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CDC’s Vision: TB Diagnostics Moving Forward

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APHL
San Diego by phone from Atlanta
June 2013
Where we are…
- Diverse laboratory perspectives at CDC, translating into different models and programs
- Field-based programmatic core through cooperative agreements
- Emphasis on access to rapid, molecular services
- Public health funding constraints

Where we might be going…
- Recognize that CDC has a biased view
- Evidence-based change
- Insistence on robust partnership
- Exploration of shared services
- Technologic advances may drive decentralization and increased testing
- Changes in health care market place
- More regulatory and policy effort needed

CDC’s “TB” Perspective
Resurgence associated with:
- Deficient infrastructure
- HIV epidemic
- Immigration
- Institutional transmission
- Multidrug-resistance (MDR) TB
- Less research

2013 Data
9,951 Cases
(Rate 3.2/100,000)
Annual CDC Domestic TB Budget
FY 1990–FY 2012*

USD (millions)

Year


CDC Federal Budget per Case

USD (millions)

Year


CPI-Adjusted

4500

5550

5
CDC’s TB Cooperative Agreements Enhance Laboratory Systems

• Introduced in the early 1990s in response to the resurgence

• In FY2012, USD 7.4 million were distributed for laboratory support in 64 jurisdictions: 8% of total DTBE cooperative agreement award

• Original purpose to provide resources for upgrade of laboratory services, shifting to “strengthening”

• Laboratory and program consultants work with public health professionals to improve laboratory systems
Plan to Combat Extensively Drug-Resistant Tuberculosis

Recommendations of the Federal Tuberculosis Task Force

Diagnostic laboratory Services
NAA Tests † and Diagnostic Delay

- Delay was a significant factor in 27 CDC-investigated outbreaks, 2002–2008*
- In 2009, PHL# performed NAA testing for *M. tuberculosis* for 14% of TB suspects
- Cautious guidelines in 1996 and 2000, due to limited evidence of programmatic effectiveness
- High cost and low demand
- In 2009, updated NAA test guidelines

† NAA tests are nucleic acid amplification tests.
#PHLs are public health laboratories.
NAA testing 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.
Other Laboratory Tests and Delay

- 28% of patients with negative sputum smears and positive sputum cultures are not started on treatment until culture result is available*
- Liquid culture—*M. tuberculosis* can take weeks to grow
- Among PHLs, 72% of specimens meet benchmark of identifying *M. tuberculosis* within 21 days of specimen receipt
- Underscores need for rapid (i.e., in hours) and accurate test for TB diagnosis, especially if AFB is smear negative
- August 1, first commercial molecular test to detect drug resistance received market authorization from FDA

CDC’s MDDR Service

• This CLIA* compliant, laboratory developed test was implemented in September 2009, after 1½ years of applied research

• Uses PCR † and DNA sequencing platforms

• Benefits clinicians and public health practitioners
  – Rapid confirmation of rifampin-resistant and MDR‡ TB
  – Second-line drug resistance information

*CLIA is Clinical Laboratory Improvement Amendments at www.cms.gov/clia; † PCR is polymerase chain reaction; ‡ MDR is multidrug-resistant, i.e., at least resistance to isoniazid and rifampin; The graphic shows a portion of a DNA sequence obtained on an Applied Biosystems 3130xl Genetic Analyzer using Foundation Data Collection version 3.0 software.
Molecular Detection of Drug Resistance Service

**Molecular Testing**

- **Isolate or Sediment**
  - PCR
  - DNA Sequencing
  - Molecular Results: TAT next business day, Interim report issued

**Conventional, growth-based DST**

- **Agar Proportion & MGIT PZA**
  - Conventional Results: 33-day average TAT, Final Report
Deployment

- Conduct translational research to establish clinical protocol, validate method, and develop reporting language
- Develop guidance document and web-based educational materials*
- Communicate directly with PHLs via webinar
- Current estimate, about 80% of MDR captured
- **TBLab@cdc.gov**, (404) 639-2455
- Evaluate service

*http://www.cdc.gov/tb/topic/laboratory/mddr.htm
Xpert MTB/RIF has high sensitivity and specificity for MTBC and RMP resistance

Low positive predictive value (PPV) for RMP resistance necessitates rapid confirmatory testing, while assuring culture, DST for other drugs, and smear

Major decentralizing shift, requiring substantial operations research and guidance development

CDC preliminary thinking: NAA test, role in infection control, and RMP resistant results

August 1, 2013: Cepheid Receives FDA Market Authorization for Xpert MTB/RIF… Revolutionary Tuberculosis Test Brings Accurate, Faster Results to U.S. Market
Policy Development

• Strategies are grounded in recommendations of the Federal TB Task Force and Advisory Council for the Elimination of Tuberculosis

• Regulation affects development of and access to molecular devices to diagnose tuberculosis
  • July 2012 FDASIA enables a more direct de novo pathway
  • Reclassification from Class III to II of molecular devices to detect MTBC may encourage development of diagnostic device

• CDC assists FDA in making the public health case for TB diagnostic tests
Genotyping

• Confirm epidemiological links, useful in outbreaks, refutes epidemiological links, separates relapse vs. re-infection, and identifies false positive laboratory results

• In 2011, performed on about 94% of the 8,042 cases with a positive culture

• Spoligotyping, 24-locus MIRU-VNTR

• CDC published “Best Practices for Genotyping-Based TB Outbreak Detection“

• This system relies on state public health staff linking the genotyping with local case data
Example, Flow of laboratory data and information

- Smear
- NAAT
- Culture & Identification
- 1st Line DST
- 2nd Line DST (38% state)

- 1st Line DST
- 2nd Line DST MDDR

- National TB Surveillance System
- Genotyping
- Electronic Report of a Verified Case
- GIMS

Clinical & Private
Local Public Health
State Public Health
CDC 19
Research and Development

• For MDDR
  • Comprehensive study* of nine loci for mutations associated with drug resistance and compared with culture-based DST data to determine accuracy
  • Analysis of the dataset serves as the basis for the MDDR clinical service
  • Research on discordant results is being continually used to improve accuracy
• For genotyping, R&D to contain cost and improve discriminatory power

APHL Is a Critical Partner

• Highly productive relationship through long-term cooperative agreement
• APHL’s NCHHSTP program manager works directly with DTBE and PHLs, across multiple programs
• Collaborate to provide an effective communication network with our public health laboratory partners
• CDC/APHL operational research provides the evidence to design interventions to enhance the system
Recent Collaborative Projects with APHL

• CDC provided one-time USD 3 million supplemental award to expand patient access to molecular diagnostics, 2010

• Expansion of NAA Testing for TB in PHL, 2011

• Based on national needs assessment, developed module-based, “Essentials for the Mycobacteriology Laboratory: Promoting Quality Practices”

• Exploring Novel Approaches to Shared TB Laboratory Services, 2012 and ongoing

• Performance Evaluation of Molecular Diagnostic Tests for Tuberculosis, 2012 and ongoing
Discussion

• As TB case rates continue to decline, but the number of specimens to examine is persist, there is a shared resource crisis in PHL

• Maintaining national momentum: cycle of laboratory R&D and uptake by PHLs, and now need for broader engagement of clinical laboratories

• Limited bioinformatics science capacity, both CDC and PHL

• Insufficient internal and external electronic, integrated data exchange, bridging clinical medicine and public health systems

• Broader “policy issues” on shared services, potential increase in decentralized testing, and Affordable Care Act (ACA)

• ACA aims to improve access (from an unstated public health framework), yet unclear how it might address laboratory services

• Changing workforce core competencies
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- CDC, DTBE: Phil LoBue, Roque Miramontes, Tom Navin
Background Slides
Focus Areas of Laboratory Capacity Team

- Focus on consultancy for strengthening laboratory systems primarily in the United States and U.S. affiliated Pacific Islands
- Comprehensive approach includes a number of essential focus areas
DTBE Laboratory Consultant Project Areas

Other Sites
Angela Starks- Houston, Los Angeles, San Diego, San Francisco, FSM, RMI, CNMI, Guam, American Samoa, Republic of Palau
Frances Tyrrell- New York City, Philadelphia, District of Columbia
Tracy Dalton- Puerto Rico

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- Tracy Dalton (tldalton@cdc.gov)
- Cortney Stafford (cstafford@cdc.gov)
Turn-around Times
Recommendations and Evaluation*

- Specimen delivery 24 hours of collection
- Report AFB smear result 24 hours of specimen receipt
- Report NAAT result 48 hours of specimen receipt
- Report identification of M. tuberculosis complex 21 days of specimen receipt
- Report first-line DST results 28 days of specimen receipt

<table>
<thead>
<tr>
<th>Measure</th>
<th>2009 % PHLs within time frame</th>
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<tbody>
<tr>
<td>Specimen receipt within 1 day</td>
<td>43</td>
</tr>
<tr>
<td>Smear result within 1 day</td>
<td>89</td>
</tr>
<tr>
<td>Positive NAAT result with 48 hours of specimen receipt</td>
<td>76</td>
</tr>
<tr>
<td>ID of MTBC within 21 days of specimen receipt</td>
<td>72</td>
</tr>
<tr>
<td>DST result within 28 days of specimen receipt</td>
<td>49</td>
</tr>
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*CDC. Tuberculosis Laboratory Aggregate Report. Atlanta, Georgia. USDHHS 2011.
Primary MDR TB
United States, 1993–2011*

*Updated as of June 25, 2012. Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.
Extensively drug-resistant TB (XDR TB) is defined as resistance to isoniazid and rifampin, plus resistance to any fluoroquinolone and at least one of three injectable second-line anti-TB drugs.
Global Distribution and Prevalence of MDR TB

Total MDR cases >500,000

Percentage among Retreatment Cases

WHO 2010 Global Report