TB Drug-Susceptibility Testing
Expert Panel Meeting
Recommendations

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National Center for Preparedness, Detection
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CCID/CDC
Outline

• Background
• WHO Interim Policy Guidelines for Second Line Drug Testing (SL-DST)
• Problems and Concerns with Current Practices in the U.S.
• TB DST Panel Recommendations
What needs to be done to address XDR-TB effectively?

- Strengthen basic TB and HIV/AIDS control, to avoid creation of MDR-TB
- Scale-up programmatic management of MDR-TB to prevent XDR-TB
- Strengthen laboratory services for adequate and timely diagnosis of MDR-TB and XDR-TB
- Expand MDR-TB and XDR-TB surveillance
- Strengthen advocacy, communication and social mobilization
- Pursue resource mobilization at global, regional and country levels
- Promote the International Standards of Care
- Promote research and development into new diagnostics, drugs and vaccines
- Introduce (or expand) infection control, especially in high HIV prevalence settings

Source: WHO/STB/THD
Drug Susceptibility Testing of Second-line Anti-Tuberculosis Drugs
Interim Policy Guidance

Background

- M(X)DR-TB serious public health threat
- Reported in all regions
- Emerging/ spread epidemics
- Specific challenges in high HIV settings
- Urgent need for scale-up of diagnosis & treatment
Policy guidance on DST of SLDs
WHO Expert Meeting, July 2007

• GLC: ‘Urgent need to develop general programmatic guidance on SLD-DST’
  - Drugs that can be reliably tested
  - Validated technologies
  - Cross-resistance issues
  - Limitations in interpreting DST results
  - Recommendations for countries with limited resources
Statement of the problem

- Conventional DST results always delayed, therefore results may not accurately reflect bacterial population at the time of sputum collection
- DST cannot exclusively be relied on to guide Rx design
- Rapid DST methodologies either still in development, at early validation or in early field demonstration phase
- No rapid DST methodologies for SLD-DST
- ‘No studies have systematically evaluated all available DST methods for all available SLDs or evaluated a large number of clinical isolates for microbiological and clinical endpoints’
Reliability and reproducibility

- Relatively good for aminoglycosides, polypeptides and fluoroquinolones

- Reliability and reproducibility of other SLDs much more limited, have not been proven, or methodology for testing does not exist

- MOST IMPORTANT: Correlation of *in vitro* SLD-DST results with clinical treatment response not yet established
Evidence base (>=2 criteria)

I  Extensive published studies, extensive multi-centre laboratory review, broad inter-method agreement, high stability of drug powder in vitro, consistent DST reliability and reproducibility, extensive clinical outcome data

II Extensive published studies, extensive multi-centre laboratory review, limited inter-method agreement, variable DST reproducibility (and therefore reliability), variable stability of drug powder in vitro, less extensive clinical outcome data

III Less extensive published studies, limited multi-centre laboratory review, limited data on DST reproducibility and reliability, limited data on drug powder stability in vitro, limited clinical outcome data

IV Limited or no published studies, limited multi-centre laboratory review, limited data or questionable DST reproducibility (and therefore reliability), instability of drug powder in vitro, no clinical outcome data

V No published studies, no multi-centre laboratory review, reproducibility and reliability impossible to assess, unknown stability of drug powder in vitro, no clinical outcome data
## Recommendations (1)

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Rational use of DST (1)

- ‘Routine DST for Group 4 drugs (ethionamide, prothionamide, cycloserine, terizidone, p-aminosalicylic acid) and for Group 5 drugs (clofazimine, amoxicillin-clavulanate, clarithromycin, linezolid) is not recommended’

- Does not imply that laboratories with current capability terminate testing; but, caution is necessary in using in vitro DST-results alone to guide Rx design or Rx adjustment
Rational use of DST (1)

Rapid R testing

• Recommended in high-risk settings (including high-burden HIV) for screening

• Conventional DST still the gold standard
Hierarchy of DST

Step 1.
Isoniazid, Rifampicin

Step 2.
Ethambutol, Streptomycin, Pyrazinamide

*1 and 2 may be merged if indicated

Step 3.
Amikacin, Kanamycin, Capreomycin
Ofloxacin (or FQ of choice in RX strategy)

*2 and 3 may be merged if indicated
XDR-TB Patient: Travel and Quarantine
May 2007

INTERIM TIMETABLE
ACTIONS TO PROTECT PUBLIC HEALTH: XDR/MDR TB CASE

LOCATE XDR/MDR TB PATIENT

TESTING

ISOLATE XDR/MDR TB PATIENT

INVESTIGATE SPREAD OF INFECTION

5/18 Georgia Department of Public Health notifies CDC that patient with MDR TB traveled internationally; CDC initiates effort to locate patient and travel itinerary. Initial step in CDC's contact tracing efforts

5/22 CDC lab's preliminary tests indicate XDR^2 TB

5/24 CDC contacts colleague working with Italian MOH to discuss isolation and treatment options for patient

5/25 CDC discusses transportation options on how to bring the patient back to the U.S. from Europe

5/25 U.S. DHHS provides formal IHR notification

5/26 CDC validates U.S. re-entry of patient in NY^2

5/26 From interview, CDC obtains patient itinerary & requests passenger info for contact tracing

5/27 CDC flies patient to Atlanta; upon arrival, serves federal isolation order

5/28 CDC engages media to notify passengers of possible exposure and direct them to CDC hotline

5/29 CDC contacts self-identified passengers who call CDC hotline

5/29-5/30 CDC discusses options for safe travel of patient to Denver

5/31 CDC receives passenger contact info from multiple sources for contact tracing to facilitate testing

5/31 CDC escorted patient to Denver under federal isolation order

5/31 Denver County issues isolation order

5/31 CDC receives passenger contact info from multiple sources for contact tracing to facilitate testing

6/2 CDC resends federal isolation order

7/3 Susceptibility testing of Mtb organisms cultured from multiple sputum specimens from patient is reported to be MDR TB

5/18-5/23 CDC contacts family, acquaintances to find patient

5/24 CDC notifies Italian MOH and WHO in Geneva

5/24 CDC requests TSA issue order to prevent patient from boarding U.S. bound flight

5/25 CDC requests TSA issue order to prevent patient from boarding U.S. bound flight

5/25 CDC obtains patient from hospital in NYC after preliminary tests indicate XDR^2 TB

5/26 CDC starts discussion on bringing the patient from NYC to ATL

5/26 CDC flies patient to Atlanta; upon arrival, serves federal isolation order

6/2 CDC resends federal isolation order

*10/09/07, Subject to Updates

All dates reflect EDT
APHL/CDC Tuberculosis Drug Susceptibility Testing Expert Consultation
Atlanta, GA
December 12-13, 2007

- John Bernardo, MD (Boston University)
- Henry M. Blumberg, MD (Emory University)
- Kenneth Castro, MD (CDC)
- Terence Chorba, MD
- Edward P. Desmond, PhD (California SPHL)
- Frances P. Downes, DrPH (Michigan SPHL)
- Lauren Grosso, MSPH (APHL)
- Bruce A. Hanna, PhD (NYU)
- Leonid Heifets, MD, PhD (National Jewish)
- Rosemary Humes, MS, MT(ASCP)SM (APHL)
- Kenneth Jost Jr., MT(ASCP) (Texas SPHL)
- Philip LoBue, MD, FACP, FCC (CDC)
- Beverly Metchock, DrPH (CDC)
- Bonnie Plikaytis, MS (CDC)
- John Ridderhof, DrPH (CDC)
- Barbara Seaworth, MD (Heartland TB Center)
- Susan E. Sharp, PhD (ASM)
- Angela M. Starks, PhD (CDC)
- Centers for Disease Control and Prevention
- Stephen Suffin, MD (Quest Diagnostics)
- Anthony Tran, MPH, MT(ASCP) (APHL)
- Karin Weyer, DSc (WHO)
- Gail Woods, MD (University of Arkansas)
Expert panel meeting for improving drug susceptibility testing (DST) to detect and control MDR and XDR TB

Meeting Objectives

• Provide recommendations for updating the Clinical and Laboratory Standards Institute (CLSI) 2003 M24 standard on susceptibility testing for mycobacteria with an emphasis on second line drug (SLD) testing practices
• Develop guidance on national strategies for assuring access for rapid and comprehensive second line drug (SLD) testing in selected referral laboratories
• Review quality standards and existing proficiency testing programs for DST and provide guidance on laboratory and program level practices to assure the accuracy of testing at all levels.
• Provide guidance on priorities for operational research to improve current practices and promote implementation of methods and algorithms for the rapid detection of drug resistance.
CDC Model Performance Evaluation Program (MPEP) for M.tb and NTM drug susceptibility testing (DST)

- Established in 1994 by Division of Laboratory Systems (DLS) to assist with transition to rapid DST methods and assess laboratory performance
- Biannual shipments of 4 \textit{M.tb} and 1 NTM strains
- Voluntary and confidential, results provided in aggregate report
- 140 participating laboratories, includes 32 laboratories outside U.S.
- Contract with Computer Sciences Corporation (CSC), National Jewish Hospital is subcontractor for strain management/distribution
- Participants often test and report SLD, but SLD resistant strains rarely included
Current Practices
Classification of MPEP
Participating US Laboratories (June 2007)

- Health Department: 64
- Hospital: 34
- Independent: 10
- Other: 1
Problems and Concerns with Current Practices

- **One Patient, Multiple Labs**: Most testing algorithms are based on referrals of specimens or isolates to reference level laboratories. Problems that can arise:
  - Mycobacteriology laboratory services are often piecemeal, dispersed among different facilities
  - Communication among laboratories may be inefficient.
  - Communication with care-giver/TB program can be limited, especially as the testing moves further away from the original lab.
- **Inefficient use of rapid methods**: A laboratory may wait for the TB isolate to grow on solid media rather than perform DST directly from broth isolate.
Mycobacteriology Services - 1999
National Sample of Mycobacteriology Laboratories

Source: APHL/CDC Mycobacteriology training needs assessment. Billie Bird
Problems and Concerns with Current Practices

• Discordant results are not uncommon:
• Lack of confidence in test results contributes to delays
  • Laboratorians are reluctant to report resistance prior to confirmation.
• Comprehensive External Quality Assessment (EQA) is lacking
  • CLIA PT is infrequent
  • PT and CDC MPEP don’t include MDR
Table 1.3: Participant Results for Culture N, *M. tuberculosis*, resistant to INH at 0.2 μg/ml and 1.0μg/ml and PZA resistant at 100μg/ml by the agar proportion method.

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### Table 1.2: Participant Results for Culture M, *M. tuberculosis*, INH resistant at 0.2μg/ml

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Table 1.2: Participant Results for Culture H, *M. tuberculosis*, resistant to rifampin and ciprofloxacin at 2.0µg/ml

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<td>3</td>
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<tr>
<td>Ciprofloxacin</td>
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</tr>
</tbody>
</table>
The number of strains with > 80% concordance among participant laboratories and the intershipment concordance range for detection of resistance were:

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Strains</th>
<th>Correlation &gt;80%* AP** BACTEC+</th>
<th>Concordance range (% concordance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid-Low</td>
<td>19</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Isoniazid-High</td>
<td>19</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>12</td>
<td>-</td>
<td>12</td>
</tr>
<tr>
<td>Rifampin</td>
<td>19</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>11</td>
<td>4</td>
<td>9</td>
</tr>
</tbody>
</table>

Total *M.tb* strains: 140.

*This is 80% agreement with the critical concentration of drug based on Clinical Laboratory and Standards Institute (CLSI) Guidelines; **AP – Agar Proportion
*BACTEC 460 - Radiometric

Ref: Williams LW, et al, Poster U-071, ASM, Boston, MA 2008
Problems and Concerns with Current Practices

*Discordant Results*

- Bacterial population (isolate vs. subculture)
  - Re-testing may result in a false susceptible result if the isolate is repeatedly subcultured, as the slower-growing resistant population may be lost.
- Differential growth kinetics in the bacterial population
- Different inoculation methods (size, clumps)
- Different methods or media
- Methodology not standardized
- Cross-contamination
- Transcription or labeling errors
- Problem strains: some isolates are more difficult to grow
- Problem drugs
- Minimal Inhibitory Concentration (MIC) of drug for some isolates is close to the critical concentration
DST Recommendations

**Proficiency**

- Encouraging Experience: Laboratories performing FL-DST should test a minimum of 50 patient isolates per year to maintain technical proficiency.
- Consolidating Specialized Testing: CDC should establish national Centers of Excellence (Centers) to perform SL-DST.
  - Establish selection criteria for a laboratory to become a Center.
  - Center should have outreach capability with TB clinicians.
  - Establishing these centers will require sufficient financial resources. Don’t redirecting current resources.
  - Centers should perform research on new tools.
  - Centers could provide international technical assistance or serve as a Supranational Reference Laboratory.
MPEP Participating US Laboratories (June 2007)
Isolates Tested Per Year

Isolates Tested Per Year

- 0-10
- 11-20
- 21-50
- 51-100
- 101-500
- > 500
Participant U.S. Laboratories
Frequency of Secondary Antituberculosis Drugs
June 2006

Percentage of Laboratories

<table>
<thead>
<tr>
<th>Secondary Drug</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethionamide</td>
<td>29</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>25</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>18</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>20</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>15</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>15</td>
</tr>
<tr>
<td>Amikacin</td>
<td>12</td>
</tr>
<tr>
<td>Other FQ</td>
<td>14</td>
</tr>
</tbody>
</table>

n = 107
DST Recommendations

**Improving Oversight**

- Existing External Quality Assessment (EQA) and quality control programs need enhancement.
  - CDC should help define criteria for FL- and SL-DST proficiency panels. Second-line drug mono-resistant strains may need to be developed to avoid the biosafety risks associated with MDR and XDR strains. Laboratories performing DST must accept MDR strains for proficiency testing.
- Currently a pan-susceptible strain of Mtb is recommended for routine quality control. CDC should develop a library of well-characterized susceptible and resistant Mtb strains to test laboratory proficiency and to evaluate and validate new methods.
DST Recommendations

Referral Patterns

• Assess Current Practices: Both APHL and CDC have recommended comprehensive assessments of available TB laboratory services in each state to identify current practices and capabilities.

• Proper Notification Needed: Clinical laboratories should notify public health laboratories when specimens and/or isolates are being referred to other laboratories (including Centers of Excellence or CDC) to ensure proper tracking and appropriate reporting.
DST Recommendations

Testing Algorithms

• Reflex to Simultaneous Testing: Some experts recommended that any TB resistance to a first-line drug should automatically reflex to simultaneous confirmatory testing and SL-DST.

• Report Resistance Promptly: First-line resistance should be promptly reported to clinicians even if confirmatory or repeat testing is being performed. The initial results would be labeled:
  • “Preliminary Report. A reference laboratory will confirm results -or- Repeat testing is being performed. Due to the complex nature of TB DST, discordant results may occur.”
DST Recommendations

Testing Algorithms

• Fast-track High Risk Patients: Some experts recommended that specimens from patients at risk of drug-resistant *Mtb* or in high-risk settings be “fast-tracked” to a laboratory capable of conducting the full spectrum of TB identification, as well as FL- and SL-DST, to avoid delays.

• Refer Specimens: Some experts recommended that all smear positive specimens be referred to a full service mycobacteriology laboratory for molecular testing to identify TB and for rapid access to DST.
DST Recommendations

Testing Algorithms

• Monitor Treatment Outcome: Repeat testing—currently recommended if a patient remains culture positive at 3 months—may be needed at 2 months or sooner if drug therapy appears to fail.

• Train Routinely: Training and education for DST laboratories and clinicians interpreting test results need to be available on a recurring basis.
DST Recommendations

Panels

• The first-line panel should always include: INH (low level), RIF, EMB and PZA.
  • It is increasingly difficult to predict PZA resistance based on historical data and geographic location, so this drug should be included in the standard FL-DST panel.
  • Based on jurisdictional needs, high level INH may be tested in the first-line panel, or as part of a second-line drug panel if INH low level resistance is detected in FL-DST.
M. tb Drug Susceptibility Performance Evaluation Participating U.S. Laboratories Primary Antituberculosis Drugs (June 2006)

4 “Primary” Drugs (INH, EMB, RIF PZA)

86 (80.4%)

3 “Primary” Drugs (no PZA)

21 (19.6%)
DST Recommendations

Panels

• The second-line panel should include ALL recommended second-line drugs, following CLSI method and drug concentration recommendations.
  • Cycloserine testing is not recommended due to reproducibility issues.
  • Fluoroquinolones hold promise as possible first-line regimens in the near future, but currently there is scarce data and lack of agreement on testing standards and reproducibility. Further research is needed to establish standard, reproducible methods.
Participant U.S. Laboratories
SLD testing capacity
June 2006

- 30 Laboratories test at least 1 SLD
- 9 Laboratories test all 6 SLD
- 16 test Kanamycin and/or Amikacin, FQ, and Capreomycin
DST Recommendations

Methods

• Resolve Known Problems: resolve BD MGIT broth to broth DST inoculation problems and update the FDA-cleared product insert with new technical procedures.

• Improve Technical Guidance: More detailed technical guidance for SL-DST agar proportion and broth methods should be developed and made available to laboratories.
  • proper use of solvents in preparing drug solutions
  • CLIA-compliant verification for SL-DST in broth systems
  • guidance should be included in updates to the CLSI M24 document.
DST Recommendations

Methods

• Study MIC Benefits: Currently, testing of multiple concentrations of drugs to determine the minimum inhibitory concentration (MIC) is not recommended for *Mtb*. Further studies needed to determine the clinical utility of MIC testing, establish standard procedures and interpretive criteria

• Improve Drug Information: The stability of second-line drug stock solutions and media is not well understood.

• Align Internationally: To the extent possible, technical guidance for SL-DST should align with the WHO technical guidelines currently in development
DST Recommendations

Resolving Discrepancies

• Guidelines for Discordant Result Interpretation: CDC and partners should explain testing discordance challenges through the development of guidelines.
  • help evaluate whether discordant results came from inherent method variability or quality issues
  • help physicians understand the limitations of the test methods
• Discordant Strain Collection: Research is needed to evaluate the variability among methods and among laboratories, as well as to identify the advantages and challenges of broth-based or molecular methods.
DST Recommendations

Costs

- Lab Capacity, Capability Assessment
- Cost Assessment
- Establishing Centers of Excellence
- Packaging, Shipping
- Improved Services
DST Recommendations

Training

• Inform clinicians and public health officials of the TB systems approach, optimal specimen referral patterns, testing algorithms, interpretation of results, and reasons for discrepant results among and within laboratories.

• Laboratorians of the TB systems approach, optimal specimen referral patterns, standardized testing methods and algorithms, quality assurance procedures, interpretation of results and reasons for discrepant results among and within laboratories.
DST Recommendations

Research

• Technical Research Opportunities
  • Development and evaluation of methods for rapid detection of resistance markers.
  • Role of molecular methods to detect primary resistance and in treatment failures.

• Operational Research Opportunities
  • Correlation of the laboratory’s proficiency at detecting resistance with the number of tests performed
  • Assessment of current laboratory practices and referral strategies to develop optimal strategies to improve TB detection and DST turn-around times.
DST Recommendations

Research

• Clinical Research Opportunities
  • Clinical correlation of *in-vitro* DST results with treatment outcomes
  • Clinical utility of testing two concentrations of INH
  • Standardized, reproducible methods and drug concentrations for detecting fluoroquinolone resistance in Mtb.
  • Utility of monitoring serum drug levels in patient management
  • Clinical utility of MIC testing; establishment of standardized procedures and interpretive criteria for laboratory and clinicians.
"The Laboratory Makes a Difference"

The US initiative in the 90’s to meet the challenge of MDR-TB

Guidelines

Programs/Reports

Workshops/Conferences

Training Materials

- Guidelines
- Programs/Reports
- Workshops/Conferences
- Training Materials
Thank You
Acknowledgements

- Rosemary Humes (APHL)
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- Laurina Williams (CDC)
- Beverly Metchock (CDC)
- David Cross (CDC)
- Tom Shinnick (CDC)

The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention