if an isolate shows susceptibility to any injectable agent, it should be included in the regimen and continued for 12 months post-culture conversion if at all possible.

CASE EXAMPLE 2

Olga, a 41-year-old female from the Ukraine, is experiencing her second episode of TB.

1986	<p>Olga was first diagnosed with TB in the Ukraine and treated with INH, RIF, and EMB for 6 months and SM daily for 6 to 8 months. Olga was hospitalized during her treatment and claims she was very adherent. After her discharge, she took INH for 2 additional years for “prophylaxis.” Drug susceptibilities of this episode are unknown.</p> <p><i>What else would you like to know about this episode?</i></p> <ul style="list-style-type: none">• <i>Does she have any written documentation or copies of radiographs?</i>• <i>Was she hospitalized the entire time (i.e., all doses observed)?</i>• <i>Were there any interruptions in any of the medications due to drug supply or tolerance?</i>• <i>How extensive was her disease and what kind of clinical and radiographic improvement did she have?</i>• <i>Why did she receive 2 additional years of INH? Had her radiograph not improved; did she still have significant symptoms?</i>
1994	<p>Olga arrives in the U.S.</p>
3/01	<p>Olga develops a cough, intermittent fever/night sweats, scant blood-tinged yellow sputum, and shortness of breath.</p>
4/14/01	<p>Olga presents to the TB clinic with those symptoms and opacification of the left lung with an air-fluid level. On initial exam, she is a thin, well-appearing female with decreased breath sounds at the left base and bronchial breath sounds at the left apex.</p>
4/17/01	<p>Treatment is started with INH, RIF, PZA, EMB, levofloxacin, and capreomycin. Four out of four sputa return culture-positive for <i>M. tuberculosis</i>, with 2 out of 4 smear-positive.</p> <p><i>Because she does not have documentation of completely observed therapy and a previously susceptible isolate, Olga is treated with an empiric “expanded” regimen including 3 drugs that she had not previously received.</i></p>
5/19/01	<p>BACTEC susceptibilities show resistance to all first-line agents, including SM.</p>
6/16/01	<p>Conventional solid agar susceptibilities show borderline resistance to EMB and SM, and full resistance to INH, RIF, and PZA. Second-line drug susceptibilities show additional resistance to capreomycin and ethionamide but susceptibility to amikacin, clarithromycin, linezolid, clofazimine, and levofloxacin.</p>

6/22/01

A 5-French percutaneously-inserted central catheter is placed for IV imipenem and amikacin.

Because of the extent of her disease and extended resistance pattern, Olga receives 7 drugs to which the isolate is susceptible. Unfortunately, 2 of the drugs are “third-line” drugs with limited track records of clinical efficacy in the treatment of MDR-TB.

Olga’s revised regimen is as follows: (weight ~110 lbs/50 kg)

Levofloxacin 750 mg qd

Cycloserine 500 mg qd

PAS granules 4 grams bid

Imipenem 1 gram IV bid

Amikacin 750 mg qd

Clarithromycin 500 mg bid

Clofazimine 100 mg qd

Clinically, the patient is doing remarkably well despite the weaknesses of her initial regimen; sputum culture conversion occurs within a month of treatment initiation.

Olga is tolerating a dose of levofloxacin that is common in treatment of MDR-TB (750 mg daily). Some patients will even tolerate 1000 mg per day.

7/01

Negative cultures (final results) are obtained. Monthly sputum smears and cultures are negative. Olga’s cough and symptoms have resolved, and from her appearance, one would never guess she has a destroyed left lung and MDR-TB.

A toxic cycloserine level of 40 mg/ml is measured on June 16. A repeat level (29.1 mg/ml) is drawn on July 1 and found to be within therapeutic range of 20 to 35 mg/ml. Olga has not shown any signs of emotional or mental instability.

9/3/01

Screening audiology exam shows significant hearing loss in the right ear compared to baseline.

Many patients experience hearing loss on long-term aminoglycosides. Olga’s loss is unilateral and not yet noticeable to her. Since she had already received more than 2 months of daily amikacin, her providers change her to 3 times weekly amikacin and are able to stabilize her hearing loss.

Follow-up chest radiograph shows minimal change. Given Olga’s destroyed left lung, she is referred to National Jewish Hospital for surgical and treatment evaluation to improve the chance of a lasting cure.

Contact investigation: Olga has been unemployed for 2 years. She is married and a mother of 2 children (12 and 7 years old). Her husband had a history of a positive tuberculin skin test (TST) prior to meeting the patient. Her older daughter was born in the Ukraine and has a history of bacille Calmette-Guérin (BCG) vaccination and positive TST (11 mm) in 1994. Olga’s younger son remains TST negative. Both children are healthy, asymptomatic, and have had recent chest radiographs that are normal. There is no evidence of household transmission from either TB episode to date.

Lessons Learned

- Drug-resistant TB should be suspected in patients from countries with high incidence of drug resistance.
- MDR-TB patients with little or no improvement in chest radiograph after completing treatment are at high risk for reactivation.
- Patients with risk for harboring a drug-resistant TB isolate (incomplete documentation of prior susceptibilities, treatment, and response to treatment) should be considered for an empiric expanded regimen with at least 3 drugs that the patient has not previously received. An aminoglycoside or injectable drug other than SM should be included in the regimen.
- Careful monitoring for toxicities can limit their impact on the viability of the regimen and prevent serious adverse events for the patient.
- Surgical intervention is sometimes considered for patients with localized disease, especially those with extensive resistance patterns or disease that is unlikely to be cured because of significant lung destruction.

CASE EXAMPLE 3

Eva is a 25-year-old Peruvian woman who emigrated to the U.S. to join her American husband. She is healthy and has no symptoms of TB.

6/4/86

Eva has a TST placed for pre-employment screening before employment in a hospital. The TST results in 20 mm induration, and chest radiograph shows right-sided pleural fluid in the right base, which layers on decubitus views. The radiographs show no infiltrates or adenopathy. The pleural fluid is aspirated and pathology shows that the fluid is an effusion only. No malignant cells are seen and cultures grow no bacteria, AFB, or fungus.

*TB can cause a pleural effusion due to hypersensitivity reaction to a pleural-based TB lesion. In this case, a pleural biopsy is required to see the granulomatous changes and to grow the AFB. Pleural fluid grows *M. tuberculosis* in the event of a pleural-based lesion eroding into the pleural space and causing an empyema with purulent pleural fluid. The diagnosis of pleural TB is often missed because of the failure to obtain a pleural biopsy. In addition, sputum culture can be helpful and is often forgotten when focusing on the effusion. Pulmonary disease may be masked by an effusion or be too subtle to be seen on the radiograph.*

7/30/86

When the AFB cultures are negative at 6 weeks, the employee health provider at Eva's hospital concludes that she has latent tuberculosis infection (LTBI) and treats her with INH.

Monotherapy with INH should never be initiated until the possibility of active TB is ruled out. This practice promotes the development of resistance.

10/20/86

Eva experiences fever and some shortness of breath, which she attributes to a viral process.

12/15/86

Eva reports the symptoms to the employee health provider when she can no longer perform her duties in the hospital. Her provider obtains a chest radiograph that shows enlargement of the pleural fluid and development of extensive infiltrates.

*Patients being treated with INH for LTBI should be screened monthly for toxicity, adherence to therapy, and **symptoms of active TB**. Eva's symptoms of active TB should have been uncovered during active screening.*

12/20/86

Eva's provider concludes that she has active TB and adds RIF and PZA to her regimen. No sputum is collected.

Extensive contact investigation is performed in the hospital and several co-workers have documented skin test conversion. Because Eva does not have direct patient care responsibilities and because transmission is apparently limited, further contact investigation is not performed.

CASE EXAMPLE 3 continued

2/26/87

After initial clinical improvement, Eva reports clinical worsening. Repeat chest radiograph shows continued worsening. Eva's provider calls the county TB controller for advice. The TB controller is quite agitated about the fact that the case was not reported when Eva was considered a TB suspect, and a pleural biopsy and sputum were not obtained for culture and susceptibility testing.

Pulmonary and extrapulmonary TB are reportable diseases in all 50 states. TB should be reported within 1 working day of clinical suspicion of the disease. Reporting should not be delayed while providers are waiting for smear and culture results. Specimens for smear and cultures should be obtained from all practical sources.

3/1/87

Sputum is collected and is smear-positive and eventually grows MDR-TB (resistant to INH and RIF).

Eva should have been presumed to have INH-resistant TB when her disease blossomed on INH alone. A TB expert, who would have treated her with 4-drug therapy, should have been involved. INH-resistant TB is treated with at least RIF, PZA, and EMB, as PZA alone does not "protect" the rifampin from development of resistance.

Lessons Learned

- Pleural TB requires a pleural biopsy for histologic and culture diagnosis unless **purulent** fluid is drained by thoracentesis.
- Monotherapy with INH should not be initiated until active TB is ruled out.
- Individuals inexperienced in TB care should refer the patient to an experienced provider **and** all providers should notify the public health department within 1 working day if they are treating a patient that they suspect has TB.
- Cultures should be collected from all practical sites.
- When INH resistance is considered, initiate **at least** RIF, PZA, and EMB.

CASE EXAMPLE 4

Sam is a 29-year-old injection drug user serving time in U.S. federal prison.

5/10/99 Sam converts his TST during an incarceration at a county jail. His chest radiograph is normal and he has no symptoms of active TB. He is diagnosed as having LTBI and completes 9 months of INH by directly observed therapy (DOT) at another facility.

6/30/01 Sam complains of an increasing cough that is not improved by antibiotics. The possibility of TB is entertained, but Sam relays to the providers that he has already received 9 months of INH.

While INH treatment for LTBI reduces the risk of progression to active TB for susceptible isolates by 85% to 90%, it has no impact on high-level INH resistance. Additionally, some patients who report prior completion of LTBI in fact have not been completely adherent; other patients have been reinfected by another strain. Patients with signs and symptoms of TB should be evaluated by chest radiography and sputum collection if indicated.

10/1/01 Sam's cough is treated for several months as reactive airways disease and on his third visit to the clinic he begins to cough up blood. The prison nurse calls for records regarding Sam's prior TB treatment and 1 month later, receives information that: 1) Sam did receive a full course of INH; and 2) after Sam's release from the first jail, an MDR-TB case and a number of conversions attributable to that case were identified. Investigations show that Sam and the MDR-TB case had been housed in areas of "shared air" and that the source case was symptomatic in the months before Sam converted his skin test.

11/3/01 Sputum is collected, the local health department is notified of the case, and Sam is treated with an expanded regimen based on the 1999 source case susceptibilities (PZA, amikacin, levofloxacin, ethionamide, and cycloserine).

*If the epidemiologic link between Sam and the MDR case had not been strong, an empiric regimen using **first-line** drugs and at least 3 drugs to which the suspected source case was susceptible could have been employed. This allows a strong regimen in case this is a pan-susceptible isolate or an MDR isolate.*

11/20/01 Sam is transferred to the county hospital for isolation and is later diagnosed with TB resistant to INH, RIF, EMB, and SM.

Comparison of drug susceptibility patterns can assist in linking cases epidemiologically. Alternatively, genotyping methods can be used if both isolates are still available.

11/30/01 The case manager meets with the county hospital staff to ensure that they are informed about the care required for drug-resistant TB (DOT of all medication, required monitoring, respiratory isolation requirements, etc.) and to establish a process for coordination of TB care.

CASE EXAMPLE 4 continued

1/3/02

The local health officer is notified that although Sam is still smear-positive, he is being transferred back to the prison to serve out his sentence because his condition is stable, he is tolerating the expanded regimen, and the prison has a room where he can continue respiratory isolation. The health department case manager contacts the prison nurse and provides information about the drug-resistant TB treatment and care required for Sam.

2/20/02

As a measure of quality assurance, the case manager asks to review Sam's health and treatment records. Through much perseverance, the case manager discovers that Sam has stopped receiving his cycloserine dose because the prison had run out of the drug, and it was improperly recorded as taken. The case manager assists with obtaining the cycloserine, provides ongoing education and instruction on required toxicity monitoring, and promptly addresses lapses in Sam's care during the several months he is in the prison.

Lessons Learned

- TST converters should be treated for LTBI once TB disease has been ruled out. In addition, inmates with positive TSTs and risk factors for progression to active TB (such as injection drug use) should be treated for LTBI. If the source case has drug-resistant TB, the LTBI regimen should be tailored to the source case susceptibility results.
- Patients who have completed LTBI treatment can still develop TB for various reasons: drug resistance, poor adherence, exogenous reinfection, or bad luck.
- Not all patients with MDR-TB are foreign-born or have previously received treatment for active TB.
- Contact investigations should prioritize activities to those with the highest level of exposure and higher risk of progression to active TB. Contacts should be sought who interfaced with the source case beginning 3 to 6 months before symptoms began.
- When a hospital notifies the health department about an active TB case, the case manager assigned to the case should meet with hospital staff to ensure that the hospital staff is informed about appropriate TB care.
- TB training is essential for correctional staff, and correctional facilities should have a TB protocol in place to be able to house inmates with active TB.

CASE EXAMPLE 5

Anna is a 57-year-old diabetic Filipino woman.

-
- 7/10/98** Anna entered the U.S. with B-notification, Class B2 status (pulmonary TB suspect) and was not considered clinically active. Sputa were not collected overseas.
-
- 7/17/98** Anna is screened at the TB clinic.
- Past history:** Treated for TB in the Philippines from 1993 to 1996 with “pills and some injections,” followed by irregular use of Rifater (combination of INH, RIF, and PZA) until the time of the exam.
- Symptoms:** Chronic cough with white sputum, fatigue, anorexia, and fever for months.
- Anna’s immigration chest radiograph (February 17, 1998) reveals extensive pathology with a right upper lobe cavitary infiltrate with volume loss and fibro-nodular infiltrates of the right lower lobe and left mid-lung field. Her repeat chest radiograph in clinic shows no significant change.
-
- 7/17/98 –
7/20/98** Two out of three sputum samples collected are AFB smear-positive and all 3 specimens eventually grow *M. tuberculosis*.
-
- 7/21/98** Anna is treated with INH, RIF, PZA, and EMB by DOT.
- Serious consideration should have been given to initiation of an expanded regimen. The irregular nature of Anna’s prior treatment and immigration from an area of high levels of resistance put her at great risk. Additionally, her cavitary disease and high bacillary load put her at risk for amplification of resistance if the wrong regimen is chosen. Delay in correct treatment also prolongs risk of transmission to contacts.*
-
- 8/30/98** Anna’s *M. tuberculosis* is found to be resistant to INH, RIF, and EMB by broth methods and the laboratory sets up confirmatory tests using the agar proportion method.
-
- 9/20/98** Anna’s case manager inquires as to the susceptibility results and is only now told of the “preliminary” susceptibility results. Anna has not appreciably improved clinically or microbiologically.
- Laboratories should notify the provider and public health department of “preliminary” results unless they have strong reasons to consider them inaccurate. In this case, Anna’s risk of resistance is so high, the laboratory could have been asked to perform direct susceptibility tests, which could have hastened the results, and first- and second-line susceptibilities could have been ordered as soon as growth of *M. tuberculosis* was detected.*
- Anna’s provider and case manager should have been suspicious when the susceptibility results were not sent several weeks after the initial growth of *M. tuberculosis* was reported.*
- Drug susceptibilities confirm resistance to INH, RIF, and EMB (the laboratory does not perform PZA susceptibility tests). Anna’s isolate is sent to a reference lab for second-line susceptibility testing, and a new sputum is sent immediately for first- and second-line susceptibility testing to determine whether amplification of resistance had occurred.

CASE EXAMPLE 5 continued

- 9/27/98** Cycloserine, SM, and levofloxacin are added; INH, RIF, and EMB are discontinued.
-
- 12/2/98** Sputum culture becomes negative 2 months after institution of an appropriate regimen. Anna has resolution of cough, fever, fatigue, and anorexia. Her weight has increased by 10 pounds.
-

Lessons Learned

- Overseas immigration screening is not always reliable. Do not allow overseas tests and evaluations to drive an immigrant's evaluation upon arrival in the U.S. A chest radiograph consistent with active disease, including cavitory lesions, requires sputum collection before immigration. Immigrants with positive sputum smears are barred from U.S. entry until they become smear-negative. Notify CDC's Division of Quarantine whenever a newly arriving "classified" immigrant is smear-positive on initial evaluation. Any immigrant with a chest radiograph consistent with active TB, whether symptomatic or not, should have TB ruled out using appropriate laboratory and clinical evaluations.
- Drug resistance should be suspected in someone with prior TB treatment, especially with irregular drug administration and limited treatment documentation.
- Once suspicious of drug resistance, utilize the resources of the lab by asking for direct susceptibilities from smear-positive sputum and ordering first- and second-line drug susceptibility testing **as soon as growth is detected**. If available, seek rapid susceptibility information with molecular techniques from smear-positive sputum, growth in broth, or colonies on agar.
- Strongly consider an expanded empiric regimen in a patient with such an irregular history of previous TB treatment and risk of resistance amplification. An initial regimen with at least 3 drugs to which the isolate is susceptible will hasten clinical improvement, lessen risk of amplification of resistance, and prevent transmission to contacts.