TB Modelling and Analysis Consortium

Paper discussion

How to critically review a modelling paper

Hsien-Ho Lin and Sophie Rhodes, with thanks to Finn McQuaid

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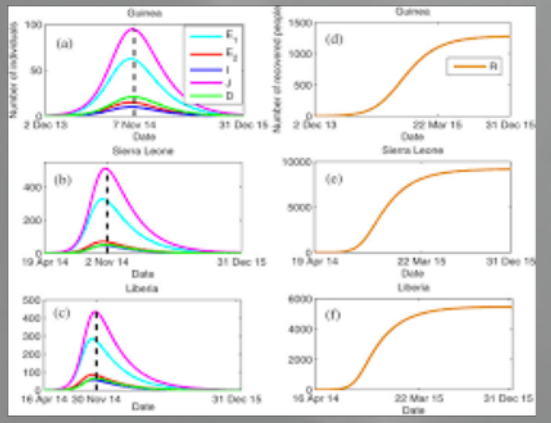
Learning outcomes

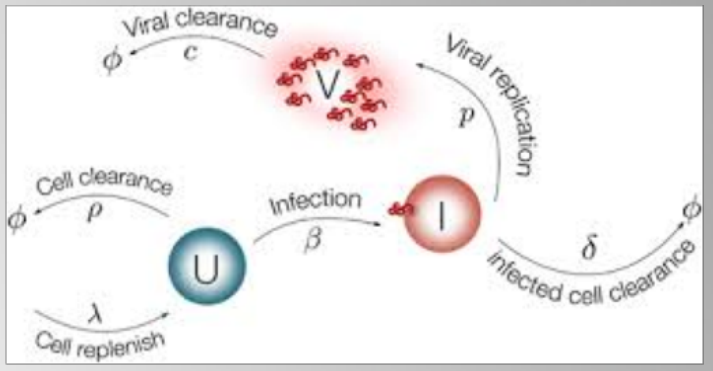
- To have read and understood a modelling paper
- To know the main components of a modelling paper
- To be able to identify the key assumptions and to critically appraise a modelling papers

Paper discussion: Introduction(s)

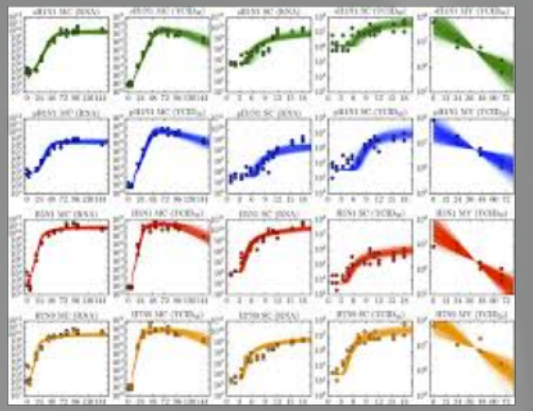
Who

- Regularly reads scientific papers?
- Has never read a modelling paper before?
- Has read this paper?





$$
\begin{aligned}
\frac{dT}{dt} &= -\beta T V_{TCID_{50}} \\
\frac{dE_1}{dt} &= \beta T V_{TCID_{50}} - \frac{n_E}{\tau_E} E_1 \\
\frac{dE_i}{dt} &= \frac{n_E}{\tau_E} E_{i-1} - \frac{n_E}{\tau_E} E_i \quad for\ i = (2, \ldots, n_E) \\
\frac{dI_1}{dt} &= \frac{n_E}{\tau_E} E_{n_E} - \frac{n_I}{\tau_I} I_1 \\
\frac{dI_j}{dt} &= \frac{n_I}{\tau_I} I_{j-1} - \frac{n_I}{\tau_I} I_j \quad for\ j = (2, \ldots, n_I) \\
\frac{dV_{TCID_{50}}}{dt} &= p_{TCID_{50}} \sum_{j=1}^{n_I} I_j - c_{TCID_{50}} V_{TCID_{50}} \\
\frac{dV_{RNA}}{dt} &= p_{RNA} \sum_{j=1}^{n_I} I_j - c_{RNA} V_{RNA} \qquad (1)
\end{aligned}
$$

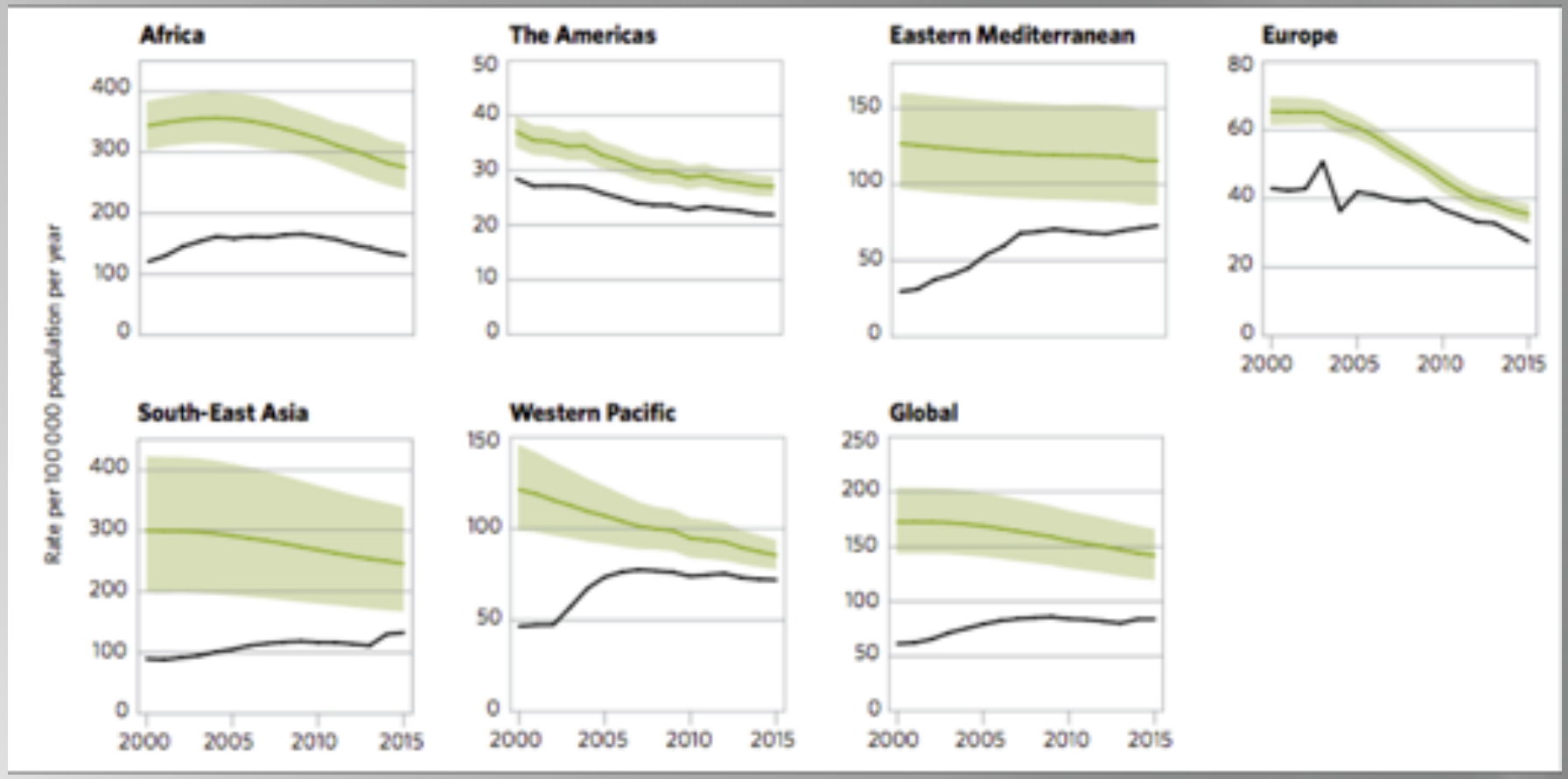


What is it? Why is that useful?

- What is a critical appraisal of a scientific paper?
  - It's a process used to identify the strengths and weaknesses of a research article in order to assess the usefulness and validity of research findings (*Young & Solomon; Nature, 2009)*
- Why critically appraise a scientific paper?
  - You might use the outcomes of modelling! Same approach for clinical trials and other studies
- What are the key things to bear in mind when reading a scientific paper?
  - An evaluation of the *appropriateness* of the study design for the *research question* and a careful assessment of the key *methodological* features of this design.
  - The suitability of the statistical methods used and their subsequent interpretation, potential conflicts of interest and the relevance of the research to one's own practice. *(Young & Solomon; Nature, 2009)*

TB Modelling

TB case detection is suboptimal



WHO, 2016

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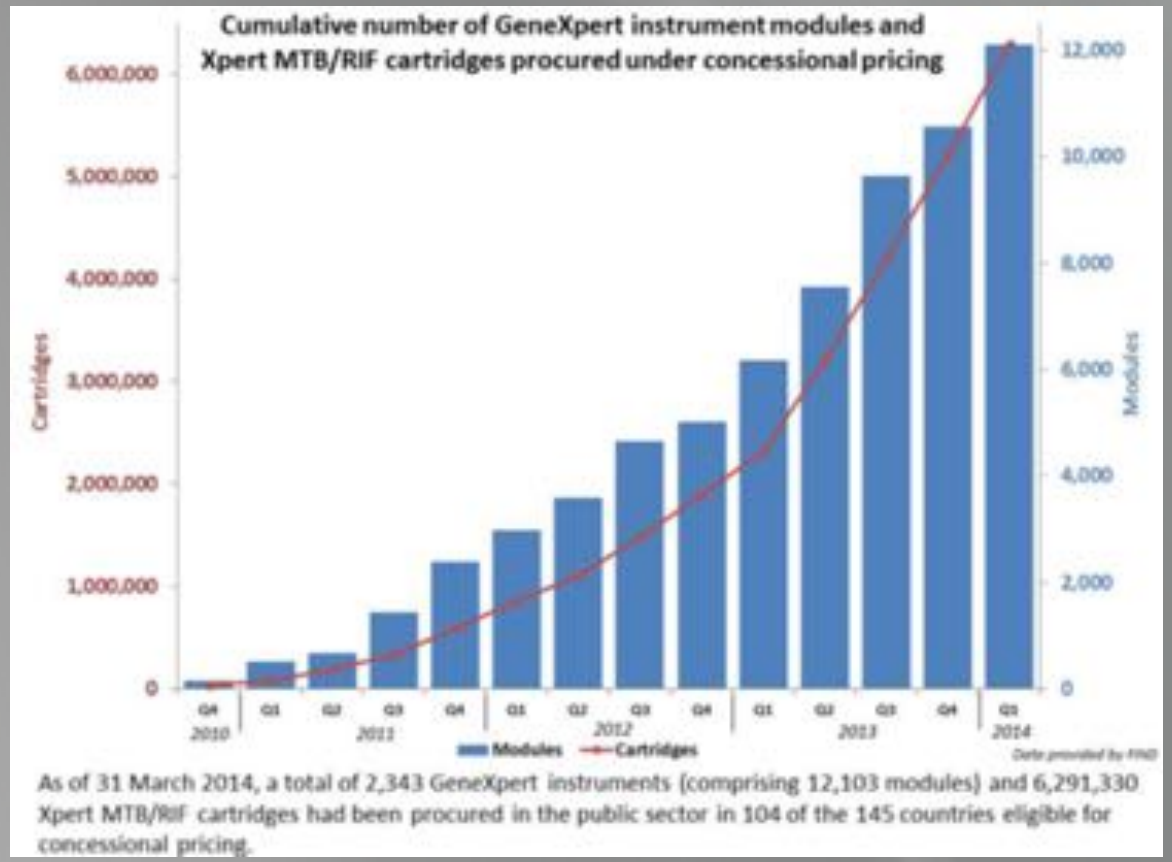
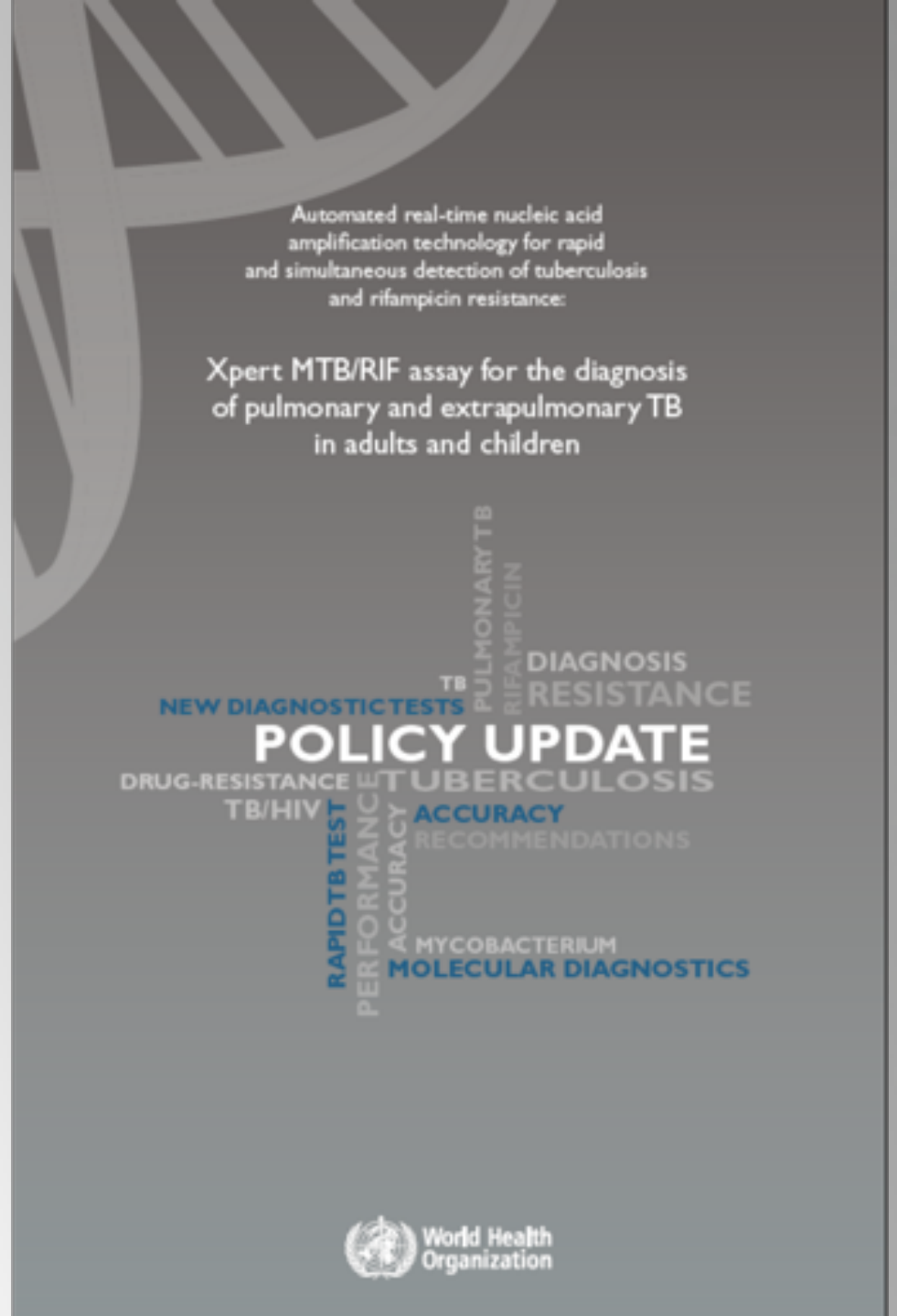
Introducing the new tool: Xpert MTB/RIF

- Automated PCR-based test
- Provides results within 2 hours
- Detects over 70% of smear-negative TB



Boehme et al, NEJM 2010

http://who.int/tb/laboratory/mtbrifrollout/en/



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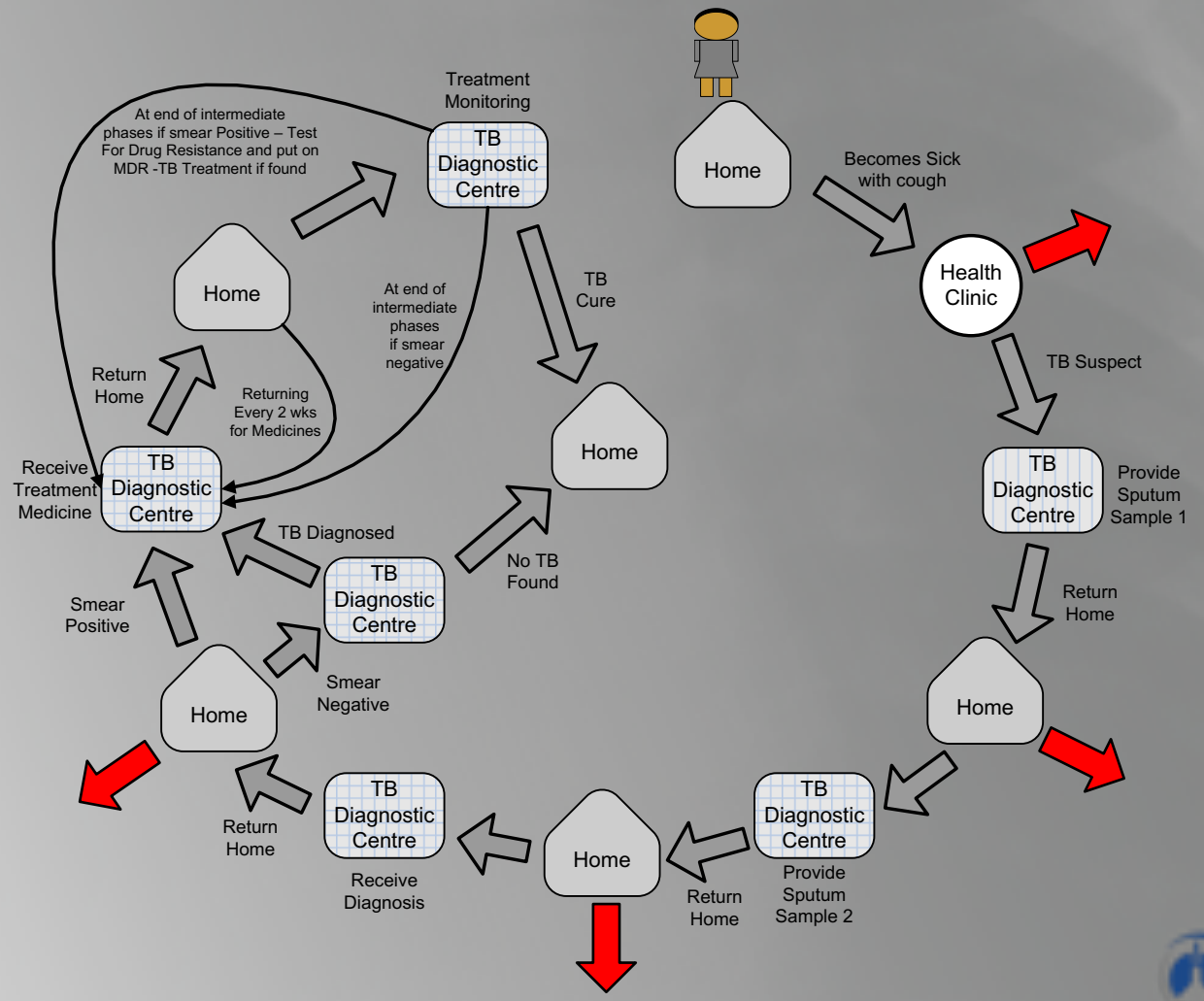
What's going to happen?

The "optimistic" view

- "The widespread introduction of new diagnostic testing platforms will allow TB to be diagnosed early and accurately"
- "Less advanced forms of TB will be diagnosed"
- "Treatment delays will be reduced"
- "Disease transmission will decrease"

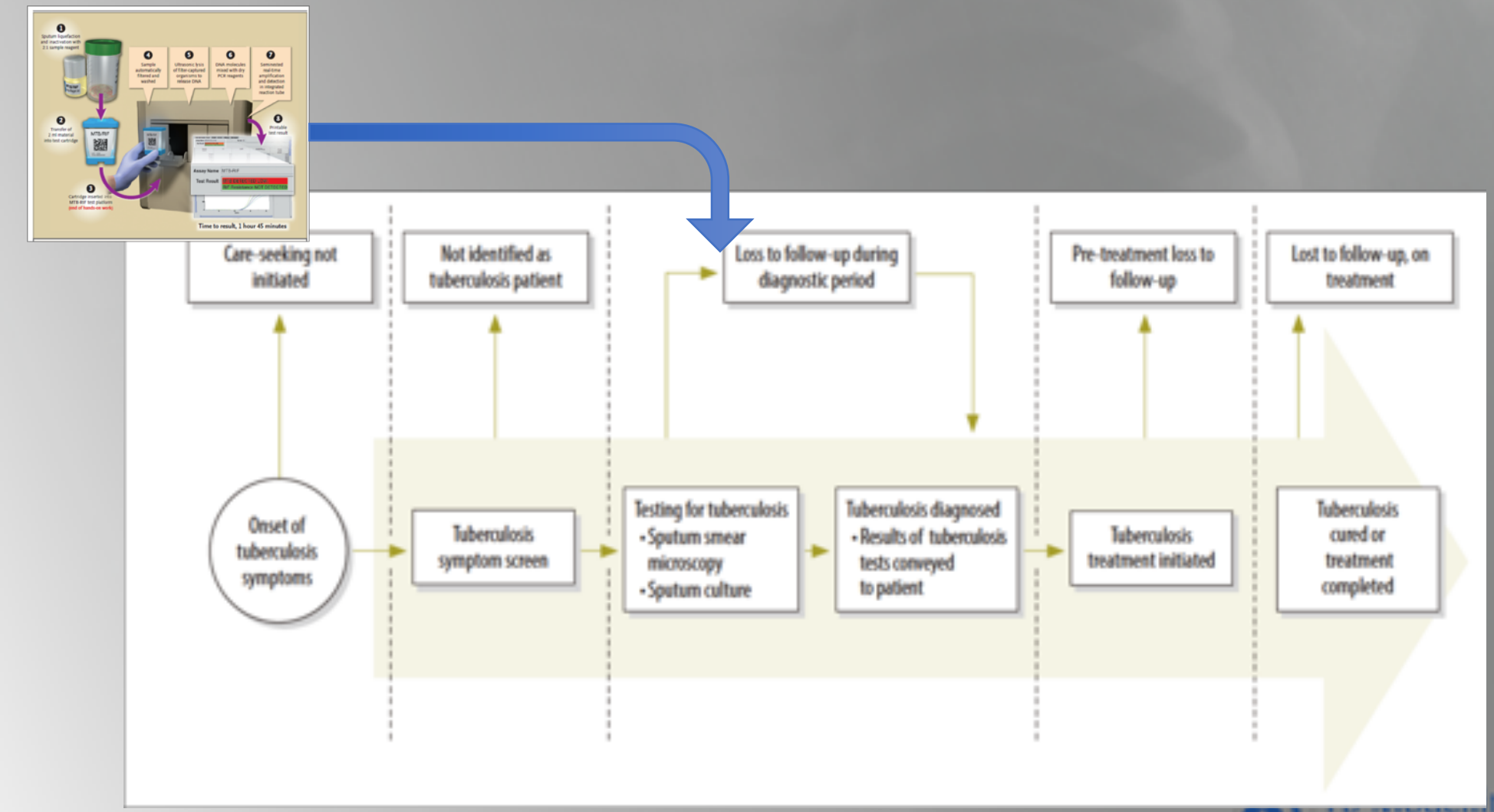
Xpert MTB/RIF implementation manual, WHO 2014

The long (and often lonely) journey of a TB patient



Courtesy of Ivor Langley

A comprehensive view of new diagnostics



Boehme et al, NEJM 2010
MacPherson et al, Bull World Health Organ 2011

Paper for today's discussion

The impact of new tuberculosis diagnostics on transmission: why context matters

Hsien-Ho Lin,[a] David Dowdy,[b] Christopher Dye,[c] Megan Murray[d] & Ted Cohen[e]

Objective To estimate the impact of new tuberculosis diagnostics on tuberculosis transmission given the complex contextual factors that can lead to patient loss before diagnosis or treatment.

Methods An epidemic model of tuberculosis specifying discrete steps along the tuberculosis diagnostic pathway was constructed. The model was calibrated to the epidemiology of tuberculosis and human immunodeficiency virus (HIV) infection in the United Republic of Tanzania and was used to assess the impact of a new diagnostic tool with 70% sensitivity for smear-negative pulmonary tuberculosis. The influence of contextual factors on the projected epidemic impact of the new diagnostic tool over the decade following introduction was explored.

Findings With the use of smear microscopy, the incidence of tuberculosis will decline by an average of 3.94% per year. If the new tool is added, incidence will decline by an annual 4.25%. This represents an absolute change of 0.31 percentage points (95% confidence interval: 0.04–0.42). However, the annual decline in transmission with use of the new tool is less when existing strategies for the diagnosis of smear-negative cases have high sensitivity and when symptomatic individuals delay in seeking care. Other influential contextual factors include access to tuberculosis care, patient loss before diagnosis, initial patient default after diagnosis and treatment success rate.

Conclusion When implementing and scaling up the use of a new diagnostic tool, the operational context in which diagnosis and treatment take place needs to be considered.

Bull World Health Organ 2012; 90:739-747A

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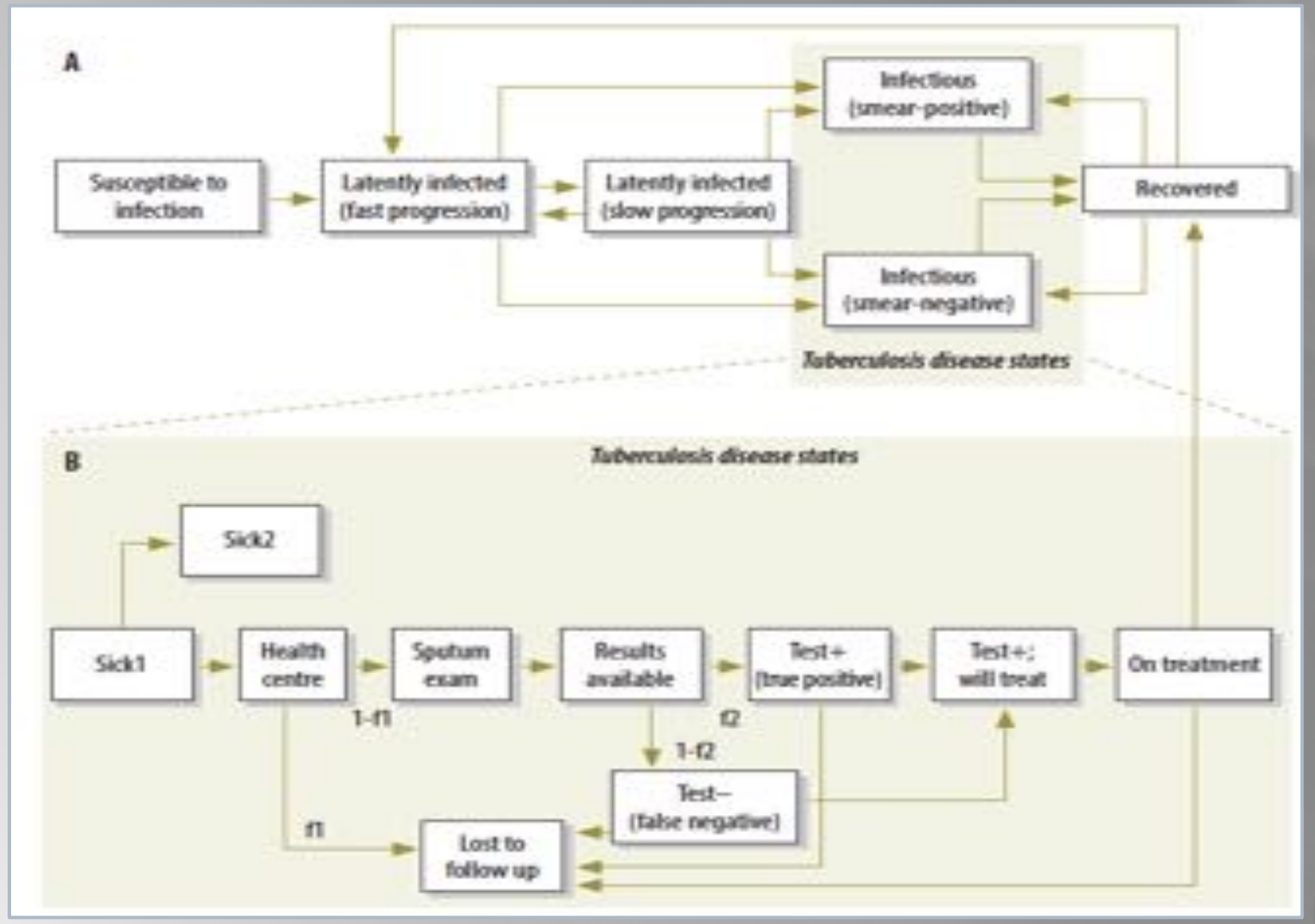
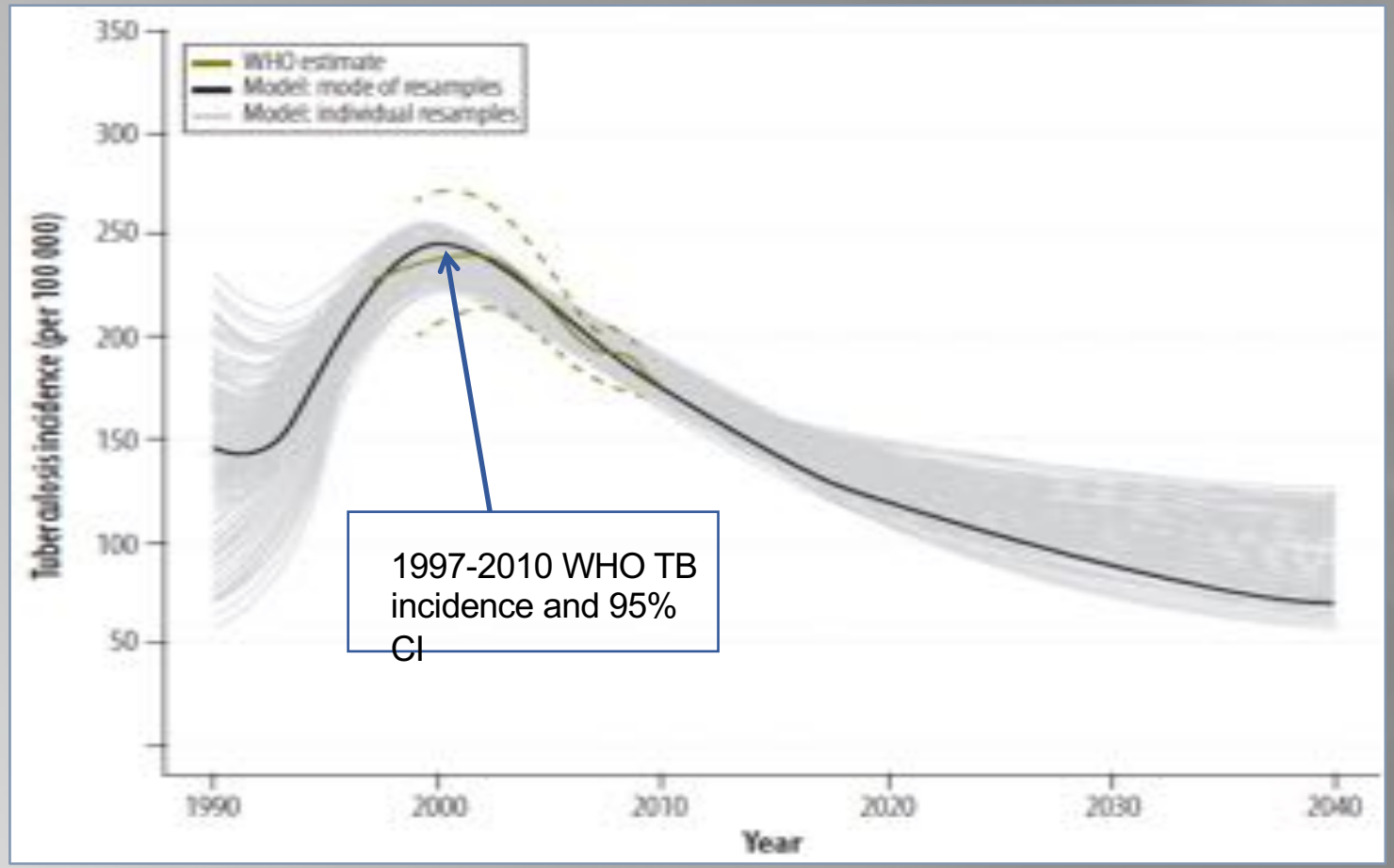
Model structure (Fig 1)



Model calibration (Fig 2)



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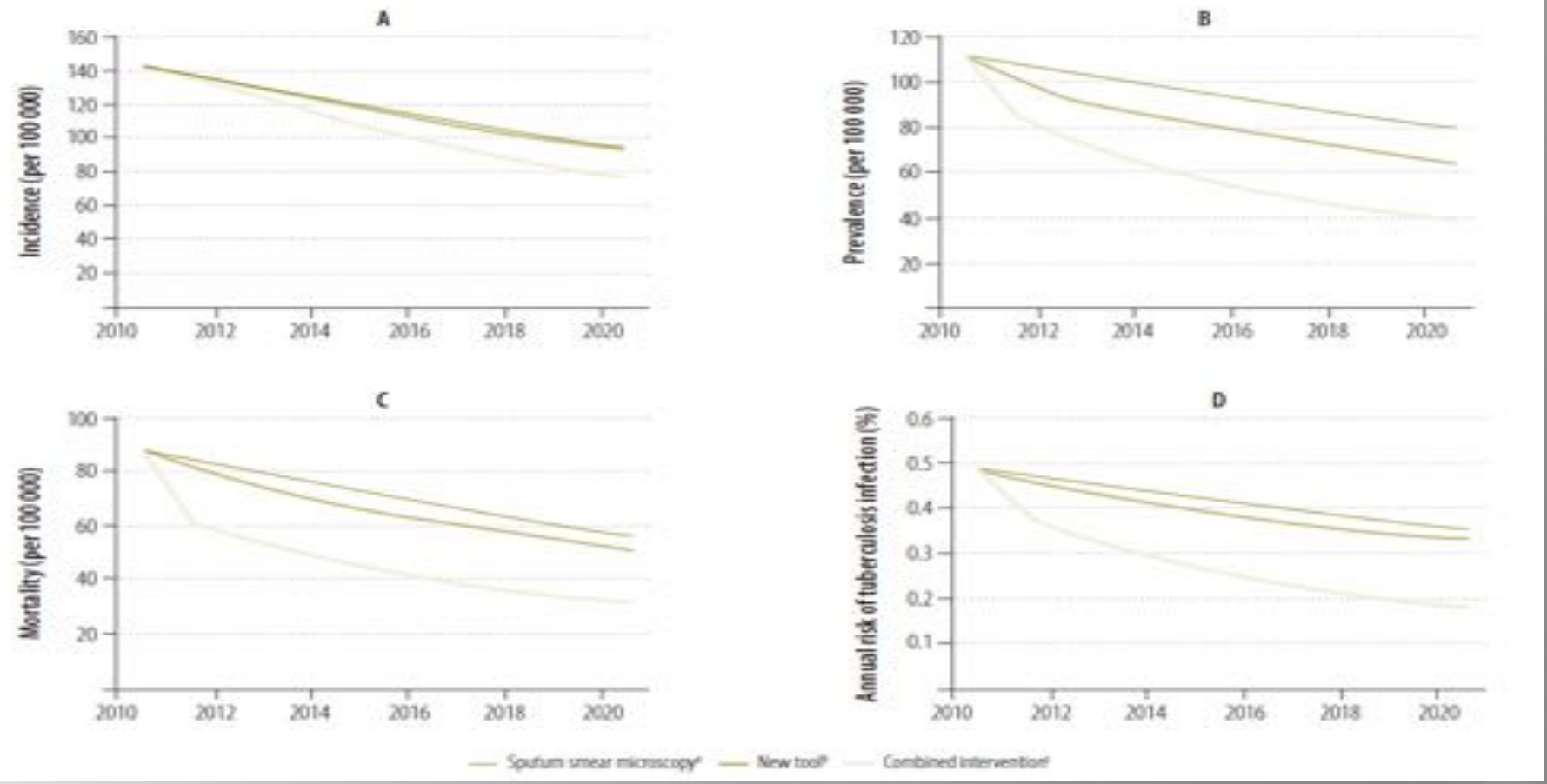
Model projections (Fig 3)

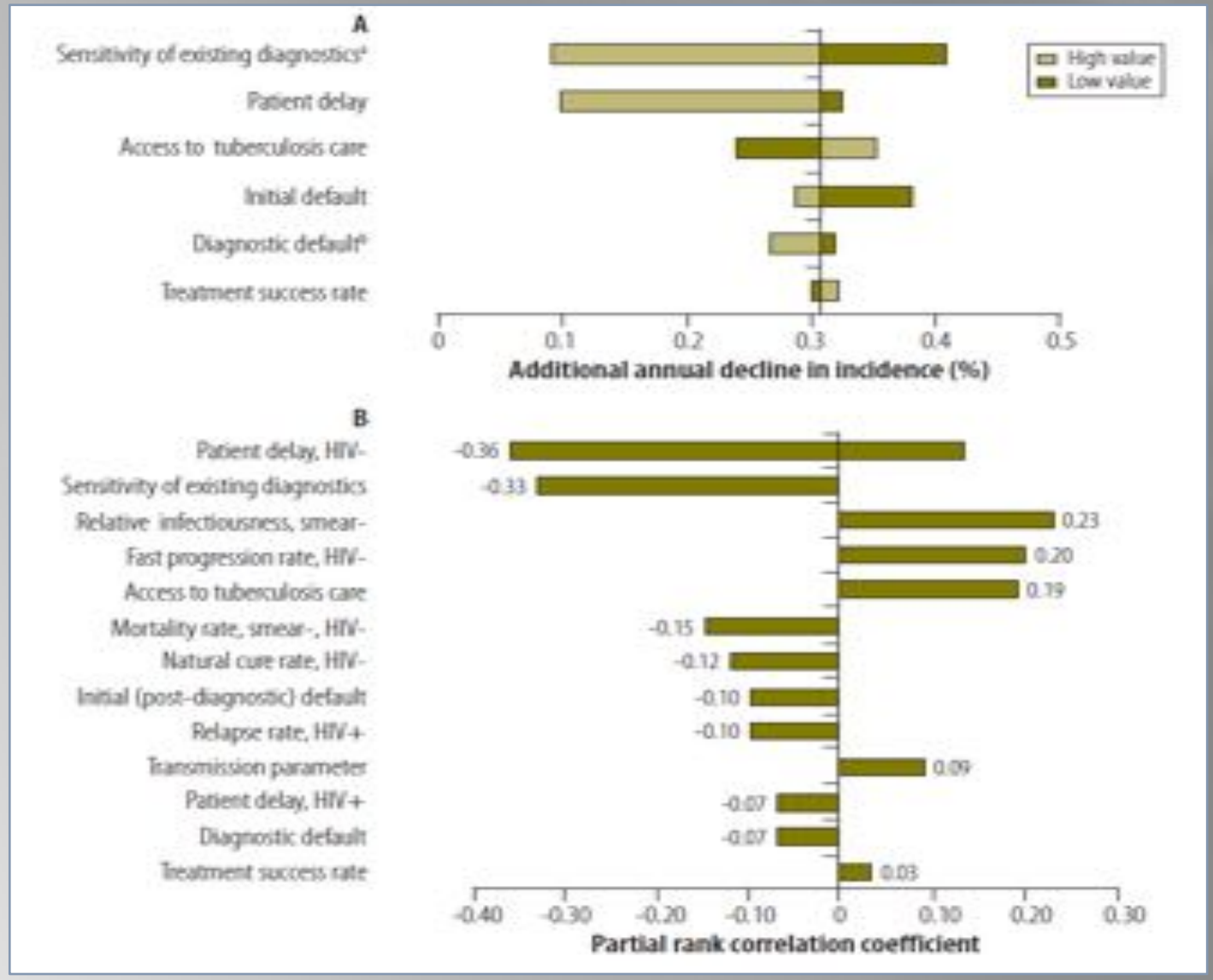


Scenario I: Sputum smear microscopy under the reference case operational scenario

Scenario II: New tool with 70% sensitivity for smear –ve and 100% for smear +ve replacing ss microscopy

Scenario III: New tool + other interventions to shorten patient delay, increase access to care and treatment success rate

Sensitivity analysis (Fig 4)



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Structure of this session

- Work in groups
- Group feedback and summary

➢3 of the most interesting/hotly debated points from the discussion (Good / Bad / Ugly)

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Aspects to consider

AREA	KEY QUESTIONS
Aims	1) Research question/hypothesis *(clearly stated?)*
Methods	2) Model structure *(what model techniques?)* 3) Model assumptions *(clearly explained?)* 4) Parameters 5) Fitting and sensitivity
Findings	6) Values and general outcomes *(what are they? original?)*
Conclusions	7) Discussion and limitations *(modelling useful to explore the research question?)*

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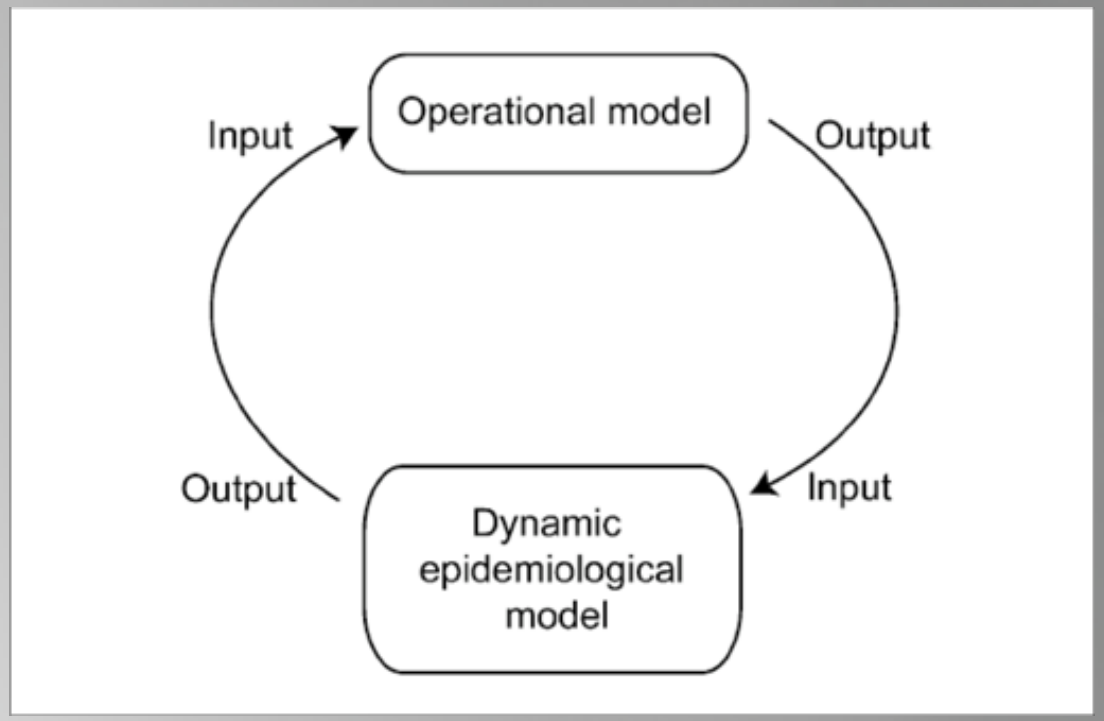
Group feedback & Summary

Further reading #1

Assessment of the patient, health system, and population effects of Xpert MTB/RIF and alternative diagnostics for tuberculosis in Tanzania: an integrated modelling approach

Ivor Langley, Hsien-Ho Lin*, Saidi Egwaga, Basra Doulla, Chu-Chang Ku, Megan Murray, Ted Cohen, S Bertel Squire*



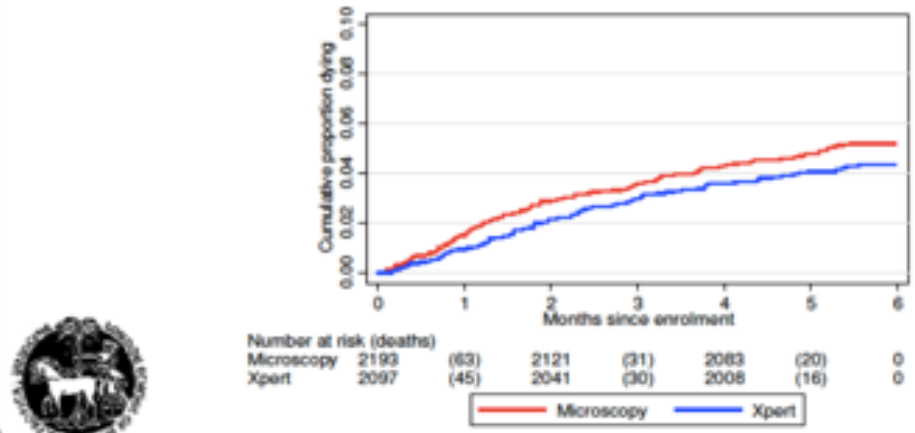
Langley et al, Lancet Global Health 2014

Further reading #2

Effect of Xpert MTB/RIF on mortality risk over 6 months

Xpert		Microscopy		Risk ratio (95% CI)	
Deaths/N	%[1]	Deaths/N	%[1]	Unadjusted	Adjusted[2]
91/2324	3.9%	116/2332	5.0%	0.86 (0.56-1.28)	1.10 (0.75-1.62)

[1]summary ignores cluster, [2]adjusted for age group, sex, body mass index group, number of TB symptoms and HIV status



Kaplan-Meier failure curves for mortality among all study participants (N=4656), by study arm

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Churchyard et al, Lancet Global Health 2015

Courtesy of Prof. Churchyard