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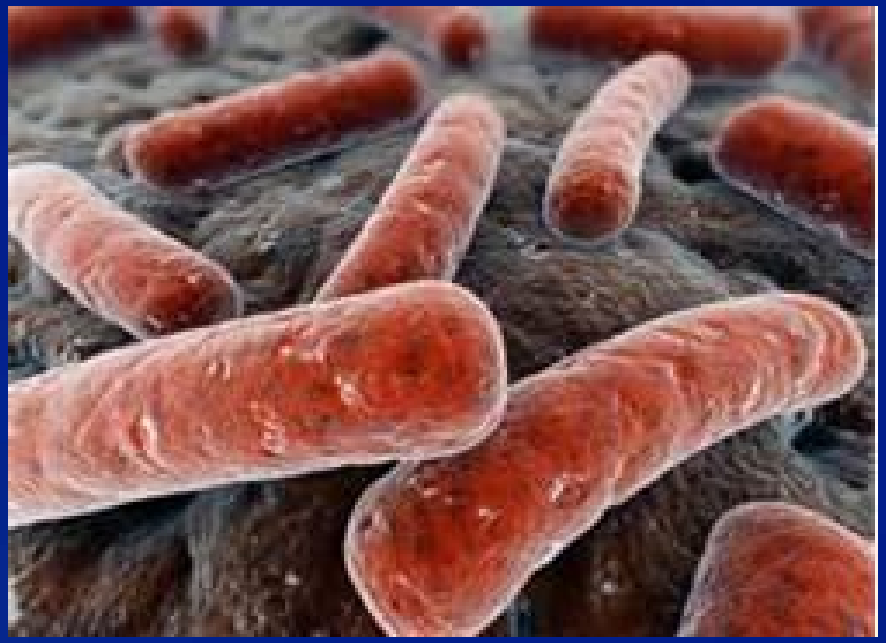
CDC's Vision: TB Diagnostics Moving Forward

Michael Iademarco, M.D., M.P.H.
Captain, U.S. Public Health Service
Chief, Laboratory Branch

APHL
San Diego by phone from Atlanta
June 2013

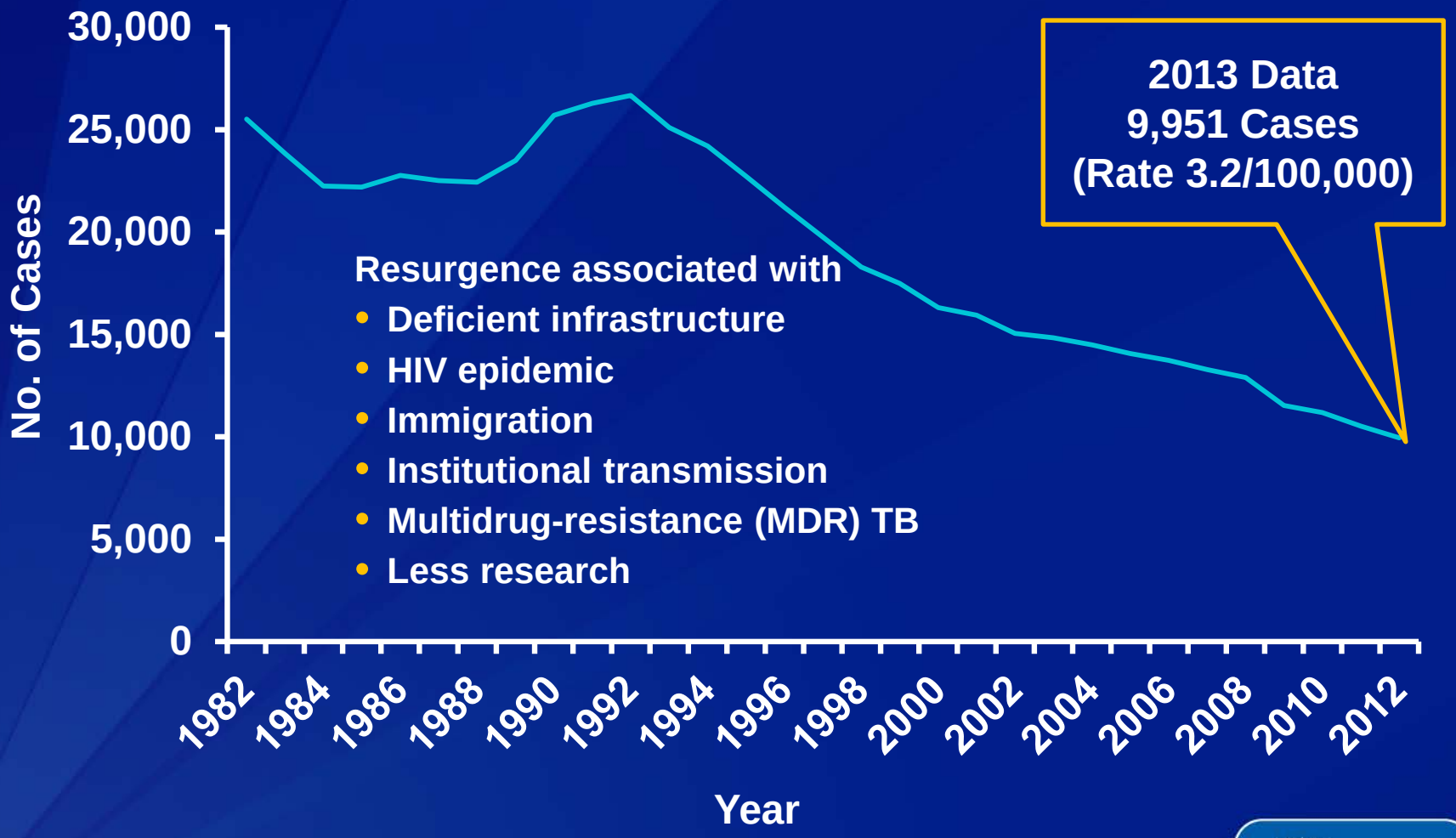


National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of Tuberculosis Elimination

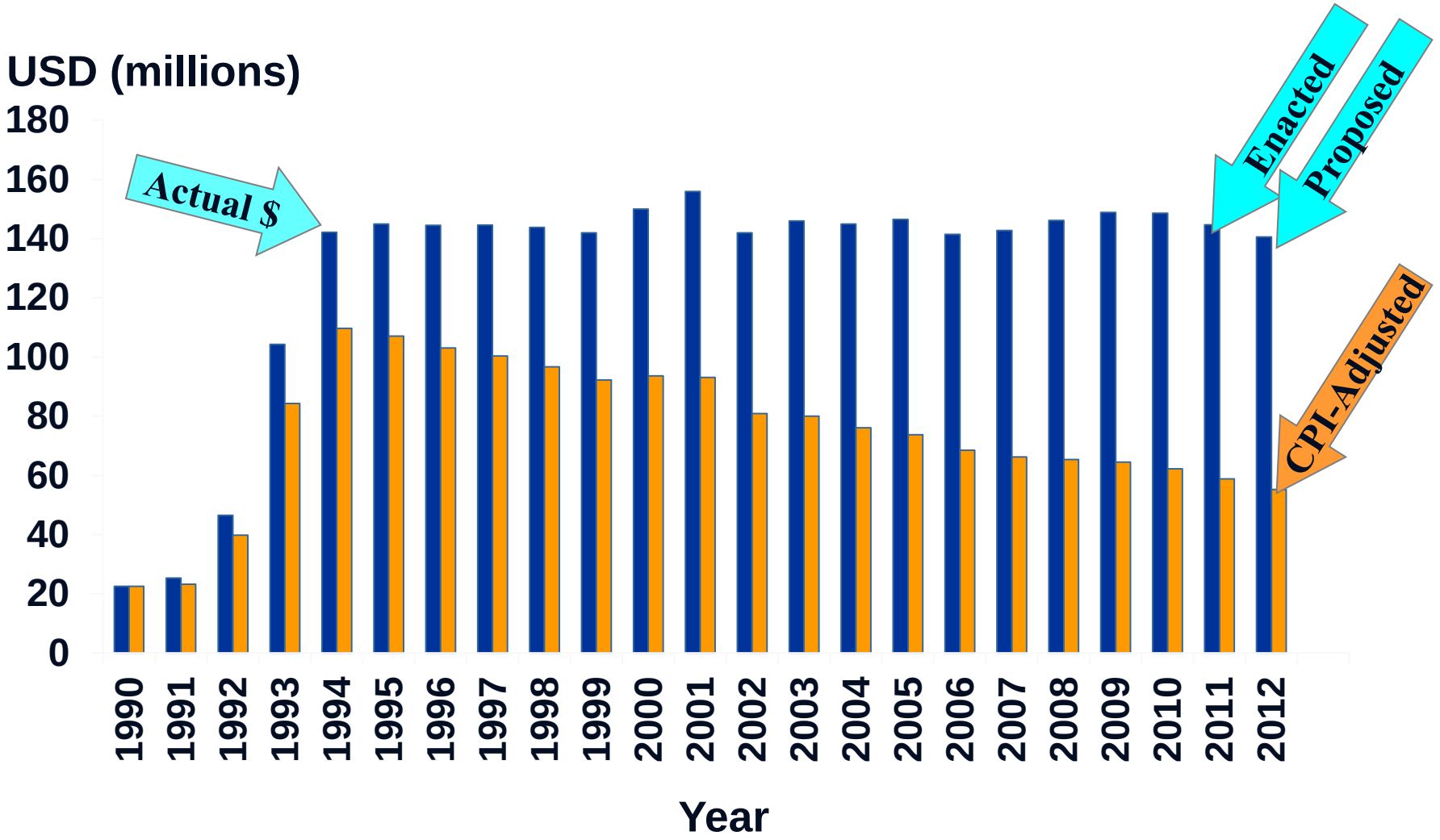
CDC's "TB" Perspective

- 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

Reported TB Cases
United States, 1982–2012

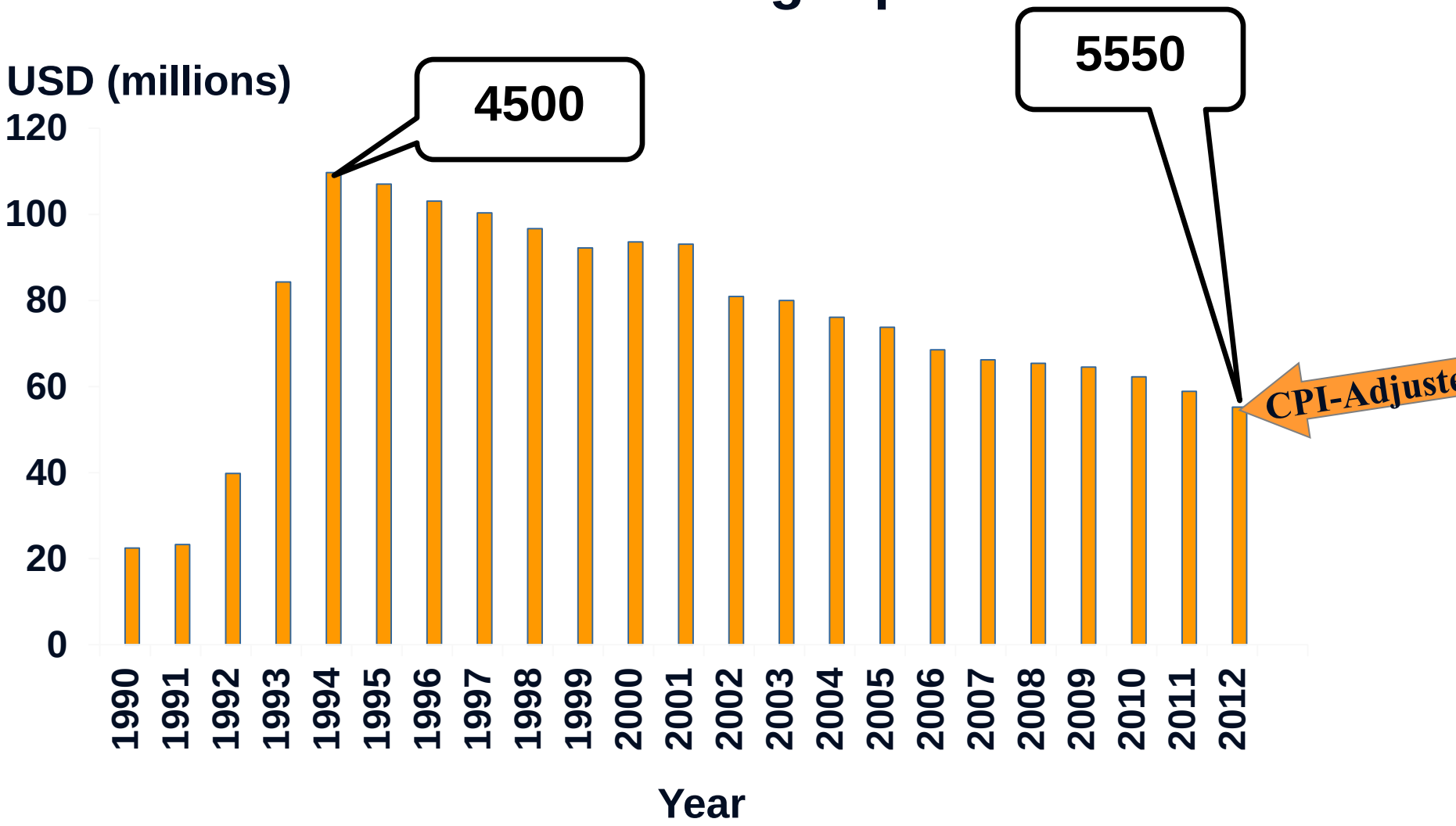


Annual CDC Domestic TB Budget FY 1990–FY 2012*



*1990 Dollars, Adjusted by Consumer Price Index for Medical Care. Includes TB/HIV and laboratory dollars. Updated 4/9/2012.

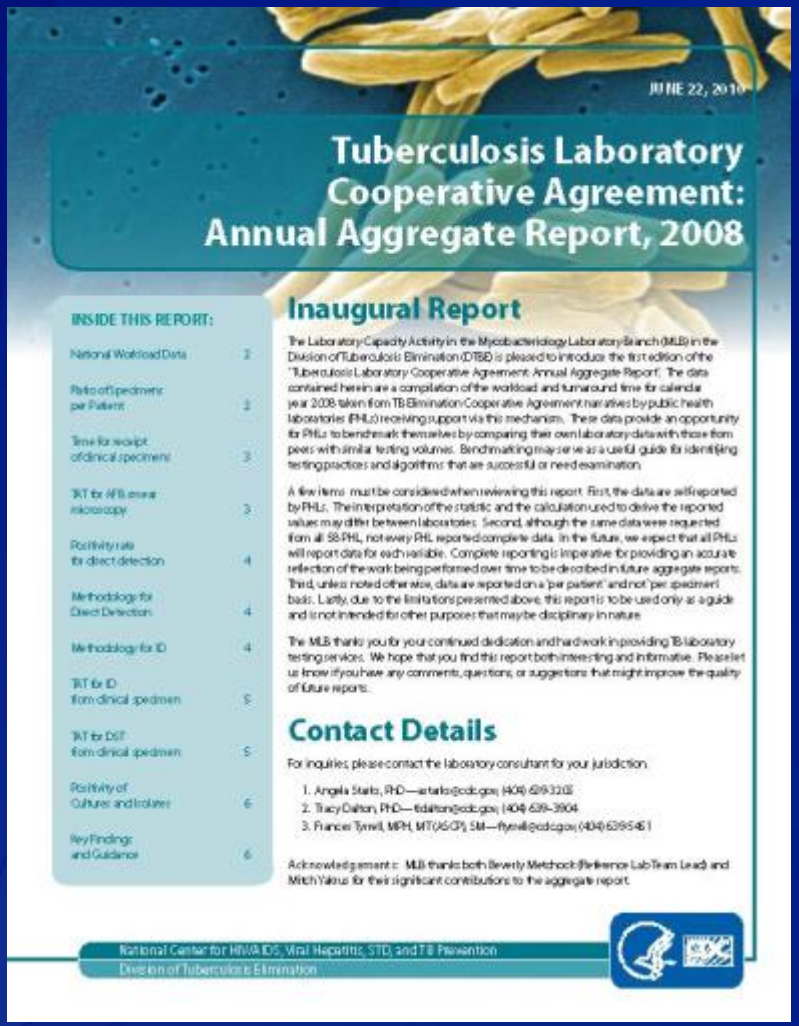
CDC Federal Budget per Case



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

Aggregate Report



JUNE 22, 2010

Tuberculosis Laboratory Cooperative Agreement: Annual Aggregate Report, 2008

INSIDE THIS REPORT:

Inaugural Report

The Laboratory Capacity Activity in the Mycobacteriology Laboratory Branch (MLB) in the Division of Tuberculosis Elimination (DTBE) is pleased to introduce the first edition of the "Tuberculosis Laboratory Cooperative Agreement: Annual Aggregate Report". The data contained herein are a compilation of the workload and turnaround time for calendar year 2008 taken from TB Elimination Cooperative Agreement narratives by public health laboratories (PHLs) receiving support via this mechanism. These data provide an opportunity for PHLs to benchmark themselves by comparing their own laboratory data with those from peers with similar testing volumes. Benchmarking may serve as a useful guide for identifying testing practices and algorithms that are successful or need examination.

A few items must be considered when reviewing this report. First, the data are self-reported by PHLs. The interpretation of the statistic and the calculation used to derive the reported values may differ between laboratories. Second, although the same data were requested from all 58 PHL, not every PHL reported complete data. In the future, we expect that all PHLs will report data for each variable. Complete reporting is imperative for providing an accurate reflection of the work being performed over time to be described in future aggregate reports. Third, unless noted otherwise, data are reported on a "per patient" and not "per specimen" basis. Lastly, due to the limitations presented above, this report is to be used only as a guide and is not intended for other purposes that may be disciplinary in nature.

The MLB thanks you for your continued dedication and hard work in providing TB laboratory testing services. We hope that you find this report both interesting and informative. Please let us know if you have any comments, questions, or suggestions that might improve the quality of future reports.

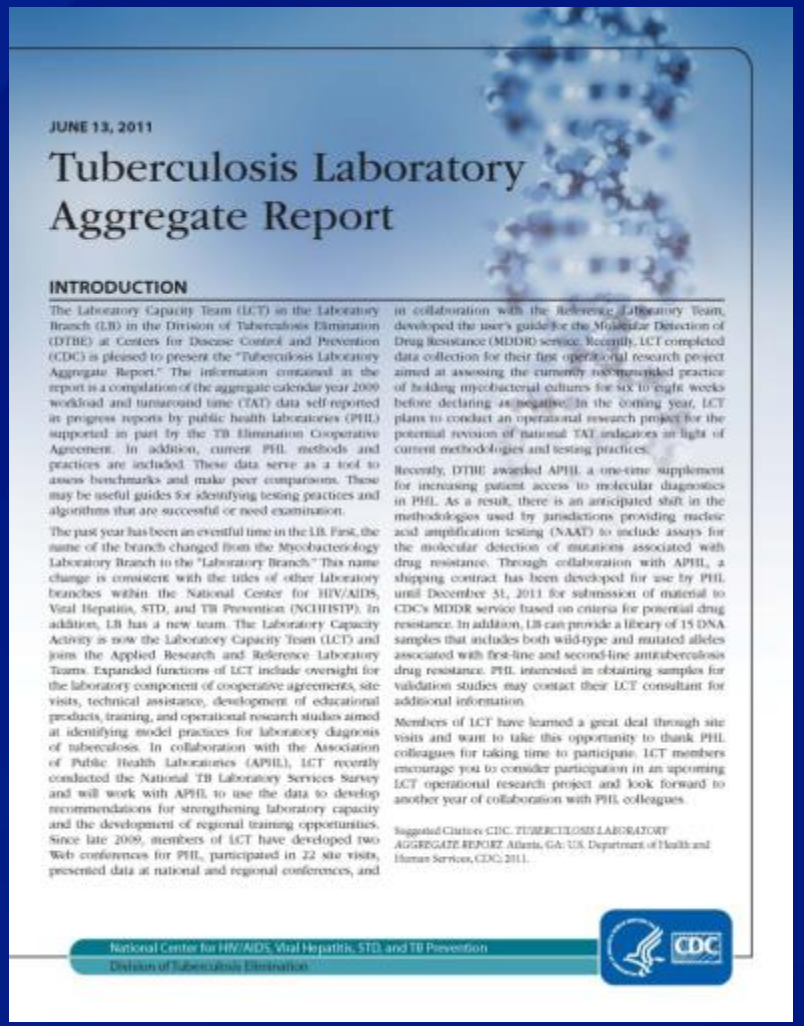
Contact Details

For inquiries, please contact the laboratory consultant for your jurisdiction.

1. Angela Starks, PhD—astarks@cdc.gov; (404) 639-3103
2. Tracy Dalton, PhD—tdalton@cdc.gov; (404) 639-3904
3. Frances Tyrrell, MPH, MT(ASCP), SM—ftyrrell@cdc.gov; (404) 639-8451

Acknowledgements: MLB thanks both Beverly Metchock (Reference Lab Team Lead) and Mitch Yakrus for their significant contributions to the aggregate report.

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of Tuberculosis Elimination



JUNE 13, 2011

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.

Suggested Citation: CDC. TUBERCULOSIS LABORATORY AGGREGATE REPORT. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2011.

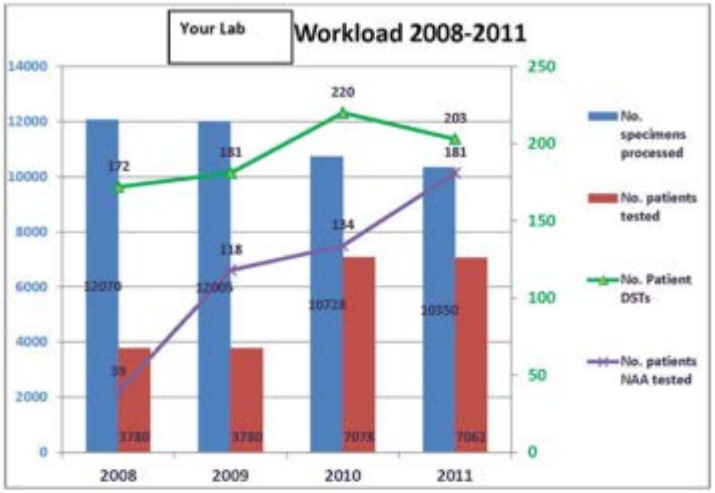
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of Tuberculosis Elimination

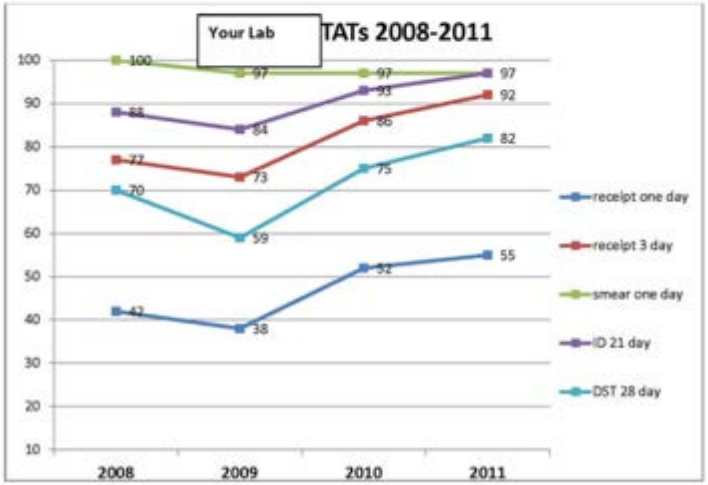
Posted to CDC website
http://www.cdc.gov/tb/publications/reportsarticles/labreports.htm

Individualized Reports for PHLs

Year	2009	% Receipt in 2 days	54
Grantee	Your Lab	% Receipt in 3 days	73
No. specimens	12005	Smear: % w/in 1 da	97
No. patients	3780	Smear: % w/in 2 da	99
No. (+) TB patients	76	Smear: % w/in 3 days	100
No. patient isolates	440	ID: % w/in 21 days	84.2
No. isolates (+) TB	84	DST: % w/in 28 days	58.9
No. patients DSTs	181	No. patients TB in 48 hrs.	42
No. patients NAAT	118	Ratio specimens to patients	3.2
No. patients (+) NAAT MTBC	53	Culture positivity	2.01
Patients genotyped	148	Isolate positivity	19.09
% Receipt in 1 day	38	NAAT positivity	44.92

Year	2011	% Receipt in 2 days	74
Grantee	Your Lab	% Receipt in 3 days	92
No. specimens	10350	Smear: % w/in 1 da	97
No. patients	7062	Smear: % w/in 2 da	97
No. (+) TB patients	93	Smear: % w/in 3 days	100
No. patient isolates	465	ID: % w/in 21 days	96.65
No. isolates (+) TB	58	DST: % w/in 28 days	81.9
No. patients DSTs	203	No. patients TB in 48 hrs.	166
No. patients NAAT	181	Ratio specimens to patients	1.5
No. patients (+) NAAT MTBC	46	Culture positivity	1.32
Patients genotyped	119	Isolate positivity	12.47
% Receipt in 1 day	55	NAAT positivity	25.41





MMWR™
Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr

Recommendations and Reports | February 13, 2009 / Vol. 58 / No. RR-3

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.
*Mitruka K, et al. Emerg Infect Dis 2011;17(3):425-431
#PHLs are public health laboratories.

MMWR™
Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr
Weekly January 16, 2009 / Vol. 58 / No. 1

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.

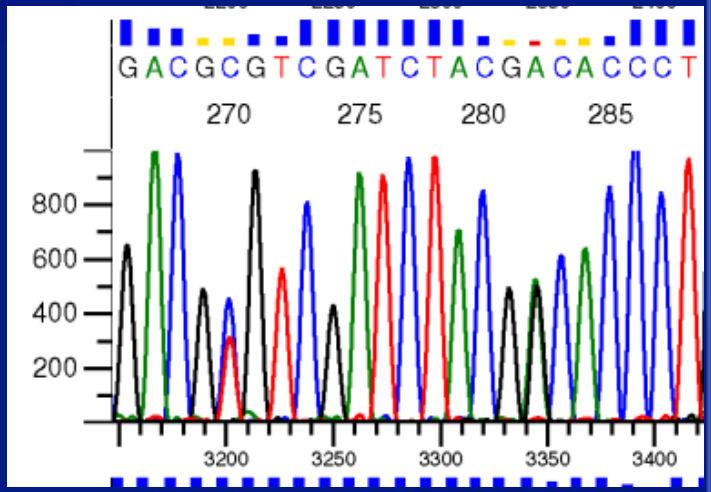
Other Laboratory Tests and Delay

- 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 2009–2010 U.S. National TB Surveillance System; unpublished Data.

CDC's MDDR Service

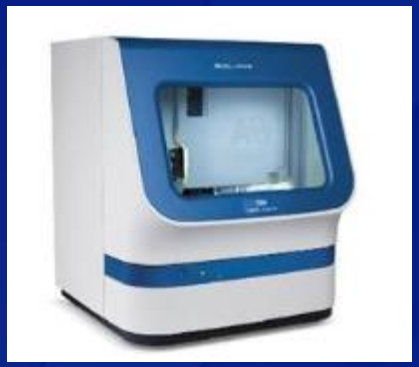
- This CLIA* compliant, laboratory developed test was implemented in September 2009, after 1½ years of applied research
- Uses PCR † and DNA sequencing platforms
- Benefits clinicians and public health practitioners
  - Rapid confirmation of rifampin-resistant and MDR‡ TB
  - Second-line drug resistance information



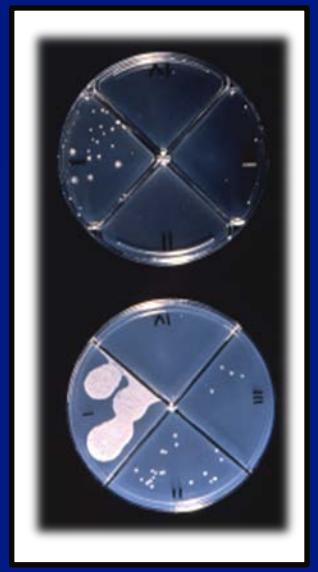
*CLIA is Clinical Laboratory Improvement Amendments at www.cms.gov/clia; † PCR is polymerase chain reaction; ‡ MDR is multidrug-resistant , i.e., at least resistance to isoniazid and rifampin; The graphic shows a portion of a DNA sequence obtained on an Applied Biosystems 3130xl Genetic Analyzer using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

Molecular Detection of Drug Resistance Service

Molecular Testing



Conventional, growth-based DST



Isolate or Sediment

PCR

DNA Sequencing

Molecular Results:
TAT next business day
Interim report issued

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

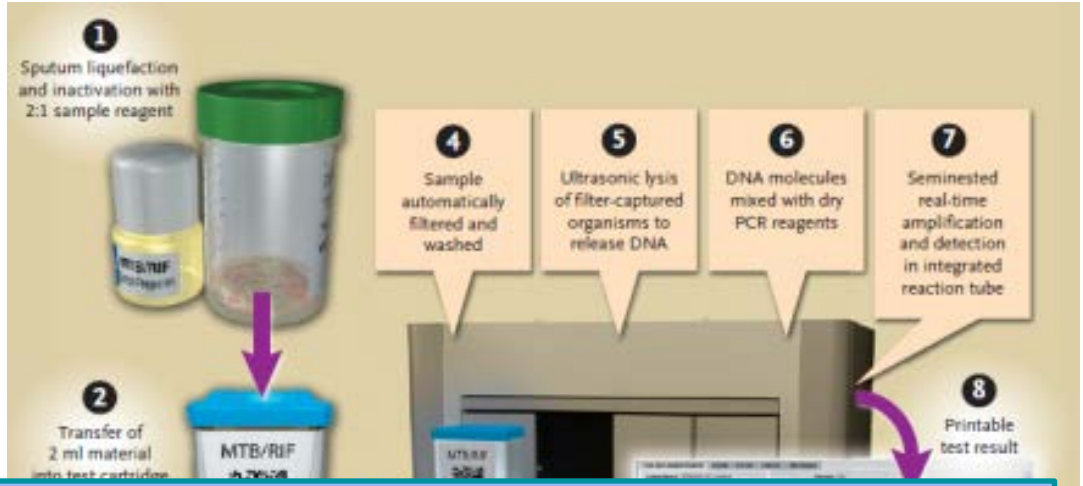
*http://www.cdc.gov/tb/topic/laboratory/mddr.htm

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 9, 2010 VOL. 363 NO. 11

Boehme CC, et al

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance



REUTERS

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

- **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**

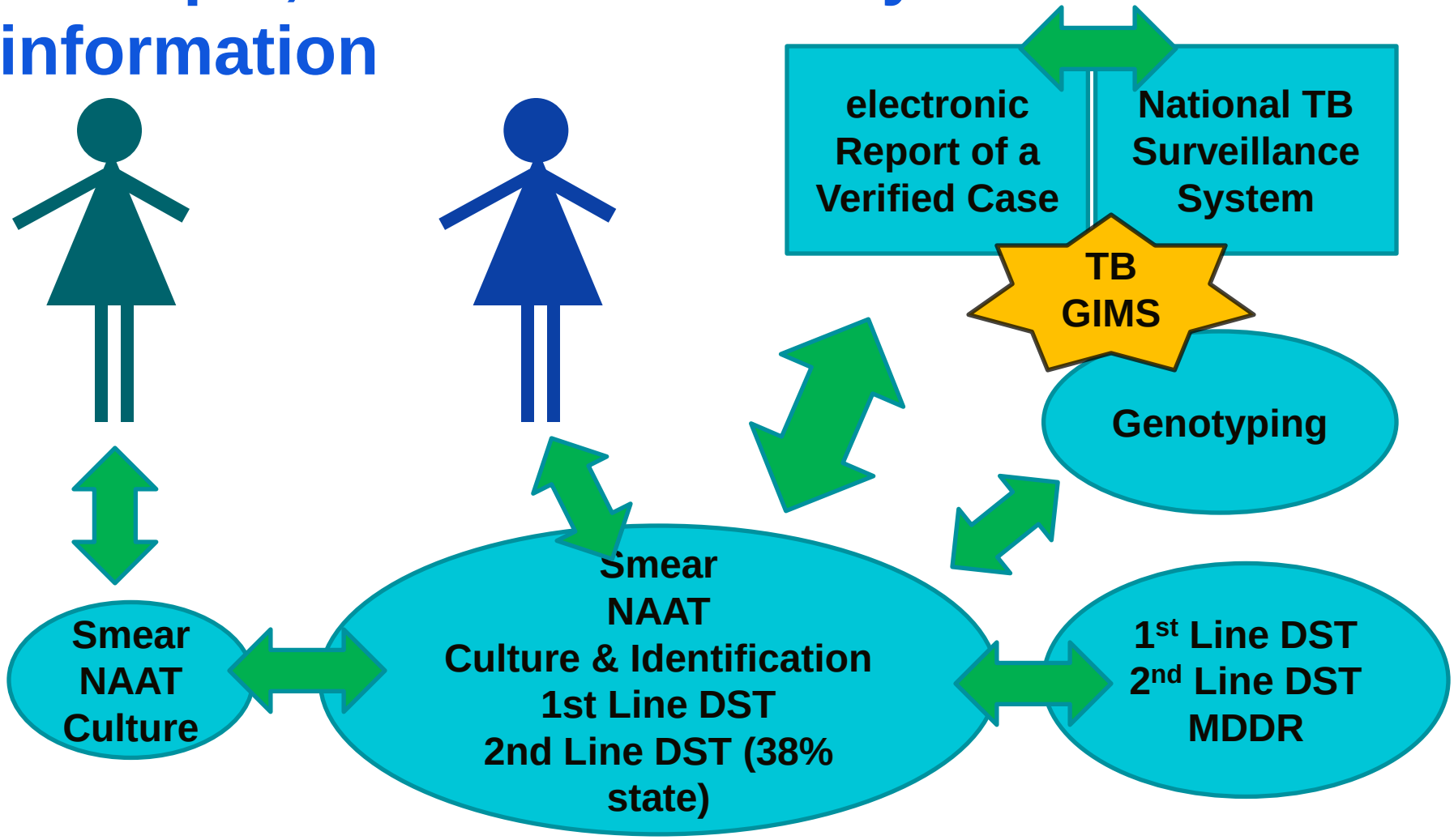
Policy Development

- 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



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

*Campbell PJ, Morlock GP, Sikes RD, Dalton TL, Metchock B, Starks AM, Hooks DP, Cowan LS, Plikaytis BB, Posey JE. 2011. Molecular detection of mutations associated with first and second-line drug resistance compared with conventional drug susceptibility testing in *M. tuberculosis*. *Antimicrob Agents Chemother.* **55**(5): 2032-41

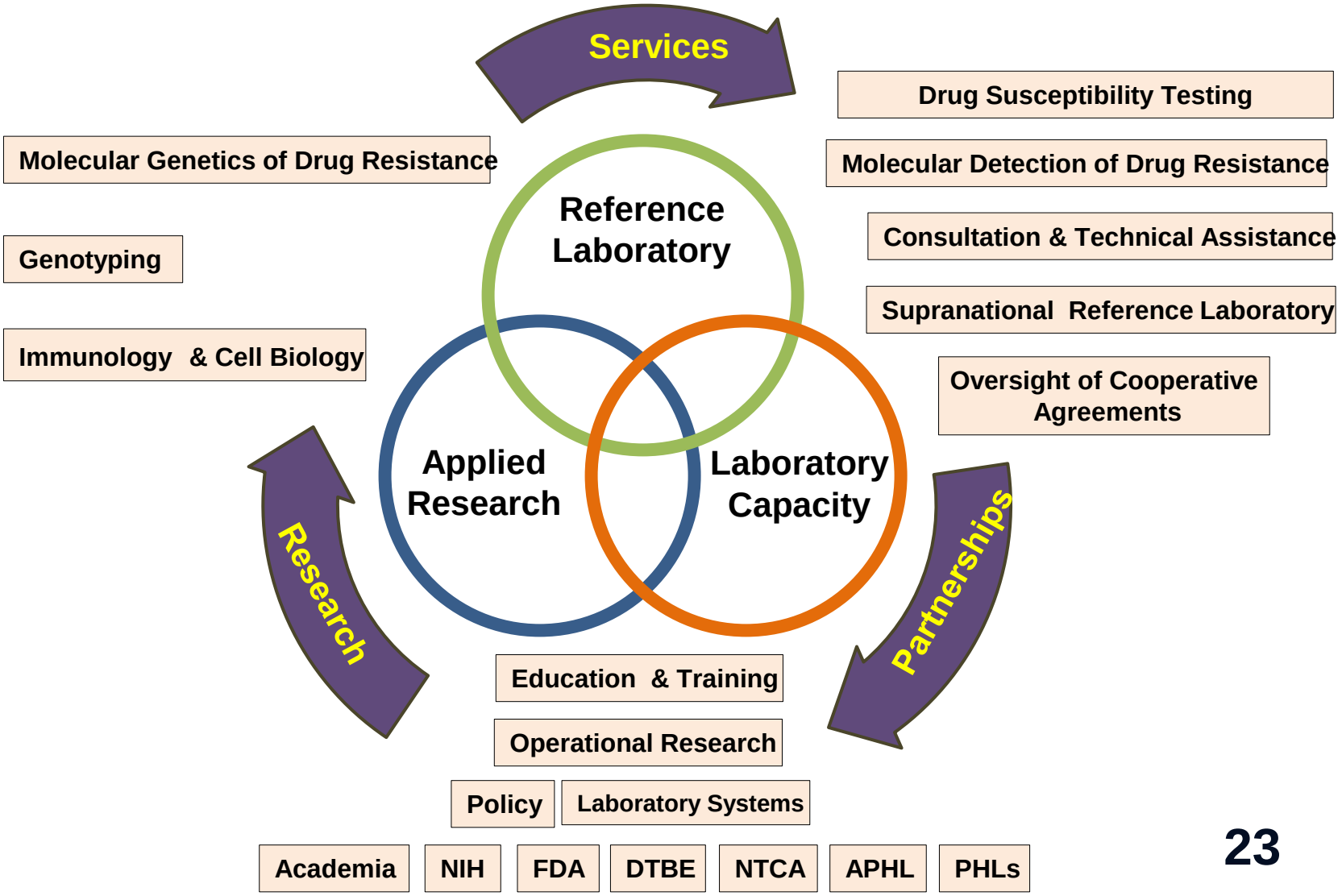
APHL Is a Critical Partner

- 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

CDC's Laboratory Branch



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

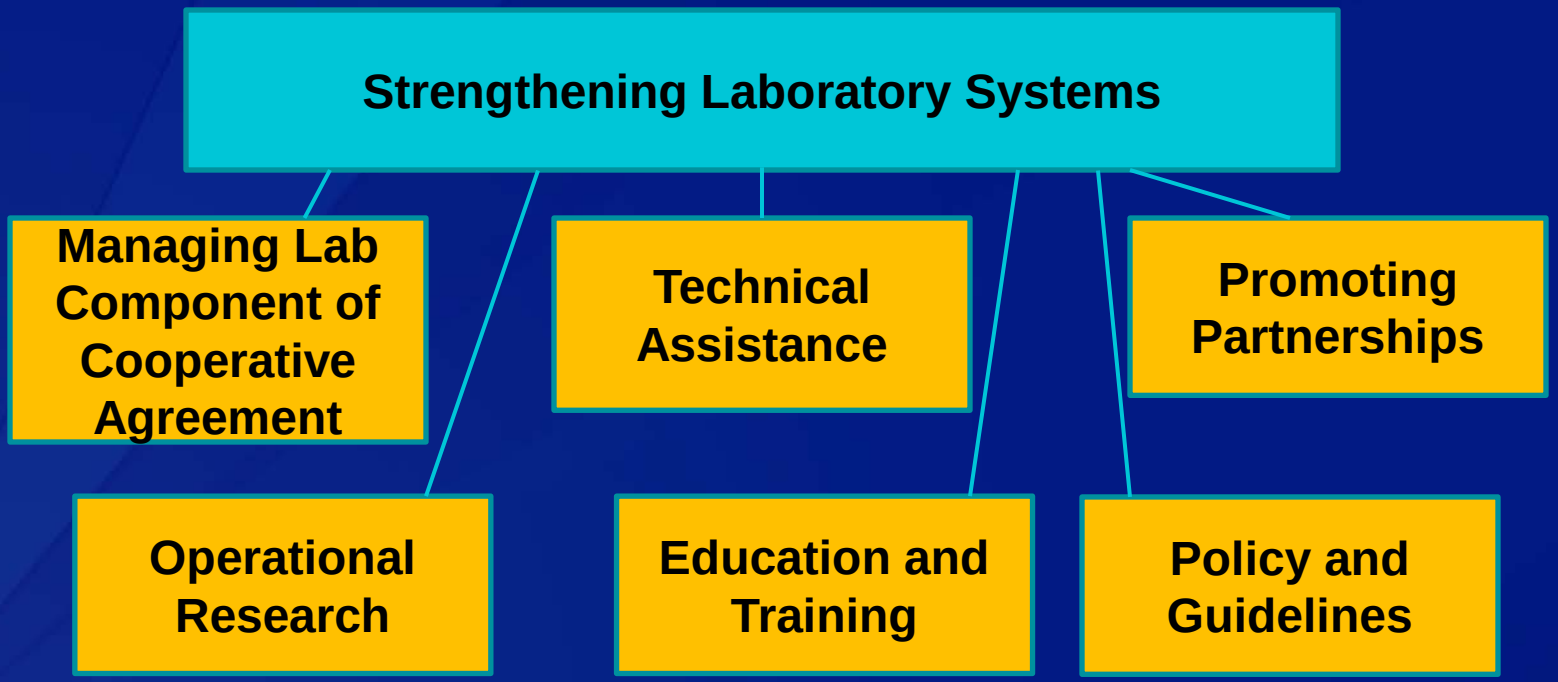
Acknowledgements

- State and Local Public Health Programs and Laboratories
- Association of Public Health Laboratories
- CDC's DTBE Laboratory Branch, Bonnie Plikaytis
  - Reference Laboratory Team, Beverly Metchock, Dr. P.H. D(ABMM), and Jeffrey Driscoll, Ph.D.
  - Applied Research, Jamie Posey, Ph.D.
  - Laboratory Capacity Team, Angela Starks, Ph.D., and Tracy Dalton, Frances Tyrrell, Mitchell Yakrus
- CDC, DTBE: Phil LoBue, Roque Miramontes, Tom Navin

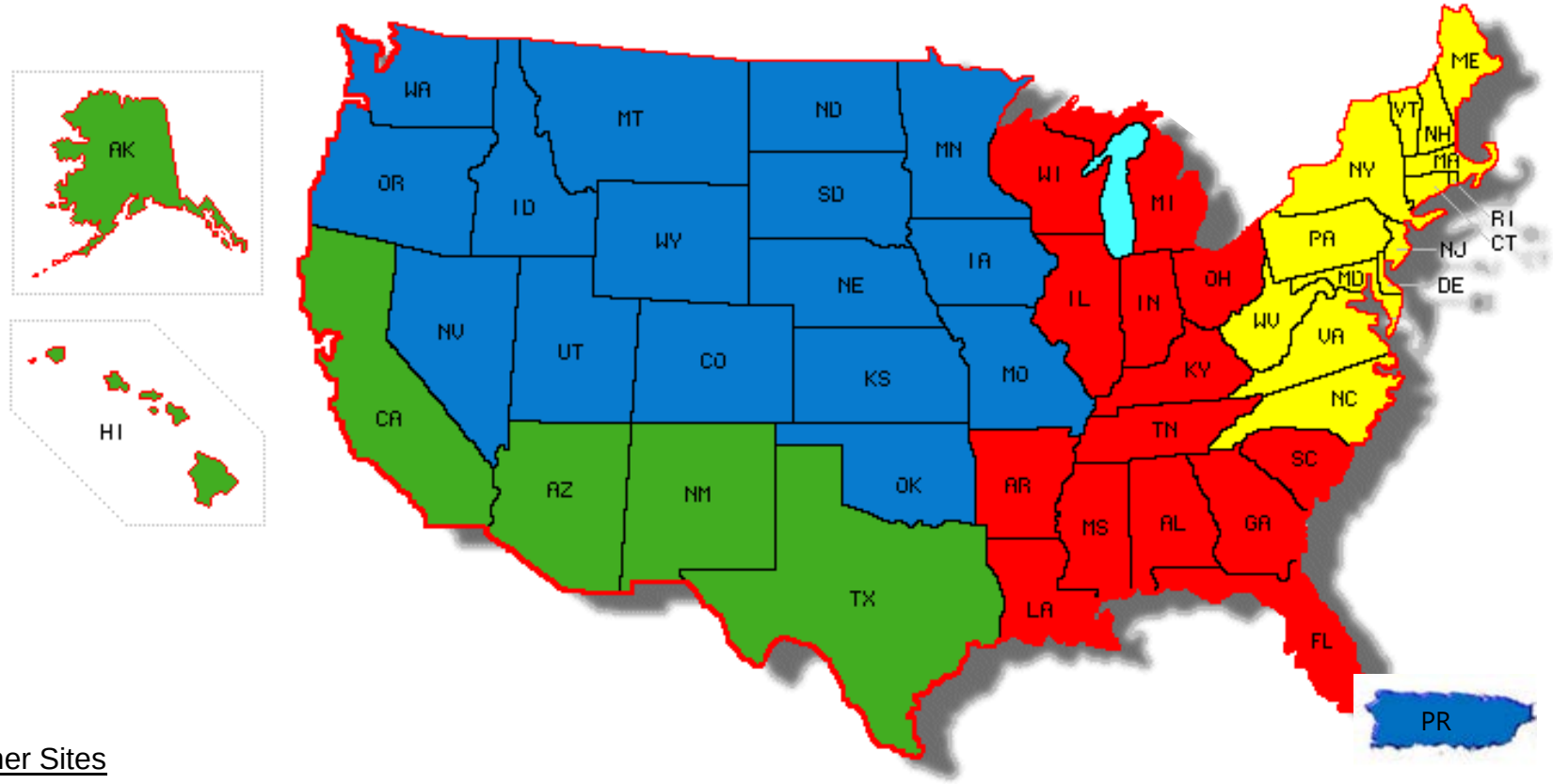
Background Slides

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

- Angela Starks (astarks@cdc.gov)
- Frances Tyrrell (ftyrrell@cdc.gov)
- Tracy Dalton (tldalton@cdc.gov)
- Cortney Stafford (cstafford@cdc.gov)

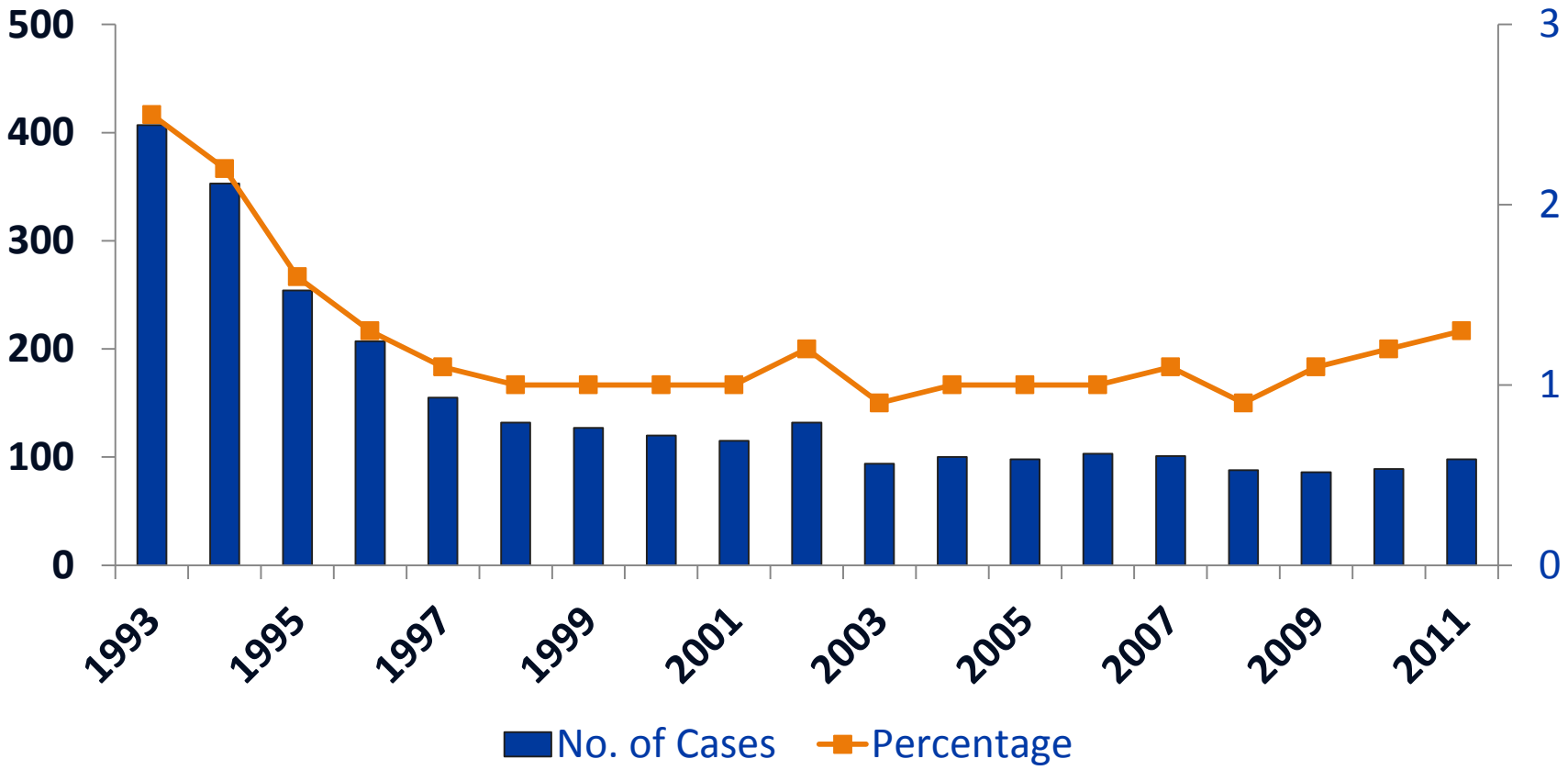
Turn-around Times Recommendations and Evaluation*

- 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

Measure	2009 % PHLs within time frame
Specimen receipt within 1 day	43
Smear result within 1 day	89
Positive NAAT result with 48 hours of specimen receipt	76
ID of MTBC within 21 days of specimen receipt	72
DST result within 28 days of specimen receipt	49

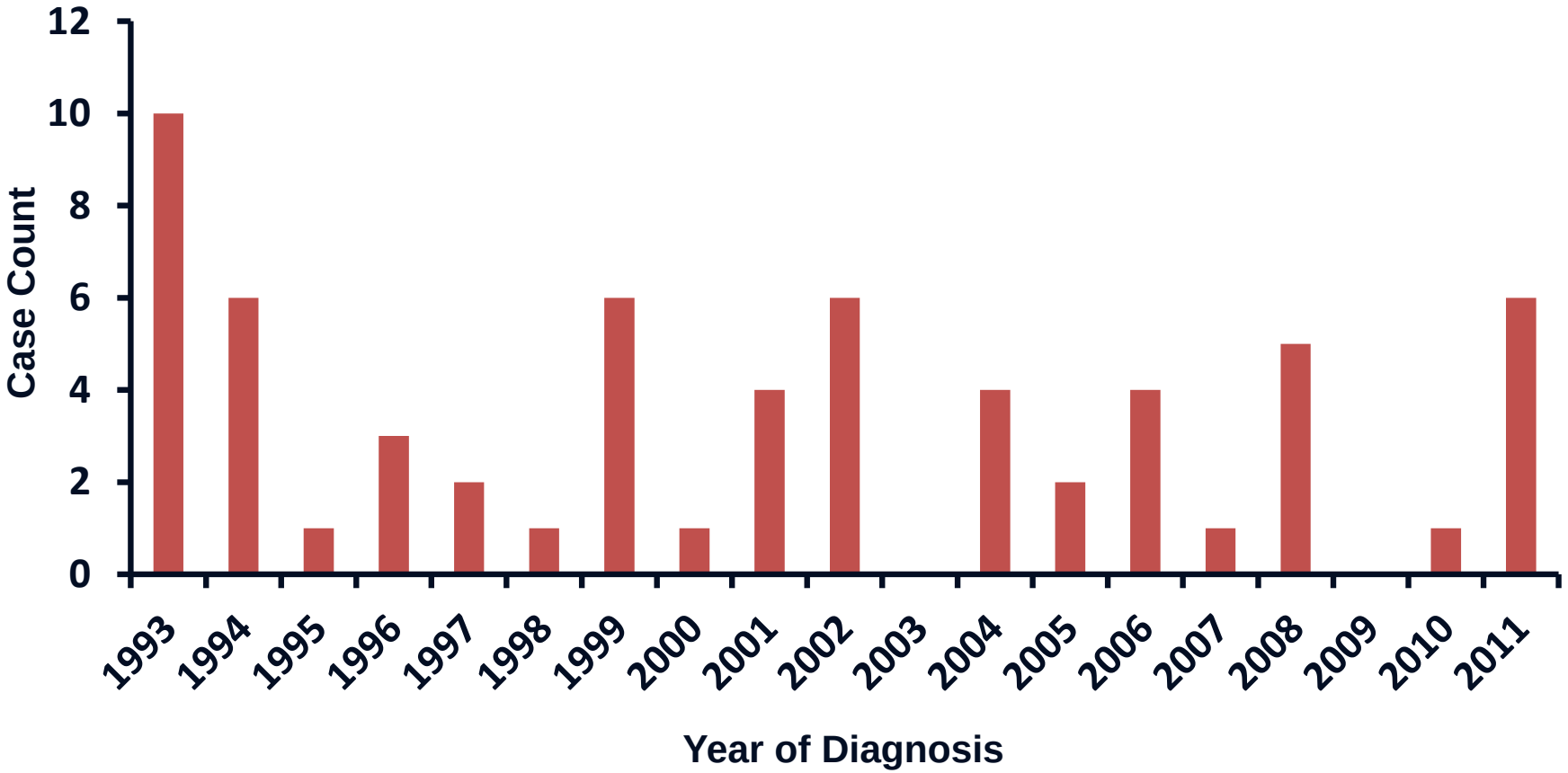
*CDC. *Tuberculosis Laboratory Aggregate Report.* Atlanta, Georgia. USDHHS 2011

Primary MDR TB
United States, 1993–2011*



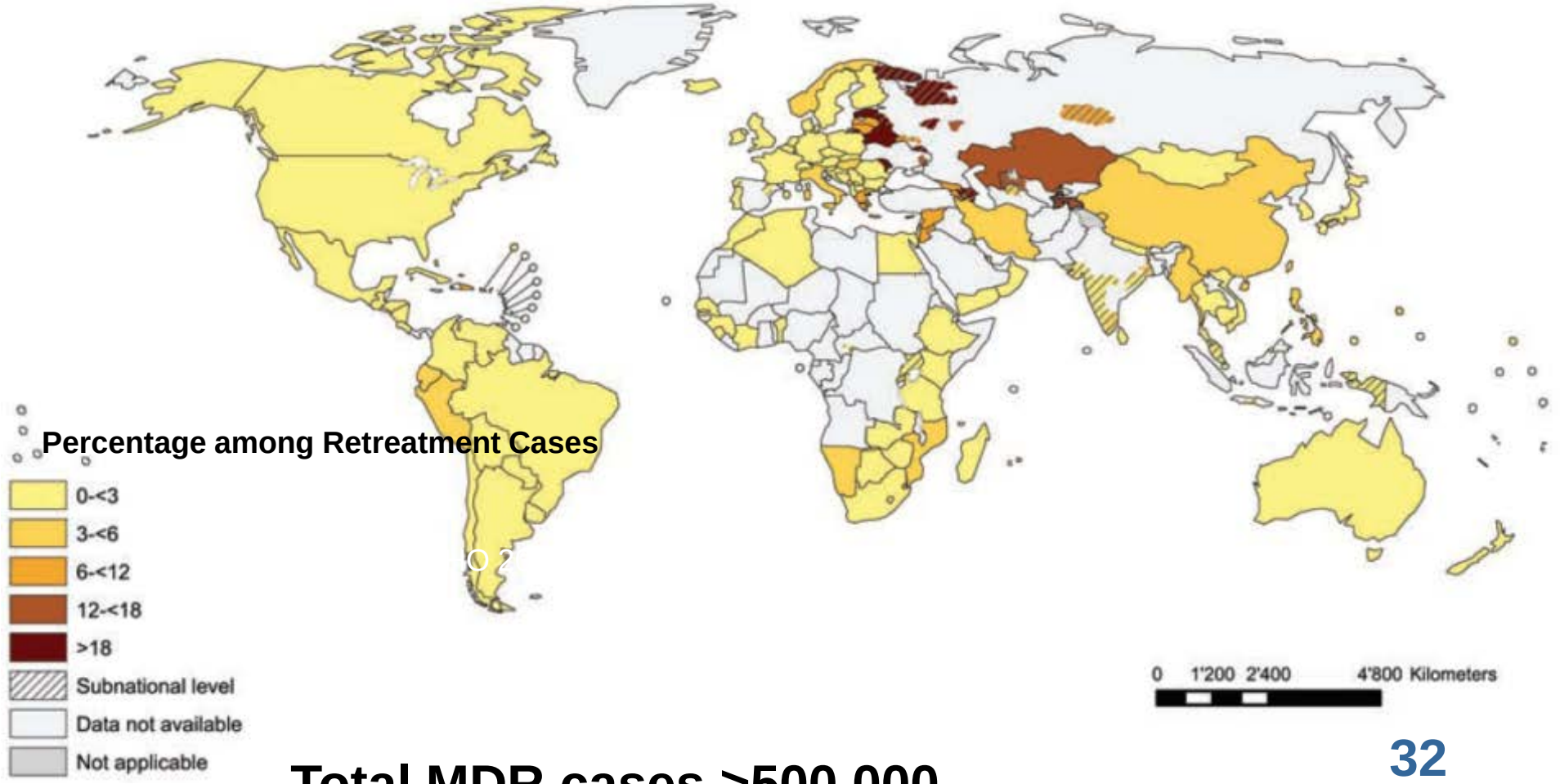
*Updated as of June 25, 2012. Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.

XDR TB Case Count Defined on Initial DST by Year, 1993–2011*



* Drug susceptibility test; Updated as of June 25, 2012; 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

WHO 2010 Global Report