Core TB Laboratory Services for Public Health Laboratories

by the APHL TB Steering Committee

APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES

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Introduction

The following document was developed for use by state public health laboratories (PHLs) in the United States. The guidelines may also apply to local public health laboratories that offer TB services.

The following document defines core TB services that public health laboratories must provide or assure access to. These services were grouped according to the 11 core functions (referred to as categories and shown in italics below) of state public health laboratories that were first defined in *Core Functions and Capabilities of State Public Health Laboratories*[1]. In the case of this document, not all 11 core functions are addressed, as some are not applicable to the diagnosis of TB. The original *Core Functions* document contained a charge encouraging "the development of a list of services for each core function by analyte and laboratory method." This document completes that charge for TB.

The *Core TB Laboratory Services* document indicates that certain services should be provided "in-house" while others may be performed at a reference laboratory. Providing a basic set of services locally within each state laboratory should improve turnaround times and permit the laboratory to provide and retain the expertise to provide leadership and consultation within each state. Where applicable, the laboratory services provided must meet turnaround time goals as described in Appendix B of *Mycobacteriology: Assessing Your Laboratory*[2].

This document does not address Nontuberculous mycobacteria (NTM). NTM disease presents challenges distinct from tuberculosis, so clarity requires a separate discussion of core tuberculosis laboratory functions. It should be noted, however, that when the smear prepared from the specimen is acid-fast smear positive or when a culture is positive for AFB, it is essential that the laboratory determine as quickly as possible whether the AFB are TB complex or NTM. This result should be reported as soon as it is available. Also note that, although NTM may not be as significant from a public health perspective, the public health laboratory may be the only available resource within a given jurisdiction for identification of these organisms, some of which are pathogenic.

DISEASE PREVENTION, CONTROL AND SURVEILLANCE: CORE FUNCTION 1

Core PHL Functions:

"Public health laboratories should have the ability to provide accurate and precise analytical results in a timely manner. Serve as a "first line of defense" in the rapid recognition and prevention of the spread of communicable diseases. Serve as a center of expertise for the detection and identification of biologic agents of importance in human disease[1]."

Core PHL TB Services:

All public health laboratories should provide instructions on specimen collection and transport to the TB control programs and health care providers that they service.

Types of specimens accepted include:

- primary specimens including pulmonary and extra-pulmonary specimens from true TB suspects in support of state programs and
- cultures for drug susceptibility testing, genotyping or identification of *M. tuberculosis* complex.

All public health laboratories should develop systems to facilitate the transport of specimens. Specimens should ideally be received in the laboratory within one day of collection.

All public health laboratories should perform acid-fast microscopy using a fluorochrome stain as the primary acid-fast staining method.

All public health laboratories should perform specimen decontamination, concentration and inoculation of cultures using at least selective liquid media.

All public health laboratories should have the capability to identify *M. tuberculosis* complex isolates using rapid method such as DNA probe, nucleic acid amplification or HPLC.

All public health laboratories should provide or ensure nucleic acid amplification testing performed directly on a clinical specimen to detect *M. tuberculosis* complex.

All public health laboratories should participate in TB genotyping, by submitting *M. tuberculosis* complex isolates to one of the contract laboratories funded by the Centers for Disease Control and Prevention (CDC) for this purpose. Additionally, all public health laboratories should assist TB Control Programs in the interpretation and utilization of genotyping data when laboratory data suggest an outbreak or possible false positive laboratory result.

On Nucleic Acid Amplification Testing (NAAT) for TB

According to the "Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis," NAAT should be performed on one specimen from each true TB suspect[3]. Each public health laboratory should work with its TB Control Program to establish a "true TB suspect" definition for its individual jurisdiction. Overutilization of this service may be common, and laboratories may have requests for AFB culture of sputum from patients who are not truly suspected of having TB. It is necessary for public health laboratories to work with program partners to establish policies assuring the appropriate utilization and interpretation of NAAT. The utilization of this testing should be carefully reviewed to determine if it is being ordered appropriately. Further information on utilization review as a core service can be found in Appendix A.

INTEGRATED DATA MANAGEMENT: CORE FUNCTION 2

Core PHL Functions:

"Public health laboratories should have the ability to serve as the focal point for accumulating, blending, and disseminating scientific information in support of TB public health programs, including: capturing laboratory data essential for public health analysis and decision-making; ensuring rapid dissemination of laboratory information to assist in identification, understanding, and controlling TB outbreaks; providing primary data necessary to provide information for and implement policy and planning; systems to collect, monitor, and analyze laboratory data for surveillance of tuberculosis and identify clusters of TB disease; serving the data needs of state epidemiologists, other laboratories, practitioners and CDC in identifying trends and sentinel events in tuberculosis; and interfacing with national data bases[1]."

Core PHL TB Services:

All public health laboratories should provide rapid reporting to providers, TB control programs and/or submitting laboratories in compliance with HIPAA confidentiality requirements.

All public health laboratories should work toward the incorporation of routine electronic reporting. Patient-centered databases are superior to sample-centered databases for this purpose.

Electronic reporting should include reporting to the tuberculosis control program as well as the test request submitter.

Electronic test ordering should be pursued for future implementation.

All public health laboratories should utilize Laboratory Information Management Systems (LIMS) as a means to maintain and manage tuberculosis data and reports. Labs should work toward systems that contain standardized data exchange language (SNOMED and LOINC codes) and systems capable for data exchange and interoperability with other systems, including CDC and PHLs.

REFERENCE AND SPECIALIZED TESTING: CORE FUNCTION 3

Core PHL Functions:

"Public health laboratories should have the ability to serve as the primary reference microbiology laboratory to: test for, and aid in the diagnosis of, unusual pathogens; confirm atypical laboratory test results; verify results of other laboratory tests; test epidemiologically-significant specimens with potential public health implications; provide reference diagnostic testing to private sector laboratories that may not have the capability to fully identify disease agents of public health importance[1]."

Core PHL TB Services:

All public health laboratories should have the capability to identify *M. tuberculosis* complex isolates using rapid methods such as DNA probe, nucleic acid amplification or HPLC.

All public health laboratories should perform or ensure species identification for *M. tuberculosis* and M. bovis (BCG). On request, identification of the BCG strain of M. bovis should be available, either at the state laboratory or as a reference service.

All public health laboratories should have the capability to identify M. tuberculosis complex isolates using rapid methods

All public health laboratories should perform or assure drug susceptibility testing for *M. tuberculosis* complex for first line drugs and second line drugs.

First line drug susceptibility testing should be performed in broth.

Second line drug susceptibility testing may not be available in all public health laboratories, but cultures should be sent to a reference laboratory for second line testing as soon as resistance to rifampin is suspected. Rapid referral is necessary when rifampin resistance is detected.

All public health laboratories should perform or assure molecular detection of resistance to rifampin in culture or smear-positive sputum sediment.

All public health laboratories should have the ability to confirm unusual or discordant laboratory results. Applied to the tuberculosis laboratory, examples include but are not limited to cases of *M. tuberculosis* complex drug resistance and cases where possible cross-contamination or false positives have occurred.

Due to the logistical limitations of currently available methods, Interferon gamma release assays (IGRA) testing is **NOT** considered a core service of public health TB laboratories. However, public health laboratories should collaborate with their TB Control Program to determine the need for IGRA in their jurisdiction and may implement or assure testing if resources are available. Other roles for public health laboratories that do not perform IGRA testing may include providing guidance to public health, hospital and independent laboratories regarding recommended uses of IGRA testing, results interpretation and quality control issues.

On the Molecular Detection of Drug Resistance

The molecular detection of resistance to rifampin is limited in its availability in the United States. Examples of methods currently in use include the Hain line probe assay or molecular beacons PCR. In the future, several "centers of excellence" laboratories may be established to provide this service.

Analysis of the impact of molecular beacons testing shows that multi drug resistant tuberculosis (MDR-TB) patients are put on the appropriate regimen and become smear negative six to eight weeks sooner when the molecular method of detecting drug resistance is used[5]. The study by O'Riordan, et al. found that MDR-TB patients who were diagnosed using rapid molecular methods for detection of drug resistance were started "on appropriate therapy a median of 51 days sooner than those diagnosed by conventional culture and sensitivity testing." Such patients are expected to be rendered non-infectious to others sooner by a similar six to eight week margin. This should significantly reduce the transmission of this serious and difficult-to-treat disease.

LABORATORY IMPROVEMENT AND REGULATION: CORE FUNCTION 6

Core PHL Functions:

"Public Health laboratories should have the ability to coordinate and promote quality assurance programs for private clinical laboratories through training and consultation. Exercise leadership and authority as the agency responsible for laboratory regulation and training in the clinical and environmental areas[1]."

Core PHL TB Services:

Public health laboratories should provide guidance regarding existing regulations to the TB Control Program and clinical laboratories within their jurisdiction.

Public Health laboratories should have the ability to coordinate and promote quality assurance programs

Public health laboratories should help to evaluate compliance and/or provide subject matter expert consultation to regulators regarding existing TB testing and specimen transport regulations.

Public health laboratories, in collaboration with TB Control Programs and other stakeholders, should participate in development of state regulations to require adequate laboratory testing for TB cases or suspects, reporting requirements, requirements to submit specimens, etc.

POLICY DEVELOPMENT: CORE FUNCTION 7

Core PHL Functions:

"Public health laboratories should have the ability to provide scientific and managerial leadership in developing state and federal public health policy, and in developing, promoting and integrating public health laboratory science into practice[1]."

Core PHL TB Services:

Public health laboratories should develop a utilization review policy to examine the over- or under-utilization of TB services offered within the laboratory. More information on the concept of utilization review can be seen in Appendix A.

Public health laboratories should evaluate laboratory specific data to inform changes in testing algorithms or monitor the utilization of tests.

Public health laboratories should engage in national policy discussions regarding TB diagnostics.

Public health laboratories should meet regularly with their TB Control program in order to foster communications surrounding the development of policies for proper utilization of diagnostic tools and other overlapping issues.

PUBLIC HEALTH RELATED RESEARCH: CORE FUNCTION 9

Core PHL Functions:

"Public health laboratories should have the ability to evaluate and implement new technologies and analytical methodologies to ensure that laboratories provide state-of-the-art, cost-effective and timely analytical and diagnostic services… This includes: Identifying the need for new laboratory methodologies for disease detection and prevention; Conducting research to improve laboratory tests for more effective disease surveillance, including rapid methods; Collaborate with academic and private sector researchers and other government agencies to adapt emerging technologies to public health surveillance[1]."

Core PHL TB Services:

As resources permit, public health laboratories should participate in the evaluation and validation of new laboratory techniques. Additionally, public health laboratories should engage in operational research, such as the cost and yield of solid culture media, value of additional specimens for the laboratory's patient population and other practical issues that may have different results in different patient populations and laboratory settings.

Public health laboratories should analyze their own data in order to guide policy decisions about required numbers of specimens, number and type of solid culture media, etc.

TRAINING AND EDUCATION: CORE FUNCTION 10

Core PHL Functions:

"Public health laboratories should have the ability to: sponsor training opportunities to improve scientific and technical skills of public health laboratory staff; provide or facilitate training courses and workshops for laboratory staff in both the private and public sectors, to continually upgrade the knowledge and skills essential for providing quality services in medical, environmental and public health laboratories[1]."

Core PHL TB Services:

Public health laboratories should provide in-depth training of new TB laboratory staff in areas including but not limited to:

- appropriate specimen collection and handling;
- appropriate utilization of services;
- technical procedures;
- safety; and
- other laboratory policies, including test ordering and turn-around-time standards.

Public health laboratories should provide continuing education to inform mycobacteriology laboratory staff in commercial and clinical laboratories of

On Training International Scientists

The limited availability of a well-trained, stable workforce in developing countries is well recognized. The provision of training on conventional and new diagnostic methods to international scientists is emphasized in the "Plan to Combat Extensively Drug-Resistant Tuberculosis Recommendations of the Federal Tuberculosis Task Force4". The plan indicates that a major component of control and prevention of XDRTB in the US includes some level of assistance with the control of TB in countries that are the source of immigrants, tourists and students visiting the US. Mycobacteriology laboratory personnel in the US may be poorly prepared to perform international training or consultation; courses in training international scientists should be made available.

up-to-date testing protocols, requirements for reporting to public health, need for submission of cultures for genotyping, etc.

Public health laboratories should participate in training and conferences provided by APHL, CDC and others to maintain proficiency and remain current on TB laboratory methods

As resources permit, public health laboratories should participate in the training of international scientists and consultants on proper TB laboratory techniques.

PARTNERSHIPS AND COMMUNICATION: CORE FUNCTION 11

Core PHL Functions:

"Public health laboratories should have the ability to develop and strengthen statewide partnerships among state, county and city public health leaders, managed care organizations, academia and private industry, to forward understanding of the important role played by public health laboratories in supporting the core functions of public health[1]."

Core PHL TB Services:

Public health laboratories should provide training of tuberculosis control staff regarding test ordering, turnaround time standards, resource limitations and result interpretation.

Public health laboratories should also cultivate partnerships with clinical laboratories for education and training related to tuberculosis laboratory work.

Public health laboratories should provide consultation to clinicians, laboratorians and TB control program personnel regarding:

- Services available and expected turnaround times.
- Content, utility and availability of current APHL Self-Assessment Tool.
- The importance of state public health laboratory systems approach. This includes partnerships with clinical laboratories to assure that up-to-date technologies are used, turnaround time goals are met, staff have adequate training and public health requirements, such as reporting of positive results and submission of cultures, are done in accordance with state regulations.

Public health laboratories should provide interpre-

Timely and accurate laboratory testing is a necessary component in achieving the goal of tuberculosis elimination in the United States.

tation of results, including results of testing performed by reference laboratories.

Be able to cite limitations of test results, sources of inaccuracies and when to request follow-up testing.

Public health laboratories should provide public health partners with requirements for reporting TB laboratory results to the health department.

Public health laboratories should ensure that a system is in place to expedite specimen/culture submission and initiation of PHL services when drug resistance is expected.

To the Future

The intent of this document is to present the groundwork for defining the core tuberculosis services that public health laboratories should offer or ensure and characterizing the role public health laboratories play in TB diagnosis. This document is also anticipated to evoke further discussion and refinement of these services and roles. Further clarification of "essential" versus "optional" functions and capabilities is also needed. Public health laboratories, public health officials, administrators and legislators must work together to ensure that laboratories are provided with the resources necessary to fulfill these core functions.

Timely and accurate laboratory testing is a necessary component in achieving the goal of tuberculosis elimination in the United States. Delayed testing or unreliable results lead to delays in therapy initiation and increased risk of transmission. Successful TB control relies on the development and maintenance of an integrated system that includes clinicians, laboratorians and TB controllers as well as a network of public and private laboratories working together to provide diagnostic testing services. Public health laboratories must lead the development of laboratory networks within their jurisdictions and work to improve and maintain communication among laboratories, clinicians and TB controllers. To the future, public health laboratories, as an essential element of tuberculosis elimination, must seek more resources and continue to promote and develop their capabilities to perform not only current, but also emerging laboratory technologies as they are developed to ensure the goal is met.

References

1 Association of Public Health Laboratories. (2000). Core functions and capabilities of state public health laboratories. Washington, DC: APHL

2 Association of Public Health Laboratories. (2009). Mycobacteriology: assessing your laboratory. Retrieved from http://www.aphl.org/aphlprograms/infectious/tuberculosis/Documents/Mycobacteria_TuberculosisAssessingYourLaboratory.pdf

3 Centers for Disease Control and Prevention. (2009). Plan to combat extensively drug-resistant tuberculosis recommendations of the federal tuberculosis task force. Morbidity and Mortality Weekly Report, 58(3), 1-43.

4 Centers for Disease Control and Prevention. (2009). Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis. Morbidity and Mortality Weekly Report, 58(1), 7-10

5 O'Riordan P, Schwab U, Logan S, et al. (2008). Rapid molecular detection of rifampin resistance facilitates early diagnosis and treatment of multidrug-resistant tuberculosis: case control study. PLoS One, 3(9), e1173.

Appendix A: Utilization Review in the TB Laboratory

Over- and under-utilization of TB services are common problems. This is especially true regarding NAAT and specimen submission. Laboratories should have policies in place that call for a periodic review examining how these services are used, resulting in subsequent education as appropriate. In addition to utilization of NAAT, laboratorians should consider periodic review of how often drug susceptibility testing is ordered on a single patient, how many specimens are collected and tested and by what methods, etc. An example of utilization review is:

Review numbers of specimens submitted per patient and tests requested.

- To assist in the diagnosis of new patients, three specimens are recommended for acid-fast smear and culture, with one specimen, preferably the first, being tested with NAAT. Inappropriate utilization could be failure to order NAAT.

- For diagnosed patients, to determine eligibility for release from isolation, three specimens are recommended, and acid-fast microscopy will generally be the only laboratory examination needed. A notable exception is patients who are known or suspected to have drug-resistant disease. For these patients, a negative culture result may be required for release from isolation. Inappropriate utilization could be ordering culture for all specimens in this category.

- For patients under treatment, specimens should be collected (often after two and five months of treatment) for **culture**, to evaluate treatment efficacy. Inappropriate utilization could be requesting nucleic acid amplification testing to attempt to monitor treatment efficacy.

Following a review of this type, results should be shared with the tuberculosis control program, and joint plans should be formulated to correct inappropriate test ordering.

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