



# Modeling TB Diagnostics: Historical Perspective & State of the Science

Advanced TB Diagnostic Research Course  
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# Objectives

- To describe the (recent) history of TB diagnostics modeling
- To discuss key published papers in the field
- To give an overview of what modeling has taught us about TB diagnostics to date



"'LUNCH?' WELL, YES--BUT WHAT ARE YOUR LONG-TERM GOALS?"

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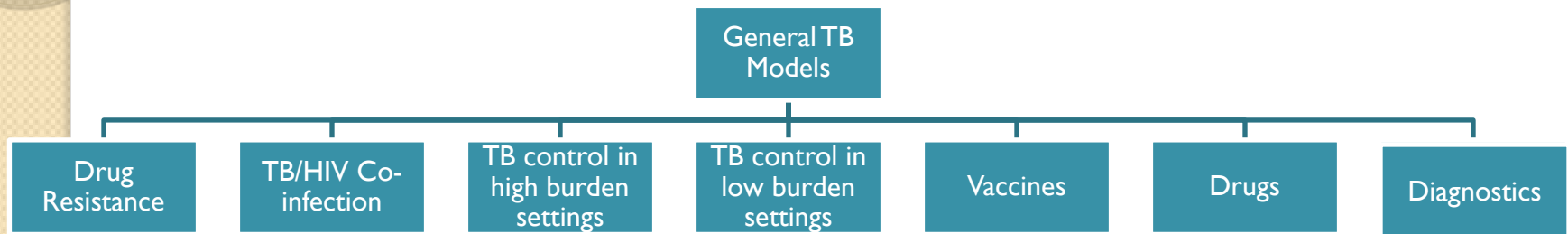
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# 4 Key Goals of Models

- **Craft policy**
  - Focus decision-makers on important issues
- **Conceptualize**
  - Help frame the problem in a new light
- **Project**
  - Quantify impact of interventions
- **Operationalize**
  - Identify parameters that are key to an intervention's success

# From last session:



## **Presentation Outline:**

Pre-2006: 1 slide

2006: 2 models

Post-2006: 4 models

Summary & Conclusions

# Early TB Diagnostics Modeling: A Timeline

- 1996: Blower et al put TB modeling on the map.
  - Treatment and prophylaxis, but no diagnosis
- 1998: Murray & Salomon are the first to model diagnostic strategies
  - Increasing smear sensitivity to 95% estimated to reduce TB mortality by only 4%
    - HIV considered only cursorily
    - Low infectivity/mortality among smear-negatives
    - Diagnostic process not actually modeled
- 1999-2005: “Dead zone” for TB diagnostics modeling
  - Focus squarely on improving DOTS coverage



**2006:**

## **Diagnostics Return to the Spotlight**


- **Global Plan to Stop TB 2006-2015**
  - Push for new drugs, diagnostics, and vaccines
- **Moore et al publish Peruvian MODS study in NEJM**
- **FIND gathers steam, contracts Cepheid**
- **Multiple systematic reviews and opinion pieces**
- **WHO begins to evaluate diagnostic tests for global recommendation**

2006:

## Diagnostics Return to the Spotlight

- 2 major modeling papers revisit the importance of diagnostics.
  - Increased understanding that DOTS alone might not be sufficient
  - Impact of HIV on TB diagnosis becoming more clear
  - Interest in developing better strategies for active case-finding






# The potential impact of enhanced diagnostic techniques for tuberculosis driven by HIV: a mathematical model

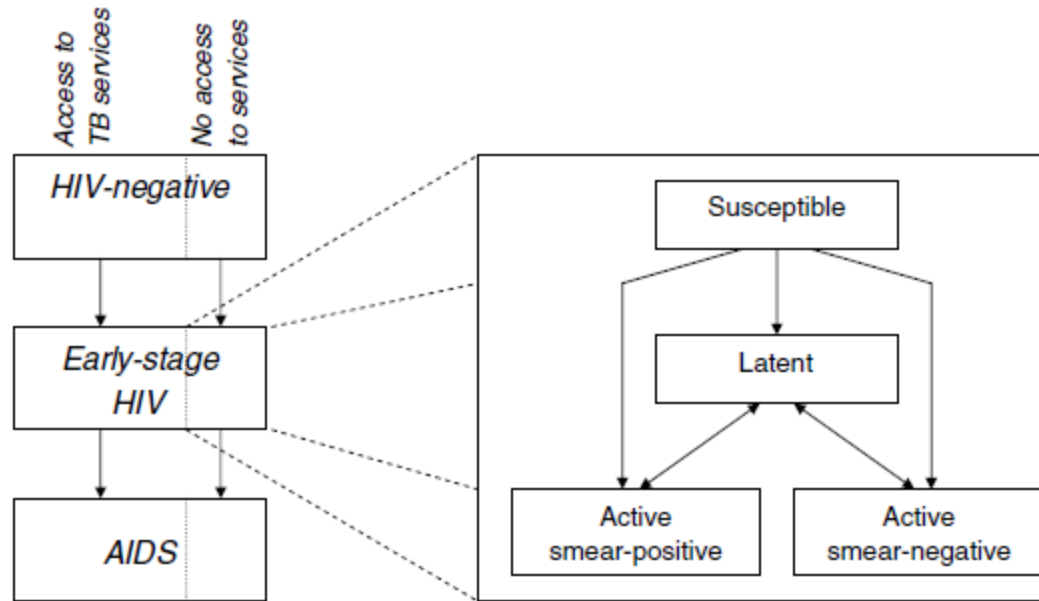
David W. Dowdy<sup>a,c</sup>, Richard E. Chaisson<sup>a,b,d</sup>, Lawrence H. Moulton<sup>b</sup>  
and Susan E. Dorman<sup>b,d</sup>

*AIDS* 2006, **20**:751–762



# AIDS 2006 model

- Focus of HIV-related TB interventions:
  - ART
  - 3 I's (IPT, ICF, infection control)
  - Not diagnostics
- Compared TB control strategies in a hypothetical HIV-endemic population:
  - Rapid molecular test (50% sens for sm-neg)
  - Culture (85% sens for sm-neg, 20% LTFU)
  - Active case-finding (33% of population)
  - ART (50% coverage)



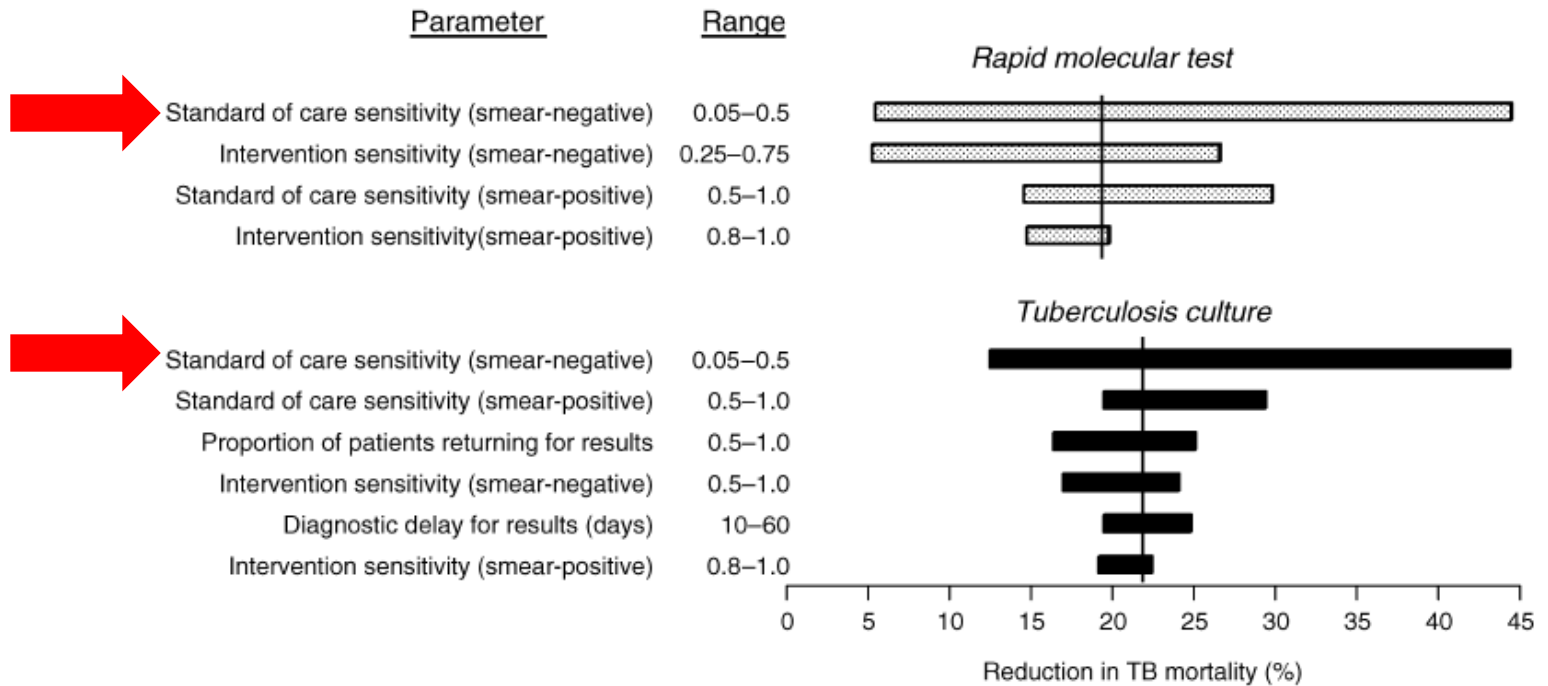
- First TB model to evaluate the diagnostic process in terms of access
- Otherwise simple structure



Table 2. Impact of modeled interventions on hypothetical tuberculosis (TB) epidemic.

Intervention	TB incidence		TB prevalence		TB mortality	
	Cases per 100 000	Reduction (%)	Annual cases per 100 000	Reduction (%)	Deaths per 100 000	Reduction (%)
1. Standard of care	406	–	288	–	221	–
2. Rapid molecular testing	371	9.3%	223	22.8%	178	19.3%
3. TB culture	370	9.6%	214	25.7%	172	22.2%
4. Community-based active case finding	348	15.0%	205	28.8%	177	20.1%
5. HIV-based active case finding	389	5.0%	261	9.6%	195	11.9%
6. Highly active antiretroviral therapy	377	7.8%	271	6.1%	205	7.4%

- Key result:
  - Realistic diagnostics can have large impact
  - 20% mortality reduction
  - Similar to 33% coverage with ACF



- Impact is most sensitive to the quality of existing diagnosis, not the accuracy of new diagnostics.
  - New diagnostics have greatest impact if deployed in areas of greatest need.

# AIDS 2006: Summary

- **Craft Policy**
  - Placed diagnostics “on the map”
- **Conceptualize**
  - Evaluated access to diagnostic services
- **Project**
  - 20% realistic mortality reduction
- **Operationalize**
  - Deploy diagnostics in settings with poor existing infrastructure

# Reducing the global burden of tuberculosis: the contribution of improved diagnostics

Authors: **Emmett Keeler,<sup>1</sup>**

**Mark D. Perkins,<sup>2</sup>**

**Peter Small,<sup>3</sup>**

**Christy Hanson,<sup>4</sup>**

**Steven Reed,<sup>5</sup>**

**Jane Cunningham,<sup>6</sup>**

**Julia E. Aledort,<sup>1</sup>**

**Lee Hillborne,<sup>1</sup>**

**Maria E. Rafael,<sup>1</sup>**

**Federico Girosi<sup>1</sup> &**

**Christopher Dye<sup>6</sup>**

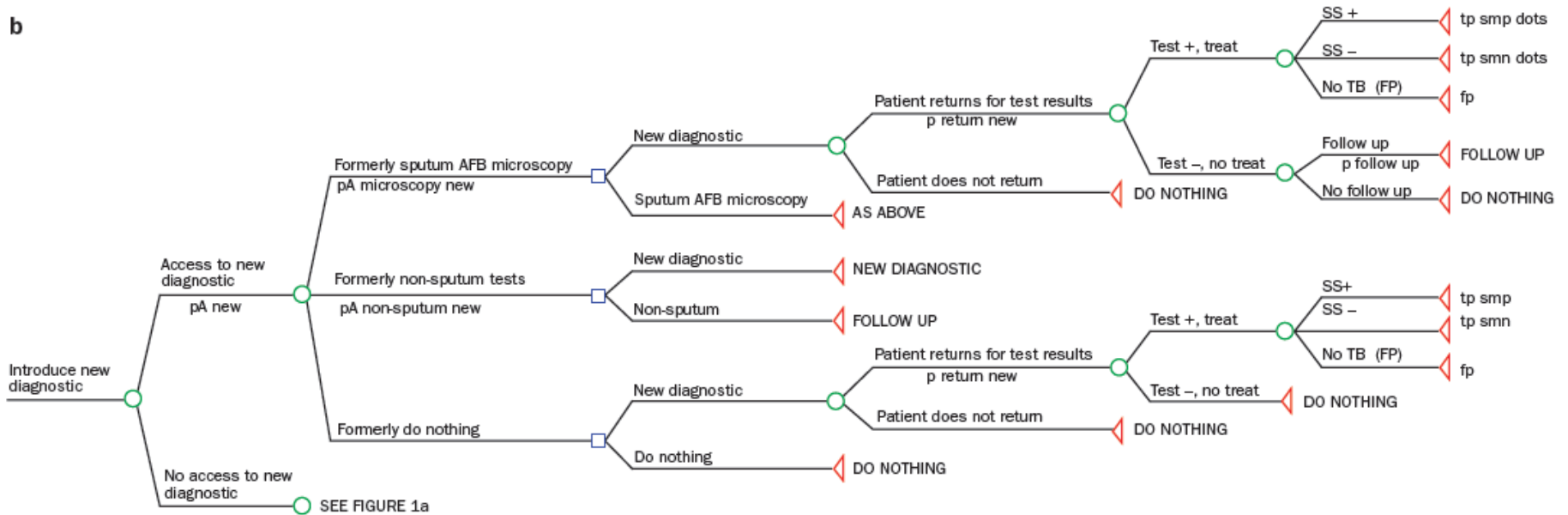
nature publishing group



# Keeler et al, Nature 2006

- Published by “who’s who” of TB diagnostics/modeling
- Nature supplement focused on impact of diagnostics on various conditions
- Remains the most widely-cited source on potential impact of TB diagnostics

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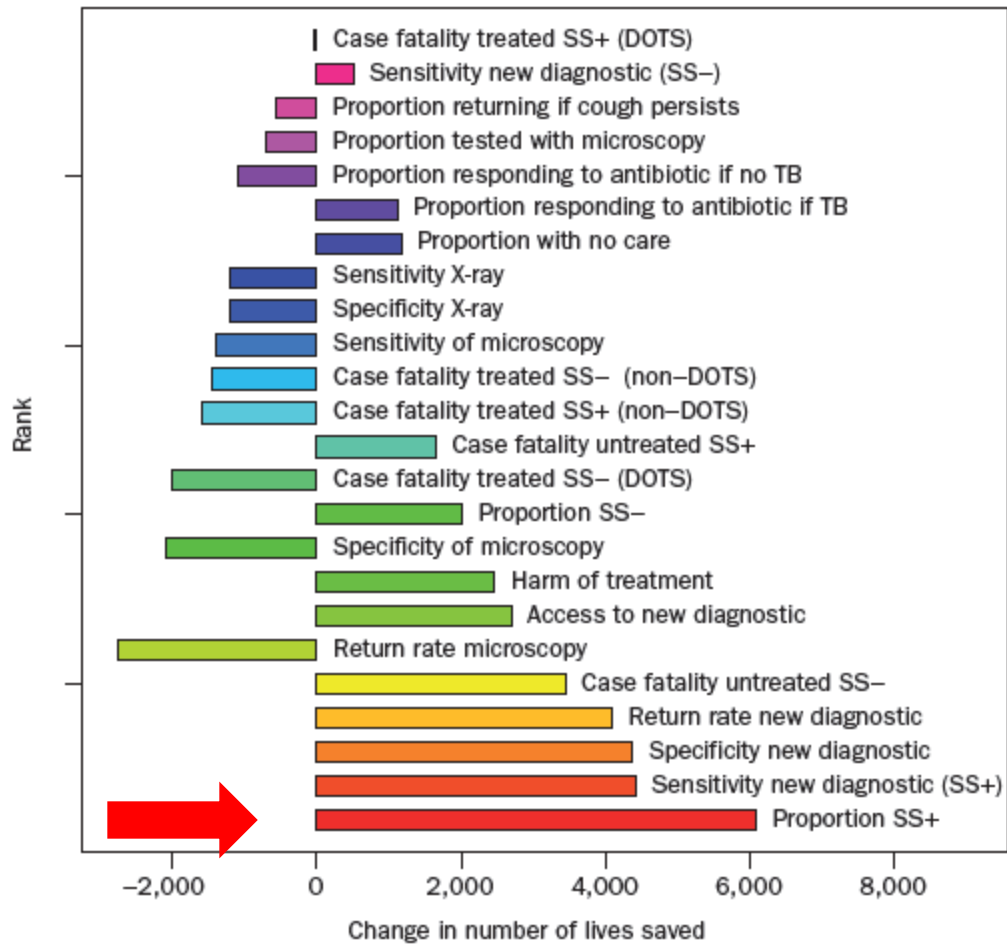


- Decision analytic model
  - (can't read figure in initial publication either)
- Also focuses on access to diagnosis
- Does not include transmission effects

**Table 2 | Worldwide attributable benefits of new diagnostics for tuberculosis\***

Test	Sensitivity to ss+ (%)	Sensitivity to ss- (%)	Specificity (%)	Loss to follow-up (%)	Annual adjusted lives saved† (thousands)	Percentage of world TB deaths††
Advanced infrastructure (16–19% access)						
1	100	100	100	0	105	6.0
TB clinic and hospitals (44–66% access)						
2	85	0	97	10–15	0	0
3	100	0	97	10–15	46	2.6
4	85	0	97	0	95	5.4
5	85	85	97	10–15	60	3.4
6	85	85	97	0	195	11.2
7	100	100	100	20	146	8.3
8	100	100	100	0	359	20.5
No infrastructure (100% access)						
9	85	0	97	10–15	133	7.6
10	85	0	97	0	263	15.1
11	85	85	97	10–15	214	12.3
12	85	85	97	0	392	22.4
13	100	100	100	20	334	19.1
14	100	100	100	0	625	35.8

TB (HIV-)



# Nature 2006: Summary Deja Vu

- **Craft Policy**
  - Placed diagnostics “on the map”
- **Conceptualize**
  - Evaluated access to diagnostic services
- **Project**
  - 20% realistic mortality reduction
- **Operationalize**
  - Deploy diagnostics in settings with poor existing infrastructure

# Post-2006: Advancing the Field

- Interest in diagnostics rising
  - Moore et al's NEJM paper on MODS published
  - Increased focus on access to diagnostics
- Modeling of diagnostics turns to more specific questions:
  - Expansion of existing diagnostics
  - Introduction of novel diagnostics
  - Diagnostics as part of integrated TB control strategy
  - Diagnostics for managing MDR-/XDR-TB

# Expansion of Existing Diagnostics

## Impact of enhanced tuberculosis diagnosis in South Africa: A mathematical model of expanded culture and drug susceptibility testing

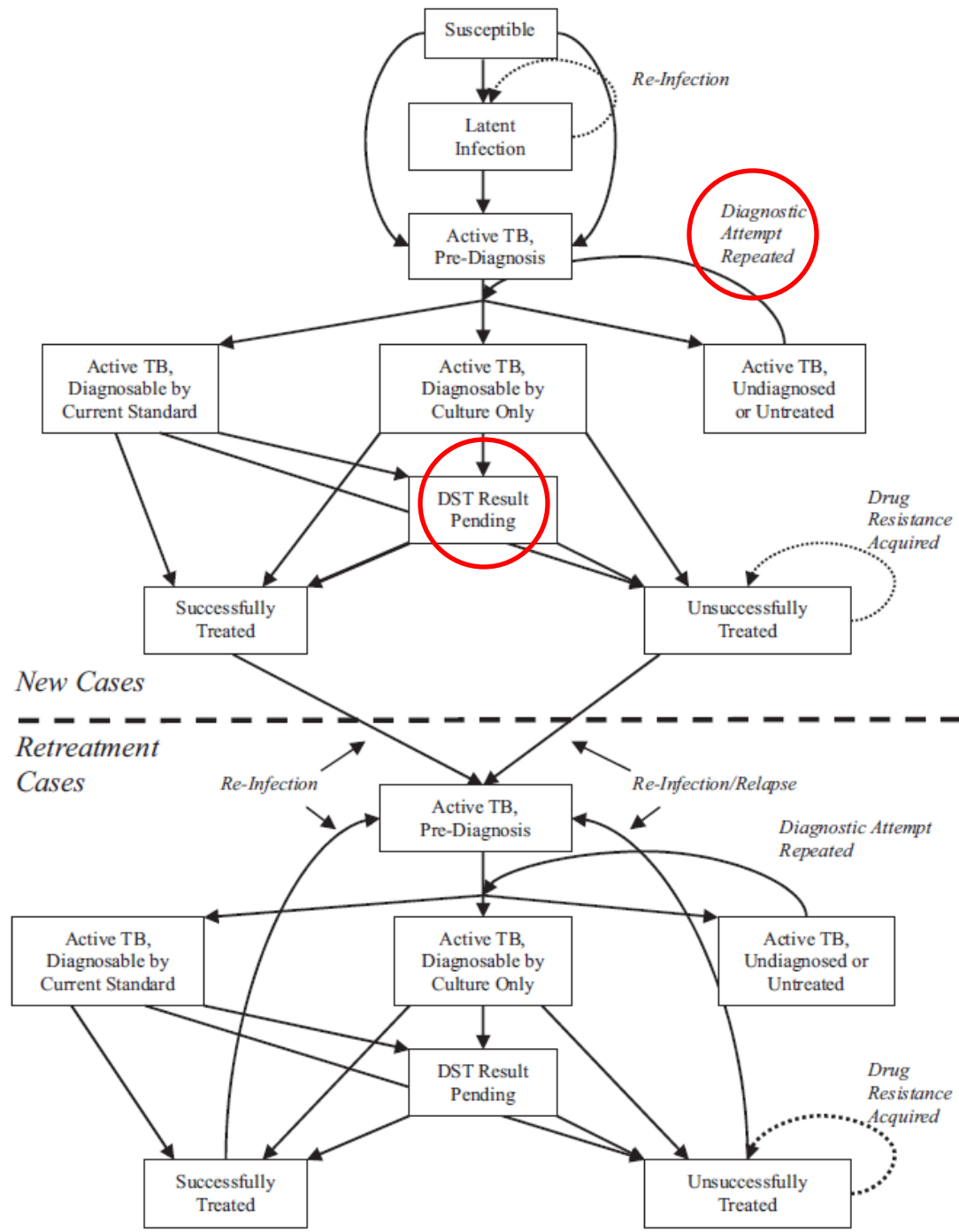
David W. Dowdy<sup>\*†</sup>, Richard E. Chaisson<sup>‡</sup>, Gary Maartens<sup>§</sup>, Elizabeth L. Corbett<sup>¶</sup>, and Susan E. Dorman<sup>\*||</sup>

<sup>\*</sup>Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, Suite W6508, Baltimore, MD 21205; <sup>†</sup>Department of Medicine, Division of Infectious Diseases, The Johns Hopkins University, 1550 Orleans Street, Room 1M.08, Baltimore, MD 21231; <sup>§</sup>Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Faculty of Health Sciences, Observatory 7925, Cape Town, South Africa; and <sup>¶</sup>Clinical Research Unit, London School of Hygiene and Tropical Medicine, Room 249, Keppel Street, Harare WC1E 7HT, United Kingdom

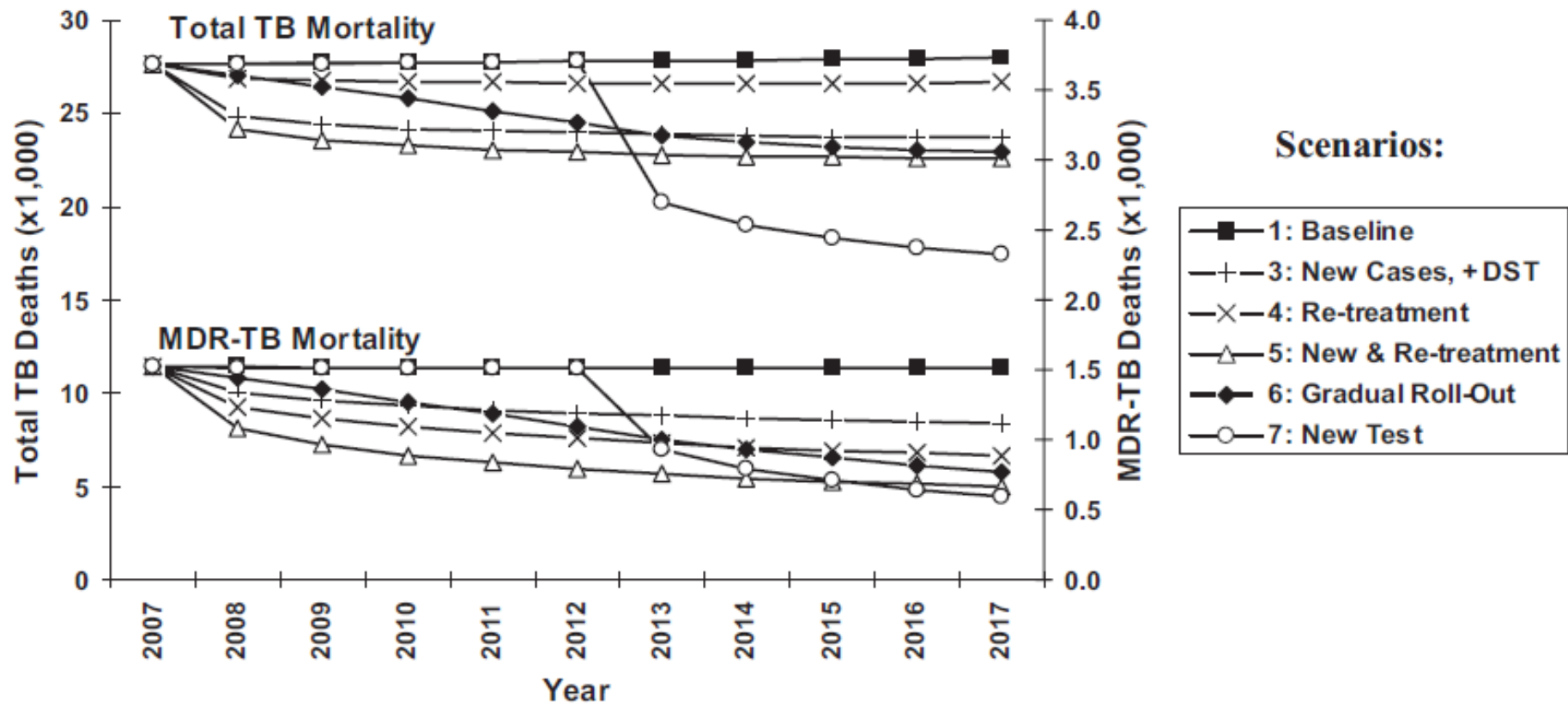
Edited by Rita R. Colwell, University of Maryland, College Park, MD, and approved April 21, 2008 (received for review January 30, 2008)

# Dowdy et al, PNAS 2008

- Motivated by discussions in South Africa regarding poor utilization of culture
- Evaluated expansion of culture and DST
  - New vs. previously-treated cases
  - Immediate vs. gradual roll-out
  - Compared against an “ideal” new test
  - Minimal evaluation of XDR-TB
- Most detailed model to date of the TB diagnostic process



Scenario	Percentage of TB suspects receiving culture*	Total TB mortality	
		Cases (×1,000)	Percent averted (95% SI)
1: Baseline	Never treated, 5%, no DST; previously treated, 37%	278	0%
2: Expanded culture, new cases (no DST)	Never treated, 37%, no DST; previously treated, 37%	243	12.6% (5.2, 19.5)
3: Expanded Culture, New Cases (+ DST)	Never treated, 37%; previously treated: 37%	240	13.6% (6.4, 20.4)
4: Expanded culture, retreatment cases	Never treated, 5%, no DST; previously treated, 85%	267	4.1% (2.2, 6.1)
5: Expanded culture, all TB suspects	Never treated, 37%; previously treated, 85%	230	17.2% (8.9, 24.4)
6: Expanded culture, gradual roll-out	Never treated, 10% (year 1), increasing by 5% per year to 37%; previously treated, 40% (year 1), increasing by 5% per year to 85%	245	11.8% (5.8, 17.4)
7: New diagnostic test <sup>‡</sup>	As in Scenario 1 (years 1–5). New test, with access as in Scenario 5 (years 6–10)	231	16.8% (10.0, 25.3)



# Dowdy PNAS 2008: Summary

- **Craft Policy**
  - Pressured gov't of RSA to expand culture
- **Conceptualize**
  - Repeated diagnostic attempts, DST
- **Project**
  - 20% mortality reduction (less for MDR)
- **Operationalize**
  - Early expansion of existing diagnostics may be preferred to late expansion of new ones.



# Introduction of Novel Diagnostics

INT J TUBERC LUNG DIS 12(9):1021–1029  
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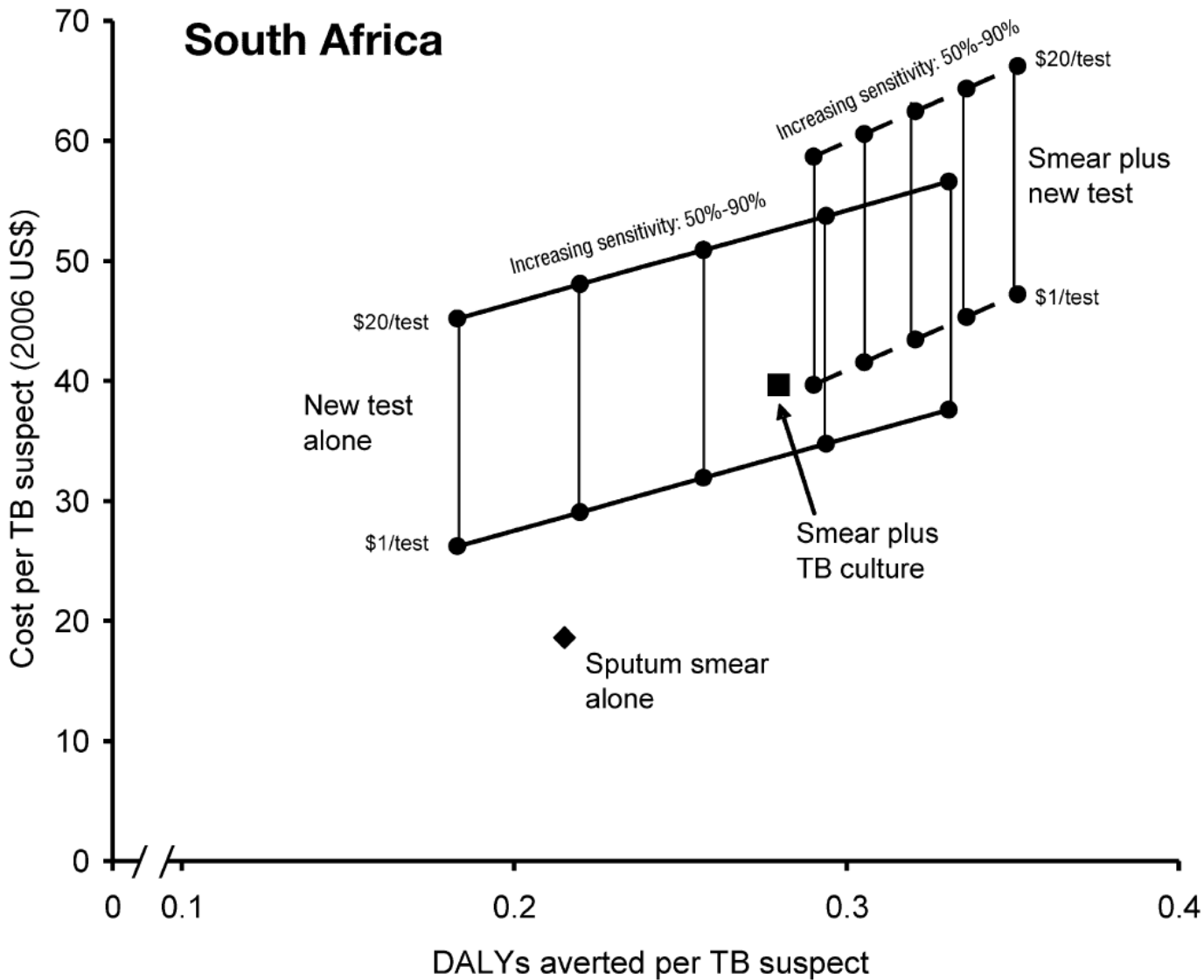
## Cost-effectiveness of novel diagnostic tools for the diagnosis of tuberculosis

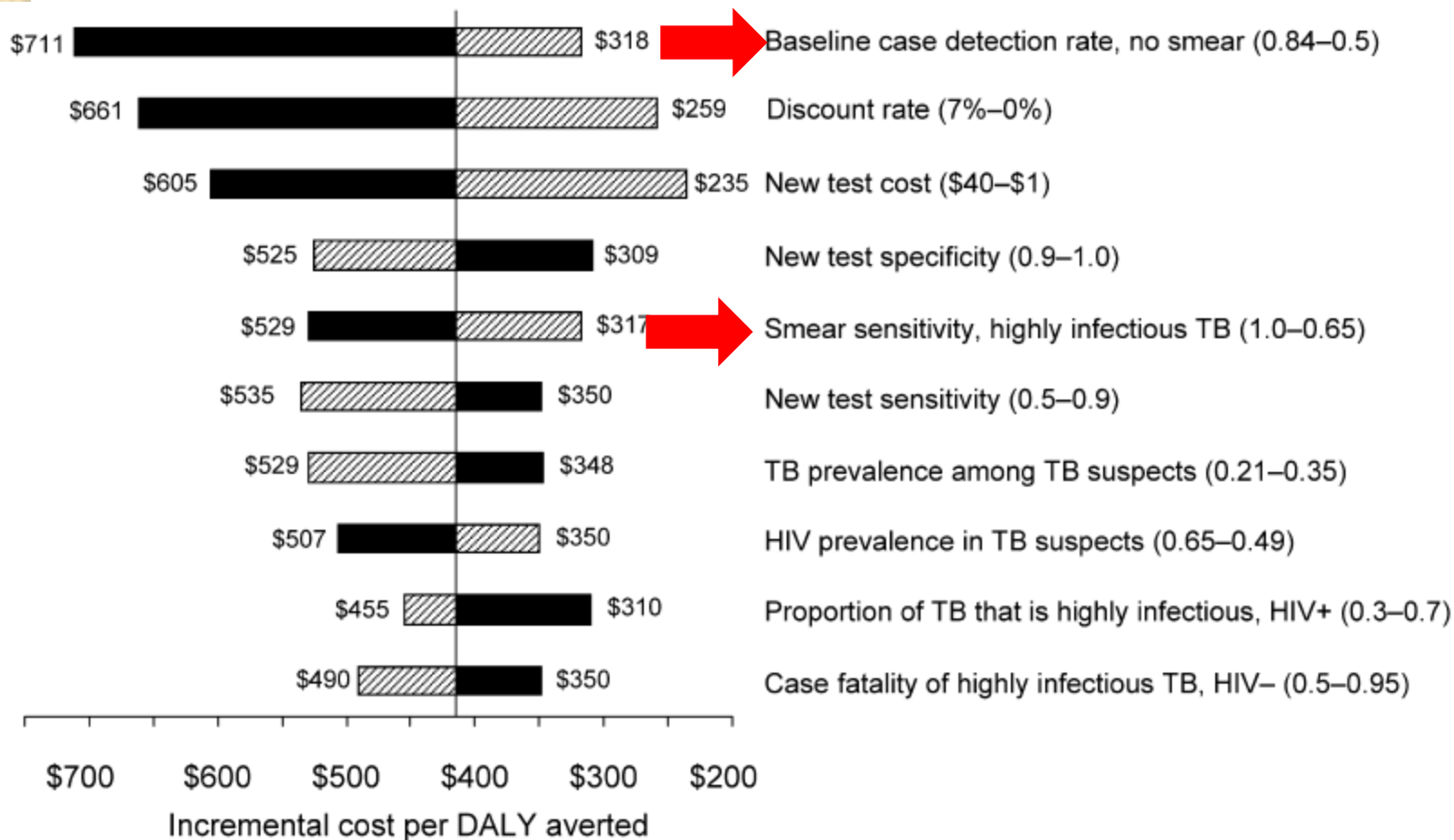
D. W. Dowdy,<sup>\*†‡§</sup> M. A. O'Brien,<sup>¶</sup> D. Bishai<sup>#</sup>

# Dowdy et al, IJTLD 2008

- Motivated by test developers who wanted to know the specifications required for a test to have impact
- Primary focus was cost-effectiveness
  - Will be discussed in next session
- Hypothetical point-of-care diagnostic in South Africa, Kenya, and Brazil
  - Sensitivity 50-90%, specificity 90-100%, price \$1-\$20
  - Later expanded to evaluate serology in India

# South Africa





# Dowdy IJTLD 2008: Summary

- **Craft Policy**
  - Demonstrated to developers that high-quality tests would be required to replace smear
- **Conceptualize**
  - Diagnostics to add on vs. replace smear
- **Project**
  - 100-200 years of life gained if a new test were added to smear for 1000 TB suspects
- **Operationalize**
  - Target areas with poor infrastructure, do not seek to replace smear

# Diagnostics in an Integrated Control Strategy

## Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics

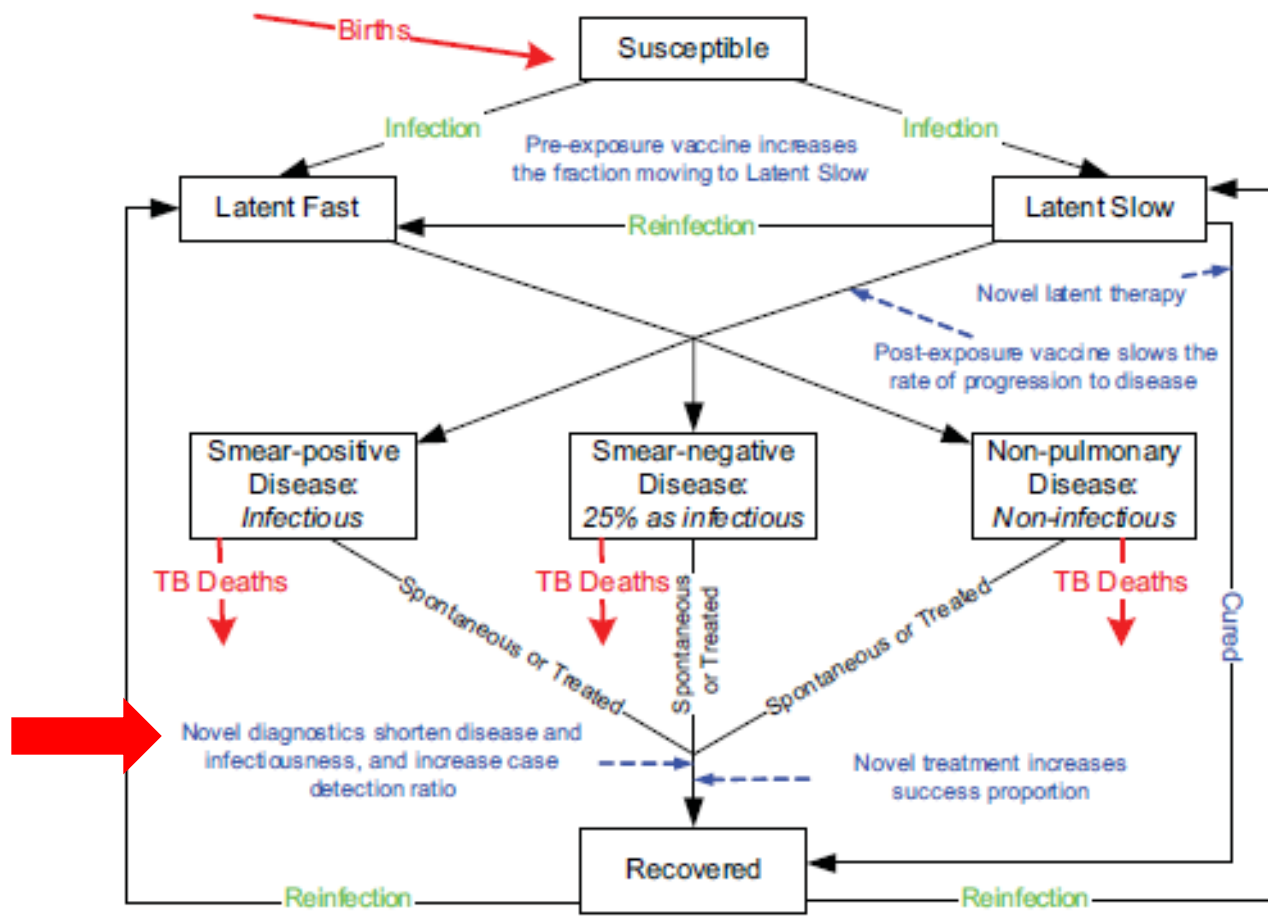
Laith J. Abu-Raddad<sup>a,1</sup>, Lorenzo Sabatelli<sup>a</sup>, Jerusha T. Achterberg<sup>a,b,c</sup>, Jonathan D. Sugimoto<sup>a,b</sup>, Ira M. Longini, Jr.<sup>a,d</sup>, Christopher Dye<sup>e</sup>, and M. Elizabeth Halloran<sup>a,d,2</sup>

<sup>a</sup>Vaccine and Infectious Disease Institute, Fred Hutchinson Cancer Research Center, Seattle, WA 98109; Departments of <sup>b</sup>Epidemiology, <sup>c</sup>Anthropology, and <sup>d</sup>Biostatistics, University of Washington, Seattle, WA 98195; and <sup>e</sup>Office of HIV/AIDS, Tuberculosis, Malaria, and Neglected Tropical Diseases, World Health Organization, CH-1211 Geneva 27, Switzerland

Edited by Simon A. Levin, Princeton University, Princeton, NJ, and approved June 4, 2009 (received for review February 18, 2009)

# Abu-Raddad et al, PNAS 2009

- Modeled diagnostics, drugs, and vaccines
- Funded by BMGF to guide portfolio development
- Focused on lower-HIV prevalence settings
- Diagnostic interventions:
  - LED microscopy: 10% increase in CDR, 1/24 month reduction in time to diagnosis
  - NAAT: 3/24 month reduction
  - Dipstick: 4/24 month reduction



**Table 1. Cumulative number of TB cases and TB-related deaths prevented between 2015 and 2050 by using different novel interventions with various strategies in the Southeast Asia region**

Intervention strategy	Prevented active TB cases, millions (%)	Prevented TB-related deaths, millions (%)
<b>Portfolio interventions</b>		
<b>Vaccination</b>		
Neonatal vaccination with adolescent boost		
Basic pre-exposure vaccine only	18.2 (18)	3.0 (17)
Basic pre-exposure vaccine with the additional effects	23.8 (23)	3.9 (22)
<b>Active disease treatment regimens</b>		
1. 4 months	8.3 (8)	2.0 (11)
2. 2 months + 90% efficacy against drug-resistant strains	19.3 (19)	4.5 (25)
3. 10 days + 90% efficacy against drug-resistant strains	22.9 (23)	5.3 (30)
<b>Diagnostics</b>		
LED	11.7 (12)	4.2 (23)
NAAT	24.4 (24)	4.2 (23)
Dipstick	39.4 (39)	8.0 (45)
<b>Combination</b>		
Neonatal vaccination with basic pre-exposure effects plus active- disease regimen 2 plus NAAT	55.3 (54)	10.4 (58)
<b>Nonportfolio strategies and combinations</b>		
<b>Mass vaccination (includes neonatal vaccination)</b>		
Basic pre-exposure vaccine only	68.2 (67)	11.5 (64)
Basic pre-exposure vaccine with the additional effects	74.0 (73)	12.4 (69)
Neonatal vaccination with 3-year mass catch-up, basic pre-exposure vaccine with additional effects	67.9 (67)	11.4 (64)
Mass vaccination with only a postexposure effect	30.1 (30)	5.0 (28)
Neonatal vaccination, basic pre-exposure with additional effects, plus mass vaccination with postexposure effect	73.2 (72)	12.3 (69)
Mass vaccination with basic pre-exposure vaccine, plus mass vaccination with postexposure effect	80.2 (79)	13.5 (75)
Mass vaccination with basic pre-exposure vaccine with additional effects, plus mass vaccination with postexposure effect	85.9 (84)	14.5 (81)
Neonatal vaccination with 3-year mass catch-up, basic pre-exposure with additional effects, plus mass vaccination with postexposure effect	83.8 (82)	14.1 (79)
Mass latent therapy	64.8 (64)	10.8 (60)
Active-disease regimen 2 plus mass latent therapy	75.6 (74)	13.1 (73)
Mass vaccination with basic pre-exposure effects plus 2-month active disease treatment regimen 2 plus NAAT	77.8 (76)	13.9 (78)
Neonatal vaccination with 3-year mass catch-up with basic pre-exposure effects plus active-disease regimen 2 plus NAAT	73.5 (72)	13.2 (74)

Without novel intervention, cumulative incidence for 2015–2050 is 101.7 million active TB cases and 17.9 million TB-related deaths.

# Abu-Raddad 2009: Summary

- **Craft Policy**
  - Helped guide development portfolio
- **Conceptualize**
  - Increase CDR vs. shorten time to detection
- **Project**
  - 20% realistic mortality reduction
- **Operationalize**
  - Diagnostics as part of an integrated package

# Diagnostics to Manage Drug-Resistant TB

## Averting epidemics of extensively drug-resistant tuberculosis

Sanjay Basu<sup>a,b,c,d,1</sup>, Gerald H. Friedland<sup>a,b,c</sup>, Jan Medlock<sup>b</sup>, Jason R. Andrews<sup>a,d</sup>, N. Sarita Shah<sup>a,e</sup>, Neel R. Gandhi<sup>a,e</sup>, Anthony Moll<sup>a,f</sup>, Prashini Moodley<sup>a,g</sup>, A. Willem Sturm<sup>a,g</sup>, and Alison P. Galvani<sup>a,b</sup>

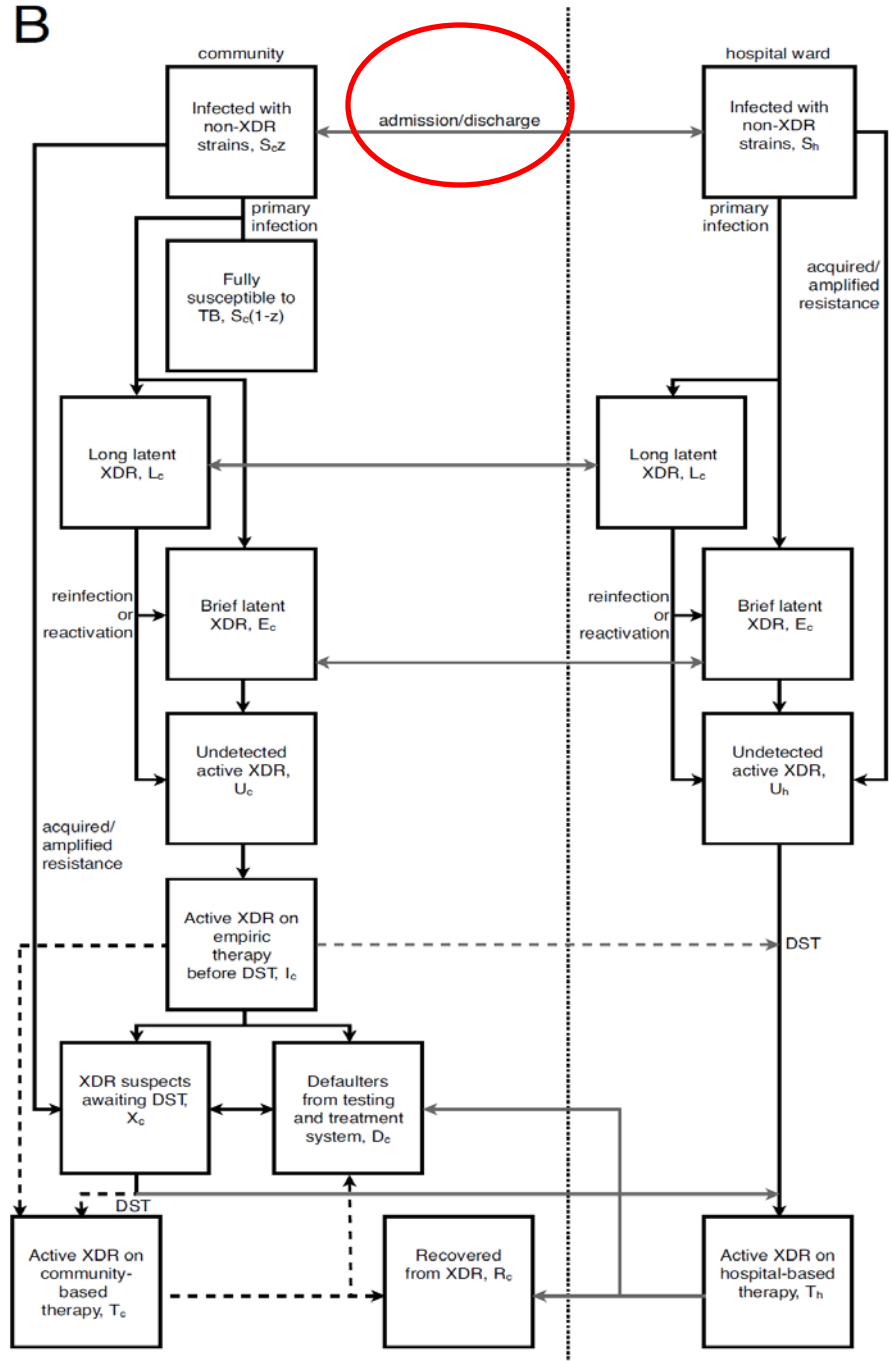
<sup>a</sup>Tugela Ferry Care and Research (TFCaRes) Collaboration, Tugela Ferry, KwaZulu-Natal 3010, South Africa; <sup>b</sup>Department of Epidemiology and Public Health and <sup>c</sup>AIDS Program, Yale University School of Medicine, New Haven, CT 06510; <sup>d</sup>Department of Internal Medicine, University of California San Francisco, San Francisco, CA 94143; <sup>e</sup>Divisions of General Internal Medicine, Infectious Diseases and Epidemiology, Albert Einstein College of Medicine, Bronx, NY 10467; <sup>f</sup>Church of Scotland Hospital, Tugela Ferry, KwaZulu-Natal 3010, South Africa; and <sup>g</sup>Department of Medical Microbiology, Nelson R. Mandela School of Medicine, Durban, KwaZulu-Natal 4013, South Africa

Edited by Rita R. Colwell, University of Maryland, College Park, MD, and approved March 11, 2009 (received for review December 8, 2008)

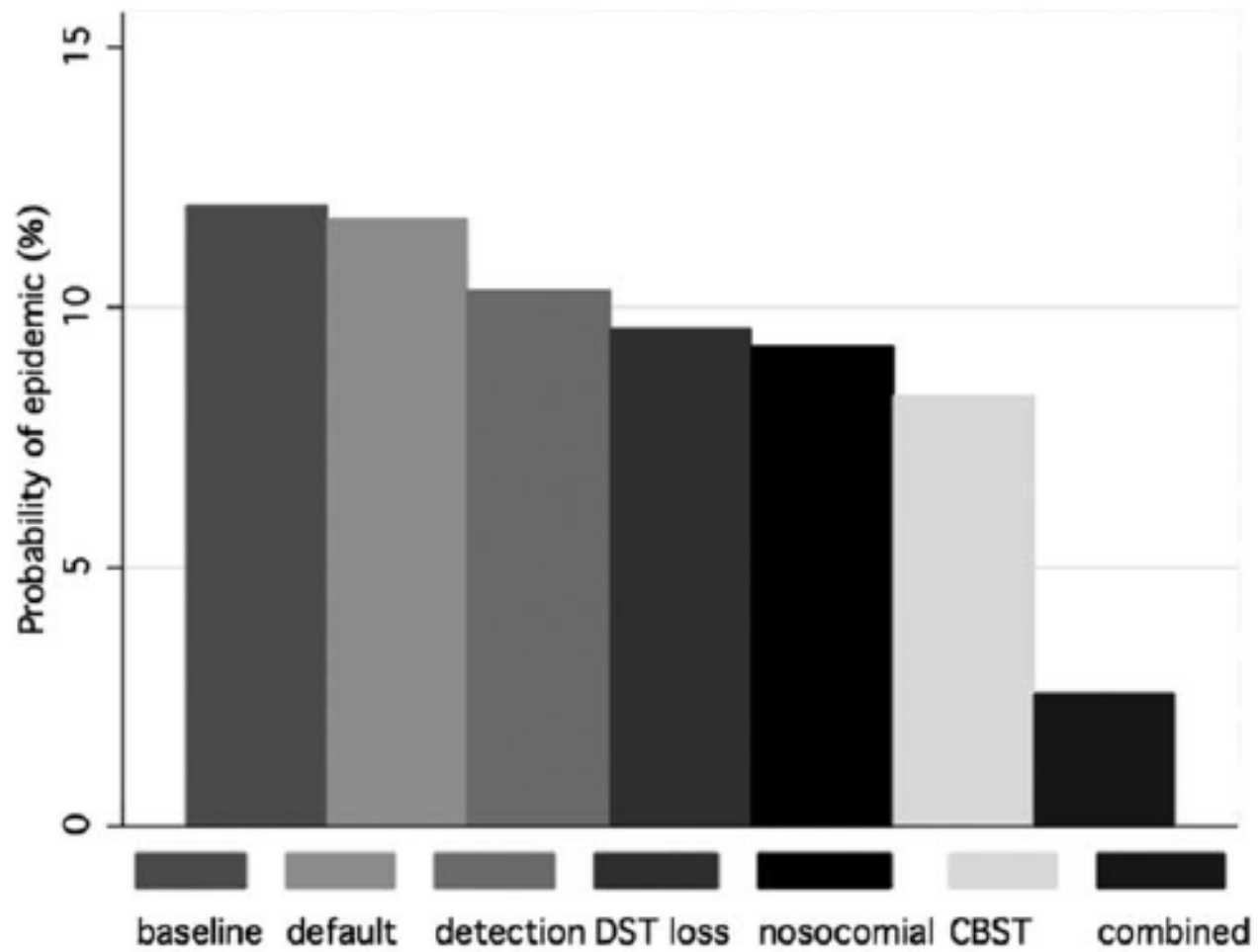
# Basu et al, PNAS 2009

- Published by Friedland's group from Tugela Ferry, South Africa (XDR-TB outbreak)
- Aimed to identify strategies for preventing XDR-TB epidemics
- Interventions:
  - Increase CDR from 55% to 70%
  - Accelerate DST from 6 wks to 1 wk
  - Infection control: prevent nosocomial spread
  - Increased access to DST (outpatient)

B



**B**



# Basu 2009: Summary

- **Craft Policy**
  - Inform XDR-TB control strategies
- **Conceptualize**
  - Importance of nosocomial epidemics
- **Project**
  - Lower risk of XDR epidemic from 12% to 8%
- **Operationalize**
  - Community-based efforts required to prevent spread of nosocomial XDR-TB outbreaks

# Conclusions:

## History of Modeling TB Diagnostics

- Modeling of TB diagnostics is a new field.
- 2006 as a turning point
  - Nature & AIDS papers, plus external forces
- Specific refinements since 2006
  - Expansion of existing diagnostics
  - Introduction of novel diagnostics
  - Diagnostics as part of integrated TB control strategy
  - Diagnostics for managing MDR-/XDR-TB

# Conclusions: 4 Goals of Models

- **Craft Policy**
  - 2006: Enhance awareness of diagnostics
  - Post-2006: Target specific audiences
- **Conceptualize**
  - 2006: Access to diagnostic services
  - Post-2006: Repeat attempts, relation to smear, speed vs. accuracy, nosocomial vs. community
- **Project**
  - 20% realistic mortality reduction
- **Operationalize**
  - Target areas with poor infrastructure
  - Diagnostics as part of a larger package

