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Tuberculosis Laboratory Aggregate Report

INTRODUCTION

The Laboratory Capacity Team (LCT) in the Laboratory Branch (LB) in the Division of Tuberculosis Elimination (DTBE) at Centers for Disease Control and Prevention (CDC) is pleased to present the "Tuberculosis Laboratory Aggregate Report." The information contained in the report is a compilation of the aggregate calendar year 2009 workload and turnaround time (TAT) data self-reported in progress reports by public health laboratories (PHL) supported in part by the TB Elimination Cooperative Agreement. In addition, current PHL methods and practices are included. These data serve as a tool to assess benchmarks and make peer comparisons. These may be useful guides for identifying testing practices and algorithms that are successful or need examination.

The past year has been an eventful time in the LB. First, the name of the branch changed from the Mycobacteriology Laboratory Branch to the "Laboratory Branch." This name change is consistent with the titles of other laboratory branches within the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP). In addition, LB has a new team. The Laboratory Capacity Activity is now the Laboratory Capacity Team (LCT) and joins the Applied Research and Reference Laboratory Teams. Expanded functions of LCT include oversight for the laboratory component of cooperative agreements, site visits, technical assistance, development of educational products, training, and operational research studies aimed at identifying model practices for laboratory diagnosis of tuberculosis. In collaboration with the Association of Public Health Laboratories (APHL), LCT recently conducted the National TB Laboratory Services Survey and will work with APHL to use the data to develop recommendations for strengthening laboratory capacity and the development of regional training opportunities. Since late 2009, members of LCT have developed two Web conferences for PHL, participated in 22 site visits, presented data at national and regional conferences, and in collaboration with the Reference Laboratory Team, developed the user's guide for the Molecular Detection of Drug Resistance (MDDR) service. Recently, LCT completed data collection for their first operational research project aimed at assessing the currently recommended practice of holding mycobacterial cultures for six to eight weeks before declaring as negative. In the coming year, LCT plans to conduct an operational research project for the potential revision of national TAT indicators in light of current methodologies and testing practices.

Recently, DTBE awarded APHL a one-time supplement for increasing patient access to molecular diagnostics in PHL. As a result, there is an anticipated shift in the methodologies used by jurisdictions providing nucleic acid amplification testing (NAAT) to include assays for the molecular detection of mutations associated with drug resistance. Through collaboration with APHL, a shipping contract has been developed for use by PHL until December 31, 2011 for submission of material to CDC's MDDR service based on criteria for potential drug resistance. In addition, LB can provide a library of 15 DNA samples that includes both wild-type and mutated alleles associated with first-line and second-line antituberculosis drug resistance. PHL interested in obtaining samples for validation studies may contact their LCT consultant for additional information.

Members of LCT have learned a great deal through site visits and want to take this opportunity to thank PHL colleagues for taking time to participate. LCT members encourage you to consider participation in an upcoming LCT operational research project and look forward to another year of collaboration with PHL colleagues.

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INSIDE THIS REPORT

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HOW TO GET THE MOST FROM THIS REPORT

Workload and TAT indicators are an integral part of an overall quality assurance program. As detailed in the TB cooperative agreement guidance document, it is important for each laboratory to set their own goals for each of the TAT indicators, to periodically analyze their laboratory data, and determine where improvements might be made. For example, a laboratory may, after carefully examining specimen delivery TAT data, notice that one particular provider is far slower at sending in specimens than others and may be batching specimens. This assessment aids in identifying an opportunity for educating the submitter on the importance of rapid transport and the potential negative clinical and public health consequences of delay on downstream testing and TAT.

In using this report, PHL can compare their TAT indicators to those of their peers with similar testing volume. With each TAT indicator, the national average has been included in the figure as indicated by the horizontal red line. Stratified TAT indicators and the corresponding national averages provide reference points from which PHL might assess their performance. For example, if your PHL performs 100 drug susceptibility tests (DST) per year, you would examine the percent of DSTs completed within 28 days of specimen receipt within the stratum of 51–100 DSTs, which is 57%, and compare the percentage calculated for your laboratory. In addition, you would compare the TAT in your laboratory to the overall national average of 49%. If your laboratory completes a higher percentage of DSTs than the stratum specific and national averages, then you know you are on target and should strive for continued improvement in TAT for this national indicator. However, if your laboratory has a lower percentage, you should investigate factors contributing to delays in TAT. Potential factors may include change or reduction in staff, change in methodologies, quality control issues, problematic isolates, or workflow impediments. Some of these factors are outside the control of the laboratory. However, others within the analytical and post-analytical phases could be identified and quality improvements implemented. A final step would be periodic reevaluation of the indicator to measure the effect of quality improvements.

This report can also serve as a quality data-checking tool; if your calculations are far above or below the averages for any of the indicators, a data re-check may be in order. Lastly, data provided in this document can and should be used to tout the accomplishments of your laboratory, or provide evidence that your laboratory may benefit from additional personnel or changes in testing algorithms, workflow, or procedures.

Any suggestions for improvements for future aggregate reports are welcomed and encouraged. For any questions regarding the data requirements for the TB cooperative agreement or your laboratory specific data provided to you with this report, please contact your LCT consultant.

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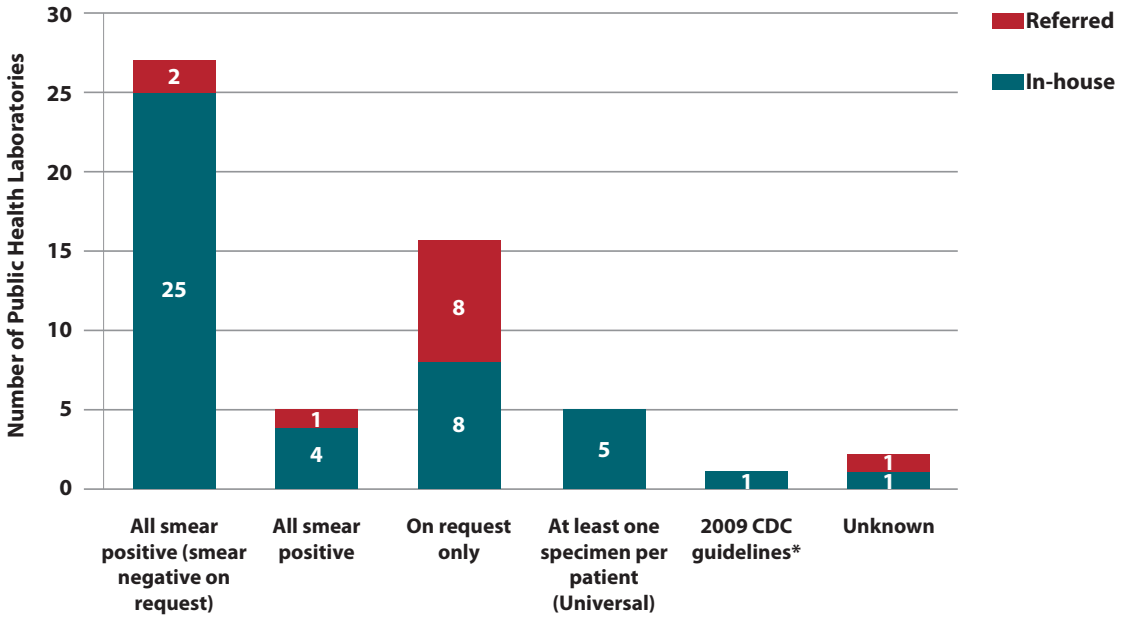
Table 1. Comparison of 2008 and 2009 National Workload Data

Variable	2008 Total number (No. PHL reporting)	2008 Median (Range)	2009 Total number (No. PHL reporting)	2009 Median (Range)	% change (p value [b])
Clinical specimens received[a]	295,416 (58)	3,228.5 (306–23,500)	272,152 (58)	3,050.5 (288–23,951)	−7.9 (≤0.05)
Patients for whom a specimen was submitted [c]	118,914 (58)	1,428.0 (124–10,934)	112,061 (57)	1,404.0 (88–10,282)	−5.8 (≤0.05)
Patients culture positive for MTBC[d]	5,745 (58)	56.0 (1–792)	5,005 (58)	40.5 (1–834)	−12.9 (≤0.05)
Patients for whom a reference isolate was submitted [e]	21,250 (58)	228.5 (0–2,575)	20,331 (58)	188.5 (0–2,739)	−4.3 (0.09)
Patients with a reference isolate identified as MTBC	3,327 (55)	28.0 (0–276)	3,871 (57)	28.0 (0–342)	14.1 (0.61)
Patients for whom DST [f] was performed	8,255 (58)	81.5 (2–895)	7,549 (58)	76.0 (2–883)	−8.6 (≤0.05)
Patients for whom a clinical specimen was tested by either NAAT[g] or other rapid test	13,745 (58)	51.5 (0–5,855)	15,827 (58)	98.5 (0–6,901)	13.2 (≤0.05)
Patients NAAT positive for MTBC	2,533 (52)	24.0 (0–567)	2,357 (56)	21.0 (0–459)	−7.0 (0.30)

[a] Processed and cultured, not including isolates referred from other laboratories, [b] Wilcoxon signed-rank test, [c] Processed and a TB culture inoculated, [d] *Mycobacterium tuberculosis* complex, [e] Received to either rule out or confirm the identification (ID) of MTBC, [f] Drug susceptibility testing, [g] Nucleic acid amplification test

For 2009 as compared to 2008, PHL reported statistically significant (p value ≤ 0.05) decreases in the number of clinical specimens received, patients for whom a specimen was submitted, patients culture positive for MTBC, and patients for whom DST was performed. The decreases in key workload categories correlate with a 10.5% decrease in reported tuberculosis cases in the United States from 2008 (12,906 cases) to 2009 (11,545 cases) reported to CDC (1). There was a significant increase of 13.2% in direct testing for MTBC from 2008 to 2009 as measured by the number of patients for whom a clinical specimen was tested by either NAAT or other rapid test.

Figure 1. Criteria for Direct Detection of MTBC in Clinical Specimens



Data presented above were taken from multiple sources including TB cooperative agreement narratives, APHL NAAT expansion grant proposals, and LB site visits. Direct detection of MTBC in diagnostic clinical specimens was performed in-house by 44 PHL and through referral by 12 PHL. Two PHL reported no access to direct detection. Of these criteria, the most utilized was testing a diagnostic specimen from all patients with a smear positive result and on request, for patients with a smear negative result.

*Performed NAAT based on updated CDC *MMWR* guidelines, which state that NAAT should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities (2).

Table 2. NAAT Workload and TAT Indicators, 2009

Number patients NAAT performed (2009)	Number of PHL	Percent of patient specimens processed at PHL that also had NAAT performed	Percent of patients with NAAT performed that were NAAT positive for MTBC	Percent of patients with culture confirmed MTBC with a NAAT positive result reported within 48 hours (HP 2020)	Percent of patients with positive NAAT result reported within 48 hours of specimen receipt
≤25	11	1%	19%	5%	35%
26–100	10	3%	30%	24%	77%
101–200	13	5%	34%	38%	72%
201–500	6	9%	23%	30%	73%
>500	5	34%	18%	54%	84%
All PHL reporting	45	8%	24%	36%	76%

Overall, 8% of patient specimens processed were tested by NAAT in 2009. Current national progress towards meeting the *Healthy People* 2020 goal (TB diagnosis within 2 days from receipt of clinical specimen for 75% of cases that are later culture confirmed) is 36%. It is important to note that when patient specimens do receive a NAAT, 76% of NAAT positive results are reported within 48 hours of specimen receipt. In general, all indicators improve as the volume of NAA testing in the laboratory increases with the exception of the proportion of specimens tested by NAAT that are NAAT positive, which is lowest in the highest volume category. One limitation to the data above is the potential for laboratories to include referred sediments that are not processed for culture in their NAAT counts.

Figure 2. First-line DST Methods

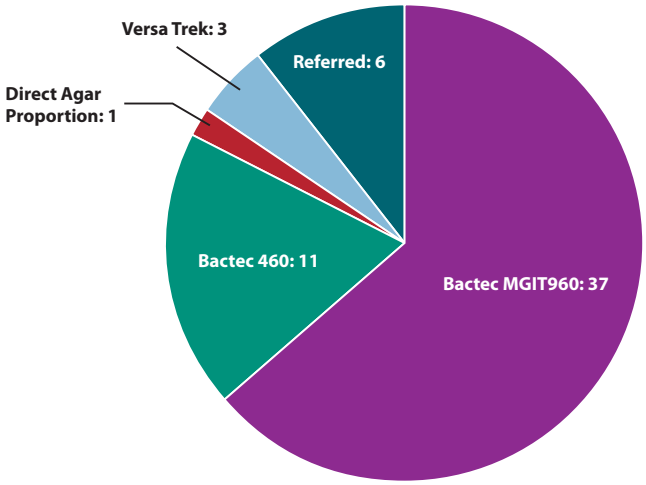
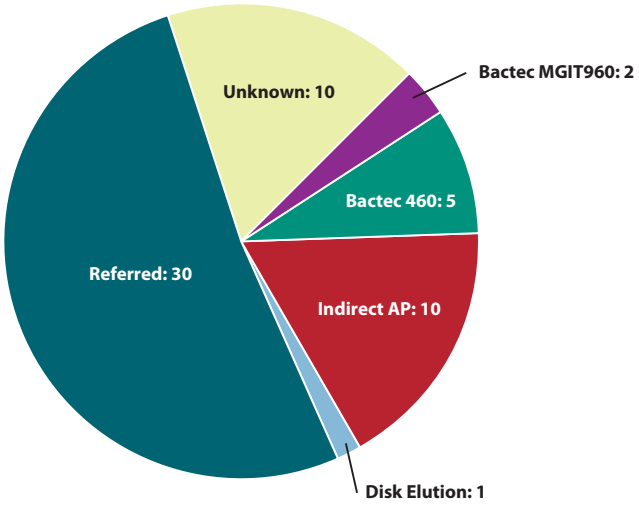


Figure 3. Second-line DST Methods



Methods used by 58 PHL for first-line and second-line DST of MTBC from culture. The proportion of laboratories using the Bactec 460 for DST will change as reagents for this platform are being discontinued in 2011. Of the 52 laboratories performing drug susceptibility in-house, 38 included pyrazinamide as part of the first-line DST panel. Five laboratories did not test for susceptibility to pyrazinamide and nine laboratories did not describe their panel for DST. Currently, 18 PHL reported performing second-line DST in-house.

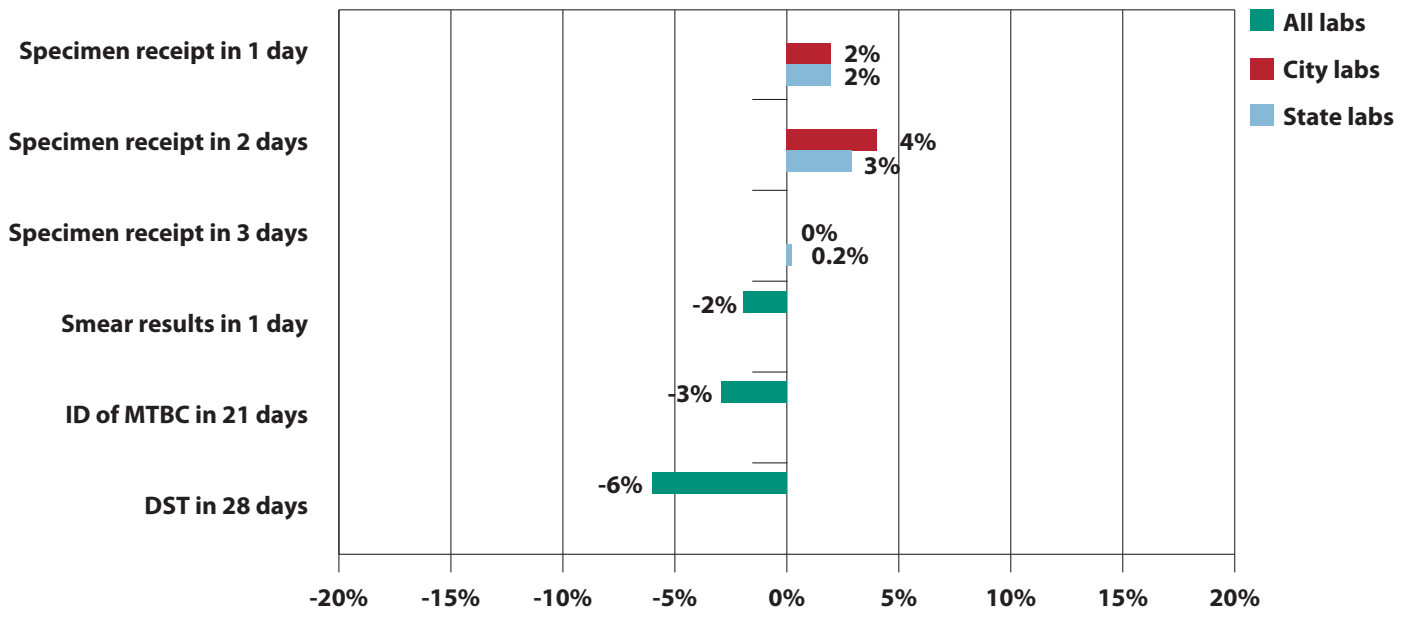
Table 3. Second–line DST in U.S. PHL

No. PHL performing SL-DST	18
No. PHL that reported SL-DST panel	16
Mean no. of SLD included in SL-DST panels	5.1
Median no. of SLD included in SL-DST panels	4.5
Range no. of SLD included in SL-DST panels	3–10
No. PHL testing at least 1 SL-INJ and 1 FQ	16
No. PHL testing >1 FQ	4
No. PHL testing all 3 SL-INJ	4
No. PHL testing 2 SL-INJ	6
KAN, CAP	4
AMK, CAP	2
No. PHL testing 1 SL-INJ	6
KAN	3
AMK	1
CAP	2

No., number; KAN, kanamycin; AMK, amikacin; CAP, capreomycin; FQ, fluoroquinolone; SL-INJ, second-line injectables

Current second-line DST (SL-DST) panels tested in-house by 16 PHL were reported. Four laboratories test all three SL-INJ (KAN, AMK, and CAP). Twelve laboratories reported testing either one or two SL-INJ. Current CLSI guidelines state that testing both AMK and KAN in addition to CAP may be desirable (3). The availability of DST for all three SL-INJ is beneficial due to incomplete cross-resistance between these drugs that could result in a missed opportunity to identify XDR-TB and potentially compromise treatment regimens (4).

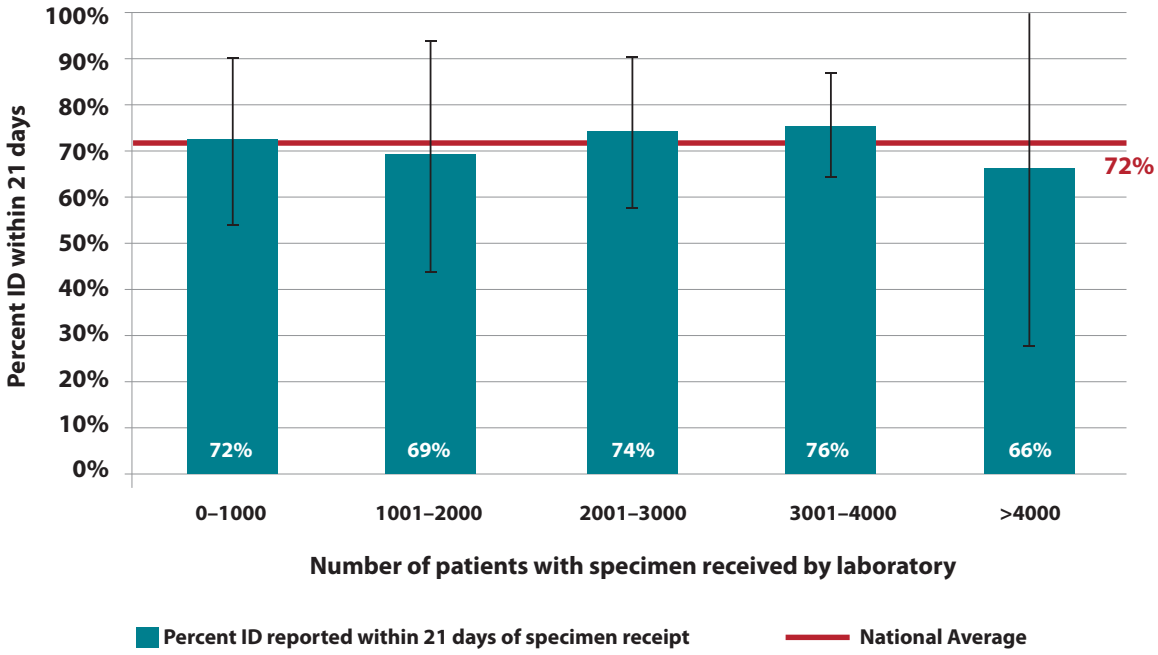
Figure 4. Changes in TAT, 2008 to 2009



Measure	Mean %, 2008 (No. PHL reporting)	Mean %, 2009 (No. PHL reporting)	Range, 2009
Receipt of specimens within 1 day			
City Laboratories	83 (5)	85 (6)	72–100
State Laboratories	37 (47)	39 (49)	0–89
Receipt of specimens within 2 days			
City Laboratories	87 (5)	91 (6)	86–100
State Laboratories	56 (41)	59 (46)	0–94
Receipt of specimens within 3 days			
City Laboratories	98 (5)	98 (6)	96–100
State Laboratories	74 (41)	74 (42)	12–100
Smear results within 1 day	91 (51)	89 (57)	54–100
ID of MTBC within 21 days of specimen receipt	75 (49)	72 (57)	0–100
DST results within 28 days of specimen receipt	55 (51)	49 (56)	0–100

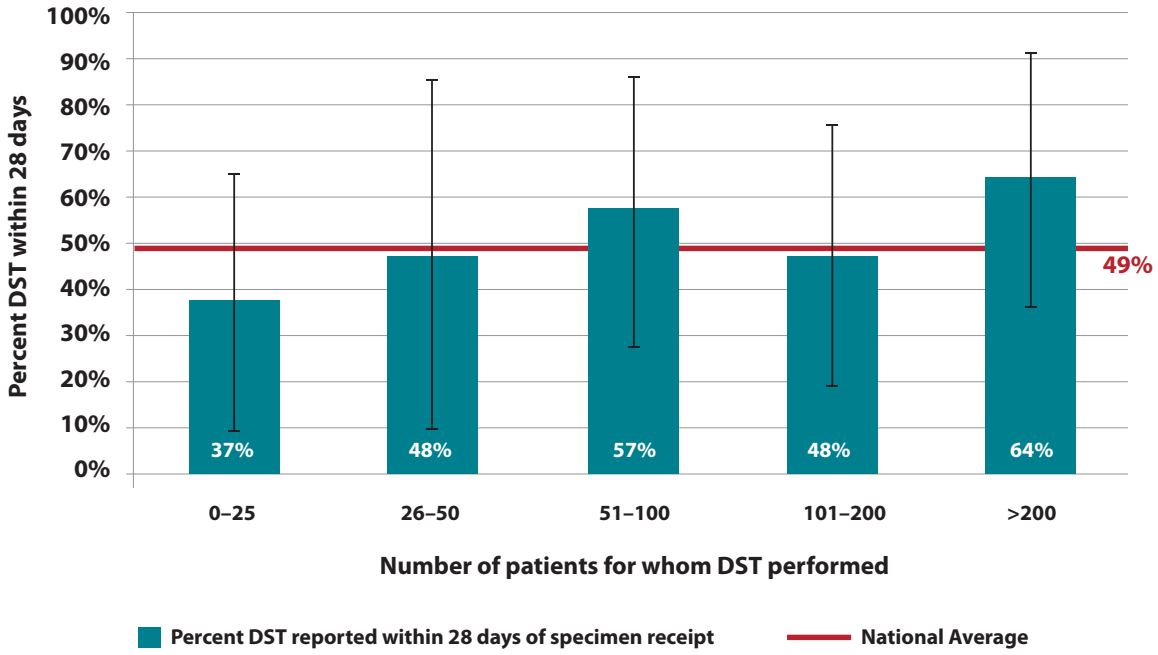
TAT for specimen receipt decreased slightly in 2009 compared to 2008. Other TAT for smear result, ID, and DST increased during this period resulting in a decreased percentage of results reported within the recommended TATs. The differences in TAT between 2008 and 2009 were not statistically significant and it is unknown if the increases truly represent slower time to reporting or whether other factors have influenced the TAT data. TATs will be periodically monitored to look for trends.

Figure 5. Percent ID Reported Within 21 Days of Specimen Receipt, Stratified by Testing Volume



The percent of isolates identified as MTBC within 21 days of specimen receipt dropped for each category in 2009 relative to 2008. As a result, the national average for turnaround time dropped from 75% in 2008 to 72% in 2009. The reasons for this decline are unknown but might include reductions in staff and batching due to economic circumstances. Laboratories should monitor this indicator and identify potential solutions to ensure continued progress in meeting national recommendations.

Figure 6. Percent DST Reported Within 28 Days of Specimen Receipt, Stratified by Testing Volume



The percentage of isolates with DST results reported within 28 days of specimen receipt increased for laboratories performing 51–100 and >200 DST per year in 2009 relative to 2008. However, slower DST TATs were reported for the other three categories and as a result, the national average for turnaround time dropped from 55% in 2008 to 49% in 2009. The reasons for this decline are unknown but are likely similar to those affecting earlier analytical processes (i.e., smear and ID). Laboratories should monitor this indicator and identify potential solutions to ensure continued progress in meeting national recommendations.

REFERENCES

1. Reported Tuberculosis in the United States, 2009: CDC TB Surveillance Report: http://www.cdc.gov/tb/statistics/reports/2009/default.htm
2. Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5801a3.htm?s_cid=mm5801a3_e
3. "Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes; Approved Standard—Second Edition," CLSI. March 2011 M24-A2, Vol. 31 No. 5.
4. "Molecular analysis of cross-resistance to capreomycin, kanamycin, amikacin, and viomycin in Mycobacterium tuberculosis," CE Maus et al., Antimicrob Agents Chemother. 2005 Aug;49(8):3192-7.

TB RESOURCES

CDC TB Website: http://www.cdc.gov/tb/

APHL TB Website: http://www.aphl.org/aphlprograms/infectious/tuberculosis/pages/default.aspx

CDC Molecular Detection of Drug Resistance (MDDR) Service: http://www.cdc.gov/tb/topic/laboratory/guide.htm

CDC Model Performance Evaluation Program: http://wwwn.cdc.gov/mpep/default.aspx

APHL TB Laboratory Self-Assessment tool: http://www.aphl.org/aphlprograms/infectious/tuberculosis/Pages/tbtool.aspx

TB Education and Training Resources: http://www.findtbresources.org/scripts/index.cfm

Evidence-Based Tuberculosis Diagnostics: http://www.tbevidence.org/

Regional Training and Medical Consultation Centers: http://www.cdc.gov/tb/education/rtmc/default.htm

Report of Expert Consultations on Rapid Molecular Testing to Detect Drug-Resistant Tuberculosis in the United States: http://www.cdc.gov/tb/topic/laboratory/rapidmoleculartesting/default.htm

Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection—United States, 2010: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm?s_cid=rr5905a1_w

Guide to the Application of Genotyping to Tuberculosis Prevention and Control: http://www.cdc.gov/tb/programs/genotyping/manual.htm

Core TB Laboratory Services for Public Health Laboratories, by the APHL TB Steering Committee: http://www.aphl.org/aphlprograms/infectious/tuberculosis/Documents/Core_TB_Services.pdf

OTHER PUBLICATIONS OF INTEREST

"Molecular detection of mutations associated with first and second-line drug resistance compared with conventional drug susceptibility testing in *M. tuberculosis,"* PJ Campbell et al., *Antimicrob Agents Chemother.* 2011 Feb 7. [Epub ahead of print]

"Monitoring the performance of mycobacteriology laboratories: a proposal for standardized indicators," KD McCarthy et al., INT J TUBERC LUNG DIS 12(9):1015–1020.

"*Mycobacterium tuberculosis* Strains with Highly Discordant Rifampin Susceptibility Test Results," A Van Deun et al., J Clin Microbiol. 2009 November; 47(11): 3501–3506.

"Validation of laboratory-developed molecular assays for infectious diseases," EM Burd, Clin Microbiol Rev. 2010 Jul;23(3): 550-76.

"Evaluation of the Cepheid Xpert MTB/RIF Assay for Direct Detection of *Mycobacterium tuberculosis* Complex in Respiratory Specimens," EM Marlowe et al., J Clin Microbiol. 2011 Apr;49(4):1621-3. Epub 2011 Feb 2.