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Mathematical Modeling of TB Diagnostics: An Introduction

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Advanced TB Diagnostics

Montreal, Canada

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

Mathematical Models: A Pre-Test

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- Take:
  - S = size of the TB-susceptible pool
  - L = size of latently-infected TB pool
  - A = size of active TB pool
- Then:
  - $dA/dt = \lambda\rho SA + \lambda\rho\varphi LA + \varepsilon L - \theta A - \mu A$
- Where:
  - λ = force of infection
  - ρ = probability of rapid progression
  - φ = protection due to latent infection
  - ε = reactivation rate
  - θ = diagnosis & treatment rate
  - μ = mortality rate for active TB

What is the purpose of this model?

- (a) To explore the balance between recent infection vs. reactivation
- (b) To evaluate long-term effects on transmission as the active pool is reduced through intervention
- (c) To project possible declines in incidence as a result of faster diagnosis and treatment
- (d) All of the above

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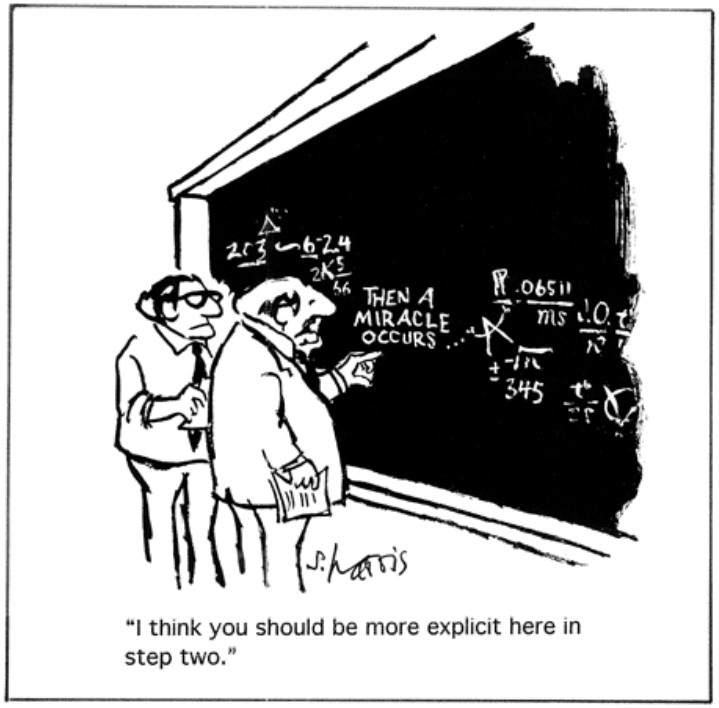
- **(d) All of the above**

Objectives

- Introduce the motivation for transmission modeling
  - Making decisions with limited resources/data
- Discuss some lessons learned from earlier transmission models of TB diagnostics
- Start to open the “black box”…

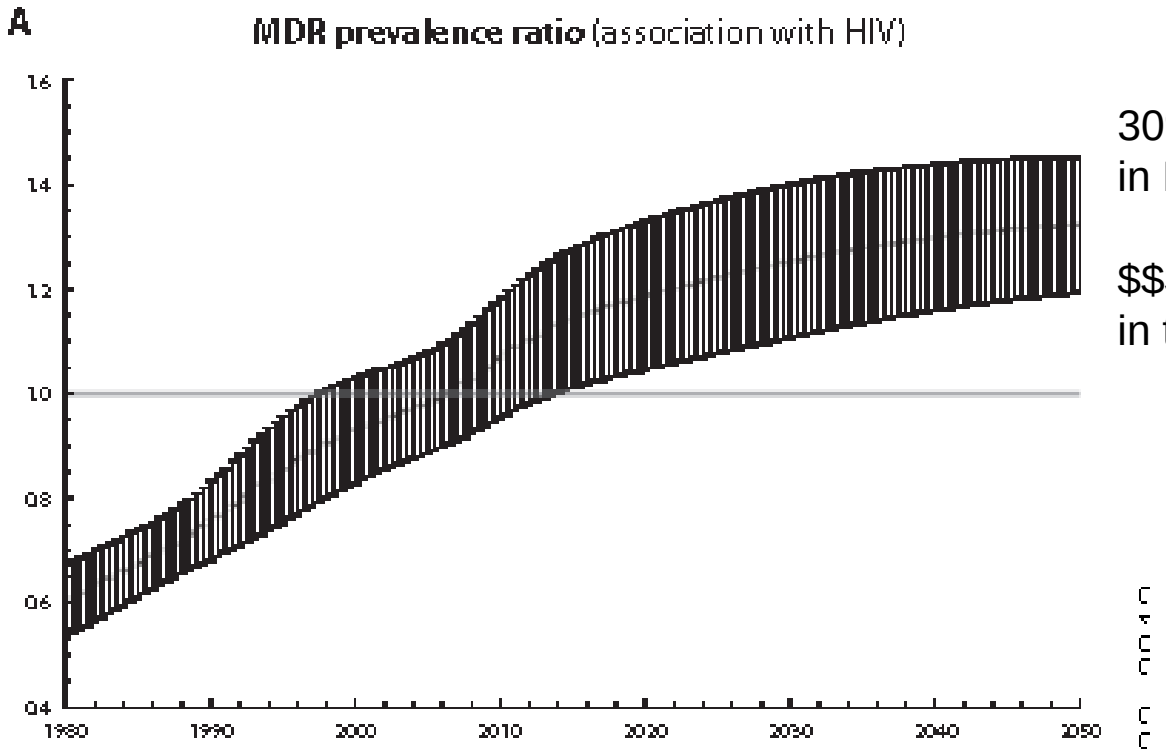


A Scenario…

- 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?



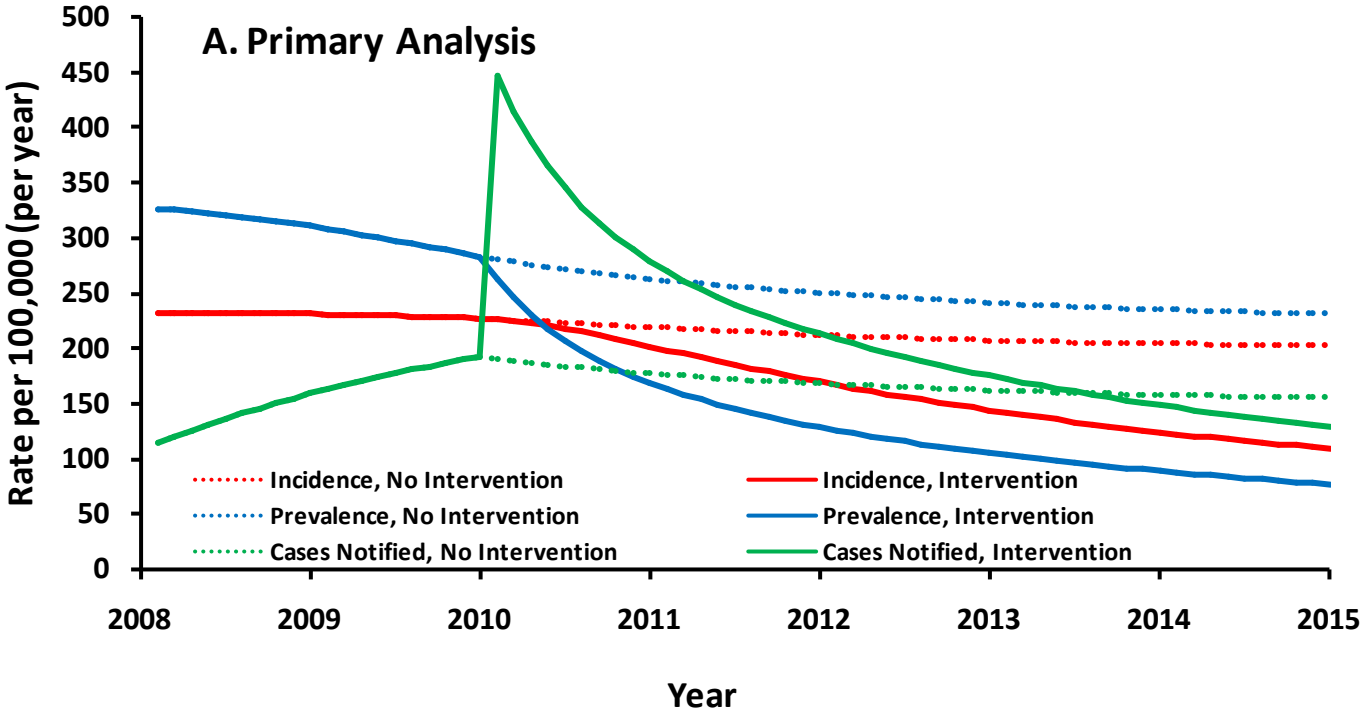
30% increase in MDR-TB =

$$$$$$$ 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?



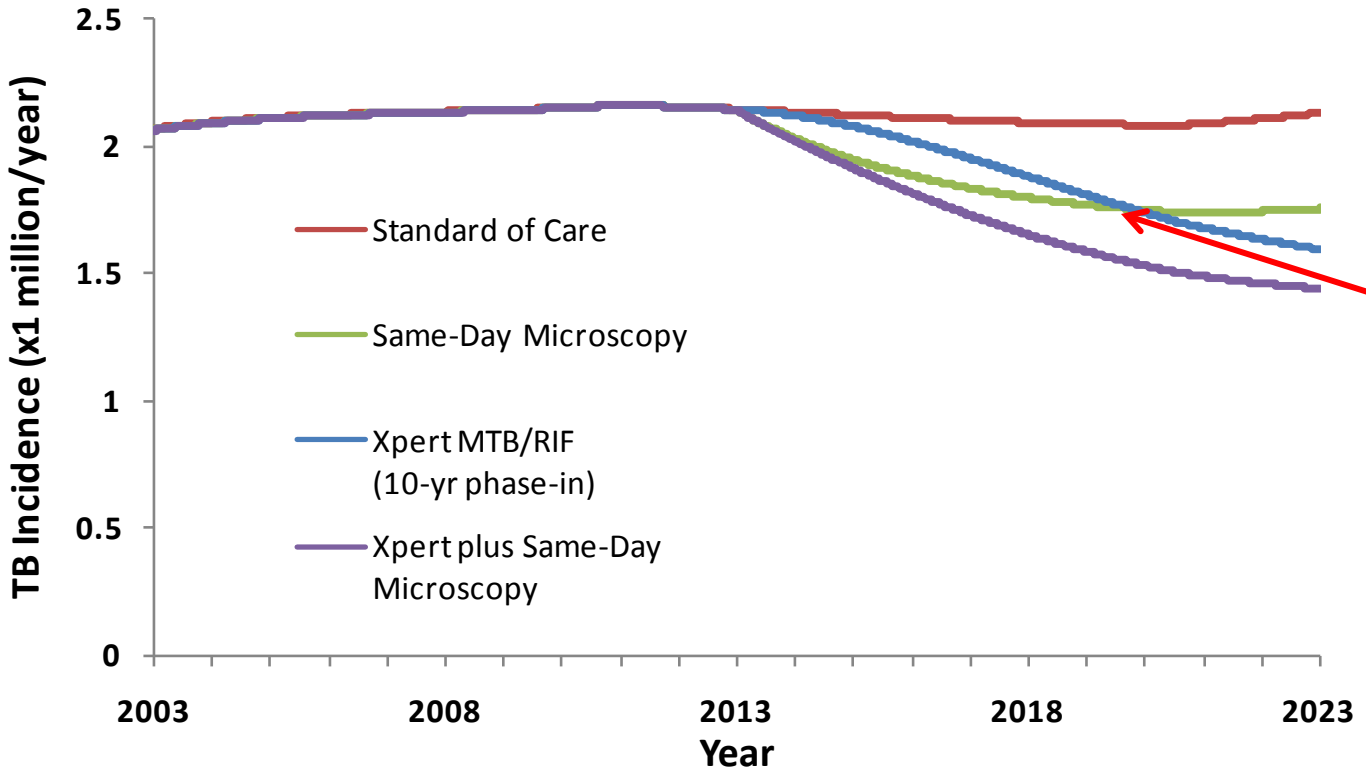
FEWER cases treated within 4 years =

$$$$$$$ 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

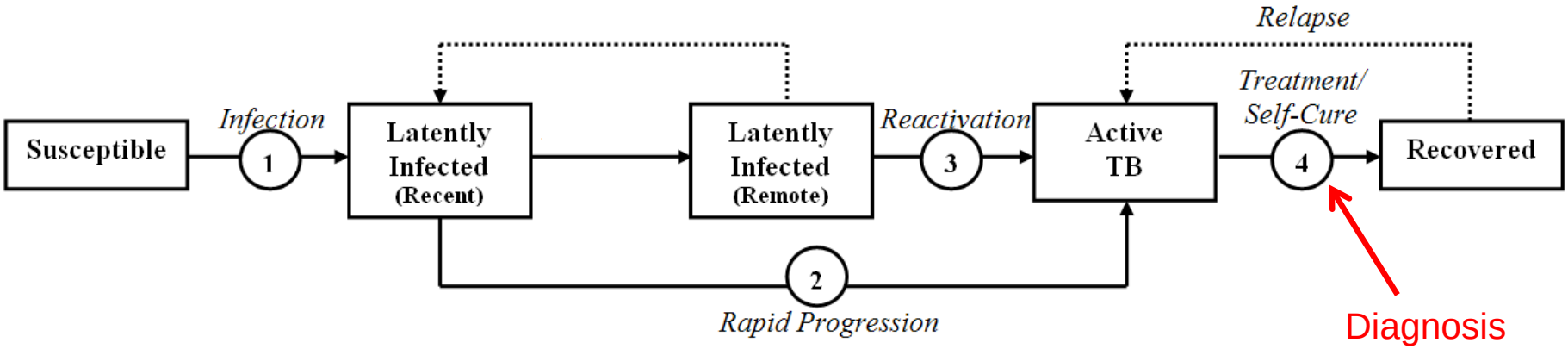
Role of Modeling

- **SIMPLIFY complex systems into something we can understand** (not just Greek letters!)**.**

- Translate existing epi data into a decision-making framework.
  - "If your assumptions are correct, these are the implications."
  - Can project alternative scenarios under different sets of assumptions.
  - Cannot predict the future, tell if assumptions are right, or replace data.

- Help to conceptualize or understand important questions.
  - What are the key drivers of cost, cost-effectiveness, impact, etc.?
  - If we change our assumptions, how much will our outcomes change?
  - What are the data that we most need to collect?

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.”

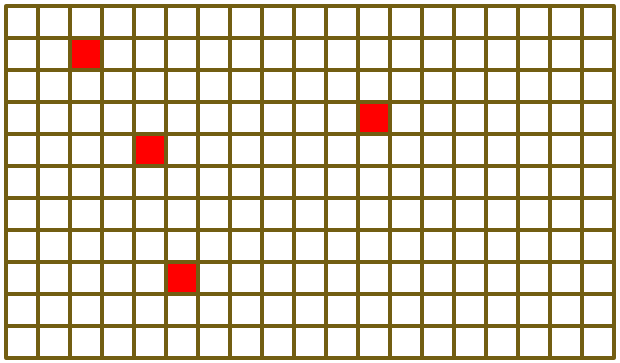
The Simple Approach…

- Evaluate a cohort of 100 people

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

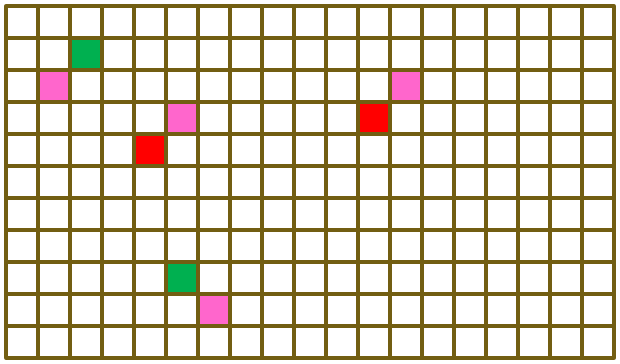
Test 2 is slightly better than Test 2 in averting deaths.

What If We're Interested in the Population?



4 TB cases in a community with test 1

Population Dynamics



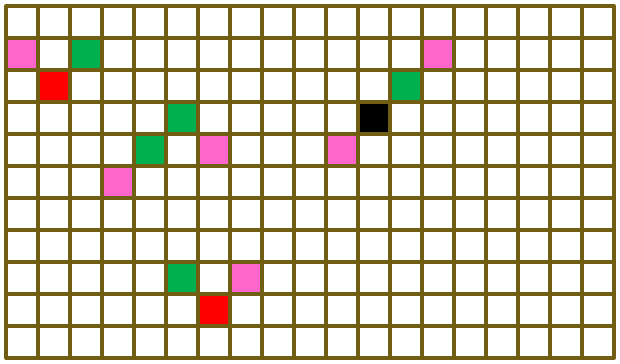
Diagnosed

Old Active

New Active

At 6 Months: 6 Active Cases

Population Dynamics



Diagnosed

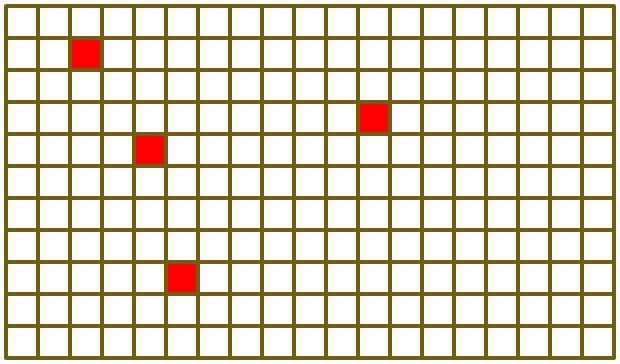
Old Active

New Active

Dead

At 12 Months: 8 Active Cases

Alternative Population Dynamics



Diagnosed

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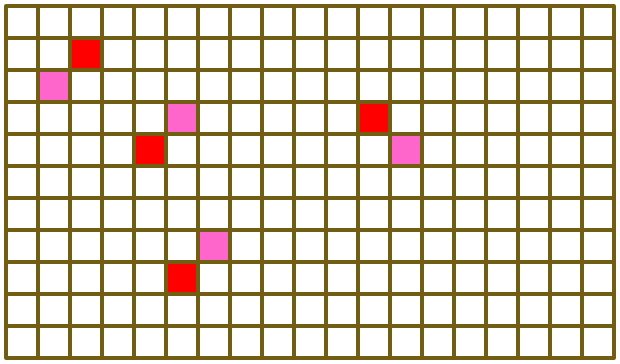
What about test 2?

Alternative Population Dynamics



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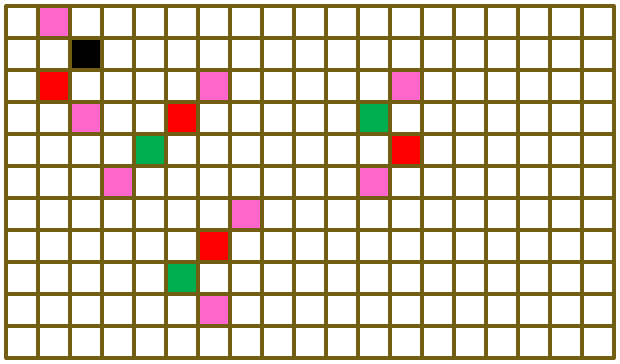


Diagnosed

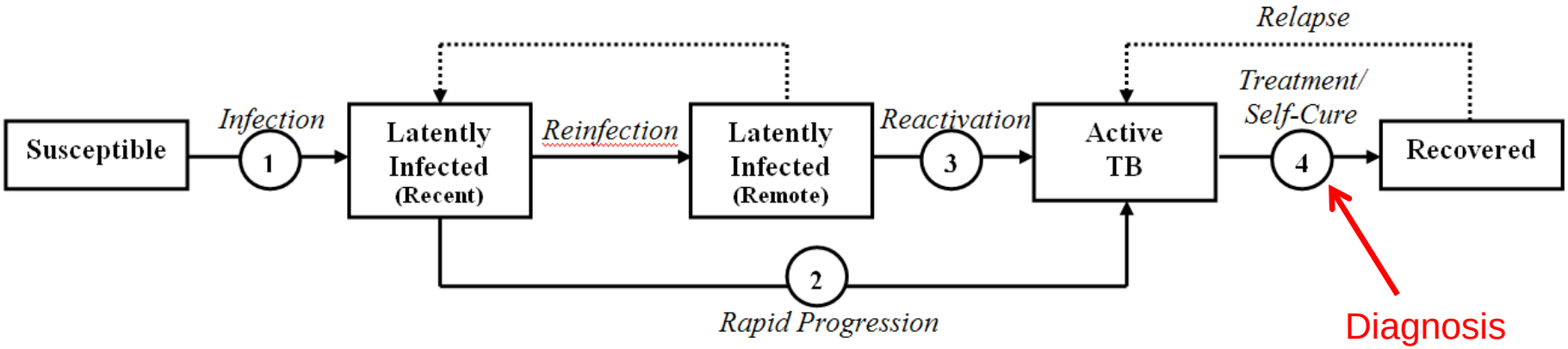
Old Active

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

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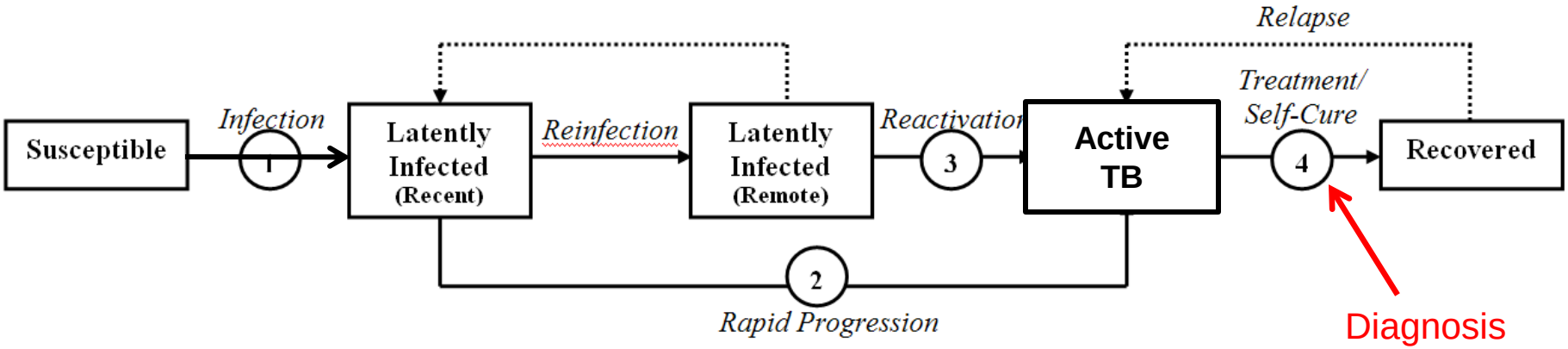


- Re-calculate the population every few days
- As the size of the active TB compartment grows, the rate of infection grows
- Allows for real-time evaluation of population-level effects on transmission

The Role of Transmission Modeling

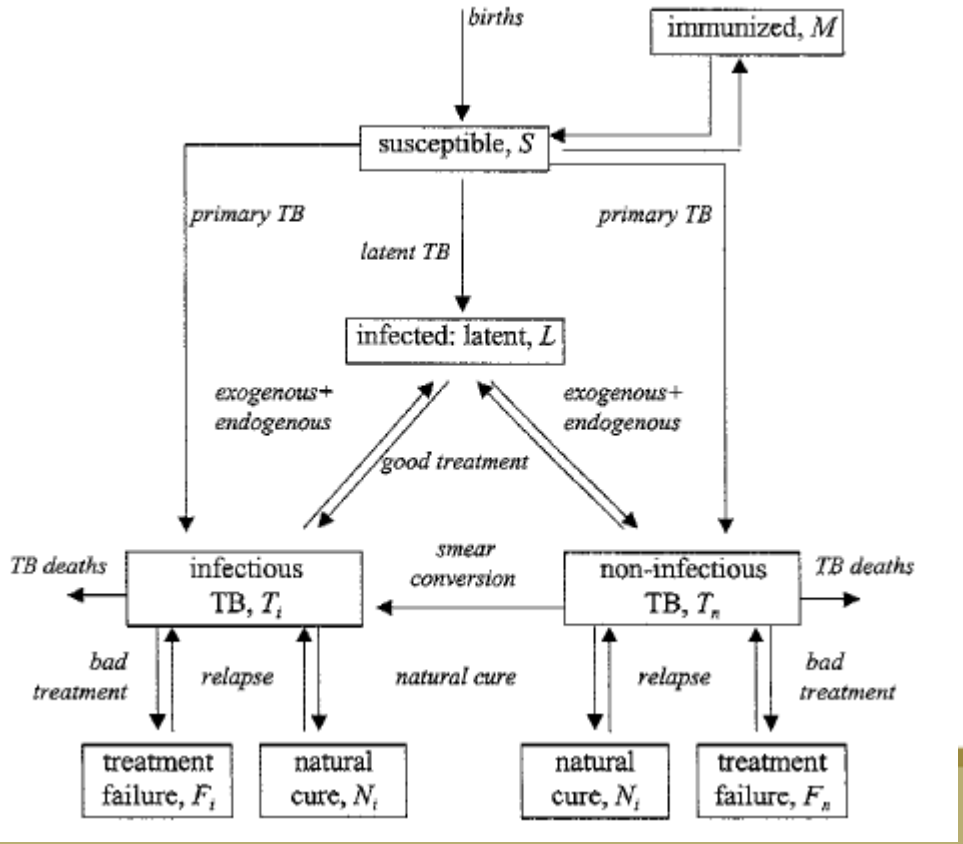
- The targets of TB diagnostic strategies are increasingly moving beyond individual (clinical) effectiveness to population-level (public health) effectiveness.
  - This is a true paradigm shift.
- If diagnostics are being deployed with a goal of population-level effectiveness in mind, models must account 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? A Brief Intro…

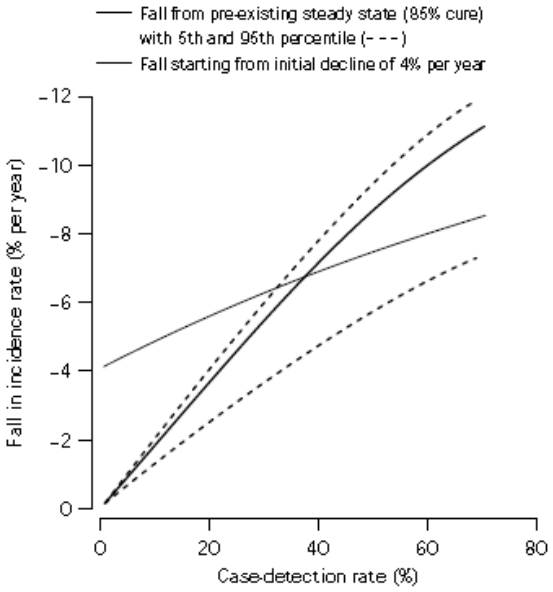
ARTICLES

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



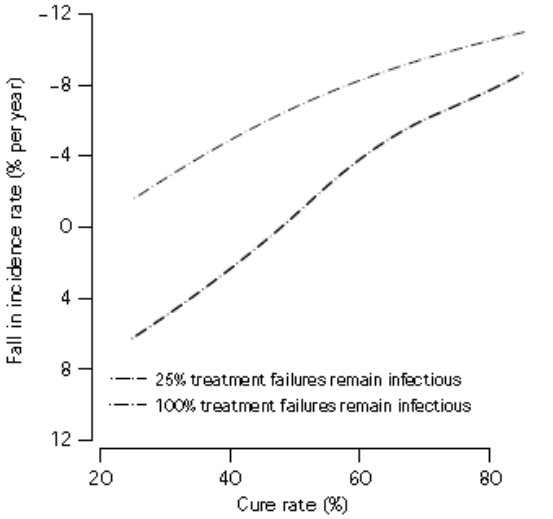


Figure 2: **Effects of case detection (top) and cure rates (bottom) on expected decline in tuberculosis incidence**

Ability of DOTS to Control TB…

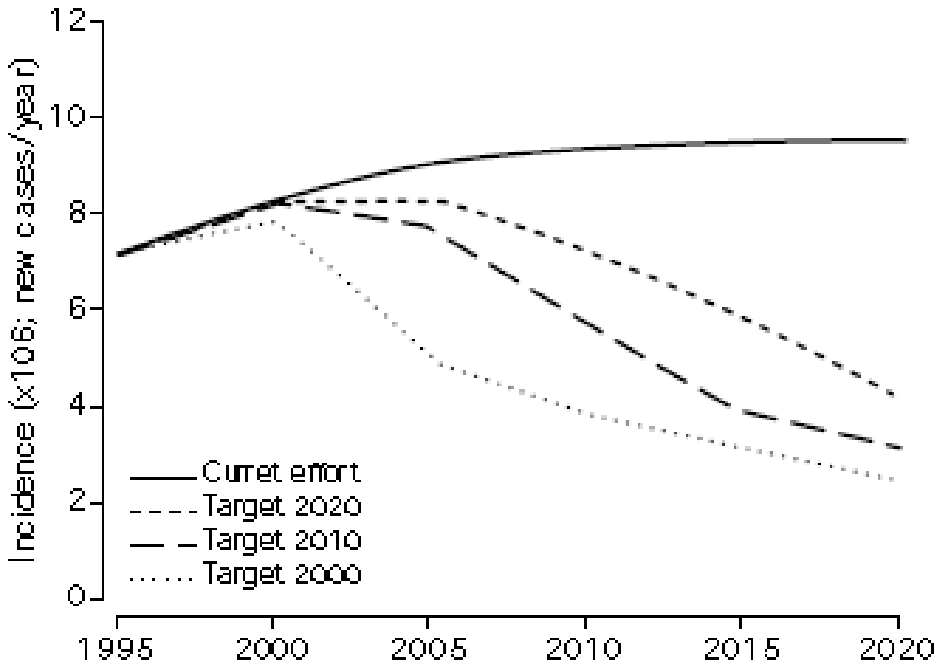


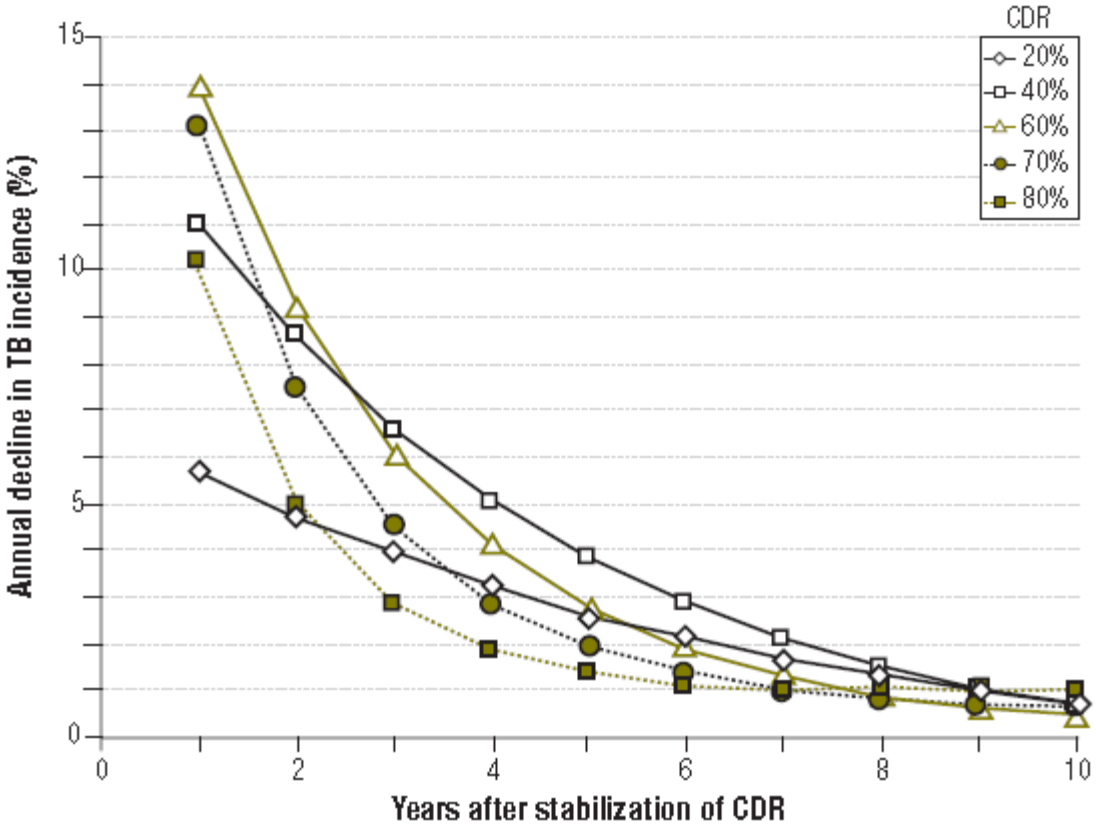
Figure 5: **Projected annual worldwide incidence of tuberculosis under assumption that WHO targets for case finding and cure are met in 2000, 2010, and 2020, compared with maintenance of current control effort**

...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]

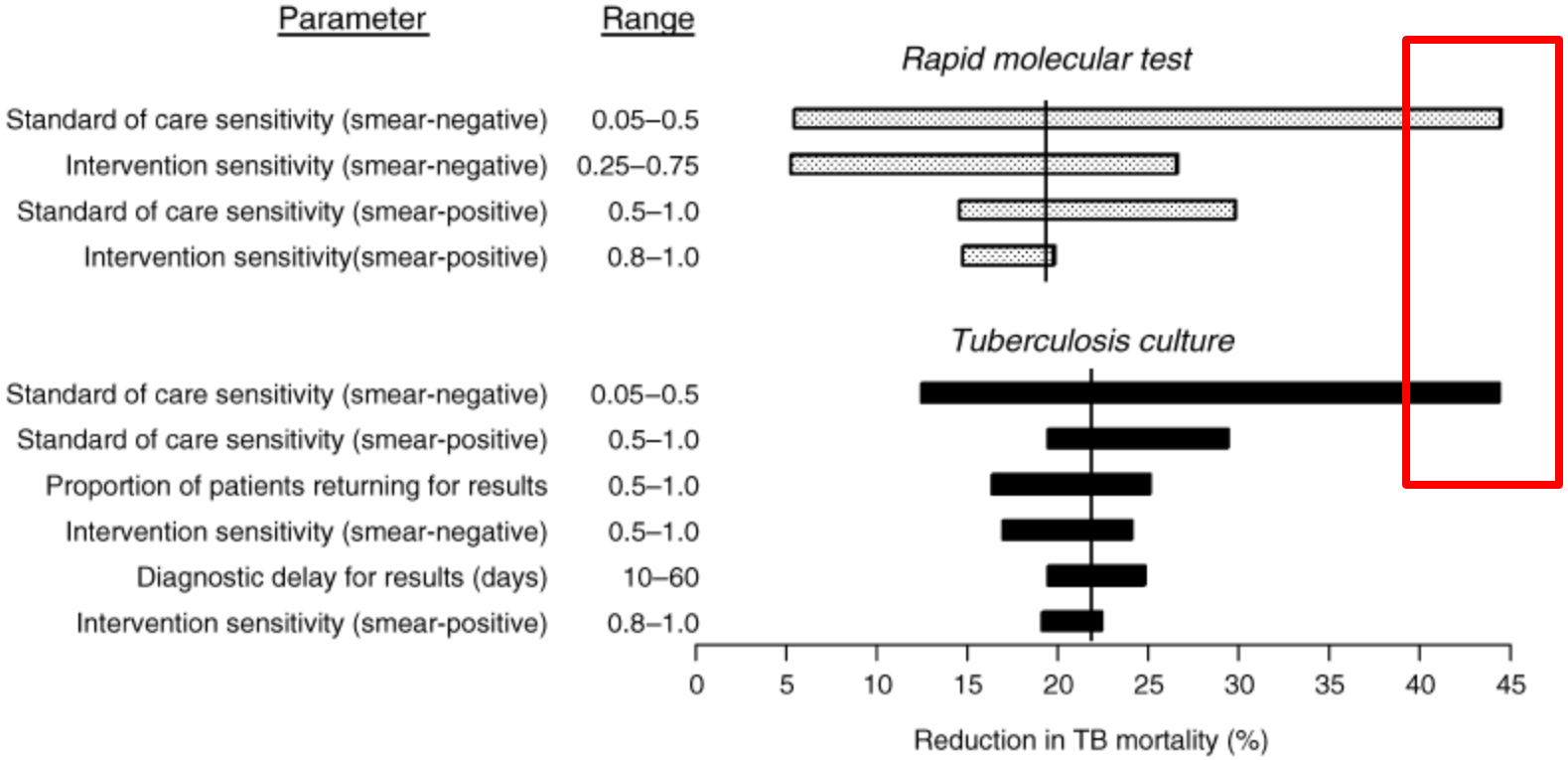
Fig. 2. **Annual decline in TB incidence under stable case detection[a]**



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

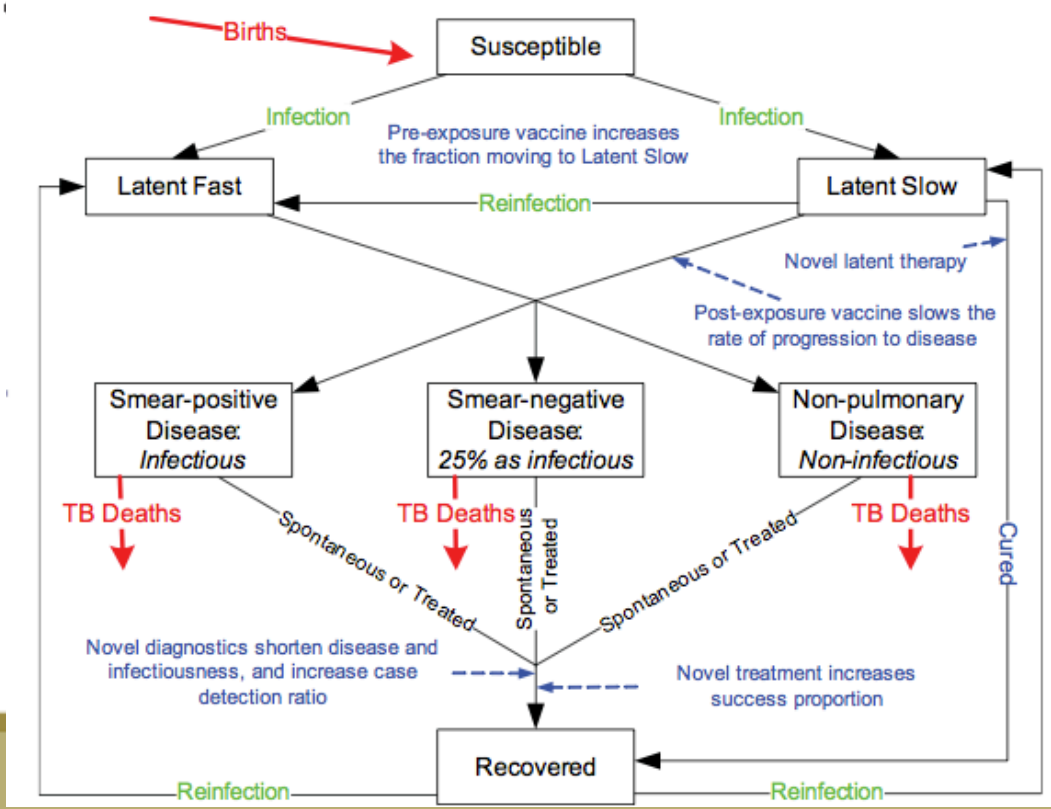
Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics

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]

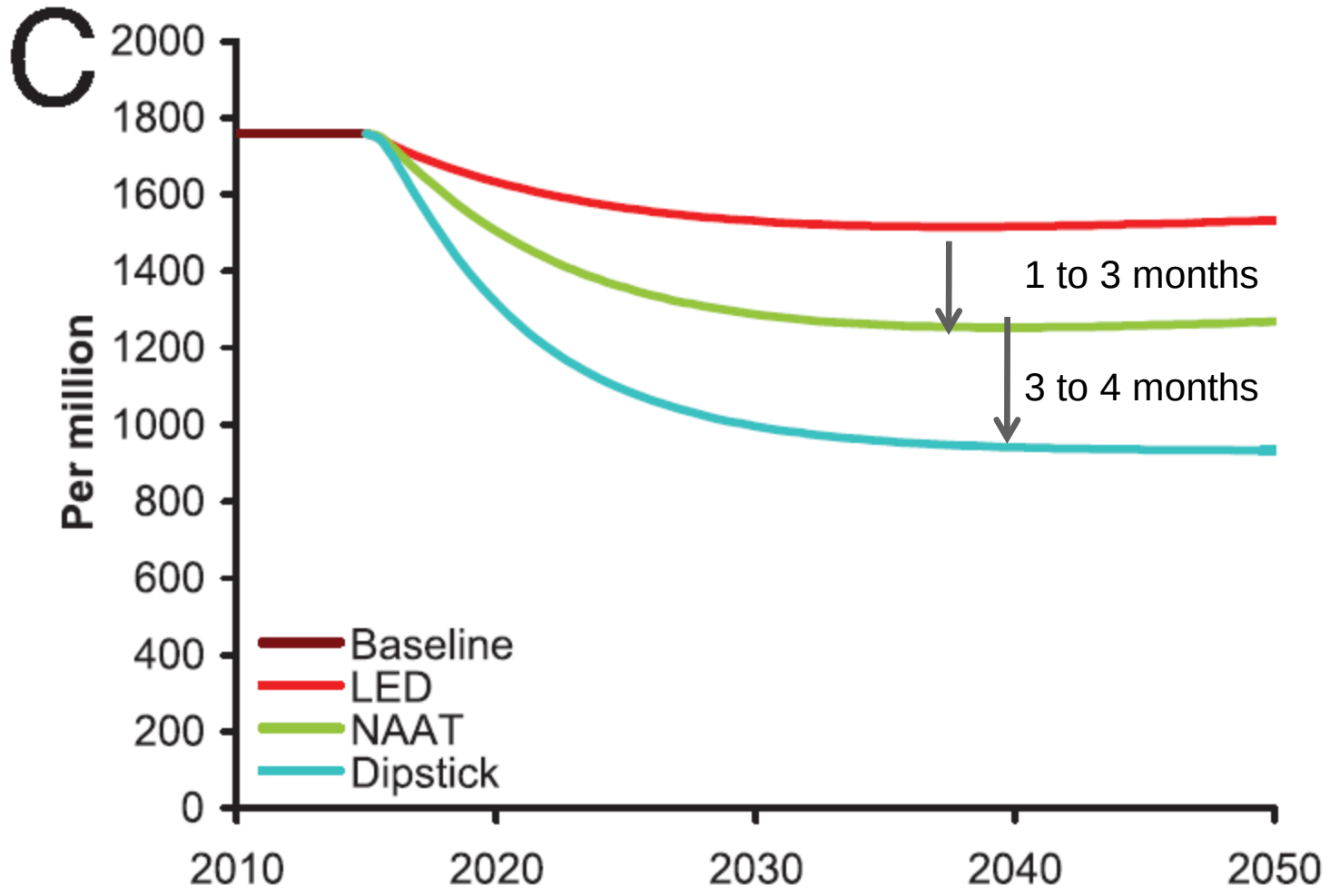
[a]Vaccine and Infectious Disease Institute, Fred Hutchinson Cancer Research Center, Seattle, WA 98109; Departments of [b]Epidemiology, [c]Anthropology, and [d]Biostatistics, University of Washington, Seattle, WA 98195; and [e]Office of HIV/AIDS, Tuberculosis, Malaria, and Neglected Tropical Diseases,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

Edited by Sim

8, 2009)



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:
  - Simplifying complex systems into something we can understand
  - Translate data into a decision-making framework
  - Help to conceptualize important questions
- 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 evaluation/cost-effectiveness models
- Current challenges & directions in modeling TB diagnostics