JOHNS HOPKINS
UNIVERSITY

JOHNS HOPKINS
BLOOMBERG
SCHOOL of PUBLIC HEALTH

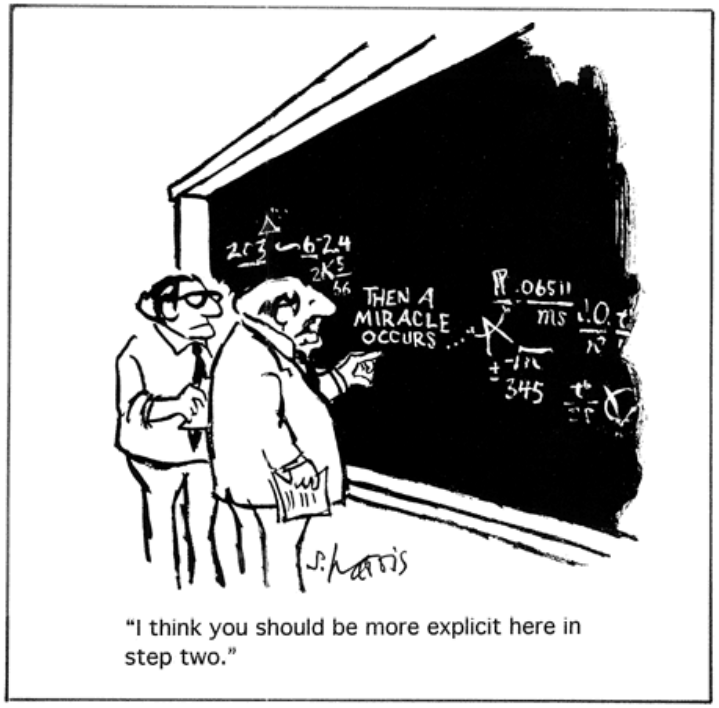
# Mathematical Modeling of TB Diagnostics: An Introduction

David Dowdy, MD PhD
Advanced TB Diagnostics
Montreal, Canada
ddowdy@jhsph.edu

Protecting Health, Saving Lives—*Millions at a Time*

# Objectives

- Introduce the motivation for transmission modeling
- Describe modeling methods (without equations)
- Discuss some insights we have gained from transmission models of TB diagnostics

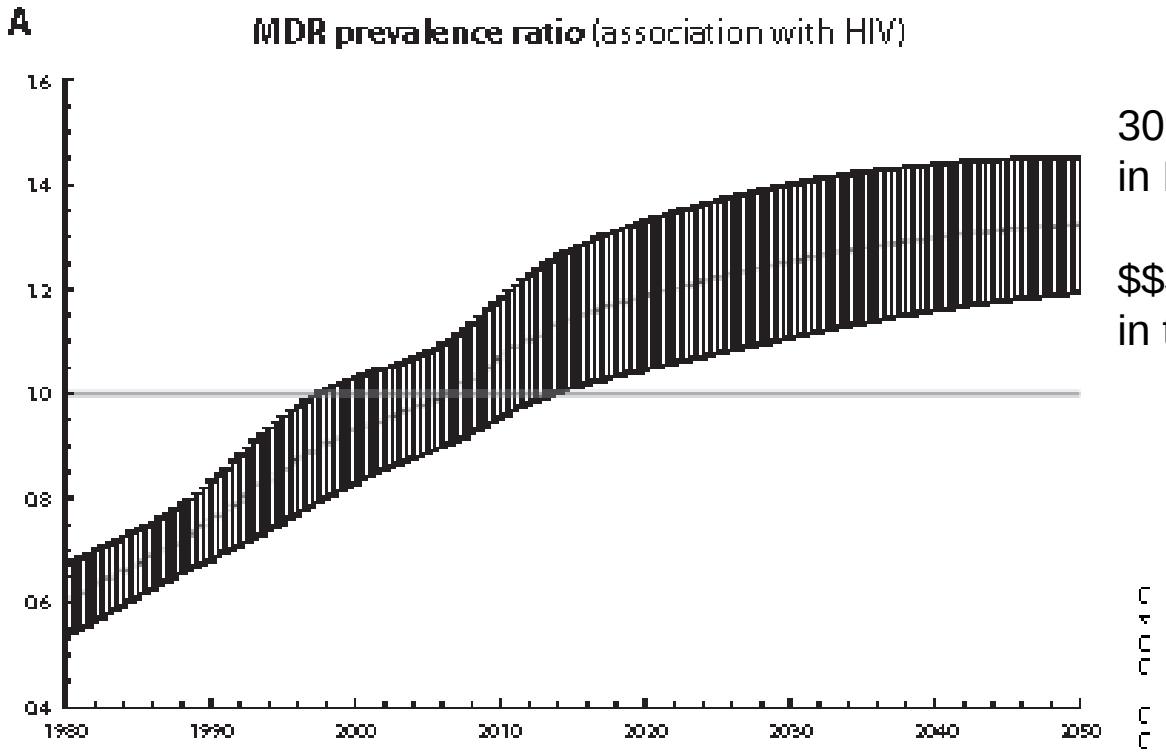


# A Scenario…

- You are the director of the NTP for a country in sub-Saharan Africa, SE Asia, etc.
- You have a total budget of $20 million, population of 100 million, and TB incidence of 100,000 new cases/year
  - 20c/person, $200/TB case
- You have no idea what your MDR-TB prevalence is, but you're worried it's high.
- You must decide how to budget your money:
  - DOTS ($100/case treated, $2/smear)
  - Optimized DOTS ($5,000/district to enable same-day microscopy)
  - Active case-finding ($25/person screened)
  - MDR-TB ($2000/case treated, $20/DST)
  - Xpert scale-up ($10/cartridge, $17,000/machine)

# How Do You Decide?

- If you neglect MDR-TB, does this happen?



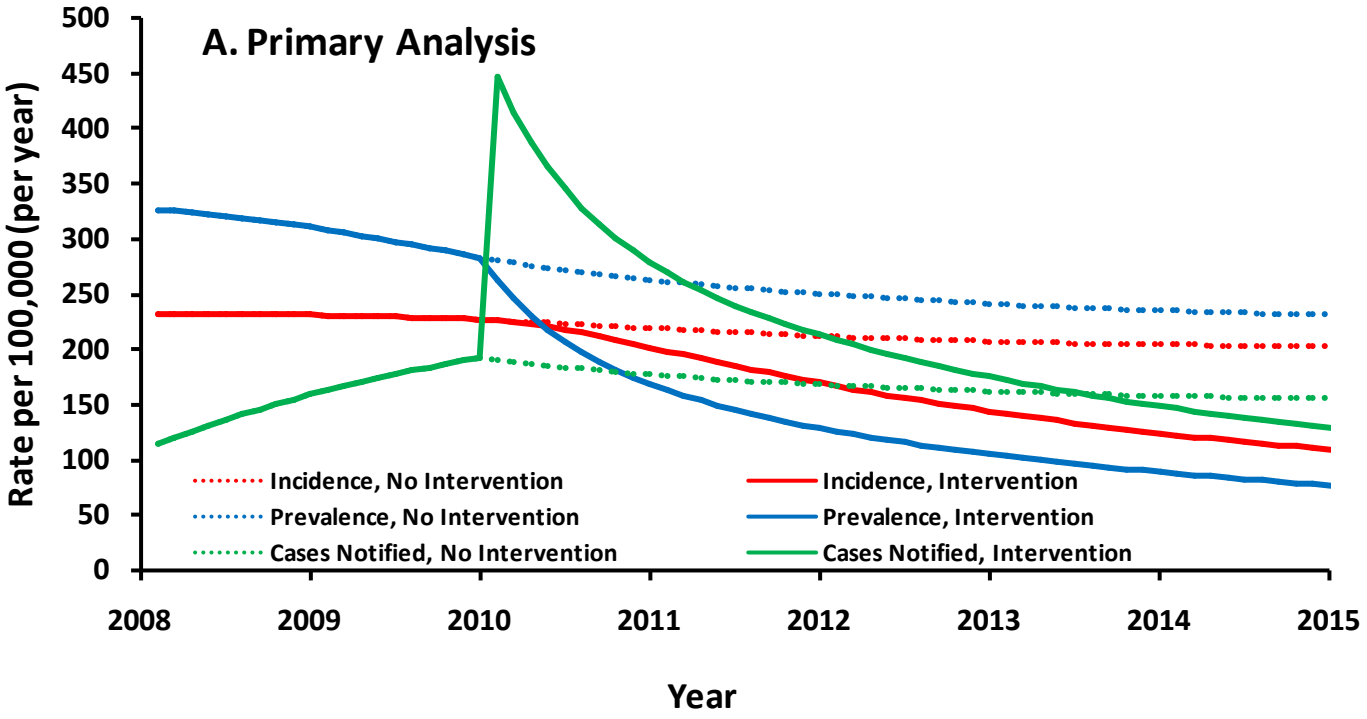

30% increase in MDR-TB =

$$$$$$$ in the future!

*Serveev R et al, Sci Transl Med 2012*

# How Do You Decide?

- If you invest in active case-finding, can you achieve this?



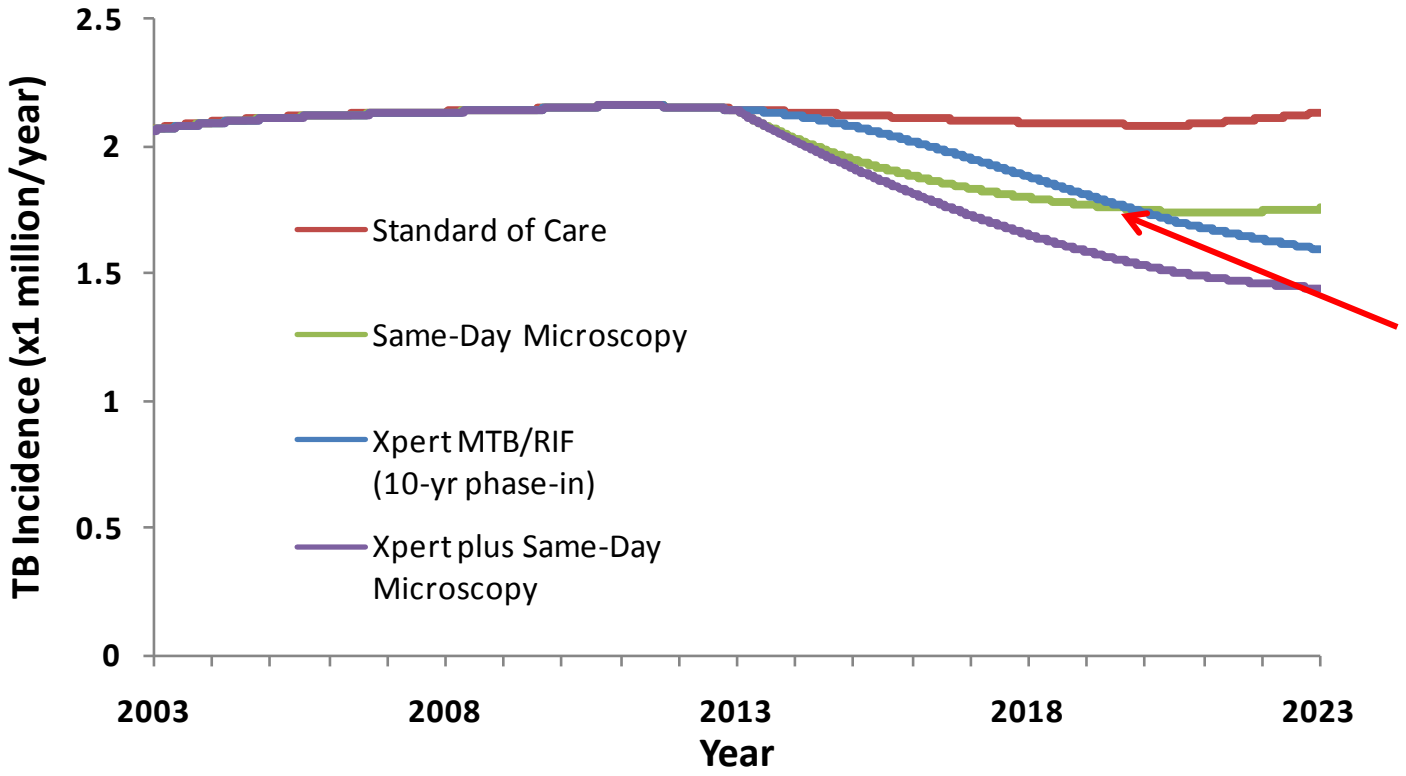

FEWER cases treated within 4 years =

$$$$$$$ in your bank

*Dowdy DW et al, in preparation*

# How Do You Decide?

- Is Xpert a good idea, or “optimize smear and wait for something better”?




*Dowdy DW et al, in preparation*

# The Role of Mathematical Modeling

- Conceptualization
  - Help understand the problem or frame it in a new light
- Operationalization
  - Identify parameters that are key to an intervention's success
- Projection
  - Quantify impact of interventions
- Informing policy
  - Bring data into decision-making
  - Focus those decisions on key issues

# What Models Cannot Do...

- Tell the future
  - The future is molded by unpredictable events.
- Precisely describe the world
  - The world is shaped by extremely complex phenomena.
- Tell us which sets of assumptions are “right”
  - Models can use different sets of assumptions to make different projections, but cannot tell which projections are the right ones.
- Make decisions for people
  - Decision-making is a political process; models seek only to bring epidemiological data to bear in that process.

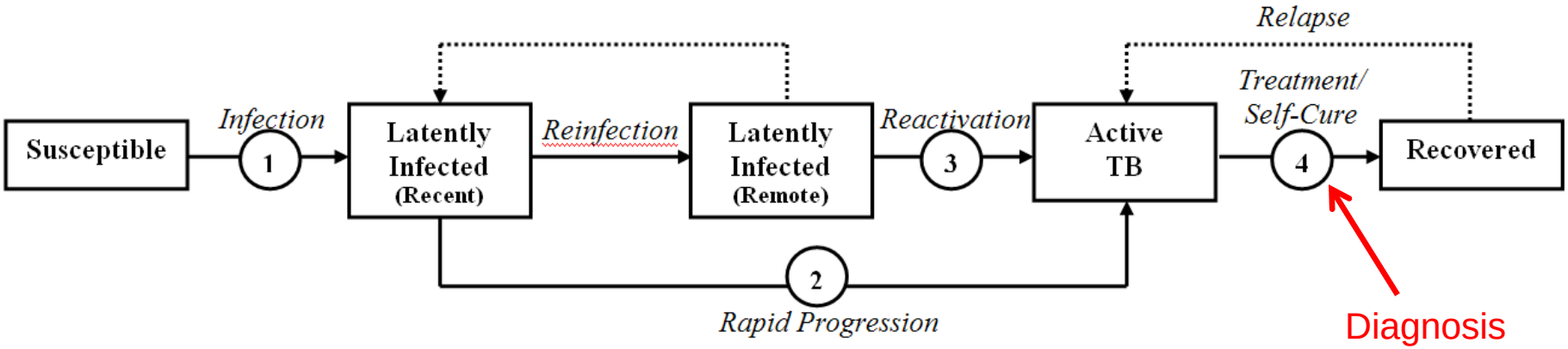
# More Complex ≠ Better

**Box 1. Costs of Complexity in TB Transmission Models**

1. **Transparency:** Complex models (e.g., one that models multiple states of HIV progression, drug resistance, demographics, spatial networking, etc.) may be less transparent than simple ones, as model output may depend on complex relationships that are not readily visible to readers (or model diagnostics).
2. **Generalizability:** Calibration of complex models to specific settings is likely to involve alteration of more parameters, making model output less generalizable to other settings with different TB epidemics.
3. **Stability:** Output of complex models may be more dependent on specific combinations of parameter values, making their results less stable (i.e., higher variance) when parameters are simultaneously varied in uncertainty analysis.
4. **Over-Parameterization:** TB transmission models are generally calibrated to existing data. Complex models have nearly as many (or more) parameters than data points for calibration, leading to potentially unreliable output.
5. **Computational Intensity:** Each division of a population into two sub-populations (e.g., strata of gender) effectively doubles the time required to run simulations. Thus, more complex models are more difficult to simulate in settings without access to advanced cluster-computing resources.
6. **Manipulability:** As with complex statistical analyses, complex transmission models have more parameters that are susceptible to manipulation by developers, who often have a bias toward presenting "positive" results.
7. **Reproducibility:** By virtue of requiring more computer code, complex models are more difficult to replicate and understand, and also more prone to unintentional error.
8. **Relevance to Decision-Makers:** As a result of many of the above issues, complex models are often less relevant to decision-makers in the field (who generally lack mathematical expertise) than are simple, easily-understood models.

*Dowdy DW, Cohen T, Dye C, submitted*

# Transmission Models of TB




- Simplify complex dynamics to focus decision-making
- Compartmental models most common
  - Differential equations describe flows between sub-populations
- Key feature: rate of infection (1) depends on the number of people with active TB at any given moment.
- Can count TB cases and deaths over time

# Why Do We Need Transmission Models?

- Consider two diagnostic tests for TB:
  - Test 1: 90% sensitive, but requires patients to self-present
  - Test 2: 50% sensitive, but can be used to screen the population once per year (in addition to self-presentation)
- A few basic assumptions:
  - Duration of TB disease before self-presentation = 1 year
  - Number of secondary transmissions per infectious person-year = 10
  - Proportion of secondary transmissions that result in active TB = 20%
    - 1 new case of active TB every 6 months
  - Mortality of TB without screening at the end of year 1:
    - 20% if detected
    - 100% if not detected
- Which test is better?

# The Dogmatic Approach...

- “Test A must be better – it’s more sensitive!”
  - “Xpert must be a better option than smear, it’s more sensitive!”
- “Test B must be better – it’s more deployable!”
  - “Xpert in clinics must be better than Xpert in labs – it’s more deployable!”
- “It’s just too complicated.”
  - “So therefore I have an excuse to ignore data and choose the test that I like best.”

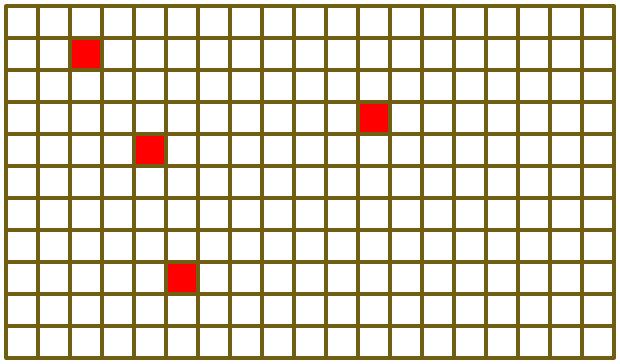
# The Simple Approach…

- Evaluate a cohort of 100 people

| Outcome | Test 1 | Test 2 |
|---|---|---|
| Screened | 50 | 0 |
| Diagnosed after 1 year<br>Survive<br>Die | 25<br>20<br>5 | 90<br>72<br>18 |
| Undiagnosed = dead | 25 | 10 |
| | | |
| **Total Alive** | **70** | **72** |
| **Total Dead** | **30** | **28** |

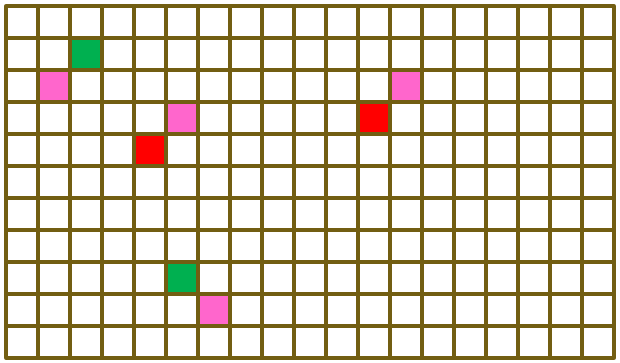
*Test 1 seems similar to Test 2 in averting deaths.*

# What If We're Interested in the Population?



**4 TB cases in a community with test 1**

# Population Dynamics



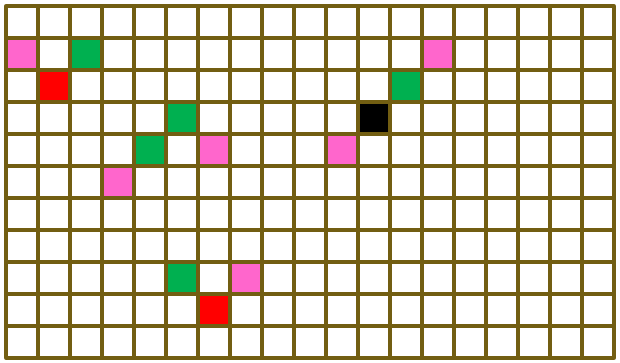
Diagnosed

Old Active

New Active

**At 6 Months: 6 Active Cases**

# Population Dynamics



Diagnosed

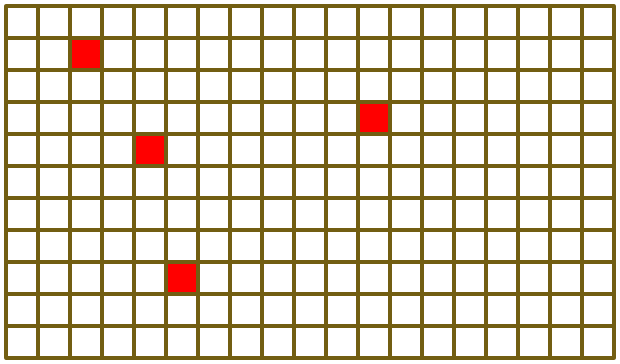
Old Active

New Active

Dead

**At 12 Months: 8 Active Cases**

# Alternative Population Dynamics



Diagnosed

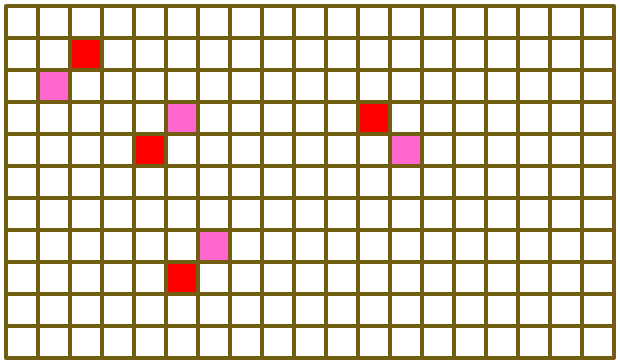
Old Active

New Active

Dead

**What about test 2?**

# Alternative Population Dynamics



Diagnosed

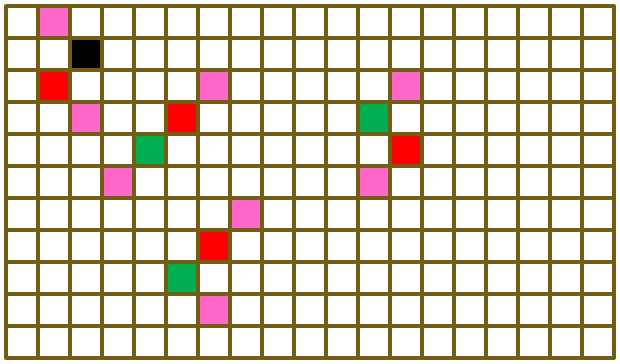
Old Active

New Active

Dead

**6 Months: 8 Active Cases**

# Alternative Population Dynamics



Diagnosed

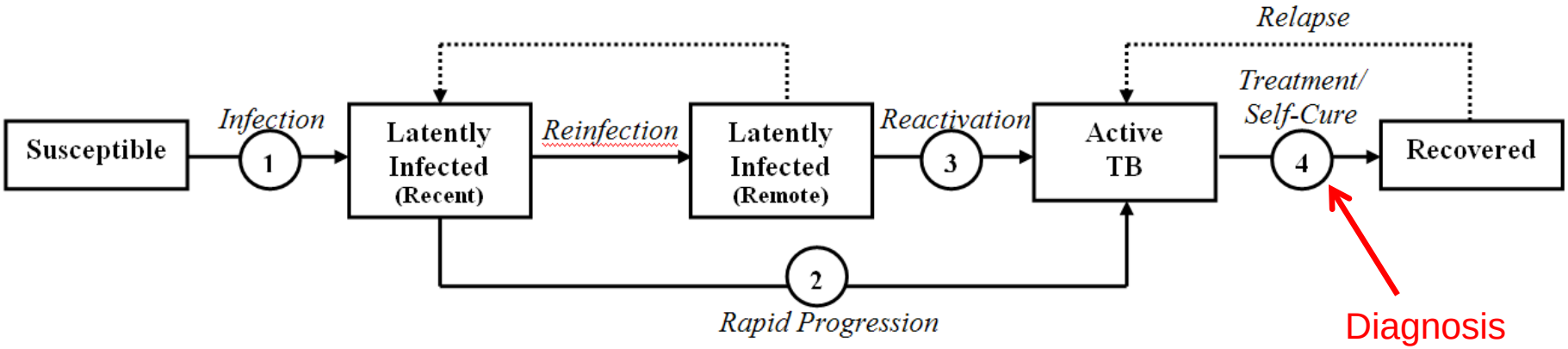
Old Active

New Active

Dead

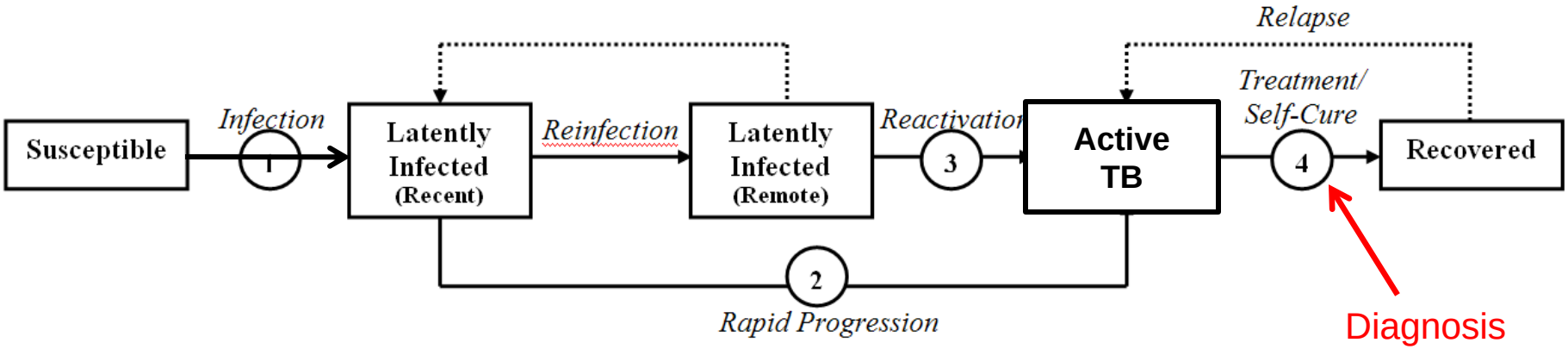
**12 Months: 12 Active Cases!**

# Transmission Models Capture These Effects




- Re-calculate the population every few days
- As the size of the active TB compartment grows, the rate of infection grows

# Transmission Models Capture These Effects




- Re-calculate the population every few days (not 6 months)
- As the size of the active TB compartment grows, the rate of infection grows
- Allows for real-time evaluation of population-level effects on transmission

# The Role of Transmission Modeling

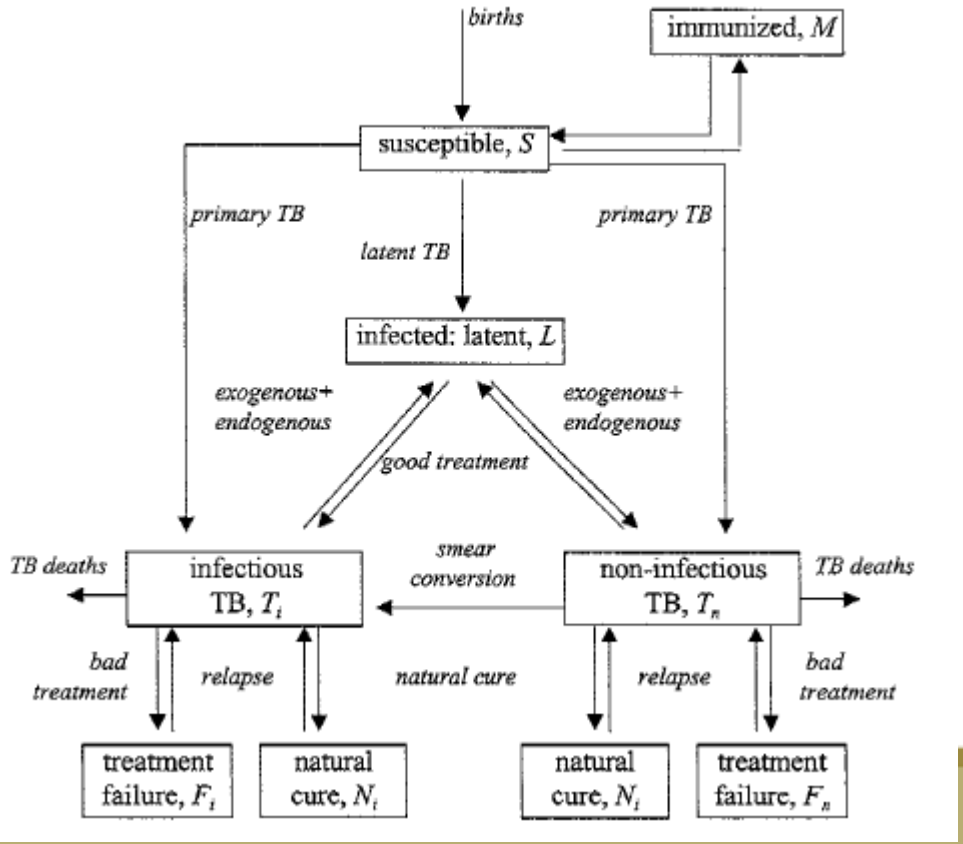
- The targets of TB diagnostic strategies are increasingly moving beyond individual (clinical) effectiveness to population-level (public health) effectiveness.
  - This is a true paradigm shift.
- If diagnostics are being deployed with a goal of population-level effectiveness in mind, models must account for the entire population.
  - Including those who have not yet been infected.
- Strategies with similar individual-level effectiveness can have dramatically different implications at the population level.
  - Differential time to diagnosis = differential transmission
- Transmission models allow us to convert assumptions about individual-level effects to the population level.

# What Have Transmission Models Taught Us About TB Diagnostics?

ARTICLES

**Prospects for worldwide tuberculosis control under the WHO DOTS strategy**

*Christopher Dye, Geoffrey P Garnett, Karen Sleeman, Brian G Williams*



# Importance of Case Detection and Cure

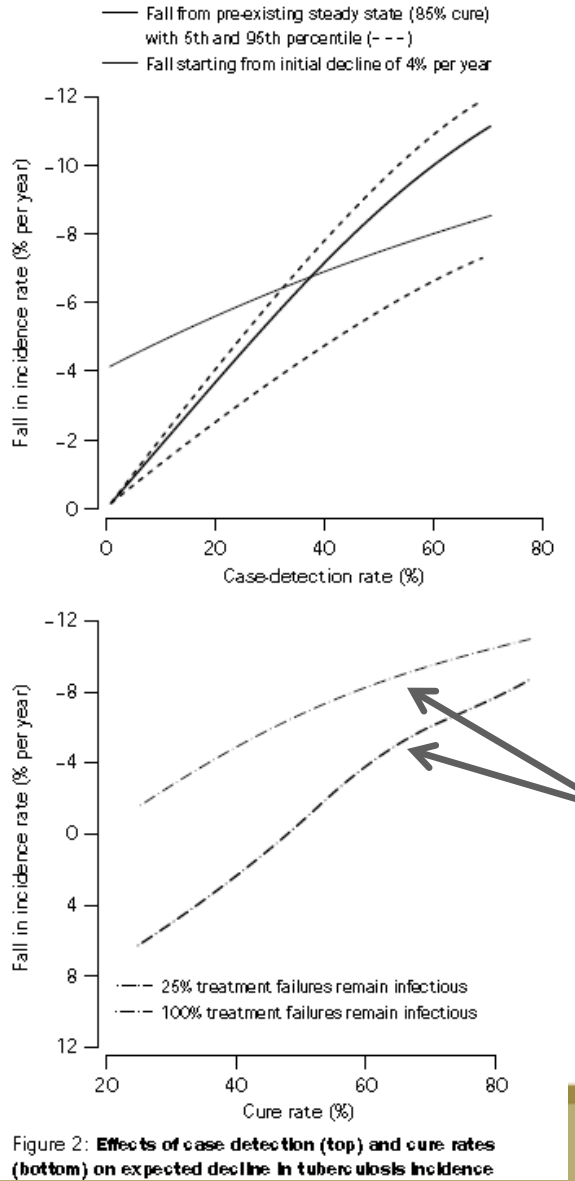



Figure 2: **Effects of case detection (top) and cure rates (bottom) on expected decline in tuberculosis incidence**

Infectiousness of treatment failures also key!

# Ability of DOTS to Control TB…

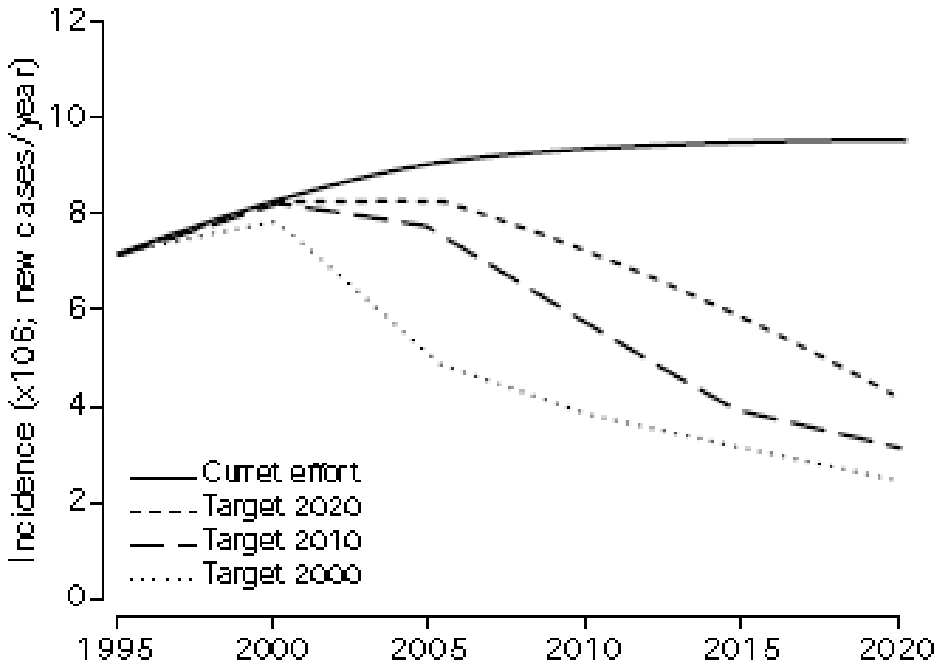


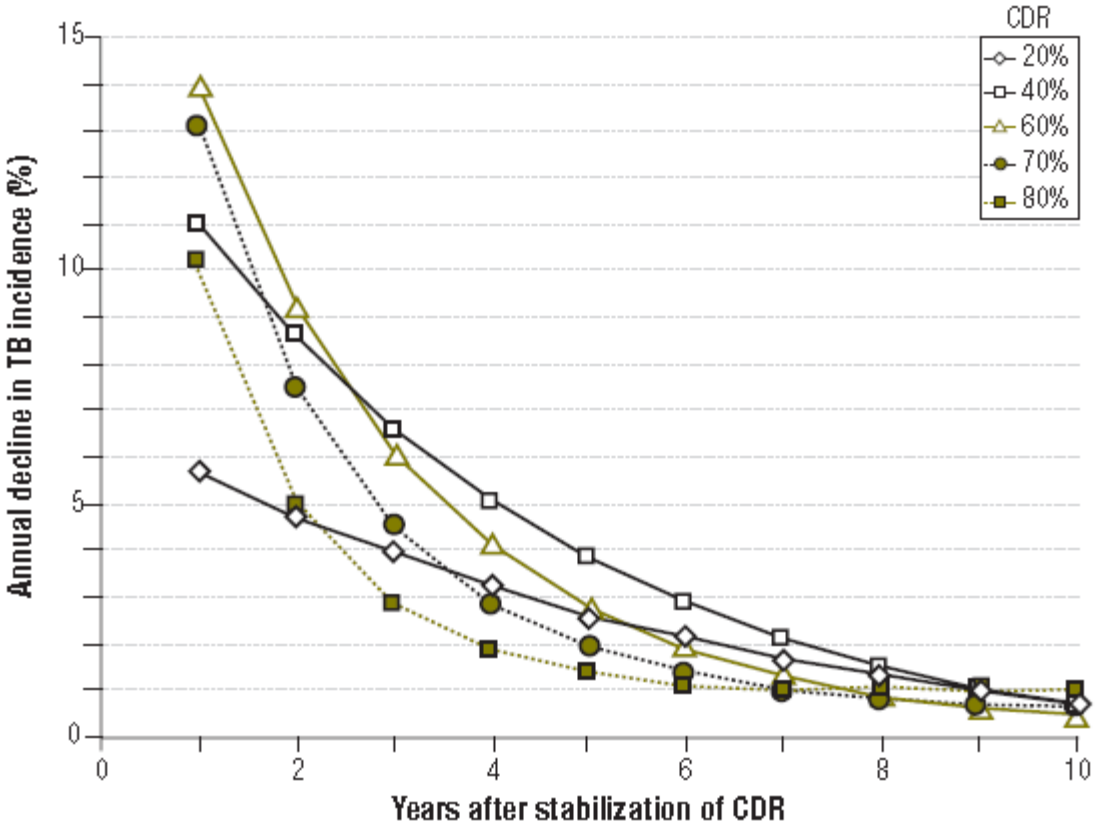

Figure 5: **Projected annual worldwide incidence of tuberculosis under assumption that WHO targets for case finding and cure are met in 2000, 2010, and 2020, compared with maintenance of current control effort**

# ...or not

**The persistence of tuberculosis in the age of DOTS: reassessing the effect of case detection**

David W Dowdy[a] & Richard E Chaisson[a]

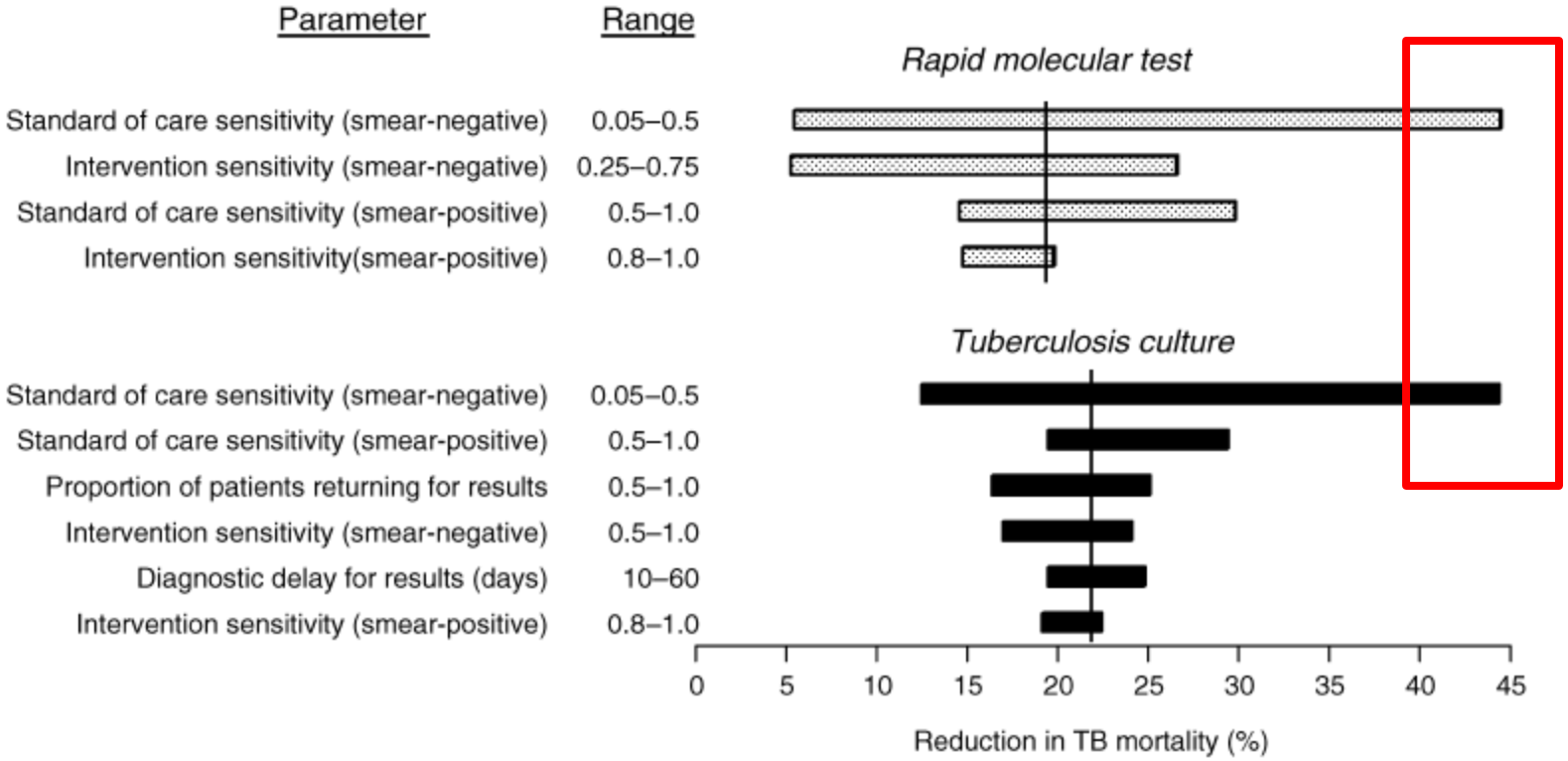
Fig. 2. **Annual decline in TB incidence under stable case detection[a]**



# Population-Level Impact of New Diagnostics Depends on the Standard of Care

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

David W. Dowdy[a,c], Richard E. Chaisson[a,b,d], Lawrence H. Moulton[b] and Susan E. Dorman[b,d]






*AIDS* 2006, **20**:751–762

# Novel Diagnostics

PNAS

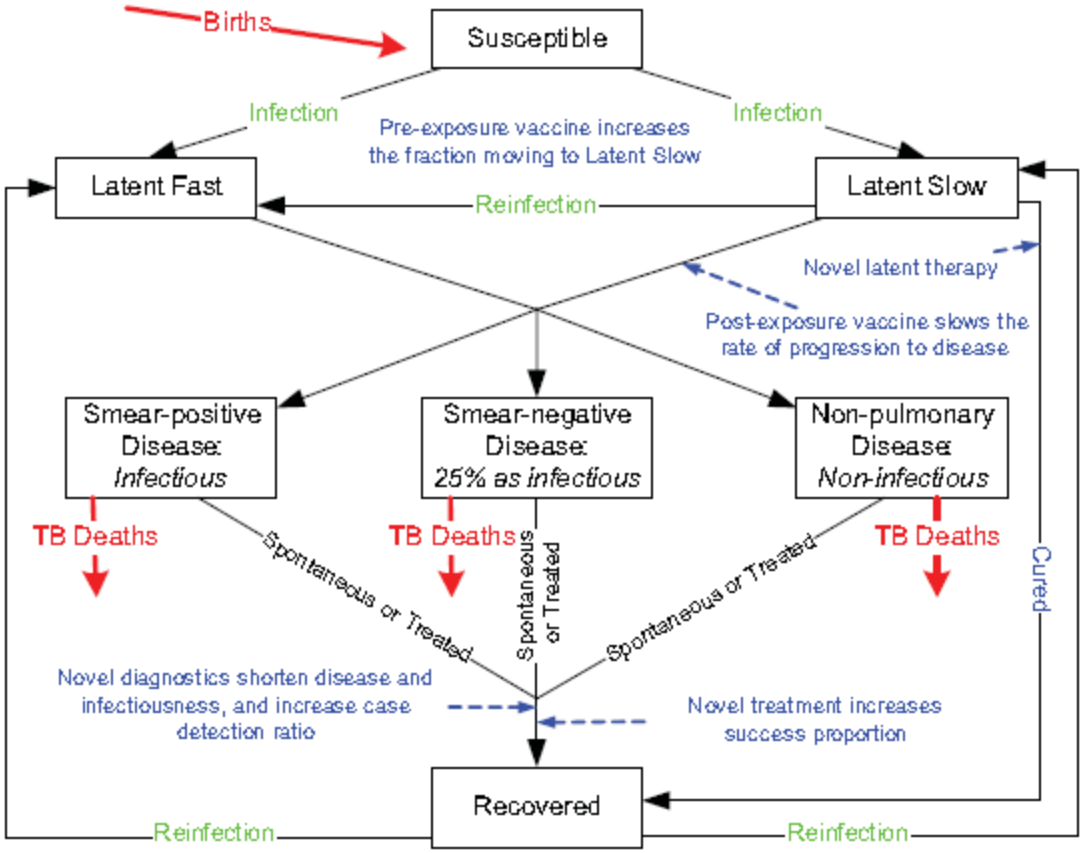
## Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics

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

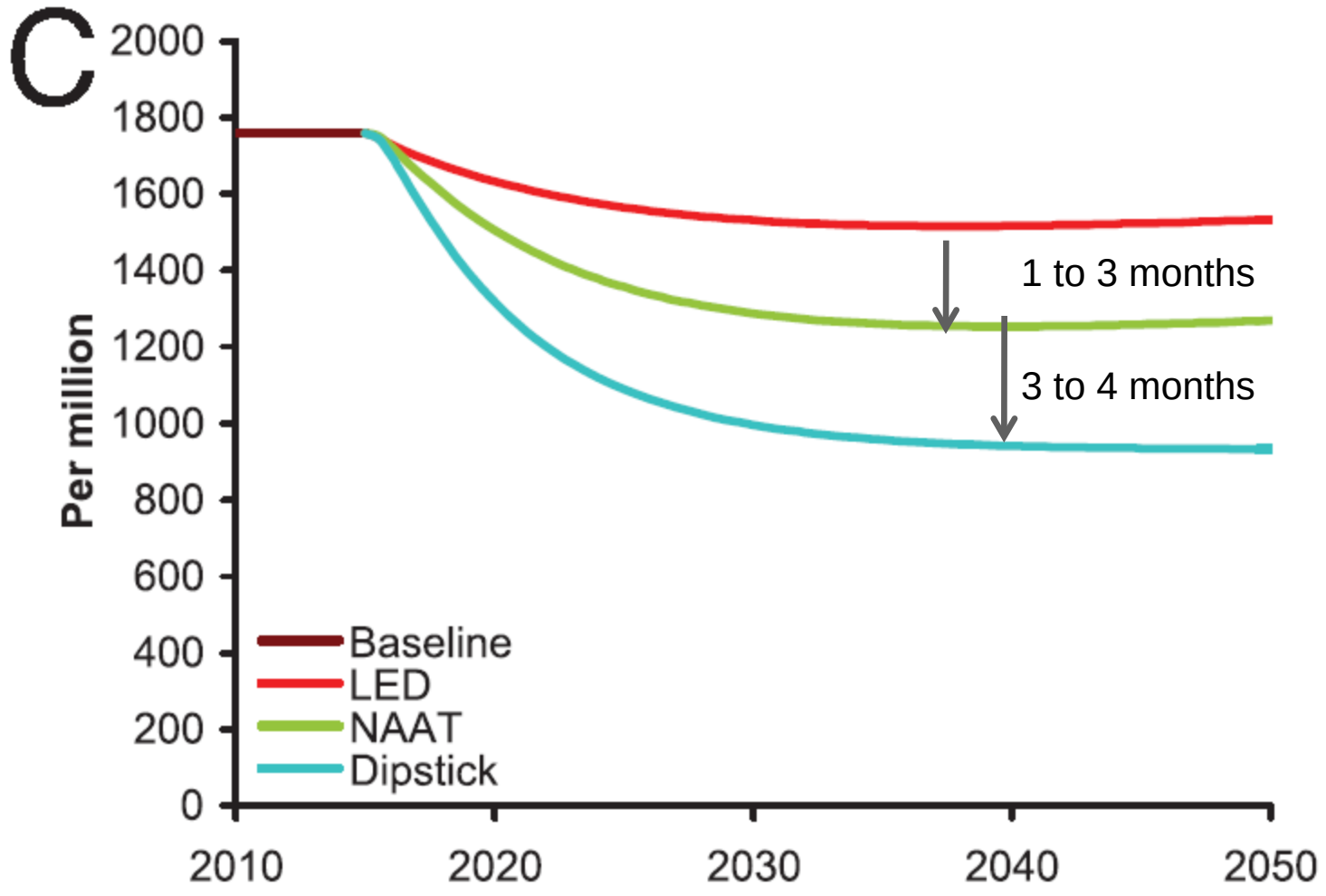
[a]Vaccine
and [d]Biost
World He

iology, [c]Anthropology,
ropical Diseases,

Edited by )



# 1 vs. 3 vs. 4 months' shortening of TTD



# Summary of Lessons Learned

- Two key elements to the population-level effectiveness of diagnostics:
  - Time to diagnosis
  - Proportion successfully treated
- Impact depends not only on where you end up, but where you start.
  - Novel diagnostics will have greater population-level impact in areas with poor existing diagnostics.
- Diagnostics tend to bring TB to a new (lower) equilibrium.
  - Difficult to achieve elimination without combining with other strategies
  - However, as diagnostics continue to improve, their proportional impact may be increasingly large.

# Conclusions


- Transmission models translate individual-level assumptions into population-level effects.
  - Account for feedback loops of transmission
- Modeling is important for:
  - **Conceptualizing** complex dynamics
  - **Operationalizing** key parameters for decision-making
  - **Projecting** (epidemiologic and economic) impact of interventions
  - **Informing policy** in TB control
- Some lessons we have learned already:
  - Two key parameters:
    - Time to diagnosis, proportion treated
  - More impact where baseline diagnostics are poor
  - Increasing effects when diagnostics are combined with other interventions or made extremely effective

# Tomorrow!

- In-depth case studies
- Economic/cost-effectiveness models
- Current challenges in modeling TB diagnostics