Modeling the Role of Novel TB Diagnostics: Black & White or Shades of Gray?

David Dowdy

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TB Modeling and Translational Epi Group

JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH

THE CENTER FOR TB RESEARCH
JOHNS HOPKINS UNIVERSITY

A Typical Question…

A Typical Question…

The Answer…Not So Simple

nature.com/diagnostics-modelling

ARTICLE OPEN

Understanding the incremental value of novel diagnostic tests for tuberculosis

Nimalan Arinaminpathy[1] & David Dowdy[2]

Table 1 | Four potential diagnostic gaps in tuberculosis (TB).

Feature of TB natural history	Description	Resultant source of transmission	Potential representation within models	Diagnostic test capable of filling gap
Latency	Prolonged latent period	Individuals who are asymptomatic or have only very mild symptoms	Asymptomatic (or mildly symptomatic) infectious state (I_0)	Test to identify who will progress to active disease, allowing targeted preventive therapy ('progression biomarker')
Slow clinical course	Early non-specific symptoms (for example, cough)	Individuals who are presenting to care, but for syndromic management	Infectious state with symptoms sufficient to drive care seeking, but with low index of suspicion for TB (I_1)	Test to rule out TB (or suggest further testing for TB) in people with a cough ('cough triage test')
Difficult microbiological confirmation	Bacilli often present in low numbers, and only in lungs or sputum; no specific antibody	Individuals who test false negative for TB	Active, care-seeking but undiagnosed state (I_2)	Test to supplant current tests with imperfect sensitivity ('smear replacement test')
Heterogeneous transmission and access to care	Transmission concentrated among those with poor access to care	Individuals who lack sufficient access to seek care rapidly	State with lower care-seeking rate (I')	Smear replacement test for use in peripheral settings with poor access ('point-of-care test')

Determinants of incremental impact (incremental transmissions averted)

1. Epidemiological setting/existing diagnostic gaps
2. Diagnostic test characteristics (accuracy, diagnostic gap targeted)
3. Existing diagnostic algorithms (incremental role of the new test)

The incremental impact of a novel diagnostic test depends not only on its sensitivity and specificity, but also on the **epidemiological setting** and **existing diagnostic approach**.

One Example: Empiric Treatment

Effect of empirical treatment on outcomes of clinical trials of diagnostic assays for tuberculosis

*Nicolas A Menzies, Ted Cohen, Megan Murray, Joshua A Salomon

	Smear scenario	Xpert scenario	Percent difference*	Absolute difference†
Tuberculosis prevalence at end 2015	880 (472 to 1536)	817 (421 to 1477)	-7·6% (-14·5 to -2·5)	-63 (-120 to -23)
Tuberculosis incidence at end 2015	802 (563 to 1151)	790 (554 to 1131)	-1·6% (-3·7 to -0·2)	-13 (-32 to -2)
Tuberculosis mortality at end 2015	315 (185 to 528)	298 (173 to 513)	-5·6% (-10·4 to -1·8)	-17 (-31 to -6)
Positive predictive value of tuberculosis diagnosis at end 2015	66% (52 to 80)	69% (55 to 82)	3·9% (-2·6 to 11·8)	2·5 (-1·7 to 6·8)
Negative predictive value of tuberculosis diagnosis at end 2015	82% (69 to 90)	91% (83 to 96)	11·7% (3·9 to 23·4)	9·3 (3·5 to 16·8)

Values indicate posterior mean for each outcome, and values in parentheses indicate equal-tailed 95% posterior intervals. *Percent differences calculated as Xpert/Smear-1. †Absolute differences calculated as number of diagnosis by smear test subtracted by number of diagnoses by Xpert.

Table 1: **Revised analysis of programme performance and tuberculosis epidemiology**

	Xpert scenario *vs* smear scenario	Percent difference* compared with original analysis[3]
Incremental costs over 10 years	US$216 000 000 (112 000 000–371 000 000)	49% lower
DALYs averted over 10 years	139 000 (50 000–280 000)	68% lower
Incremental cost-effectiveness ratio over 10 years	$1554 (858–4202)	62% higher
Incremental costs over 20 years	$572 000 000 (279 000 000–1134 000 000)	49% lower
DALYs averted over 20 years	473 000 (142 000–973 000)	67% lower
Incremental cost-effectiveness ratio over 20 years	$1208 (621–3995)	55% higher

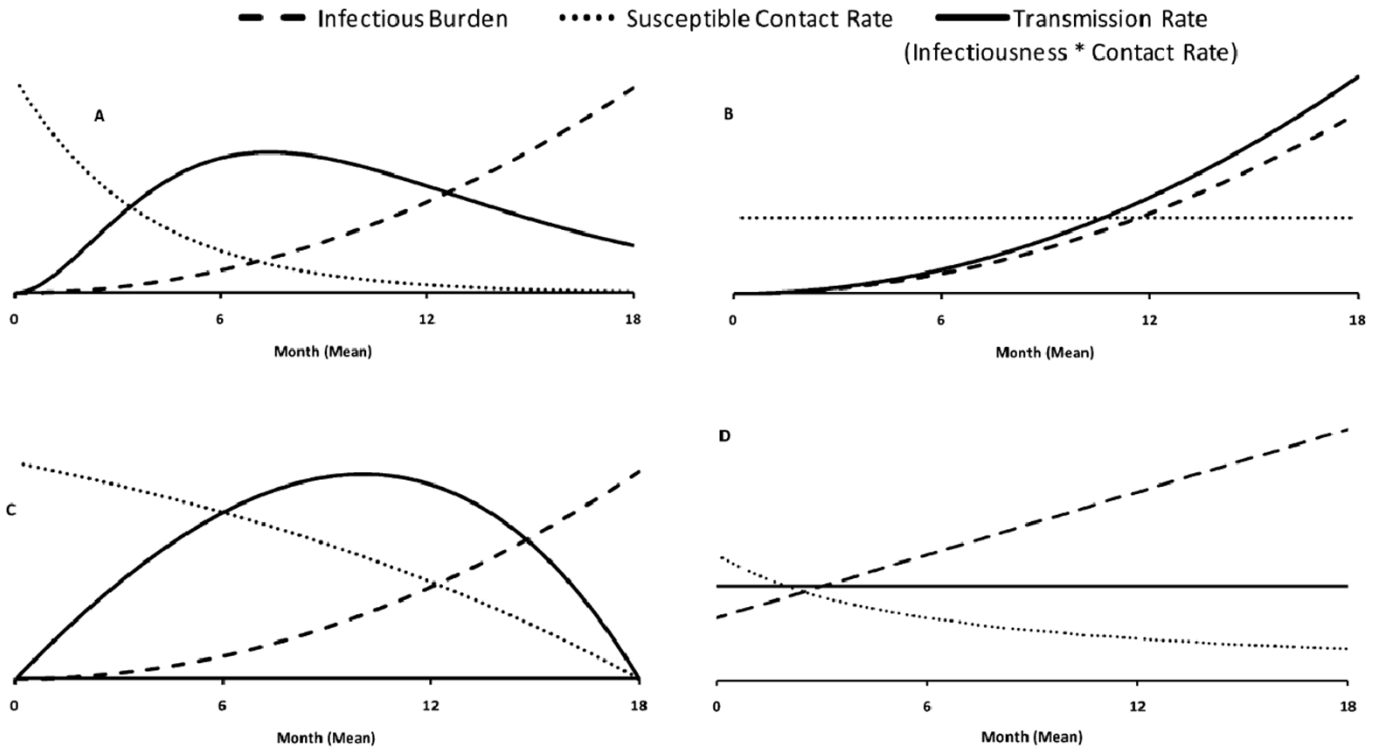
An annual discount rate of 3% applied to incremental costs and DALYs averted. Parentheses indicate equal-tailed 95% posterior intervals. DALYs= disability-adjusted life years. *Values calculated as a percentage of result obtained in original analysis.[3]

Table 2: **Revised analysis of incremental outcomes and cost-effectiveness of Xpert scenario versus smear scenario**

Incremental impact of novel diagnostics also depends on when & where transmission occurs.

Is Passive Diagnosis Enough?
The Impact of Subclinical Disease on Diagnostic Strategies for Tuberculosis

David W. Dowdy[1,2], Sanjay Basu[3,4], and Jason R. Andrews[5]



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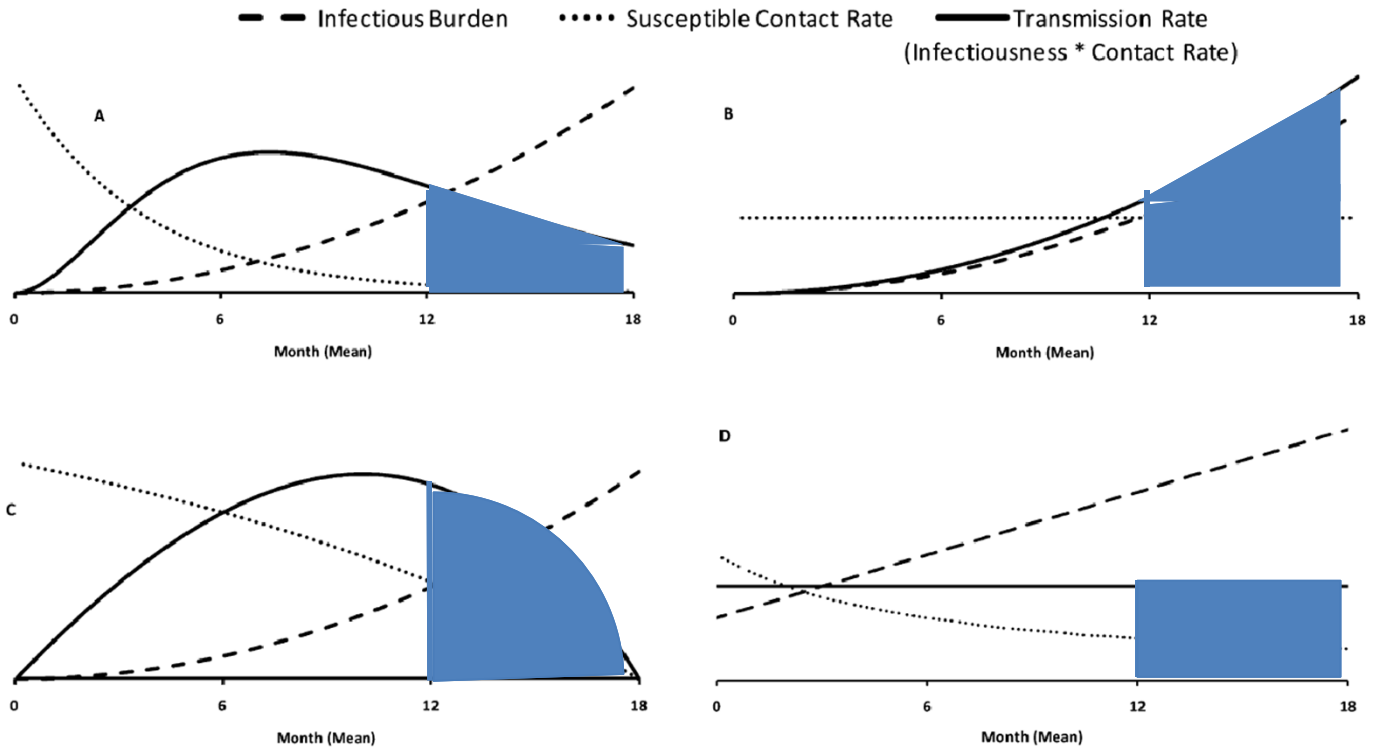

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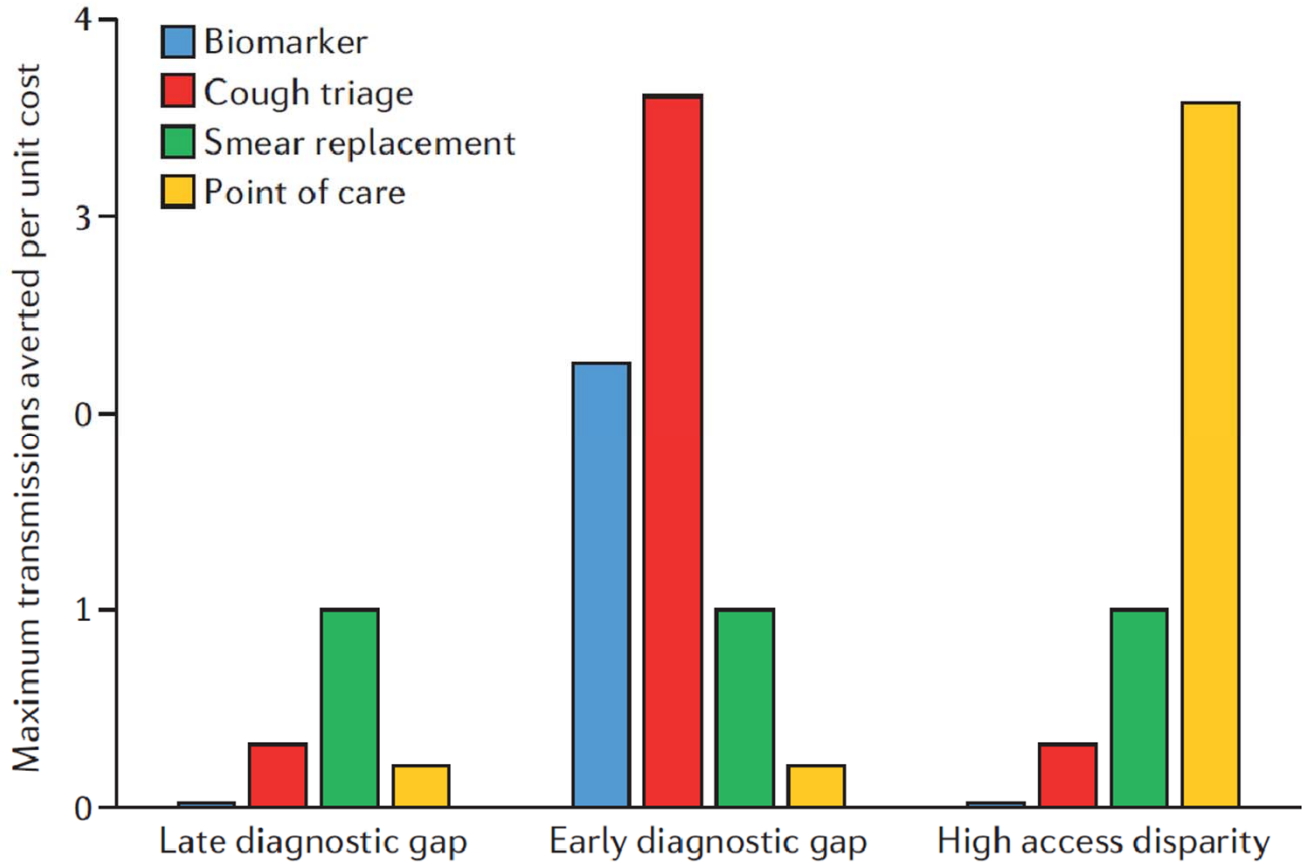


Estimating the incremental impact of a novel diagnostic test therefore requires data/assumptions on:

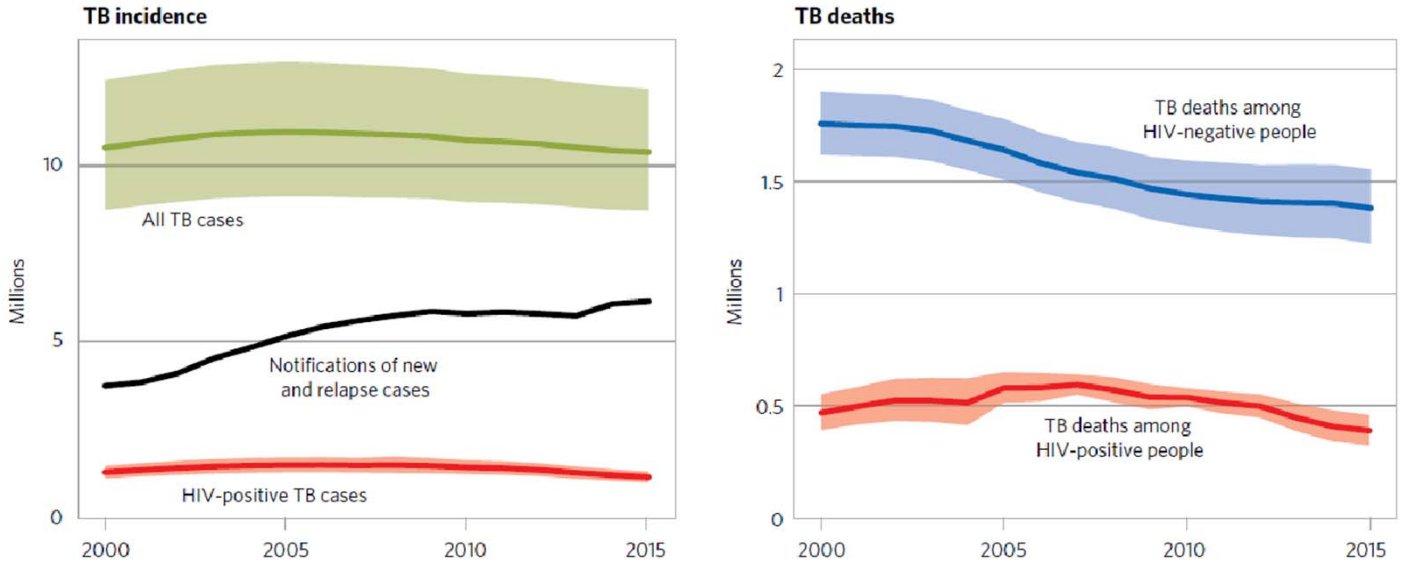
- Epidemiological setting
- Existing diagnostic approach
- Patterns of transmission (temporal/geographic)
- Intended niche/incremental value of the test
- Test accuracy (when implemented in the intended niche)

How can we improve efforts to estimate the population-level impact of novel TB diagnostics?

- Data on when & where transmission occurs

:: FIG. 3.5

Global trends in the estimated number of incident TB cases and the number of TB deaths (in millions), 2000–2015. Shaded areas represent uncertainty intervals.



Better diagnosis appears to have substantially reduced mortality, but not incidence.

How can we improve efforts to estimate the population-level impact of novel TB diagnostics?

- Closer investigation of successes and “failures”

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Original Contribution

Age- and Sex-Specific Social Contact Patterns and Incidence of *Mycobacterium tuberculosis* Infection

Peter J. Dodd, Clare Looker, Ian D. Plumb, Virginia Bond, Ab Schaap, Kwame Shanaube, Monde Muyoyeta, Emilia Vynnycky, Peter Godfrey-Faussett, Elizabeth L. Corbett, Nulda Beyers, Helen Ayles, and Richard G. White*

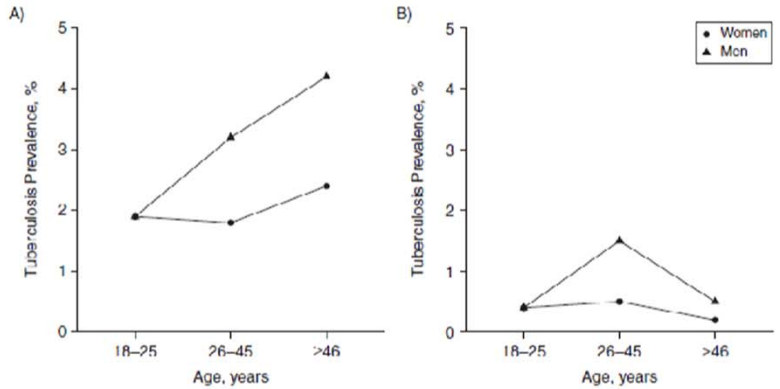
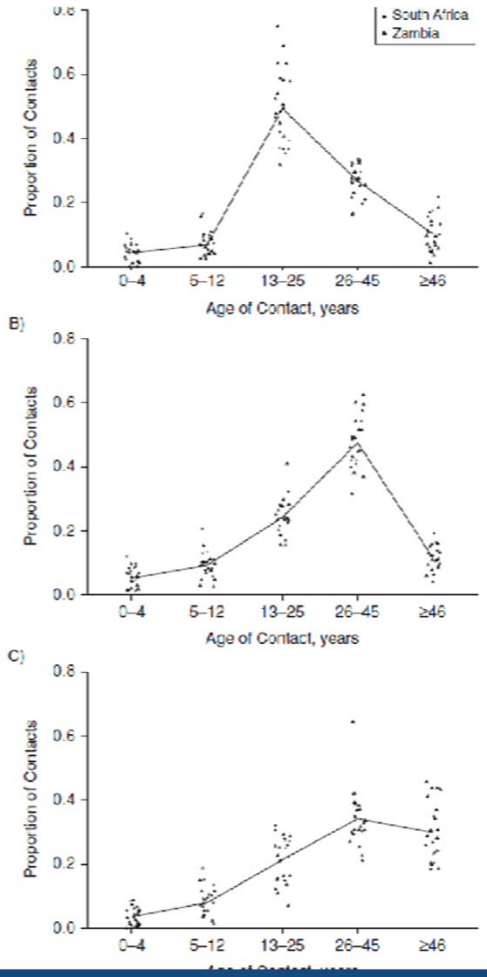
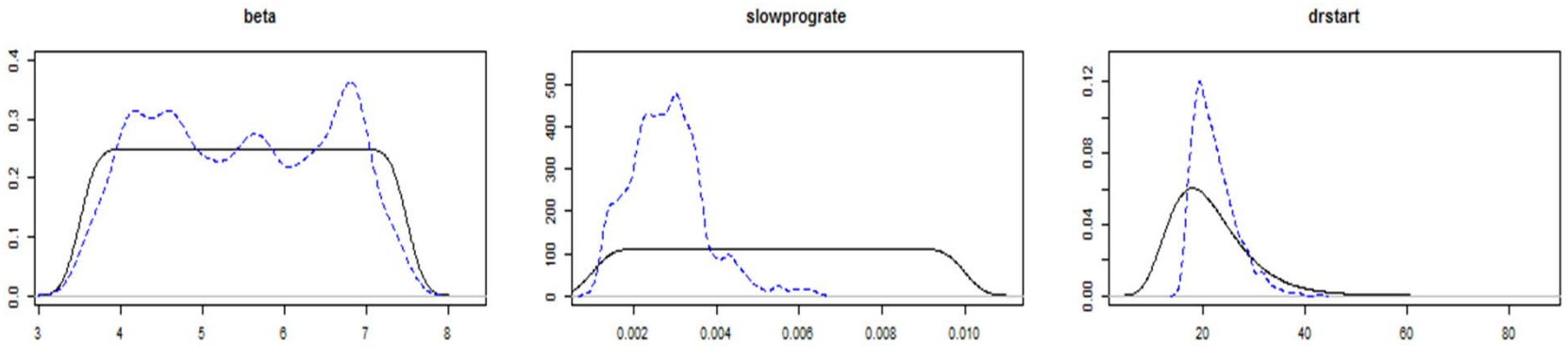


Figure 2. Prevalence of culture positive tuberculosis disease among adults in the Western Cape, South Africa (A) and Zambia (B) from the 2011 Zambia-South Africa TB and AIDS Reduction Study final prevalence survey (35), shown by age, sex and setting. This is used as a model input for estimating *Mycobacterium tuberculosis* infection rates in adults.



How can we improve efforts to estimate the population-level impact of novel TB diagnostics?

- Models that investigate the implications of empirical data in different settings



Summary

- To estimate the **incremental impact** of novel diagnostic tests, we need data or assumptions on:
  - Epidemiological setting
  - Existing diagnostic approach
  - When and where transmission occurs
  - Intended use of the test
  - Test accuracy when used as intended

- Estimates of novel tests' impact can be improved through:
  - Data on patterns of transmission
  - Deeper dives into past case-finding/diagnostic efforts
  - Models to query population-level implications of individual-level assumptions/observations