

Highlights of 2011 *CDC PZA Day* Conclusions and Action Items

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**Demystifying Pyrazinamide—Challenges and
Opportunities**
Baltimore, Maryland
September 5, 2012

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

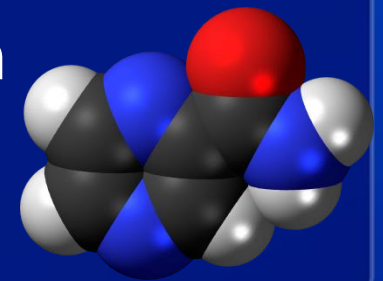


Purpose, Enhance U.S. Government Coordination

- **Convened by U.S. TB Federal Task Force**
- **Principally, CDC, FDA, and NIH, with participation of Global Alliance for TB Drug Development**
- **Review CDC activity and interest**
- **Seek NIH and FDA input**
- **Look for more efficient ways forward**
- **Plan next steps with outside partners**

Status of Proposed Actions

- CDC continuing R&D for PZA resistance testing for clinical reference service and trials
- CDC and NIH fostering development of mutation database including defining essential components
- Diagnostic Research Forum discussed plan for rapid *pncA* sequencing for use in clinical trials; DAIDS and partners now implementing
- NIH hosting PZA meeting in 2012, with partners



CDC Presented...

- **Preliminary analysis of PZA-resistant TB in National TB Surveillance System**
- **PZA experience in CDC's national reference services, including molecular detection of drug resistance**
- **PZA experience of the Preserving Effective Treatment Study (PETTS)**
- **Applied basic laboratory research, aimed at a mechanistic understanding of PZA resistance and a better approach to testing (Posey)**

PZA Resistance, United States

- **National TB Surveillance System***
 - **38 states , routine testing, 1999–2009**
 - **MDR TB cases, 38%; non-MDR, 2%**
 - **Increase mono-resistance, not related to *M. bovis***
- **TB Epidemiologic Studies Consortium****
 - **About one-third of U.S. MDR TB cases enrolled, including from three large states, using source documents, 2005–2007**
 - **47% (vs. 42% for NTSS), but through treatment**

* Kurbatova and Cegielski personal communication

** Marks, S, TO28 preliminary results, presented to study staff, May, 2012

Reference Laboratory Perspectives

- **Change in method from Bactec™ 460 TB to non-radiometric MGIT™ 960 system and introduction of VersaTREK® Myco system**
- **Increase in referral volume for PZA DST**
- **CDC's Model Performance Evaluation Program able to compare same strains over time, some evidence of increase in false resistance***
- **Increasing reports, e.g., Simons et al, JCM 2012, emergence of false resistance**

*Angra, P, JCM, 2012

PETTS

- **Almost 1300 baseline isolates from MDR TB patients, from 8 countries***
- **PZA testing put on hold due to concerns for false resistance and then delayed due to work load**
- **In a preliminary set, 112 of 174 (64%) were resistant to PZA (range among countries, 45–78%)**
- **Currently examining PZA DST and *pncA* in core set of 249 patients**

* Dalton et al, Lancet, August 30, 2012

Acknowledgements

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NIH: Richard Hafner, Barbara Laughon, Peter Kim, Christine Sizemore, Sharon Williams

Background Slides

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
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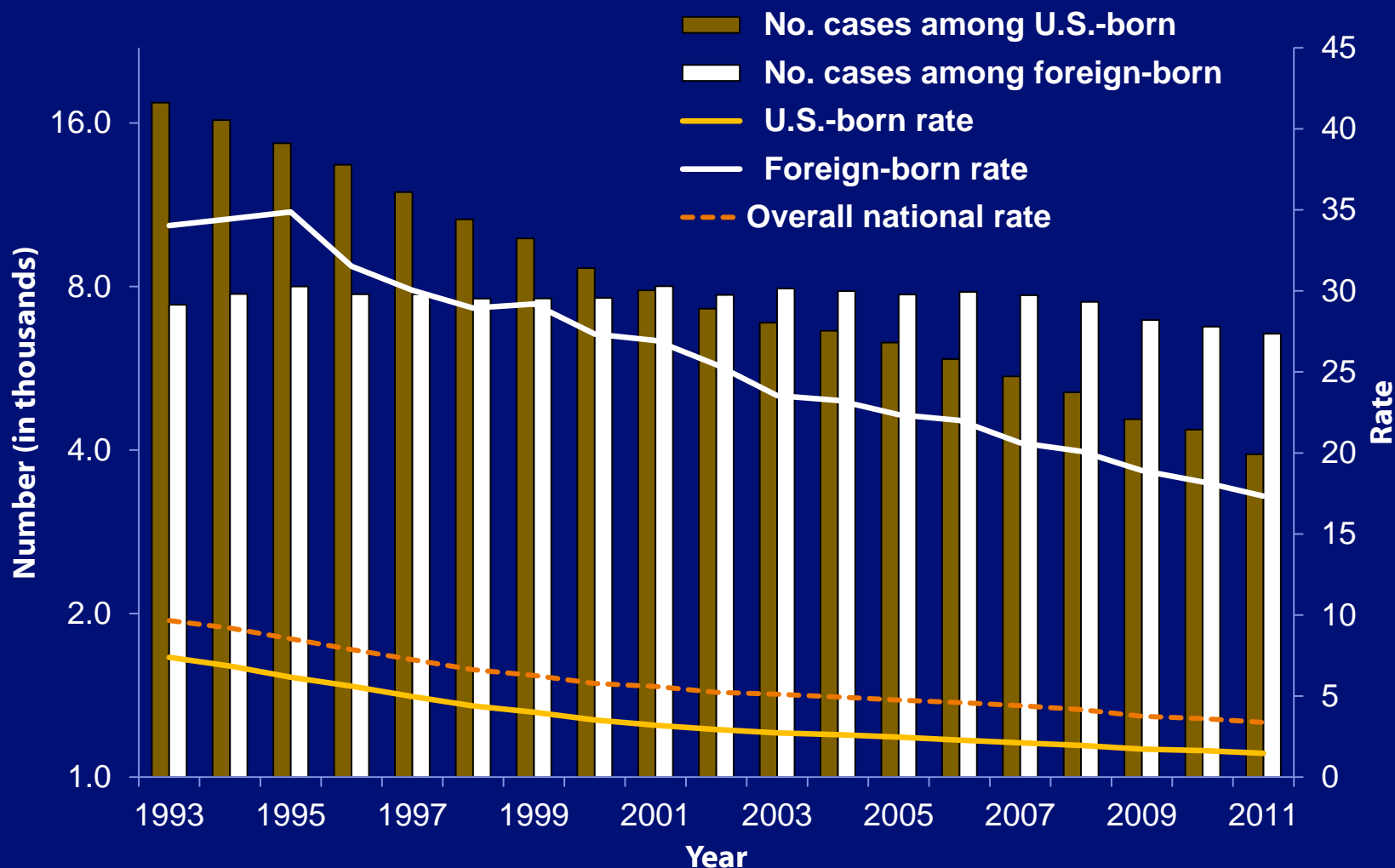
Reported TB cases United States, 1982–2011*



*Updated and provisional for 2012 as of February 22.



Number and rate* of TB cases, by year reported, by birth location, United States, 1993–2011†



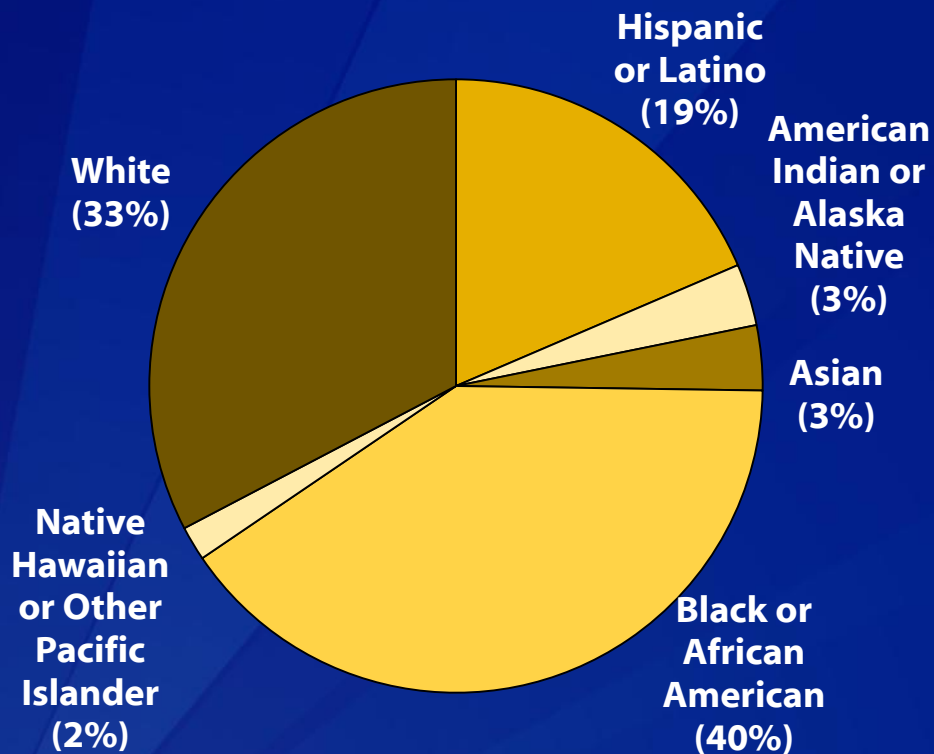
SOURCE: National TB Surveillance System

* Per 100,000 population

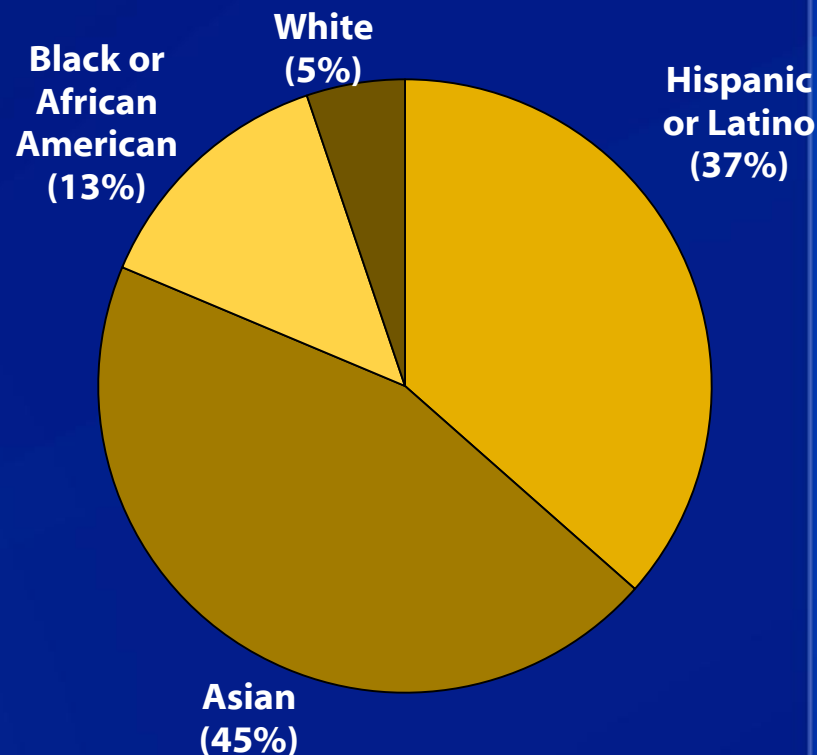
† Data are updated as of February 22, 2012. Data for 2011 are provisional.

Reported TB Cases by Origin and Race/Ethnicity,* United States, 2010

U.S.-born



Foreign-born**

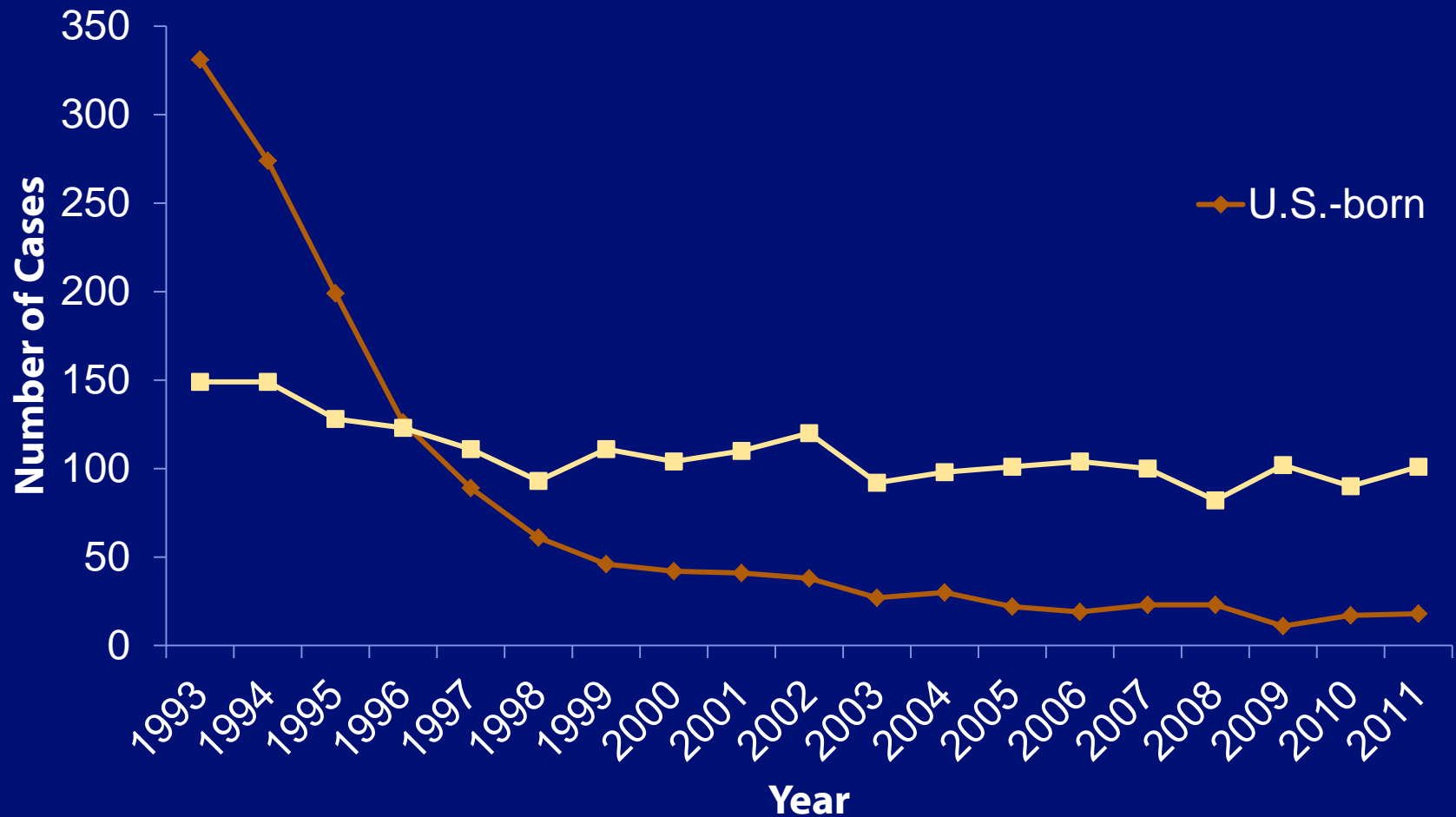


*All races are non-Hispanic. Persons reporting two or more races accounted for less than 1% of all cases.

** American Indian or Alaska Native and Native Hawaiian or Other Pacific Islander accounted for less than 1% of foreign-born cases and are not shown.



Multidrug-resistant TB cases, by country of birth, 1993–2011*



*Cases provisional as of February 22, 2012.

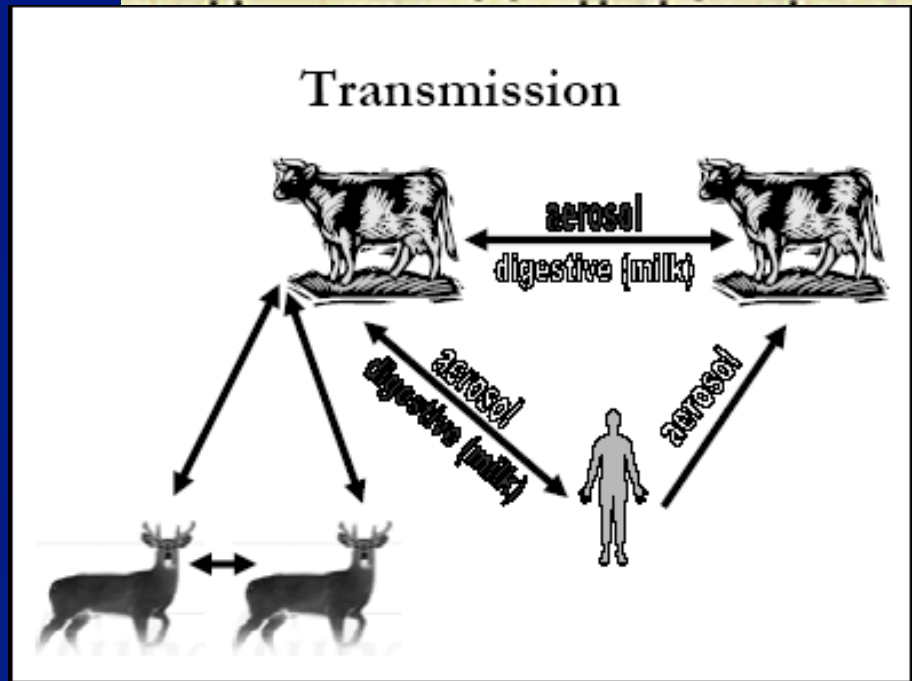
TST survey,* United States, 1999–2000, NHANES

Characteristic	Prevalence positive %	Number
All participants	4.2%	11,213,000
Birthplace		
United States	1.8%	4,154,000
Foreign	18.7%	6,888,000

*Sample of non-institutionalized persons; NHANES is National Health and Nutrition Examination Survey

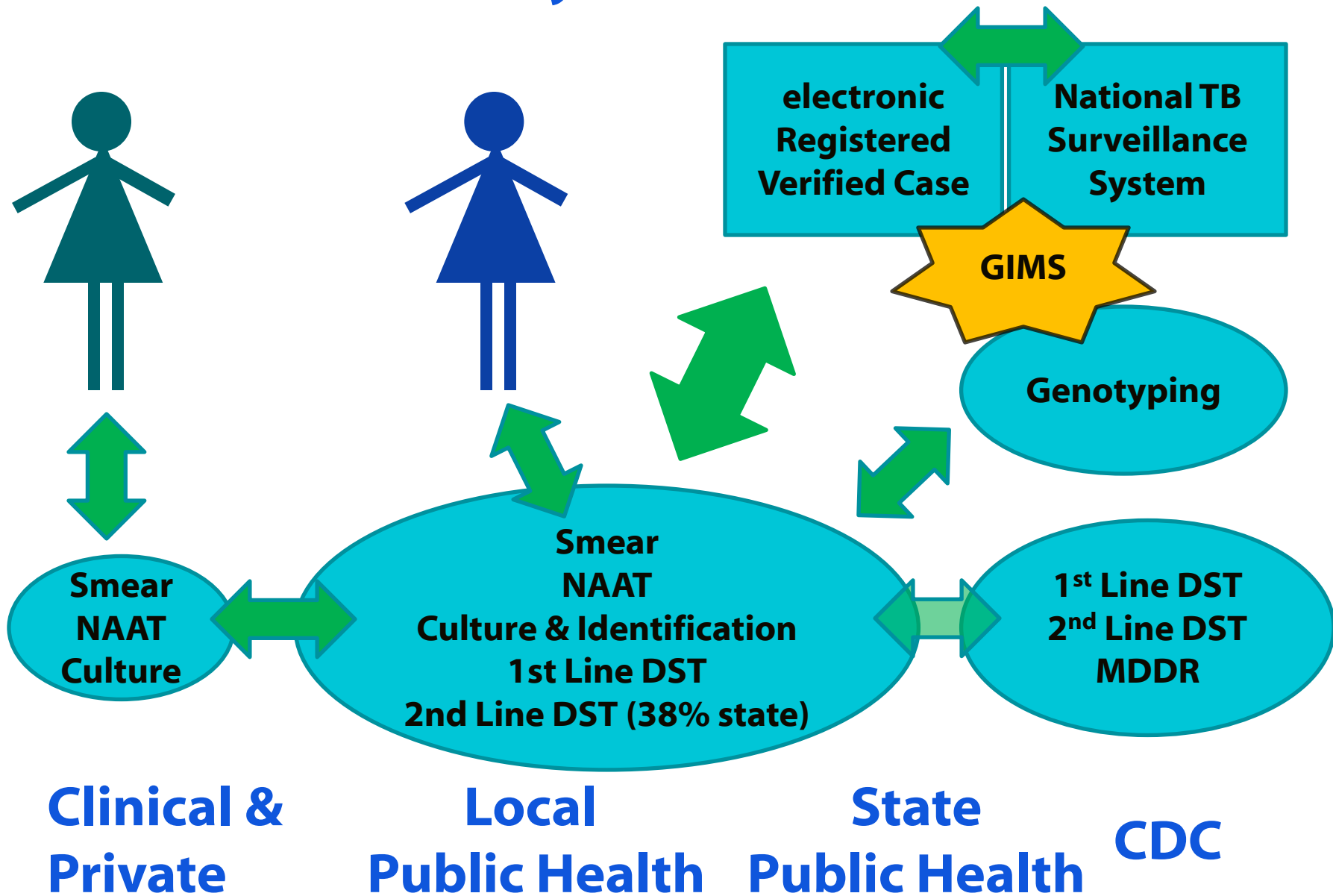
M. bovis, United States

- By genotyping, 1.4% all TB, 1995–2005*
- Higher in some areas, e.g., San Diego, 4–11%
- Risk: younger, Hispanic, extrapulmonary, and HIV infection
- Foodborne transmission, non-pasteurized dairy products



*Hlavsa et al. Clin Infect Dis. 2008 Jul 15;47(2):168-75

Flow of laboratory data and information

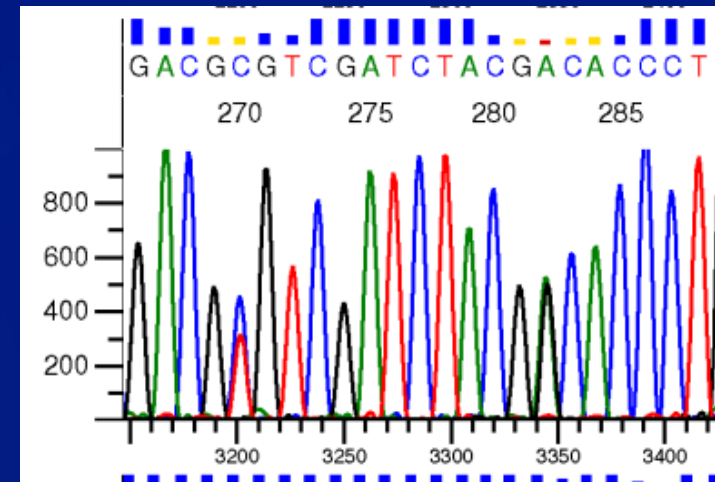


Genotyping

- **Confirm epidemiological links, useful in outbreaks, relapse vs. re-infection, and false laboratory results**
- **Performed on about 90% cases with a positive culture**
- **Spoligotyping, 24-locus MIRU-VNTR, and if needed RFLP**
- **CDC published best practices guidelines**
- **In our system, state public health staff have to link the GT with epidemiological data**
- **R&D to contain cost and improve discriminatory power**
- **About \$ 1.5 million annually, 10,000 isolates**

CDC's Molecular Detection of Drug Resistance 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

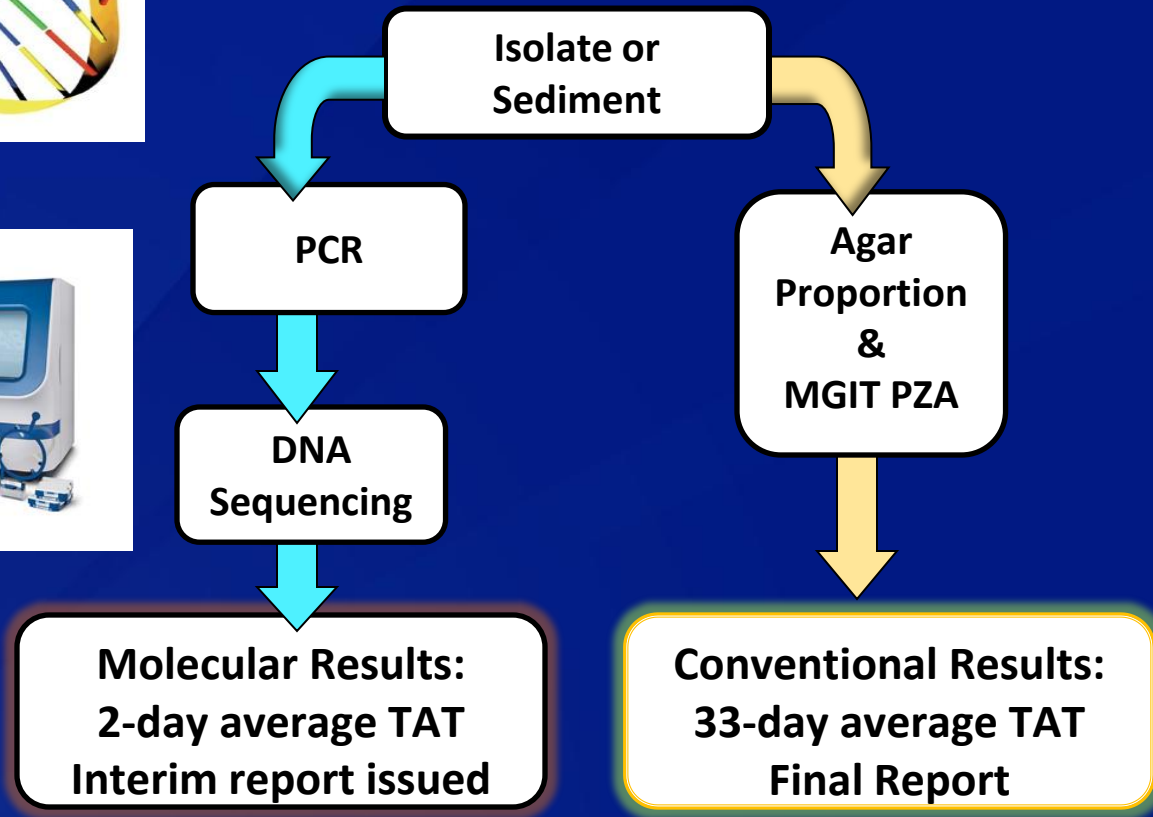


*CLIA is Clinical Laboratory Improvement Amendments at www.cms.gov/clia; † PCR is polymerase chain reaction; ‡ MDR is multidrug-resistant, that is resistant to at least isoniazid and rifampin; The graphic shows a portion of a DNA sequence obtained on an Applied Biosystems 3130xl Genetic Analyzer using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

Molecular Detection of Drug Resistance Service

Molecular Testing

Conventional, growth-based DST



*DST is drug susceptibility testing.

Genes

embB (Met306, Gly406)

pncA (promoter & CDS)

rpoB (81bp region)

inhA (-8, -15)

katG (Ser315)

gyrA (QRDR)

rrs (nt1401/1402,1484)

eis (promoter region)

tlyA (CDS)

First Line
(HRZE)

MDR

XDR

Drugs

Ethambutol

Pyrazinamide

Rifampin

Isoniazid

Isoniazid

Fluoroquinolones

Amikacin, Kanamycin,
Capreomycin

Kanamycin

Capreomycin

CONVENTIONAL DRUG SUSCEPTIBILITY TESTING

Indirect Agar Proportion Method (7H10 medium)

Amikacin (4 µg/ml)

Capreomycin (10 µg/ml)

Ciprofloxacin (2 µg/ml)

Ethambutol (5 µg/ml)

Ethionamide (10 µg/ml)

Isoniazid (0.2 & 1.0 µg/ml)

Kanamycin (5 µg/ml)

Ofloxacin (2 µg/ml)

PAS (2 µg/ml)

Rifabutin (2 µg/ml)

Rifampin (1 µg/ml)

Streptomycin (2 & 10 µg/ml)

MGIT 960

Pyrazinamide (100 µg/ml)

TB Example of CDC Role in Laboratory System

