

**CDC's**  
**Molecular Detection of Drug Resistance (MDDR)**  
**Service and *Mycobacterium tuberculosis* DST**  
**Model Performance Evaluation Program (MPEP)**

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June 22, 2010

# MPEP for *Mycobacterium tuberculosis* Drug-Susceptibility Testing

- ❑ MMWR—January 14, 1994/43(1)17-18
- ❑ Assess the DST process of laboratories for MDR strains of Mtb
- ❑ Not designed to satisfy regulatory requirements
- ❑ Voluntary and free of charge
- ❑ Anonymity of individual laboratory contributions is maintained

<http://wwwn.cdc.gov/mpep/mtbds.aspx>

# MPEP for *Mycobacterium tuberculosis* Drug-Susceptibility Testing

- ❑ Benefits to participants:
  - Opportunity to conduct a free, anonymous self-assessment that will improve testing processes
  - Additional (although) voluntary proficiency testing program for labs, beyond what is mandated by federal regulations
  - Increase DST competency
  - OPPORTUNITY for education/self-improvement
  
- ❑ 2 challenges/year (4-5 MtbC isolates)
- ❑ ~100 US labs participate

# MPEP Reports

## □ Descriptive information about participant laboratories

- Type of laboratory
- Testing volume
- Laboratory practices and procedures

## □ Results

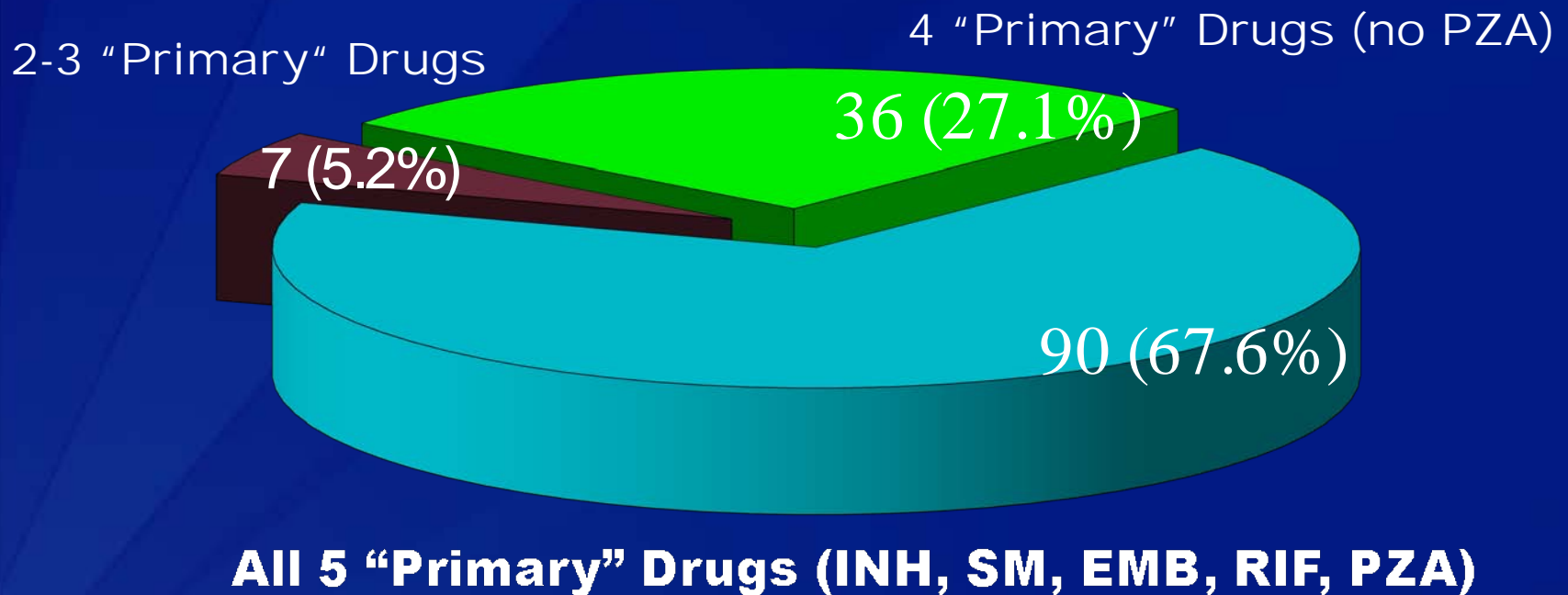
- Narrative for each strain
- Tables with aggregate test results for each strain

**Table 1.2:** Participant Results for Culture H, *M. tuberculosis*, resistant to rifampin at 1.0 µg/ml.

DRUG	Conc	Test Method																
		AP Results			BACTEC Results			LJ Prop Results			MGIT Results			Other Tests Results				
		S	R	SumS	S	R	Sum	S	R	SumS	S	R	Sum	S	R	Sum		
Isoniazid	0.01												1		1			
Isoniazid	0.05															1		1
Isoniazid	0.10				39		39						68	1	69	4		4
Isoniazid	0.20	23		23	2		2	5		5			1		1	1		1
Isoniazid	0.40				11		11						26		26	3		3
Isoniazid	1.00	25		25	1		1	3		3								
Isoniazid	2.00	1		1														
Isoniazid	5.00	4		4														
Isoniazid	10.00							1		1								
Isoniazid	100.00							1		1								
Rifampin	0.50												1		1			
Rifampin	1.00	8	19	27	3	1	4	1		1			56	13	69	3		3
Rifampin	2.00				21	15	36											
Rifampin	5.00	3		3	1		1	1		1								
Rifampin	8.00															1		1
Rifampin	10.00				1		1						1		1			
Rifampin	16.00															1		1
Rifampin	32.00															1		1
Rifampin	40.00							4		4								
Rifampin	50.00							1		1			1		1			
Pyrazinamide	64.00															1		1
Pyrazinamide	100.00				36	1	37	1		1			58	1	59	1		1
Pyrazinamide	300.00															3		3
Pyrazinamide	400.00							1		1								
Ethambutol	1.00							1		1								
Ethambutol	1.60															1		1
Ethambutol	2.00							5		5								
Ethambutol	2.50				35		35						1		1			
Ethambutol	3.20															1		1
Ethambutol	5.00	22		22	4		4	1		1			67	2	69	3		3
Ethambutol	6.40															1		1
Ethambutol	7.50	1		1	8		8						1		1			
Ethambutol	8.00															3		3
Ethambutol	10.00	9		9									1		1			
Streptomycin	1.00							1		1			53	1	54			
Streptomycin	2.00	27		27														
Streptomycin	2.00				35		35											
Streptomycin	4.00							4		4			12		12			
Streptomycin	5.00							1		1								
Streptomycin	6.00				7		7											
Streptomycin	7.50															1		1
Streptomycin	10.00	24		24				1		1								
Streptomycin	15.00															1		1
Streptomycin	30.00															1		1

What have we learned about  
TB DST in US labs from MPEP?

# MPEP Participating U.S. Laboratories Primary Antituberculosis Drugs (July 1999)

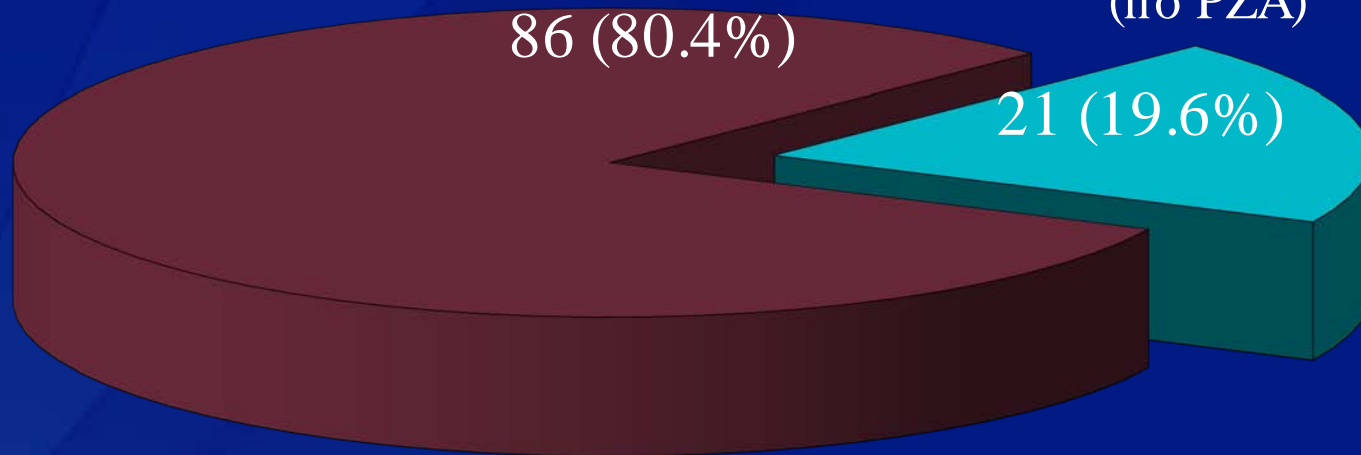


**n = 133**

# MPEP Participating U.S. Laboratories Primary Antituberculosis Drugs (June 2006)

4 "Primary" Drugs (INH, EMB,  
RMP, PZA)

3 "Primary" Drugs  
(no PZA)

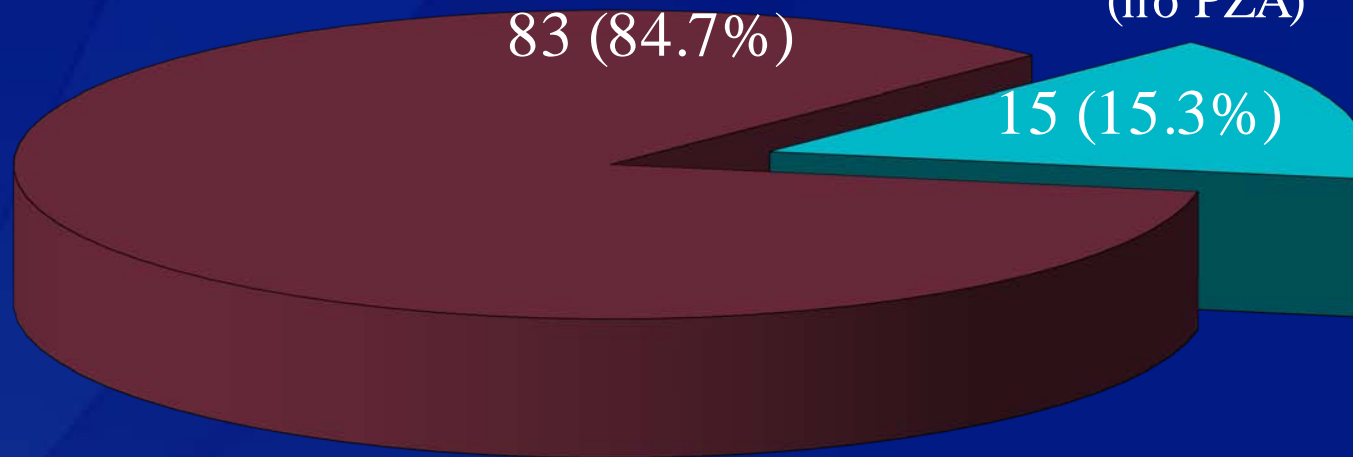


n = 107

# MPEP Participating U.S. Laboratories Primary Antituberculosis Drugs (November 2009)

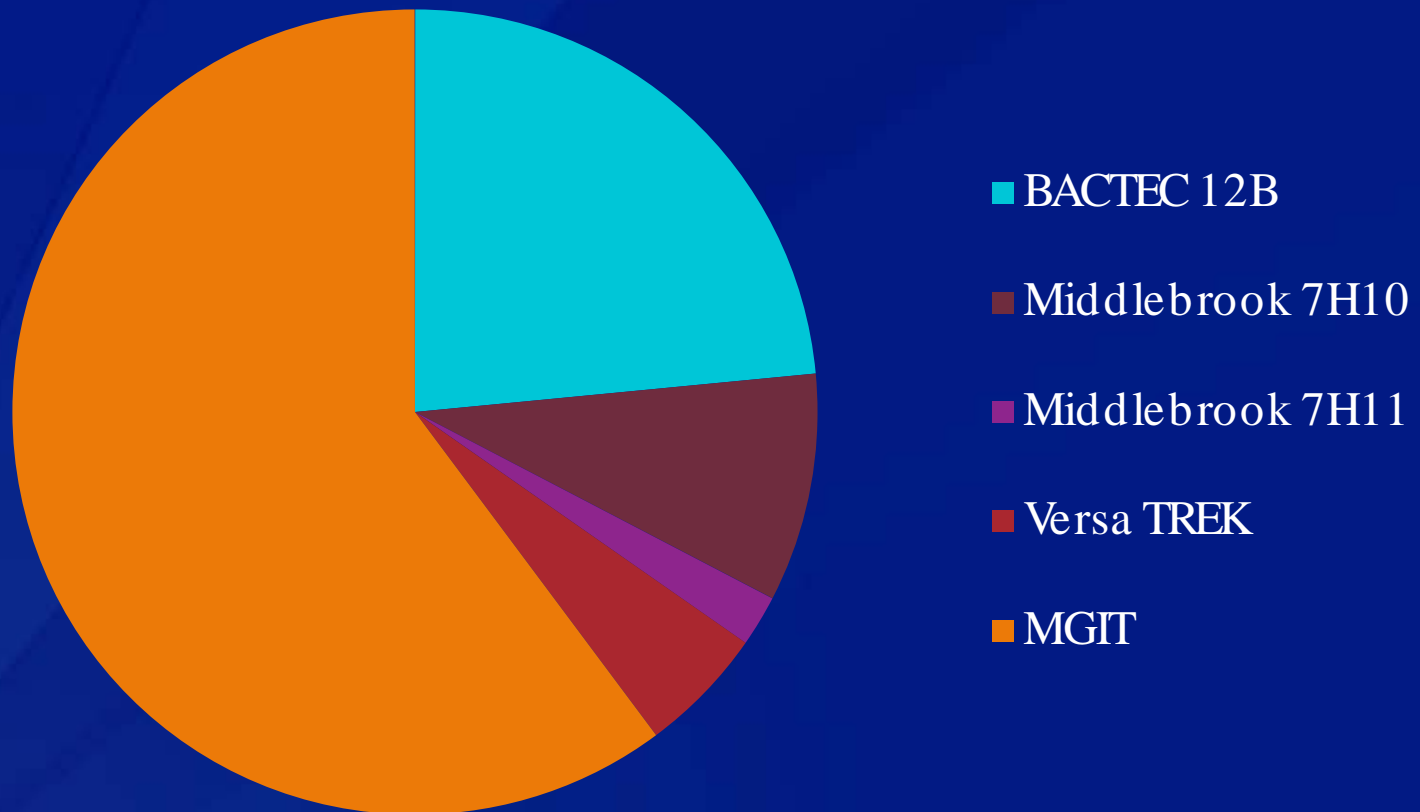
4 First Line Drugs (INH, EMB,  
RMP, PZA)

3 First Line Drugs  
(no PZA)



**n = 98**

# Primary Method – MPEP Participants (Nov. 2009)\*



- \* 21 laboratories used 2 methods and 2 laboratories used 3 methods for INH and RMP

## Case Definition for XDRTB

Resistance to at least INH and RMP (MDR) plus resistance to fluoroquinolones (FQ) and one of the second-line injectable drugs (amikacin, kanamycin, or capreomycin)

Participant U.S. Laboratories (CDC MPEP) SLD testing capacity (November 2009) – Of 98 participants:

- 34 Laboratories test at least 1 SLD (other than STR)
- 30 test at least one injectable drug and a FQ
- 10 test kanamycin, capreomycin, amikacin, and a FQ

# Comprehensive Long-term report on MPEP (1994-2008)\*

- Among >65,000 tests at respective critical concentrations, BACTEC 460 and MGIT combined (96.5% success) were comparable to Agar Proportion (96.8% success)
  - Labs do a great job on “easy” samples (>95% success)
  - Labs/methods do have problems with challenging specimens such as low-level INH-R and low-level RMP-R isolates ( $\leq$  80% success)
  - EMB is a problem (~80% success)

\* J. Ridderhof, T. Taylor, P. Angra, R. Astles

# Problems/Concerns with Current Practices that may be addressed through the MPEP

- ❑ Discordant results – inter- and intra-lab, different methods, etc. – including molecular methods
- ❑ How do participant laboratories use the results/strains?
  - Analysis
  - Procedural changes
  - Training
  - Method verification

# Molecular Detection of Drug Resistance (MDDR) Service

- ❑ Implemented in September 2009
- ❑ DNA sequencing - ABI 3130xl
- ❑ Clinical/TB Program
  - Make rapid confirmation of RMP-resistant and MDR TB available
  - Make laboratory testing data available to clinicians about SLD resistance in cases of RMP-resistant or MDR TB
- ❑ Routine DST performed in addition to sequencing

# Sensitivity and Specificity of Loci\*

Drug	Gene(s)	Sensitivity	Specificity
RMP	<i>rpoB</i>	96	93.5
INH	<i>inhA, katG</i>	89.6	98
FQ	<i>gyrA</i>	81.9	97.3
KAN	<i>rrs, eis</i>	86.5	95.1
AMK	<i>rrs</i>	87.3	97.1
CAP	<i>rrs, tlyA</i>	56.6	87.8
<b>MDR</b>	<b><i>rpoB, inhA, katG</i></b>	<b>89.6</b>	<b>94</b>

\* Analysis of 254 clinical isolates from MLB collection (2000-2008)

# Indications for MDDR Testing

	First month (Sep 2009)	First 6 months (Sep 2009-Feb 2010)
	13 requests	59 requests
Country with high risk	7	23
Known MDR or RMP-R	7	20
Previous treatment	4	14
Mixed with NTM/non-viable	2	8
Suspect RMP-R or MDR	0	5
Other	2	16
>1 indication	8	17

# Turn-Around Times for MDDR and DST\*

	First month (Sep 2009)	First 6 months (Sep 2009-Feb 2010)
	10 requests	56 requests
MDDR	1.9 d (1-4 d)	1.9 d (1-5 d)
DST	34.4 d (27-40 d)	38.3 d (26-93 d)

\*from date of isolate receipt at CDC until report issued

# Turn-Around Time for Isolate Receipt\*

First month  
(Sep 2009)

10 requests

4.3 d (1-8 d)

First 6 months  
(Sep 2009-Feb 2010)

47 requests

3.7 d (1-11 d)

\*from date that request approved until isolate receipt at CDC

# Comparison of DST and MDDR – INH and RMP

	INH-R	INH-S
Mutation	27	1
No Mutation	1	21

Agreement 48/50 (96.0%)

	RMP-R	RMP-S
Mutation	21	2
No Mutation	1	26

Agreement 47/50 (94.0%)

# MDDR Expansion – near future

- ❑ Incorporation of embB and pncA
- ❑ Addition of moxifloxacin to DST panel
  
- ❑ Continue to validate direct specimen testing

## Conclusions:

MDDR provided useful information for treatment guidance ~ 36 days earlier than AP DST.

Logistical issues around shipping of isolates and laboratory staffing may negatively impact turn-around times of MDDR and AP DST.

Delays in requesting MDDR are common (data not shown).

**Please visit Poster #1 (A. Lentz) and Poster #8 (G. Morlock)**

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

## Comments/Suggestions

- We want feedback
  - Is MPEP useful? How can we improve?
  - Experiences with MDDR