Modeling TB Diagnostics: Evaluating the Diagnostic Process

Advanced TB Diagnostic Research Course

July 12, 2013

David Dowdy, MD PhD
Dept. of Epidemiology
Johns Hopkins Bloomberg School of Public Health

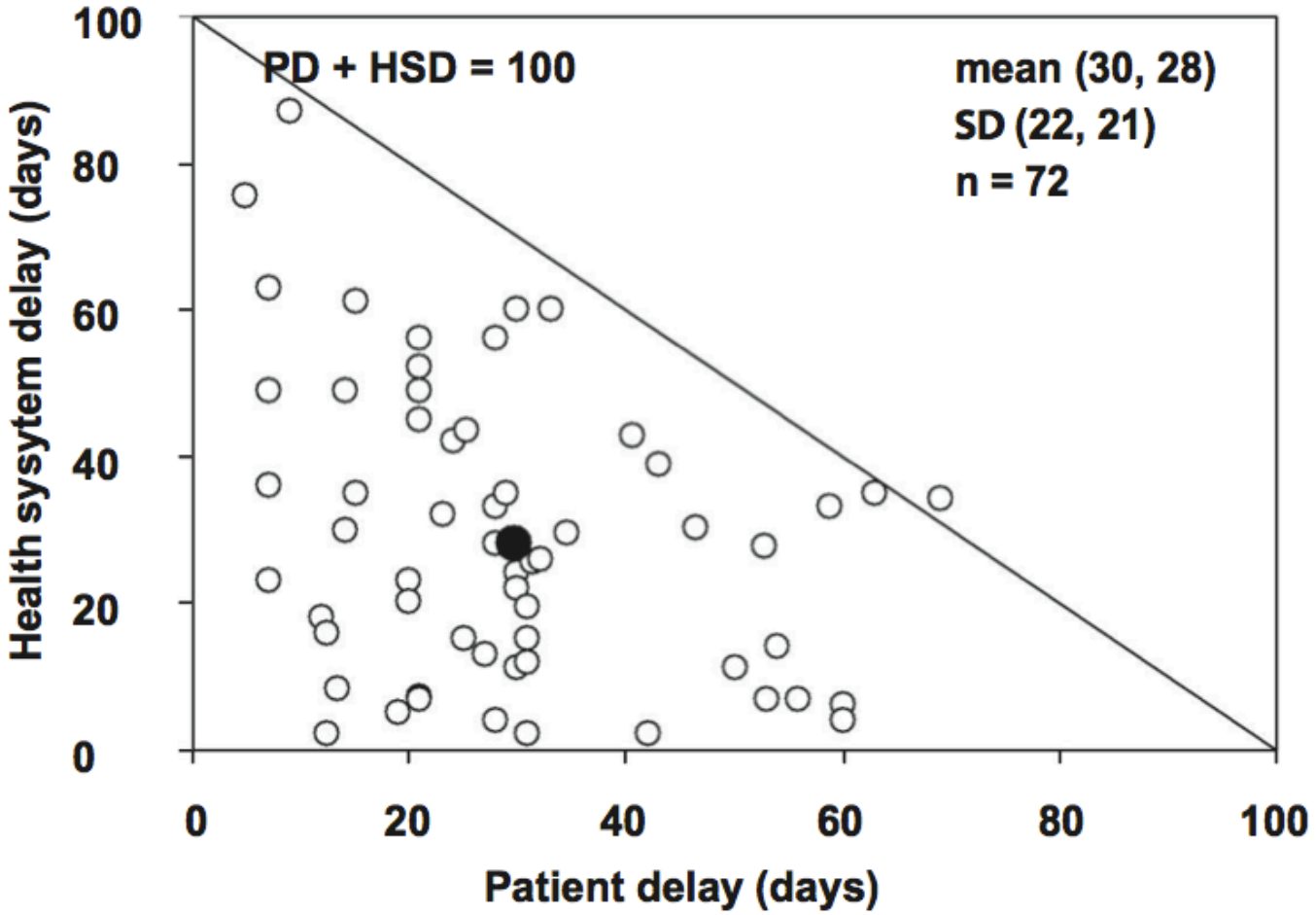
Indian J Med Res 135, May 2012, pp 737–74

The potential impact of new diagnostic tests on tuberculosis epidemics

Christopher Dye

HIV/AIDS, Tuberculosis, Malaria & Neglected Tropical Diseases Cluster, World Health Organization, Geneva, Switzerland

***Methods*: A behavioural model of patient-doctor interactions embedded in an epidemiological model of *Mycobacterium tuberculosis* transmission, linked to fied data, was used to investigate the effects of early diagnosis in preventing future TB cases.**



The approach was, first, to formulate a model of the behavioural interactions between patients and health providers (qualified doctors, pharmacists, laboratories and quacks, henceforth referred to as "doctors"). This

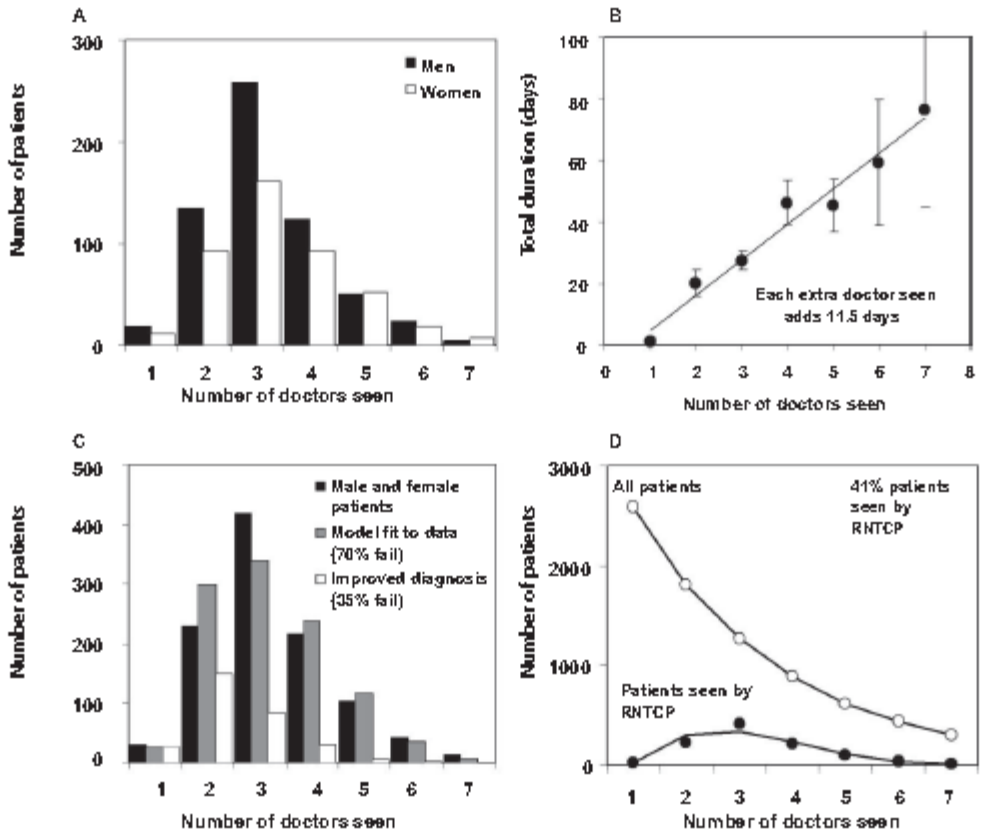


Fig. 2. A. The number of doctors seen by 1049 male and female patients in Bangalore (mode 3, range 1-7), as reported to the RNTCP. **B.** Cumulative duration of health system delays in relation to the number of doctors seen. The slope of the line indicates that each doctor seen adds 11.5 days to the diagnostic delay. **C.** Fit of model 1 (grey) to the total number of male and female patients (black), assuming a failure rate at each point (and survival to visit the next doctor), *f*, of 0.7. The alignment of black and grey bars indicates a good fit of the model to the data. Open bars show the distribution of the number of doctors seen if a new diagnostic procedure reduced *f* to 0.35. **D.** Fit (lower line) to the data (filled circles) in A and C, and the estimated total number of patients (open circles) in this setting in Bangalore. Data from the study by Pantoja *et al*[13].

Impact of improved diagnostics

- Diagnostic applied only at RNTCP would be limited
- If the proportion of "failed" attempts could be reduced from 0.7 to 0.35:
  - Number of doctors seen declines from 2.7 to 1.5
    - Even fewer encounters with RNTCP
  - Duration of illness ("health system delay") shortened from 31.1 days to 17.6 days
    - 43% reduction

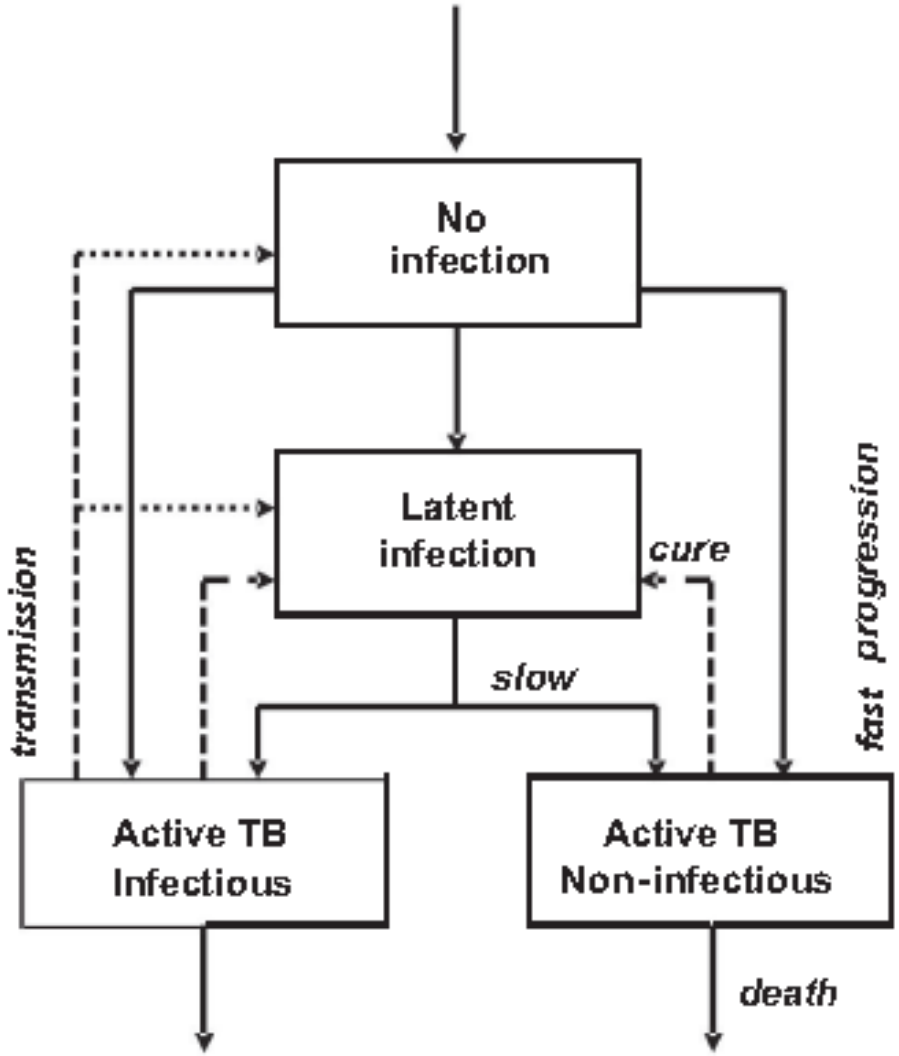

No infection
Latent infection
cure
transmission
slow
fast progression
Active TB Infectious
Active TB Non-infectious
death

Table. Parameters and control variables of the TB transmission model depicted in Fig. 3

Model parameters	Value	Units or dimensions
Contact rate between infectious TB cases and others in the population (β)	14	Per TB patient per year
Rate of progression from latent to active TB in the absence of reinfection (v)	0.001	Per infected person per year
Proportion of infected people that progress quickly to active TB (q)	0.15	Proportion
Proportion of incident TB cases that are infectious (s)	0.45	Proportion
Proportion of latently infected people who develop active TB on reinfection (x)	0.5	Proportion
Mortality rate from causes other than TB (μ)	0.015	Per person per year
Mortality rate from infectious TB (μi)	0.2	Per TB patient per year
Mortality rate from non-infectious TB (μn)	0.15	Per TB patient per year
Control variables		
Rate at which TB cases make first contact with health services	0.5	Per TB patient per year
Proportion of TB patients correctly diagnosed with active disease (sensitivity)	0.5	Proportion
Proportion of treated patients who are cured	0.7	Proportion

Annexure. Epidemiological model of tuberculosis

With state variables U = uninfected, L = latently or sub-clinically infected, N = non-infectious active TB and I = infectious active TB , and $U + L + N + I = 1$, the model defined in Fig. 3 and Table can be written as a set of time-dependent ordinary non-linear differential equations:

$$\frac{dU}{dt} = -\beta UI + \mu + \mu_n N + \mu_I I - \mu U$$

$$\frac{dL}{dt} = \beta(1-q)UI + \delta\tau\kappa(N+I) - (\mu + \nu + \beta\chi I)L$$

$$\frac{dN}{dt} = \beta q(1-s)UI + (1-s) - (\nu + \beta\chi I)L - (\delta\tau\kappa + \mu + \mu_n)N$$

$$\frac{dI}{dt} = \beta qsUI + s(\nu + \beta\chi I)L - (\delta\tau\kappa + \mu + \mu_I)I$$

Annexure. Epidemiological model of tuberculosis

With state variables U = uninfected, L = latently or sub-clinically infected, N = non-infectious active TB and I = infectious active TB, and $U + L + N + I = 1$, the model defined in Fig. 3 and Table can be written as a set of time-dependent ordinary non-linear differential equations:

$$\frac{dU}{dt} = -\beta UI + \mu + \mu_n N + \mu_I I - \mu U$$

$$\frac{dL}{dt} = \beta(1-q)UI + \delta\tau\kappa(N+I) - (\mu + \nu + \beta\kappa I)L$$

$$\frac{dN}{dt} = \beta q(1-s)UI + (1-s) - (\nu + \beta\kappa I)L - (\delta\tau\kappa + \mu + \mu_n)N$$

$$\frac{dI}{dt} = \beta qsUI + s(\nu + \beta\kappa I)L - (\delta\tau\kappa + \mu + \mu_I)I$$

Infection

Annexure. Epidemiological model of tuberculosis

With state variables U = uninfected, L = latently or sub-clinically infected, N = non-infectious active TB and I = infectious active TB, and $U + L + N + I = 1$, the model defined in Fig. 3 and Table can be written as a set of time-dependent ordinary non-linear differential equations:

$$\frac{dU}{dt} = -\beta UI + \mu + \mu_n N + \mu_I I - \mu U$$

$$\frac{dL}{dt} = \beta(1-q)UI + \delta\tau\kappa(N+I) - (\mu + \nu + \beta\chi I)L$$

$$\frac{dN}{dt} = \beta q(1-s)UI + (1-s) - (\nu + \beta\chi I)L - (\delta\tau\kappa + \mu + \mu_n)N$$

$$\frac{dI}{dt} = \beta qsUI + s(\nu + \beta\chi I)L - (\delta\tau\kappa + \mu + \mu_I)I$$

Mortality

Annexure. Epidemiological model of tuberculosis

With state variables U = uninfected, L = latently or sub-clinically infected, N = non-infectious active TB and I = infectious active TB, and $U + L + N + I = 1$, the model defined in Fig. 3 and Table can be written as a set of time-dependent ordinary non-linear differential equations:

$$\frac{dU}{dt} = -\beta UI + \mu + \mu_n N + \mu_i I - \mu U$$

$$\frac{dL}{dt} = \beta(1-q)UI + \delta\tau\kappa(N+I) - (\mu + \nu + \beta\kappa I)L$$

$$\frac{dN}{dt} = \beta q(1-s)UI + (1-s) - (\nu + \beta\kappa I)L - (\delta\tau\kappa + \mu + \mu_n)N$$

$$\frac{dI}{dt} = \beta qsUI + s(\nu + \beta\kappa I)L - (\delta\tau\kappa + \mu + \mu_i)I$$

Reinfection & Reactivation

Annexure. Epidemiological model of tuberculosis

With state variables U = uninfected, L = latently or sub-clinically infected, N = non-infectious active TB and I = infectious active TB, and $U + L + N + I = 1$, the model defined in Fig. 3 and Table can be written as a set of time-dependent ordinary non-linear differential equations:

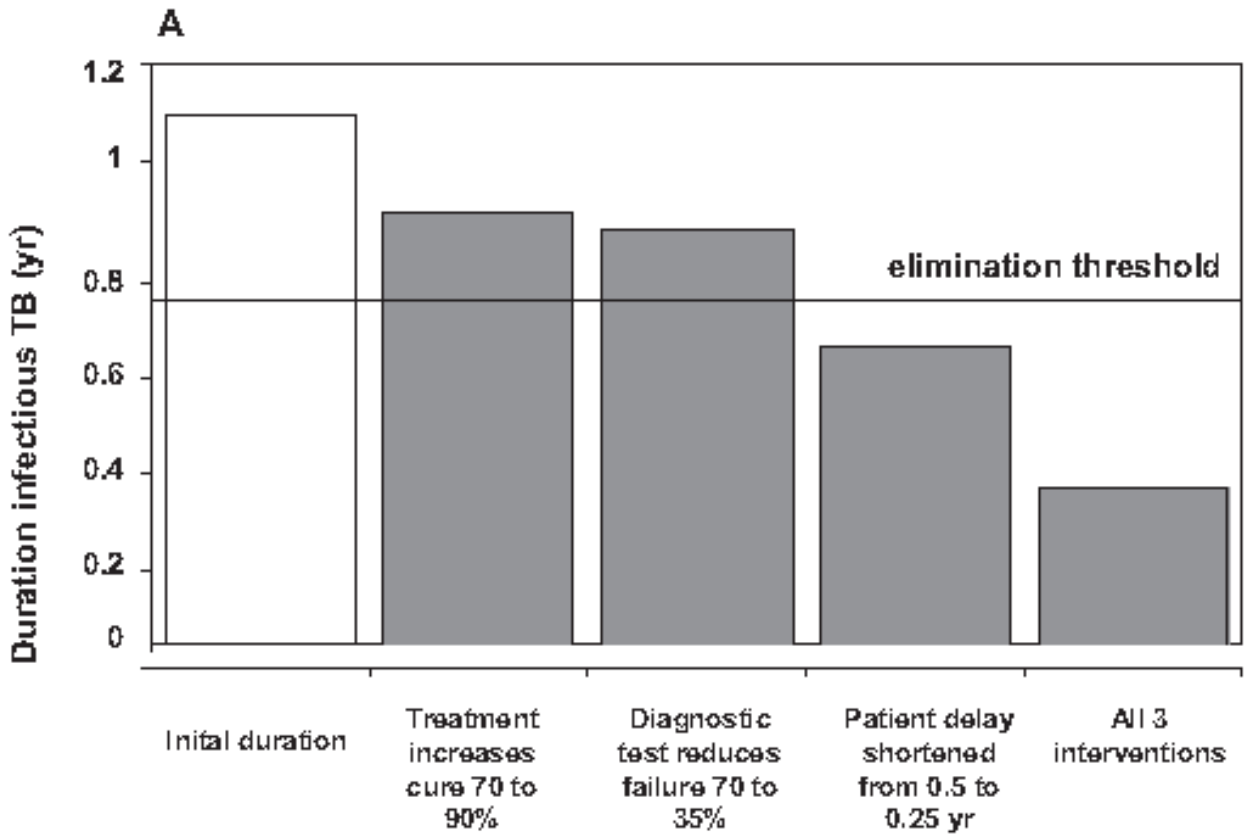
$$\frac{dU}{dt} = -\beta UI + \mu + \mu_n N + \mu_i I - \mu U$$

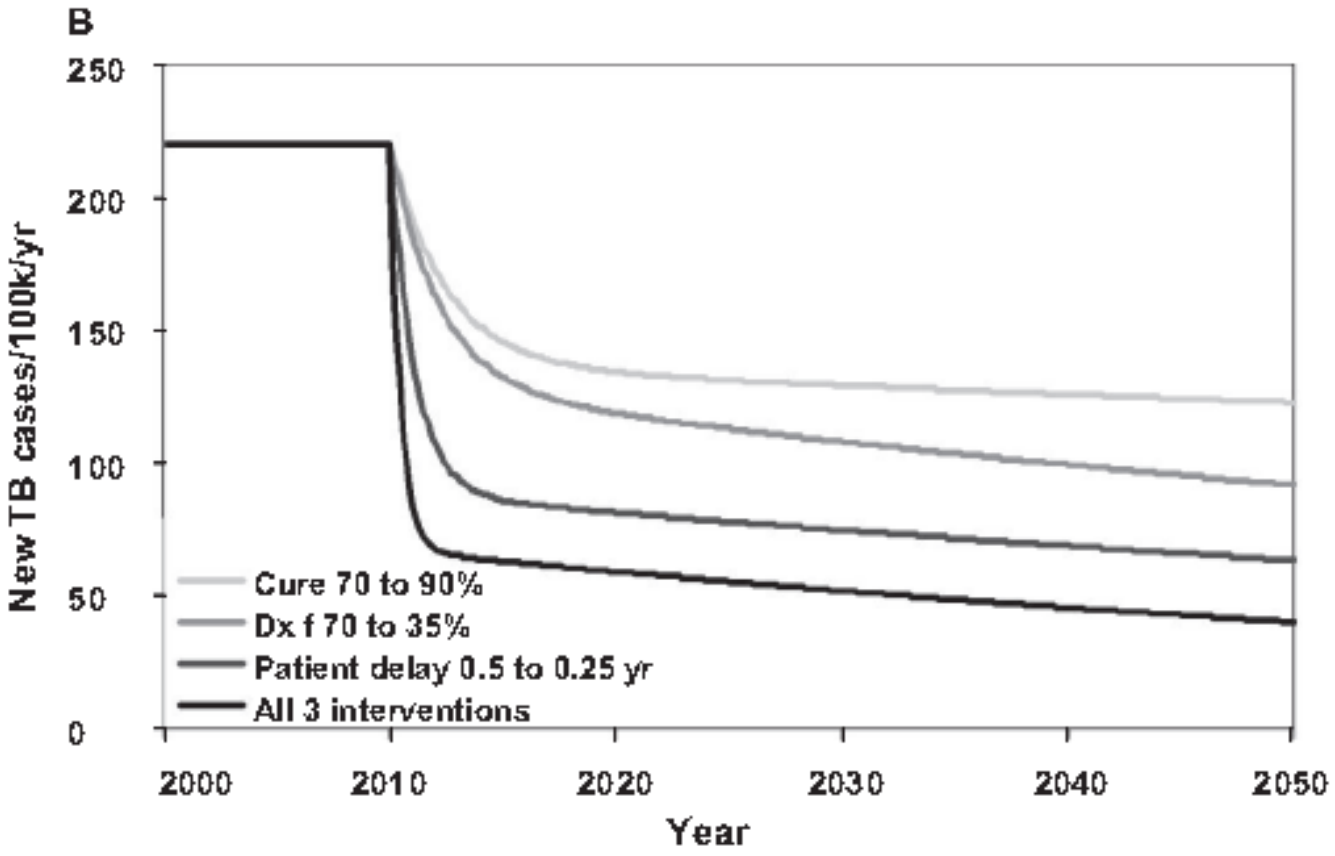
$$\frac{dL}{dt} = \beta(1-q)UI + \delta\tau\kappa(N+I) - (\mu + \nu + \beta\chi I)L$$

$$\frac{dN}{dt} = \beta q(1-s)UI + (1-s) - (\nu + \beta\chi I)L - (\delta\tau\kappa + \mu + \mu_n)N$$

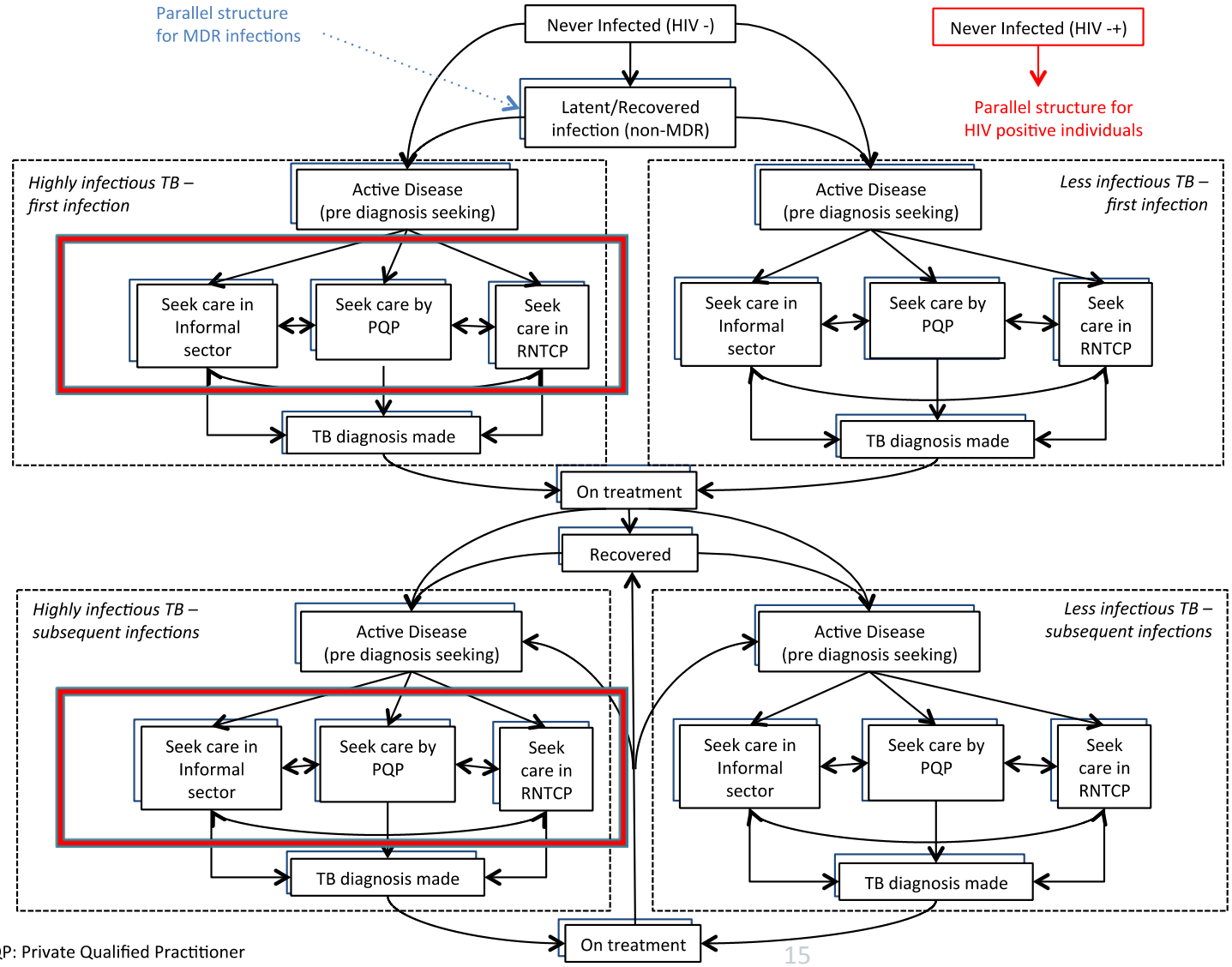
$$\frac{dI}{dt} = \beta qsUI + s(\nu + \beta\chi I)L - (\delta\tau\kappa + \mu + \mu_i)I$$

Treatment rate = (1/delay) * Sensitivity * Treatment success


A
1.2
1
0.8
0.6
0.4
0.2
0
Duration infectious TB (yr)
elimination threshold
Inital duration
Treatment increases cure 70 to 90%
Diagnostic test reduces failure 70 to 35%
Patient delay shortened from 0.5 to 0.25 yr
All 3 interventions

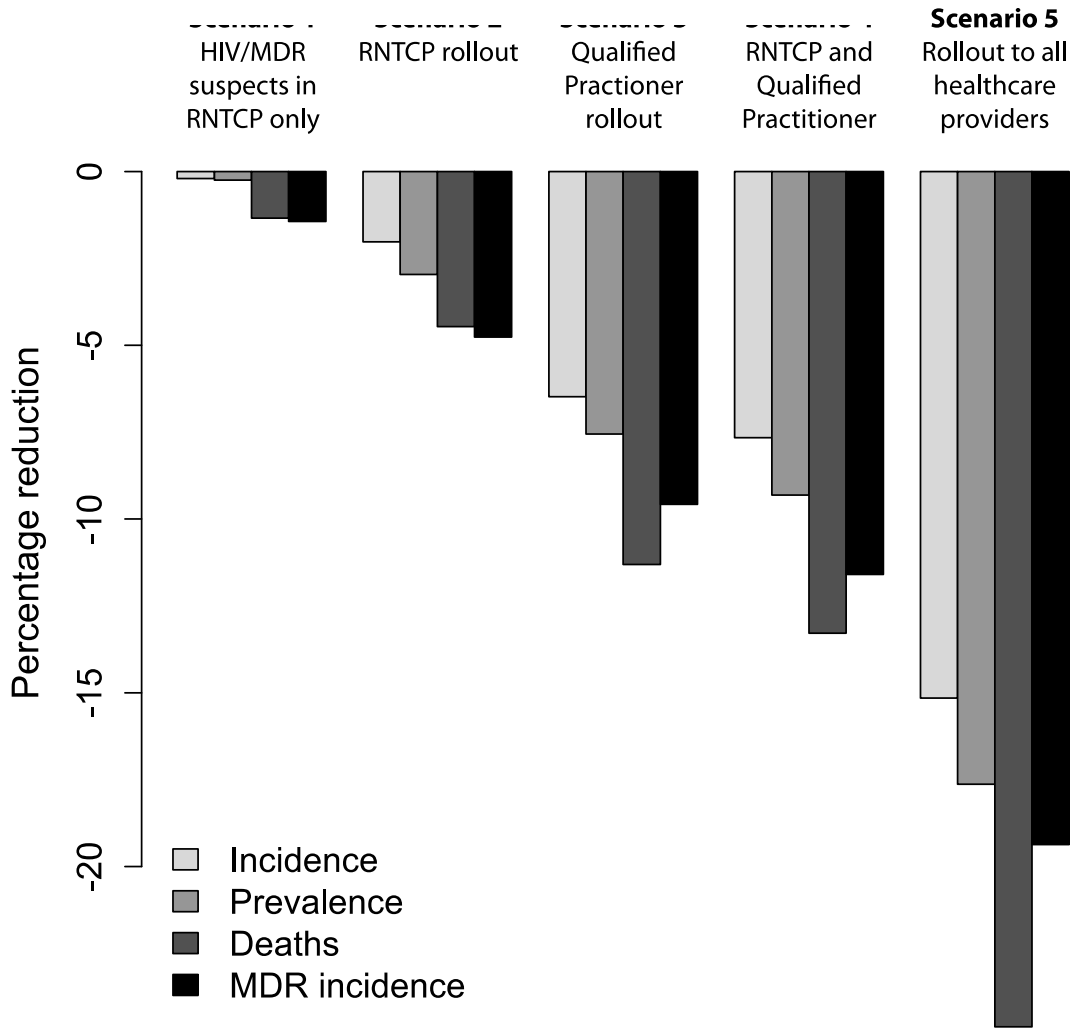

B
250
200
150
100
50
0
New TB cases/100k/yr
Cure 70 to 90%
Dx f 70 to 35%
Patient delay 0.5 to 0.25 yr
All 3 interventions
2000
2010
2020
2030
2040
2050
Year

Expansion of this Concept



PQP: Private Qualified Practitioner
RNTCP: Revised National Tuberculosis Control Program

Same Test, Different Rollout



Compared to baseline scenario (2% annual decline in incidence)

Caveats and Challenges

- **1. Model simplicity**

- Unclear that model outputs would replicate a real epidemic.
  - No incorporation of HIV, MDR, etc., etc.

- Which do you find to be more helpful: the complex or the simple approach?

Caveats and Challenges

- **2. Model calibration & uncertainty**

- No estimates of uncertainty provided.
  - But this is partially because uncertainty is so great.

- Can show us where data are lacking and inform future empirical studies.

Caveats and Challenges

- **3. Model generalizability**

- Data come from one study in Bangalore.
- Health systems vary dramatically between countries…and variation may be important.
  - How do we try to incorporate that heterogeneity?
  - Cannot construct models of every location…

Conclusions

- Better diagnostics will have more impact if they are used early.
  - Not just a matter of sensitivity and specificity; the same test can have very different impact.
- Improved diagnosis is not just a function of the test, but the system into which that test is deployed.