Meeting of Microbiology Devices Panel
Medical Devices Advisory Committee
Gaithesburg, Maryland
June 29, 2011

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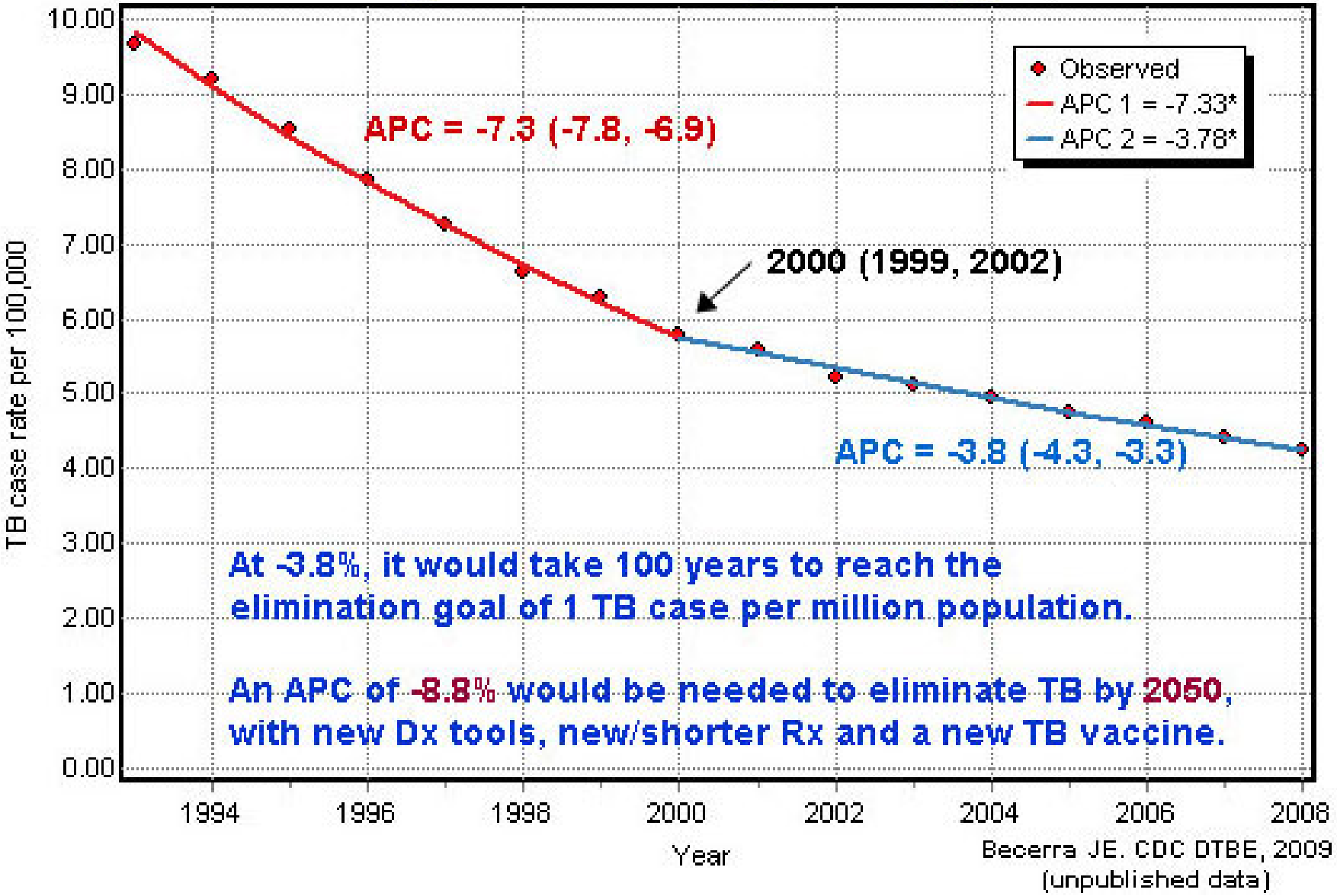
CDC/Public Health Perspective New TB Diagnostic Tests

- TB elimination is an important and worthwhile social objective
- Accrual 15 years experience with molecular diagnostic tests
- Opportunities with substantial advances in technology
- Must address perceived barriers and market impediments for new tools, in setting of declining U.S. TB rates
- Public health risk of diagnostic delays if providers lack access to new TB tools in the United States
- CDC plays a central and effective role in mitigating inaccurate diagnostic tests results through
  - Development of evidence-based guidance
  - Support of the national laboratory network
  - Provision of referral laboratory services
- Today's focus—assessment of potential benefits of new tests, risks of inaccurate diagnosis, and risk mitigation

TB Trends in the United States: 1993-2008

[APC = Annual Percentage Rate Change]



Public Health and Tuberculosis Three Priorities

1. Persons with pulmonary tuberculosis are often contagious and the source of transmission to others; therefore prompt diagnosis and effective treatment in the clinical realm are a primary public health intervention
2. Early detection of drug resistance and HIV infection are essential given the high cost in terms of morbidity, mortality, and transmission
3. Diagnosis and treatment of persons at high risk of progression from LTBI to disease is critical for progress towards elimination

Elimination: Scope of the Challenge

- Approximately 75% TB cases due to remote infection and 25% due to recent transmission*
- Almost 20% of TB cases due to transmission from persons with AFB sputum-smear-negative TB
- TST+ prevalence in U.S. estimated at 4.2% by NHANES 1999–2000 (representative national survey)
- Clinical realm for diagnosis and treatment is critical for public health – about 200,000 TB suspects/year*
- Public health realm – contact investigations (about 100,000 persons/year*) and targeted testing
- Diagnostic and treatment delays at every step
- New tools – including rapid and accurate diagnostic tests – critical for elimination

* CDC Unpublished data, 2011

Types of Diagnostic Delays

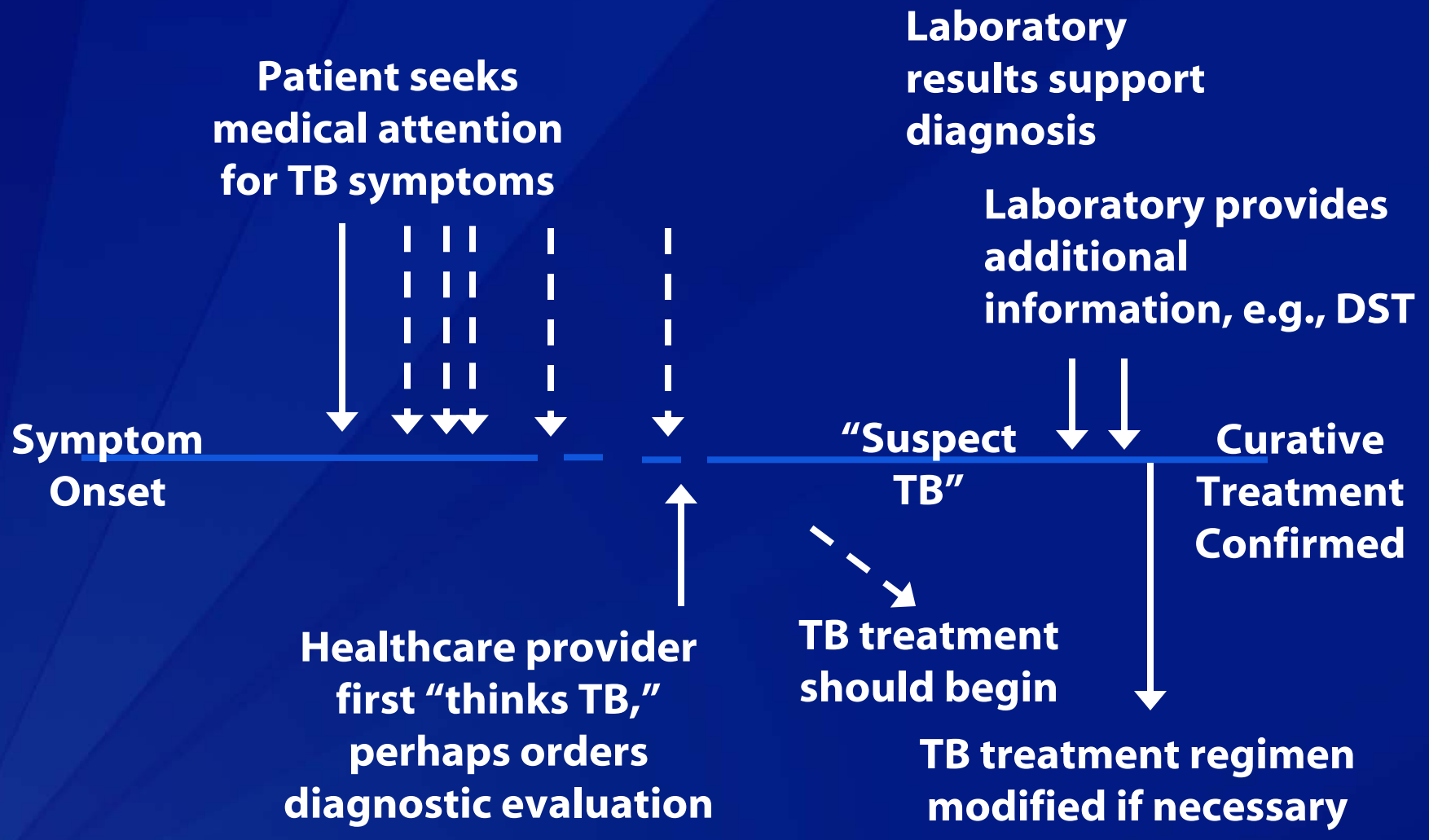
- Patient – health seeking practices
- Relevant, effective access; multiple provider settings
- Health care or "provider"
  - Diagnostic
    - Delay in "Thinking TB"
    - Getting specimen properly to the laboratory
    - Laboratory pre-analytical, analytical, and post-analytical phases
    - Provider seeing the results
    - Treatment initiation
    - Inter-related systems delays, e.g., private and public sector interaction; delay is not linear

U.S. TB Outbreak Investigations, CDC, 2002–2008*

- Most frequent contributing factor – prolonged infectiousness due to delayed diagnosis
- Patients delayed seeking medical attention for symptoms and, once they did, healthcare providers did not initially suspect TB
- U.S.-born, males, and substance abuse characterized most outbreaks
- New tools that offer additional opportunities for prompt diagnosis would decrease cumulative delay and decrease transmission and associated drug resistance

*Mitruka K, et al. Emerg Inf Dis, 2011;17(3):425-31

U.S. TB Outbreak Investigations, CDC, 2002–2008*
Timeline to TB Diagnosis and Treatment



*Mitruka K, et al. Emerg Inf Dis, 2011;17(3):425-31

Importance of Timely Laboratory Results

Symptom Onset — "Suspect TB" — Curative Treatment Confirmed

TB treatment
should begin,
but some healthcare providers wait
for confirmatory laboratory findings,
adding further delay

Importance of Timely Laboratory Results

Symptom Onset — "Suspect TB" — Curative Treatment Confirmed

If drug resistance not initially suspected, initial choice of treatment regimen likely inadequate, prolonging infectiousness and exposure risk to others

Infected contacts also placed on inadequate regimens

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.

Example of Delay Related to Laboratory Testing

- 28% of patients with negative sputum smears and positive sputum cultures are not started on treatment until culture result is available*
- Liquid culture — MTBC can take weeks to grow
- 72% of PHLs meet benchmark of identifying MTBC 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

* CDC 2009–2010 U.S. National TB Surveillance System. Unpublished Data.

IVD* Classification Rests on Theoretical Risk of an Inaccurate Result

CDC Considers Four Levels

- Individual patient level, potential new test alone
- In context of other diagnostic tests in recommended diagnostic algorithm
- Epidemiological context, examining PPV and NPV, considering practice and prevalence
- Public health context, given elimination strategy, situation of an individual patient is associated with transmission and risk to others

*IVD= *in-vitro* diagnostics

National Laboratory Network Mitigates Risk

- Supported in part by CDC (~$ 9 million annually)
- Approximately 1,500 public and private laboratories provide some level of mycobacteriology service
- About 300,000 specimens in DTBE-funded public health sector annually; likely millions if private sector included
- Local legal and regulatory framework
- Workforce training with APHL
- External quality assurance (e.g., CDC's Model Performance Evaluation Program)
- Infrastructure and logistics (e.g., specimen transport)
- Evidence-based guidance, APHL, CDC, CLSI, CMS, FDA, NIH, OSHA

CDC Sequencing "MDDR" Service* Drugs and Genes for Panel

- Rifampin
- Isoniazid
- Isoniazid

MDR TB

- Fluoroquinolones
- Amikacin, Kanamycin
- Capreomycin
- Kanamycin
- Capreomycin

XDR TB

- Ethambutol
- Pyrazinamide

Added Oct 2010

- *rpoB* (81bp region)
- *inhA* (-15)
- *katG* (Ser315)
- *gyrA* (coding region)
- *rrs* (nt1401/1402,1484)

- *eis* (promoter region)
- *tlyA* (coding region)
- *embB* (Met306, Gly406)
- *pncA* (promoter and coding regions)

* MDDR= Molecular Detection of Drug Resistance

Comparison of Turn-Around Times, MDDR and Conventional DST

Test Method	Mean* (Range)	Median
MDDR**	2.4 d (1–9 d)	2 d
Conventional DST**	36.8 d (2–112 d)	33 d

* From date of isolate receipt at CDC until report issued, calculated from > 375 samples, 44 states and territories

** MDDR= Molecular Detection of Drug Resistance, DST= Drug Susceptibility Test

Individual Patient Level, Potential New Test Alone

	MTBC	Drug Resistance
False-positive result	*Toxicity of first-line drugs*	*Less effective, more toxic second-line drugs*
Risk mitigation, via ATS, CDC, IDSA Guidelines	*Minimize harm of AEs* *Culture*	*Minimize harm of AEs* *Conventional DST*
False-negative result	*Increased morbidity and mortality*	*Increased morbidity and mortality*
Risk mitigation, via Guidelines	*Emphasis on clinical diagnosis* *Culture*	*Clinical monitoring of response to Tx* *Conventional DST*
Benefit	*Prompter initiation Tx, decreases morbidity and mortality* *Decreases risk of unnecessary testing (e.g., bronchoscopy) and therapy*	*Prompter customized Tx* *Decreases risk of acquired drug resistance and its amplification*

In Context of Other Tests in Recommended Diagnostic Algorithm

	MTBC	Drug Resistance
False-positive result	*Greater accuracy than smear-microscopy, therefore less overall risk*	*Multiple methods decrease overall risk*
Risk mitigation, via Guidelines	*All tests are adjuncts Dx*	*CDC's MDDR Service*
False-negative result	*Less chance of increased morbidity and mortality*	*Less chance of increased morbidity and mortality*
Risk mitigation, via Guidelines	*Need for clinical diagnosis emphasized* *All tests are adjuncts Dx*	*Clinical monitoring* *If at risk, CDC's MDDR Service*
Benefit	*Greater PPV relative to smear, less drug toxicity*	*Improved overall accuracy, conventional DST imperfect* *Prompt change in therapy improves trust and medication adherence*

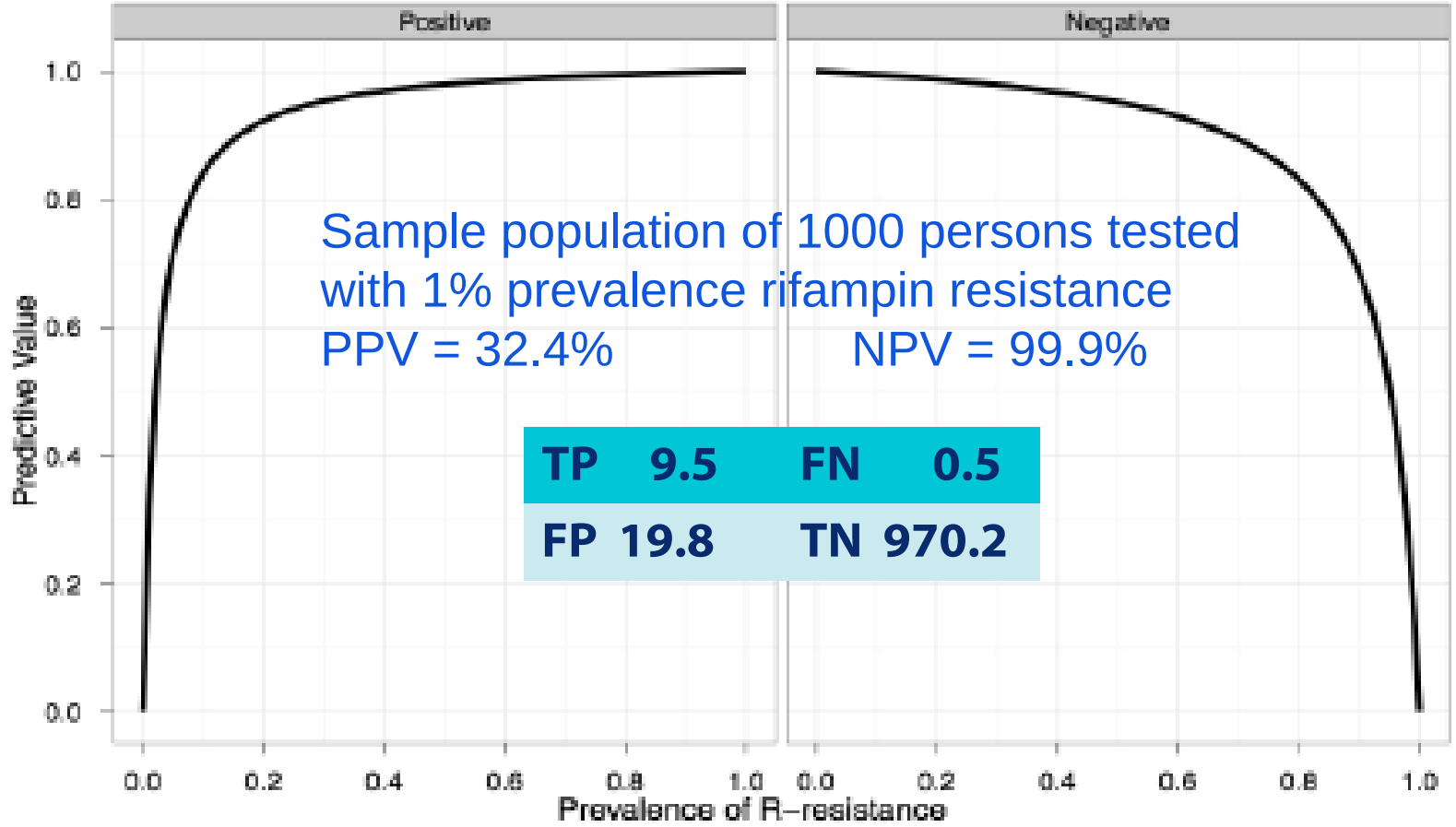
In Epidemiological Context, Examining PPV and NPV, Considering Practice and Prevalence

	MTBC	Drug Resistance
False-positive result	*Low prevalence and therefore lower PPV (percent of suspects)*	*Low prevalence and therefore lower PPV*
Risk mitigation, via Guidelines	*Confirmatory and repeat testing* *Labeling*	*Confirmatory, repeat, and targeted testing* *Labeling*
False-negative result	*NPV is high, little risk*	*NPV is high, little risk*
Risk mitigation, via Guidelines	*Need for clinical diagnosis emphasized* *All tests are adjuncts Dx*	*Clinical monitoring* *If at risk, MDDR Services*
Benefit	*Reduced cost infection control* *More accurate surveillance*	*Prompter suspicion of MDR* *Rules out MDR* *More accurate drug resistance surveillance*

In Public Health Context, Transmission

	MTBC	Drug Resistance
False-positive result	*Cost of lower utility contact investigation*	*Cost of lower utility interventions*
Risk mitigation	*Culture* *National genotyping*	*Conventional DST* *MDDR services*
False-negative result	*Little to none*	*Little to none*
Risk mitigation, via Guidelines	*Strategies to prioritize clusters and guide contact investigations* *NTSS-GT aberration detection*	*Strategies to assess risk of drug resistance in clusters and guide contact investigations*
Benefit	*More accurate, prompter results relative to smear microscopy, less transmission to others*	*Less transmission*

Positive and Negative Predictive Values of PCR Test to Detect Rifampin resistance, by Prevalence of Rifampin Resistance



Sample population of 1000 persons tested with 1% prevalence rifampin resistance

PPV = 32.4%

NPV = 99.9%

TP	9.5	FN	0.5
FP	19.8	TN	970.2

Sensitivity 0.95, Specificity 0.98 for the diagnosis of Rifampicin resistance

Diagnosis of LTBI

	LTBI	Public Health
False-positive result	*Toxicity of drugs*	*Cost of lower yield interventions*
Risk mitigation, via Guidelines	*Targeted testing*	*Strategies to determine targeted testing algorithms*
False-negative result	*Higher risk of progression to disease*	*Increased transmission*
Risk mitigation, via Guidelines	*HIV testing* *Risk factor assessment*	*Strategies for targeted testing*
Benefit	*Decreased morbidity and mortality*	*Important contribution to elimination*

Conclusions, Public Health Perspective

- In considering theoretical risk focused on device indications, public health case argues for a larger perspective in balancing benefits and risks
- CDC and partners have strong precedent for establishing clinical and public health practice through guidance
- Adjunctive approach to rapid TB diagnostic tests and CDC laboratory networks largely mitigates risk
- Risks for devices that diagnose TB, drug resistance, and LTBI are not high and can be further mitigated with general and special controls guidance
- There is an integral relationship between public and private investment, R&D for new diagnostic tools, and public health and regulatory frameworks
- Without new TB tools, which capitalize on advances in technology, we place the public at increased risk and delay elimination

Acknowledgements

- Luke Davis, Masae Kawamura, UCSF providing 2011 ATS presentation
- Dick Menzies, McGill University for references on delays
- CDC/DTBE: Becerra, Cegielski, Garrett, Gibson, Haddad, Hill, Iademarco, Jereb, Langer, LoBue, Mac Kenzie, Mazurek, Menzies, Metchock, Miramontes, Navin, Peterson, Plikaytis, Pratt, Starks, Vernon, and Winston