JOHNS HOPKINS
UNIVERSITY

JOHNS HOPKINS
BLOOMBERG
SCHOOL of PUBLIC HEALTH

THE CENTER FOR TB RESEARCH
JOHNS HOPKINS UNIVERSITY

Modeling for Decision-Making

David Dowdy, MD PhD
<ddowdy@jhsph.edu>

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

The Key Question

How do we make models useful for actual decision making in the field of TB diagnostics?

The Xpert Example

OPEN ACCESS Freely available online PLOS | MEDICINE

Population Health Impact and Cost-Effectiveness of Tuberculosis Diagnosis with Xpert MTB/RIF: A Dynamic Simulation and Economic Evaluation

Nicolas A. Menzies[1,2*], Ted Cohen[3,4], Hsien-Ho Lin[5], Megan Murray[3], Joshua A. Salomon[1,6]

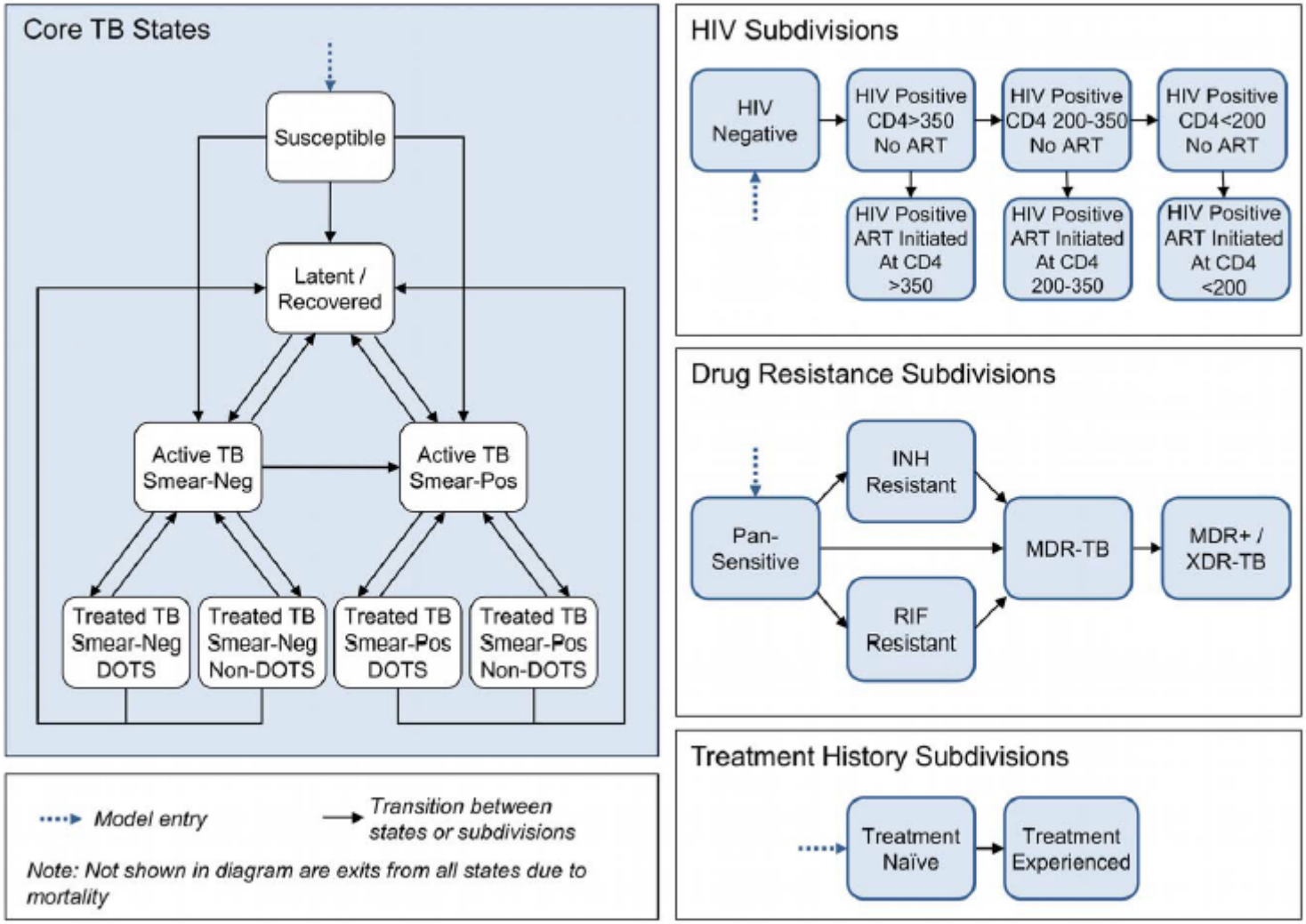
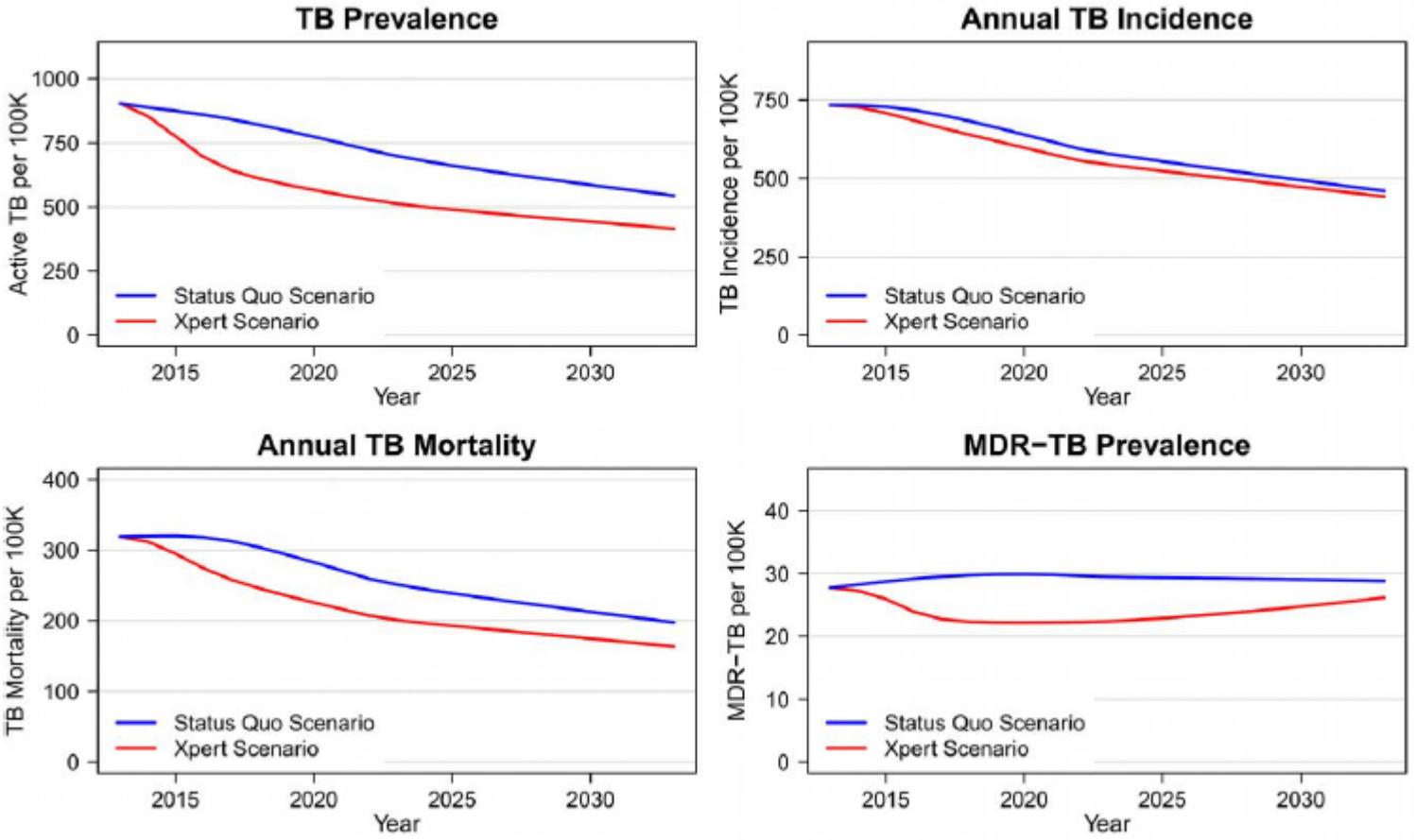


Figure 1. Model states, subdivisions, and transitions.

Main Results



How Is This Model Used?

- Conclusion: “Implementation of Xpert would avert 132,000 TB cases in southern Africa over 10 years…at a cost of $460 million.”
  - Will the Minister of Health for “southern Africa” please stand up?

- Are we simply spinning our academic wheels and making nice publications, but with no impact on decisions?
  - Remember that the entire goal of modeling should be to better understand systems, and to help with decision-making!

- What are the barriers to using models for decision-making?

Barrier 1: Complexity

Appendix Table 2: Base-case parameter values and ranges.

Description	Base-case value	Range[†]	Source
Parameters related to η_t			
New entrants at time t	Time-varying	—	[21]
Parameters related to λ_t			
Transmission parameter for individuals with (pan-sensitive) smear-positive TB in 1950 (β_{1950})			
Annual percentage decline in transmission parameter			
Infectivity of smear-negative TB, relative to smear-positive TB (q_1)			
Fitness cost for drug-resistant TB strains (r_s):			
Mono-INH resistant			
Mono-RIF resistant			
MDR-TB			
MDR+/XDR-TB			
Parameters related to γ_{0i} and γ_{ki}			
Rate of attending TB testing site, for individuals with active TB			
Rate ratio of attending TB testing, for individuals without active TB compared to those with active TB			
Parameters related to γ_{0k} and γ_{kk}			
Sensitivity of sputum smear microscopy:			
Smear-negative TB			
Smear-positive TB			
Specificity of sputum smear microscopy			

Description	Base-case value	Range[†]	Source
Sensitivity of sputum culture	1.0	—	Assumed
Specificity of sputum culture	0.984	[0.978-0.989]	[28]
Sensitivity of Xpert for TB:			[26]
Smear-negative TB	0.725	[0.655-0.788]	
Smear-positive TB	0.982		
Specificity of Xpert for TB	0.992		
Sensitivity of Xpert for RIF resistance	0.976		
Specificity of Xpert for RIF resistance	0.981		
Probability of sputum culture following a negative sputum smear (status quo algorithm):			
Treatment-naïve patients	0.20		
Treatment-experienced patients	0.80		
Probability of DST following a positive TB diagnosis (status quo algorithm):			
Treatment-naïve patients	0.00		
Treatment-experienced patients	0.80		
Sensitivity of clinical diagnosis	0.209		
Specificity of clinical diagnosis	0.953		
Parameters related to h_{0ji} and h_{kji}			
Probability of loss to follow-up between initial presentation and treatment initiation:			
With prompt diagnosis (smear, Xpert)	0.15		
With delayed diagnosis (culture, DST)	0.25		
Parameters related to δ_{ji}			
Treatment default rate, DOTS	Time-varying		
Treatment default rate, non-DOTS	0.58		
Parameters related to g_{ji}			
Probability of treatment success, for individuals with pan-sensitive TB completing first-line regimen	Time-varying		
Risk ratio of treatment success, relative to pan-sensitive TB treated with first-line DOTS regimen:			
First-line regimen, partially-sensitive strain	0.88		
First-line regimen, non-sensitive strain	0.44		
Second-line regimen, sensitive strain	0.93		
Second-line regimen, non-sensitive strain	0.44		
Non-DOTS regimen, non-MDR strain	0.72		
Non-DOTS regimen, MDR strain	0.44		
Parameters related to μ_j			
Background mortality rate, (ages 15+)	Time-varying		
Excess mortality rate for active TB (μ_{TB}):			
Smear-negative	0.21		
Smear-positive	0.30		
Excess mortality rate for HIV (μ_{HIV}):			
CD4 >350 cells/μl, no ART	0.008		
CD4 200-350 cells/μl, no ART	0.030		
CD4 <200 cells/μl, no ART	0.230		
On ART initiated at CD4 >350 cells/μl	0.008		
On ART initiated at CD4 200-350 cells/μl	0.023		
On ART initiated at CD4 <200 cells/μl	0.050		

Description	Base-case value	Range[†]	Source
Excess mortality rate for advanced HIV (CD4 <200) and active TB without ART ($\mu_{TB\text{-}HIV}$)	0.80	[0.472-1.272]	[14,15]
Parameters related to m			
Partial immunity afforded by prior infection:			[2,3,5,47]
HIV-negative	0.65	[0.37-0.87]	
HIV-positive, CD4 >350 cells/μl, no ART	0.45	[0.23-0.68]	
HIV-positive, CD4 200-350 cells/μl, no ART	0.25	[0.14-0.39]	
HIV-positive, CD4 <200 cells/μl, no ART			
Parameters related to p			
Probability of fast breakdown to active TB, for new infections:			
HIV-negative			
HIV-positive, CD4 >350 cells/μl, no ART			
HIV-positive, CD4 200-350 cells/μl, no ART			
HIV-positive, CD4 <200 cells/μl, no ART			
Parameters related to f			
Probability of smear-positivity, for incident TB cases:			
HIV-negative			
HIV-positive, CD4 >350 cells/μl, no ART			
HIV-positive, CD4 200-350 cells/μl, no ART			
HIV-positive, CD4 <200 cells/μl, no ART			
Parameters related to τ			
Rate of breakdown from latent/recovered to active TB (per 100,000):			
HIV-negative			
HIV-positive, CD4 >350 cells/μl, no ART			
HIV-positive, CD4 200-350 cells/μl, no ART			
HIV-positive, CD4 <200 cells/μl, no ART			
Parameters related to α			
Rate of conversion from smear-negative to smear-positive active TB			
Parameters related to σ			
Rate of self-cure for active TB:			
HIV-negative			
HIV-positive, CD4 >350 cells/μl, no ART			
HIV-positive, CD4 200-350 cells/μl, no ART			
HIV-positive, CD4 <200 cells/μl, no ART			
Parameters related to κ_j			
Duration of TB treatment ($1/\kappa_j$):			
First-line			
Mono-INH resistant			
Mono-RIF resistant			
MDR-TB			
MDR+/XDR-TB			
Non-DOTS (averaged)			
Parameters related to ν			
Probability that failed treatment cases are correctly identified and returned to treatment			
Additional parameters related to TB strain subdivisions			

Description	Base-case value	Range[†]	Source
Rates of acquisition of TB drug resistance:			[31]
Pan-sensitive → Mono-INH resistant, first-line regimen	0.020	[0.012-0.032]	
Pan-sensitive → Mono-RIF resistant, first-line regimen	0.003	[0.002-0.005]	
Pan-sensitive → MDR-TB, first-line regimen	0.010	[0.006-0.016]	
Mono-RIF or Mono-INH resistant → MDR-TB, appropriate second-line regimen	0.020	[0.012-0.032]	
Mono-RIF or Mono-INH resistant → MDR-TB, inappropriate second-regimen			
MDR-TB → MDR+/XDR-TB, appropriate second-line regimen			
MDR-TB → MDR+/XDR-TB, inappropriate second-line regimen			
Rate ratio of acquired resistance, pan-sensitive, non-DOTS regimen			
Additional parameters related to HIV subdivisi			
HIV incidence			
Rate of HIV progression for individuals not on AI			
From CD4 >350 cells/μl to CD4 200-350 cells/			
From CD4 200-350 cells/μl to CD4 <200 cells/			
Historical ART coverage for treatment-eligible H positive individuals			
Future ART coverage for treatment-eligible HIV- positive individuals			
Effectiveness of ART in reversing effect of HIV o natural history (all TB transition parameters subdivided by HIV status, excluding mortality)			
Proportion of HIV negative individuals with prio HIV test result			
Additional parameters related to costs and he			
Per-test cost of Xpert			
Per-test cost of smear diagnosis:			
Botswana			
Lesotho			
Namibia			
South Africa			
Swaziland			
Per-test cost of culture:			
Botswana			
Lesotho			
Namibia			
South Africa			
Swaziland			
Per-test cost of chest X-ray:			
Botswana			
Lesotho			
Namibia			
South Africa			
Swaziland			
Per-test cost of drug sensitivity testing:			
Botswana			
Lesotho			
Namibia			
South Africa			
Swaziland			

Description	Base-case value	Range[†]	Source
Cost of outpatient diagnostic visit:			[81]
Botswana	$10.32	[6.09-16.40]	
Lesotho	$2.94	[1.73-4.67]	
Namibia	$7.99	[4.71-12.70]	
South Africa	$10.30	[6.08-16.39]	
Swaziland	$6.21	[3.66-9.87]	
Cost of outpatient treatment visit:			[81]
Botswana	$6.85	[4.04-10.89]	
Lesotho	$1.95	[1.15-3.10]	
Namibia	$5.31	[3.13-8.44]	
South Africa	$6.85	[4.04-10.89]	
Swaziland	$4.13	[2.44-6.57]	
Cost of inpatient care, per day:			[81]
Botswana	$38.99	[23.00-61.99]	
Lesotho	$8.78	[5.18-13.96]	
Namibia	$28.76	[16.97-45.73]	
South Africa	$39.38	[23.23-62.61]	
Swaziland	$21.91	[12.93-34.84]	
Monthly TB regimen cost:			[41]
First-line	$5.86	[3.46-9.32]	
Mono-INH resistant	$18.02	[10.63-28.65]	
Mono-RIF resistant	$33.91	[20.01-53.92]	
MDR-TB	$119.37	[70.43-189.79]	
MDR+/XDR-TB	$179.06	[105.64-284.70]	
Monthly frequency of treatment activities, averaged over treatment course:			[1]
Clinic visits (first-line)	5.9	[3.5-9.4]	
Clinic visits (second-line)	22.3	[13.2-35.4]	
Monitoring smears (first-line)	1.0	[0.6-1.6]	
Monitoring smears (second-line)	1.0	[0.6-1.6]	
Sputum cultures (second-line)	0.43	[0.25-0.68]	
Chest X-rays (second-line)	0.14	[0.08-0.22]	
Number of months of inpatient care with MDR-TB treatment	4.0	[2.4-6.4]	[82]
Monthly cost of ART:	$104.97	[84.80-128.48]	[41,83-87]
Botswana	$69.63	[57.22-83.92]	
Lesotho	$94.68	[76.78-115.52]	
Namibia	$102.53	[82.90-125.40]	
South Africa	$81.20	[66.25-98.52]	
Swaziland			
Disability weights:			[43,44]
Active TB	0.271	[0.151-0.422]	
HIV-positive, CD4 >350 cells/μl, no ART	0.135	[0.078-0.213]	
HIV-positive, CD4 200-350 cells/μl, no ART	0.320	[0.176-0.496]	
HIV-positive, CD4 <200 cells/μl, no ART	0.505	[0.252-0.757]	
HIV-positive, ART initiated at CD4 >350 cells/μl	0.135	[0.078-0.213]	
HIV-positive, ART initiated at CD4 200-350 cells/μl	0.151	[0.087-0.238]	
HIV-positive, ART initiated at CD4 <200 cells/μl	0.167	[0.096-0.262]	
Discount rate	3.0%	[0-10%]	[88,89]

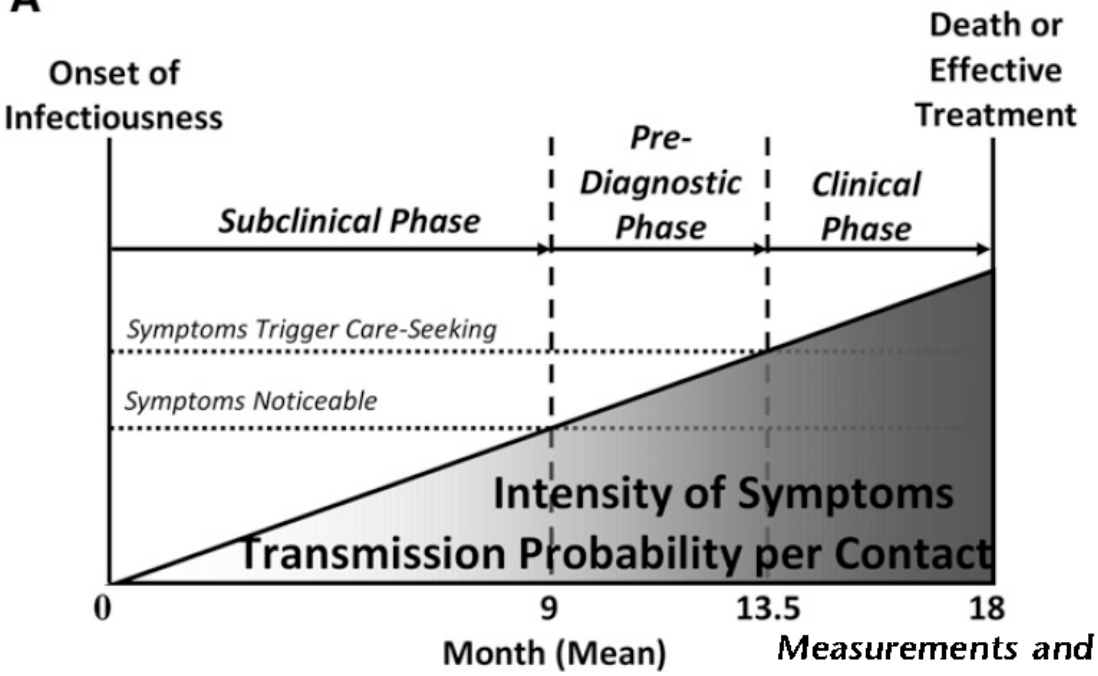
Barrier 2: Uncertainty

Is Passive Diagnosis Enough?

The Impact of Subclinical Disease on Diagnostic Strategies for Tuberculosis

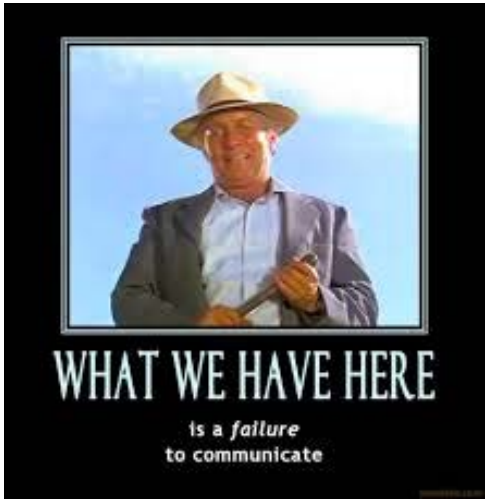
David W. Dowdy[1,2], Sanjay Basu[3,4], and Jason R. Andrews[5]

A



Measurements and Main Results: If the subclinical phase was ignored, as in most models, the passive strategy was projected to reduce TB incidence by 18% (90% uncertainty range [UR], 11–32%) by year 10, compared with 23% (90% UR, 14–35%) for the enhanced strategy and 18% (90% UR, 11–28%) for the active strategy. After incorporating a subclinical phase into the model, consistent with population-based prevalence surveys, the active strategy still reduced 10-year TB incidence by 16% (90% UR, 11–28%), but the passive and enhanced strategies' impact was attenuated to 11% (90% UR, 8–25%) and 6% (90% UR, 4–13%), respectively. The de-

But The Real Barrier Is…



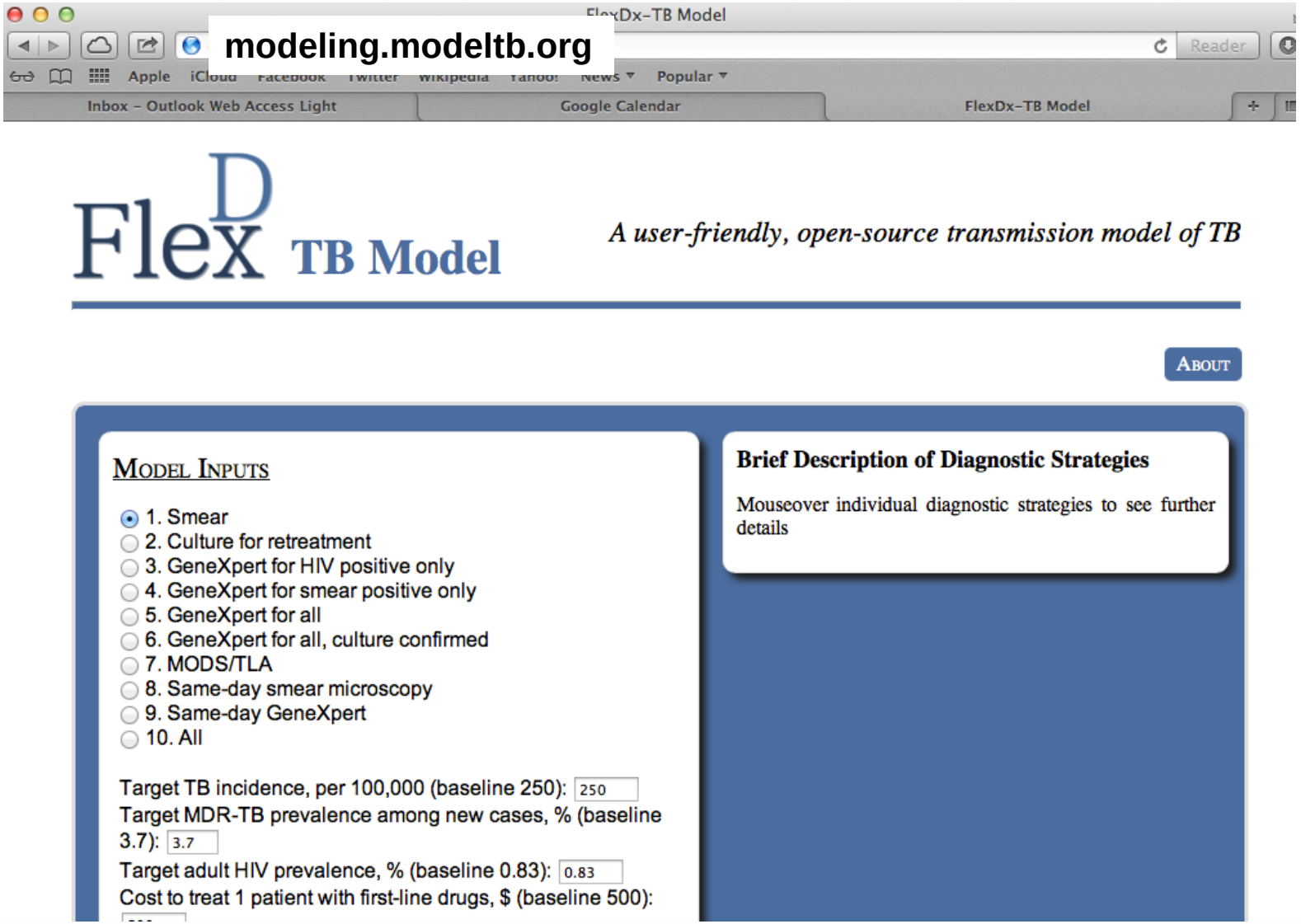
What models are providing are good for headlines…but not what decision-makers actually need.

- *Flexibility, local relevance, interpretability, actual decisions at hand*
- *Generally can only be done through long-term partnership*

One Solution

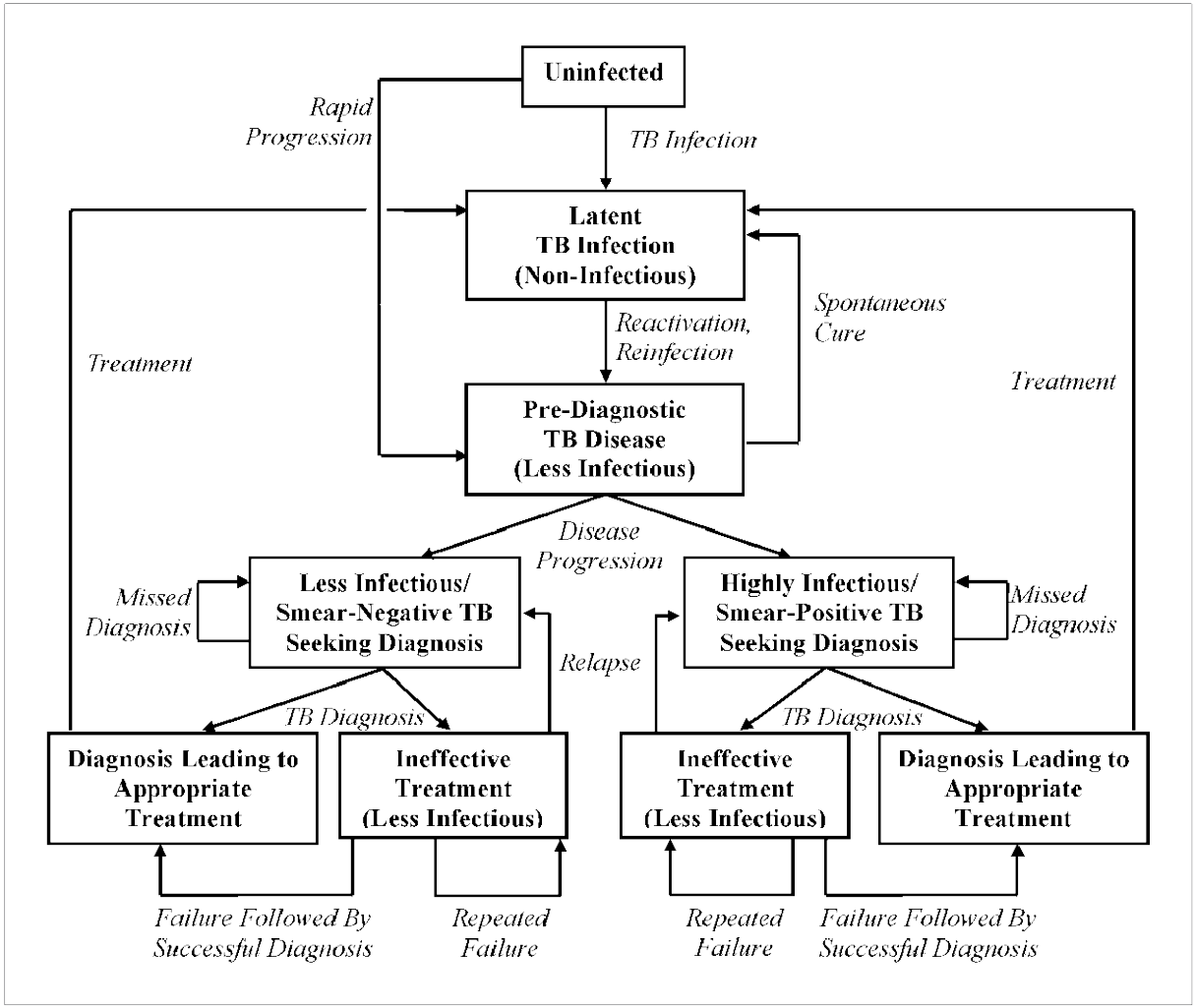
- Go to the Web
- Input your population's TB incidence, MDR-TB incidence, HIV prevalence, costs
- Have a program create a simulated epidemic that reflects your local scenario
- Use that epidemic to evaluate the impact of control interventions from a menu of possibilities
- Change any model assumptions that don't reflect your local situation, and run the model again
- Get results within seconds

User Interface

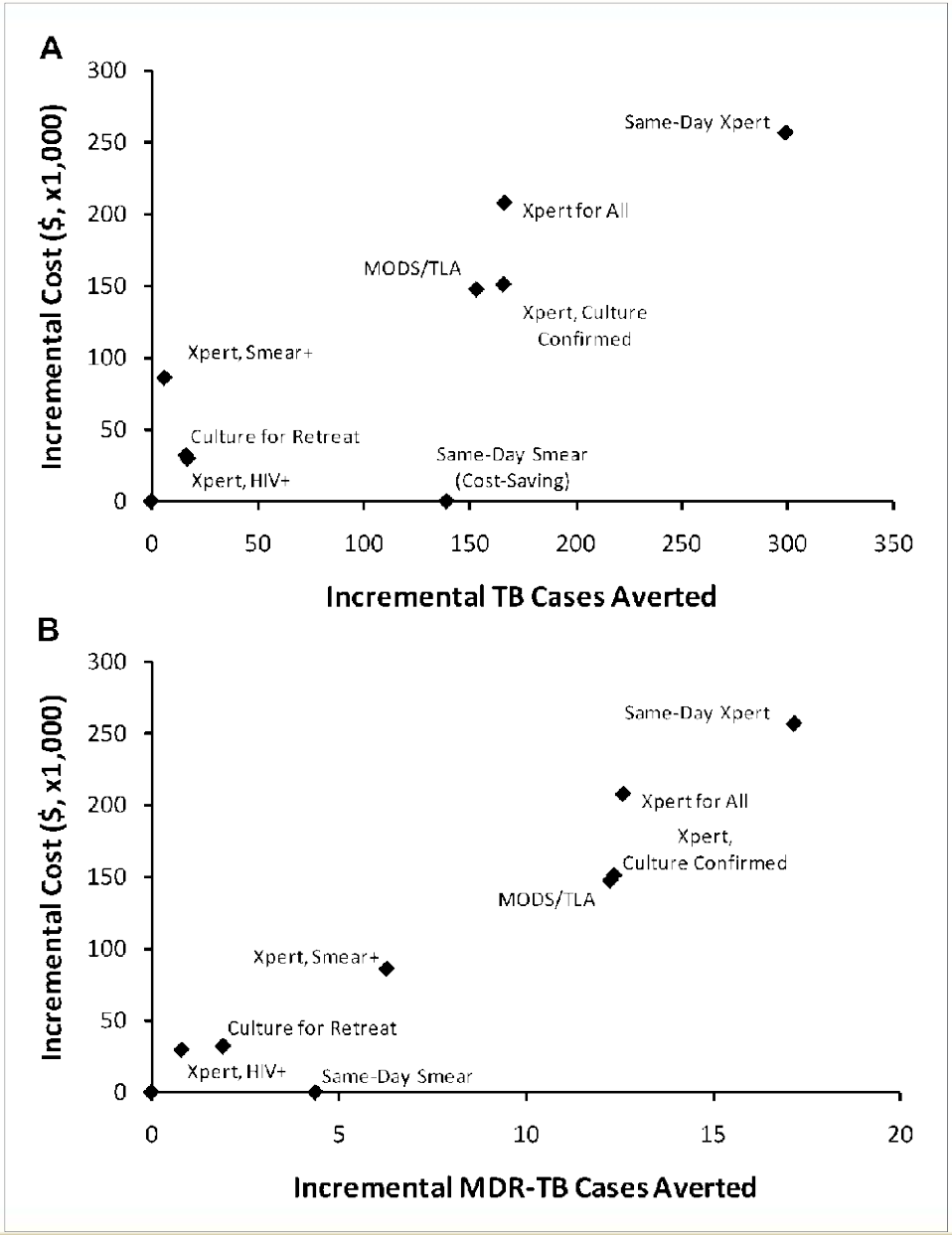


http://ec2-50-19-25-22.compute-1.amazonaws.com

Underlying Model

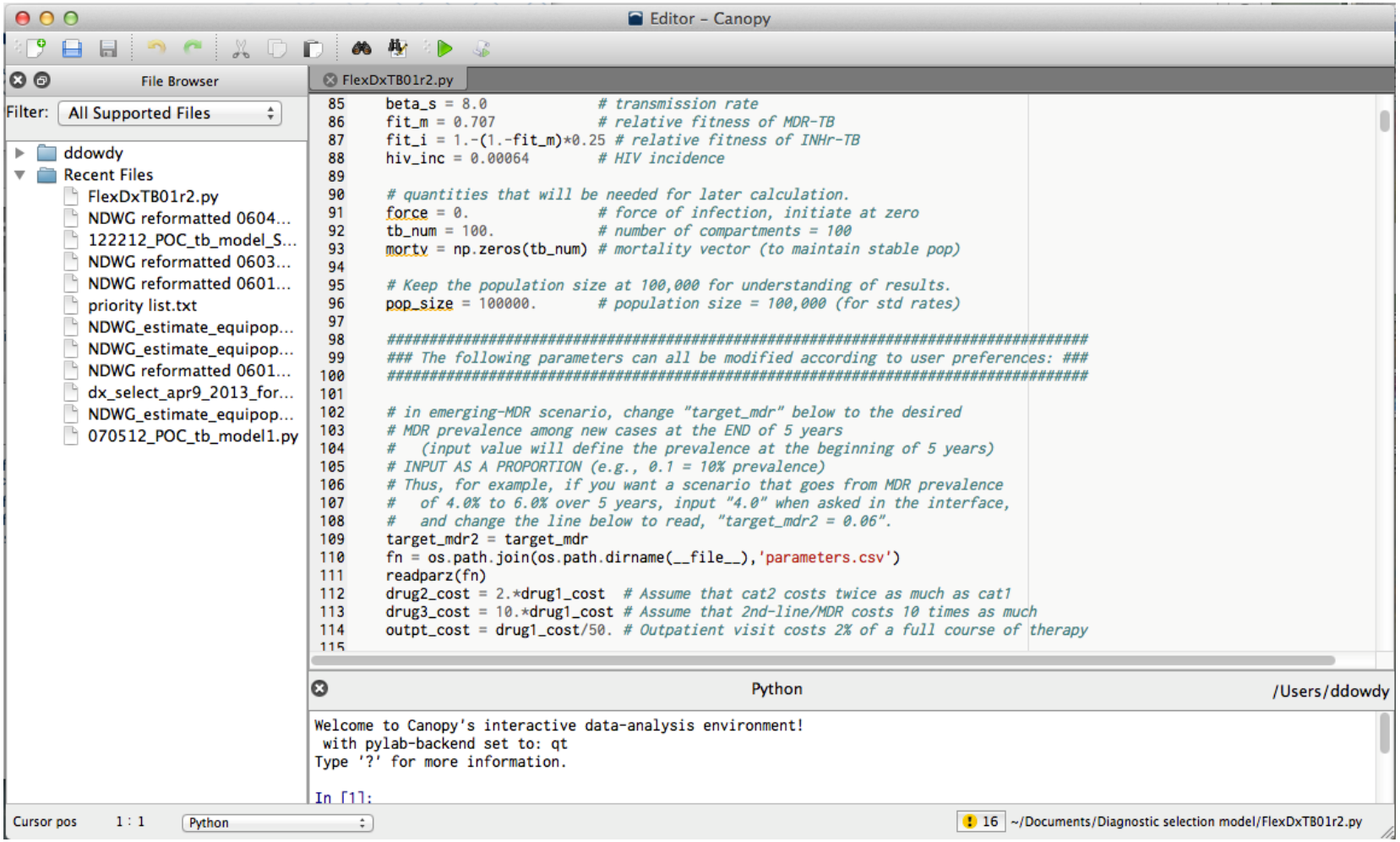


Output


A
Incremental Cost ($, x1,000)
300
250
200
150
100
50
0
Same-Day Xpert
Xpert for All
MODS/TLA
Xpert, Culture Confirmed
Xpert, Smear+
Culture for Retreat
Xpert, HIV+
Same-Day Smear (Cost-Saving)
0
50
100
150
200
250
300
350
Incremental TB Cases Averted
B
Incremental Cost ($, x1,000)
300
250
200
150
100
50
0
Same-Day Xpert
Xpert for All
Xpert, Culture Confirmed
MODS/TLA
Xpert, Smear+
Culture for Retreat
Xpert, HIV+
Same-Day Smear
0
5
10
15
20
Incremental MDR-TB Cases Averted

Comparison

Open-Source Program Available



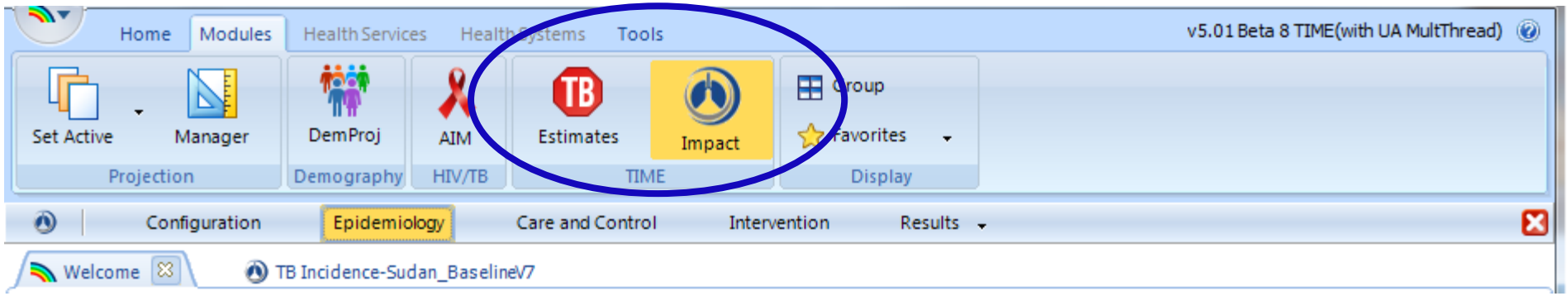
LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

TIME

TB Modelling and Analysis Consortium

(TB Impact Model and Estimates)

A new country-level and user-friendly tool for TB-HIV estimates and impact projections



Developed in collaboration with

TB Modelling and Analysis Consortium; Futures Institute; Global TB Programme/WHO; UNAIDS; Stop TB partnership

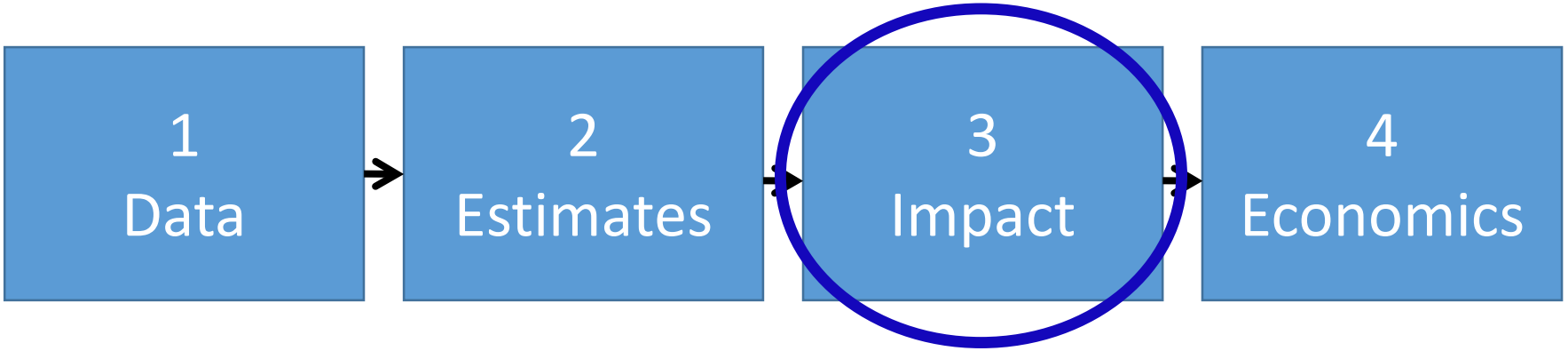
Contact: Rein.Houben@lshtm.ac.uk

BILL & MELINDA GATES foundation

Futures INSTITUTE

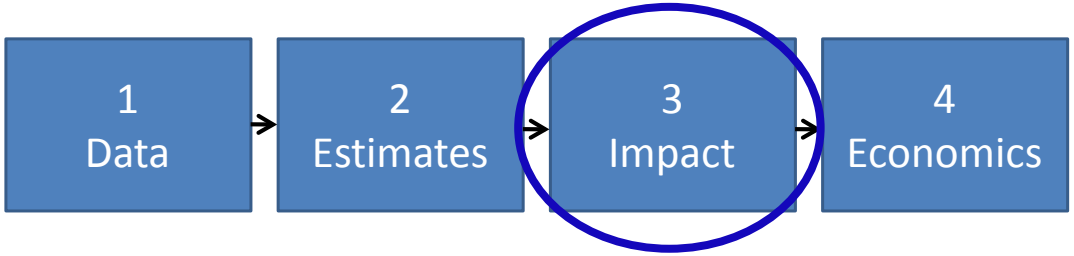
TIME

Country-level tool for TB(-HIV) estimates and projections



Set of modules for user

1. Data review, quality assessment and certification
2. Estimation of current burden and past trends
3. Projection and epidemiological impact
4. Cost-effectiveness and resource needs



TIME Impact

Data pulled in automatically (sources)

Demography (UN pop div)

TB (GTB)

TIME Estimates

HIV (UNAIDS)

TIME Impact is stratified by Treatment History, MDR, HIV/ART/CD4

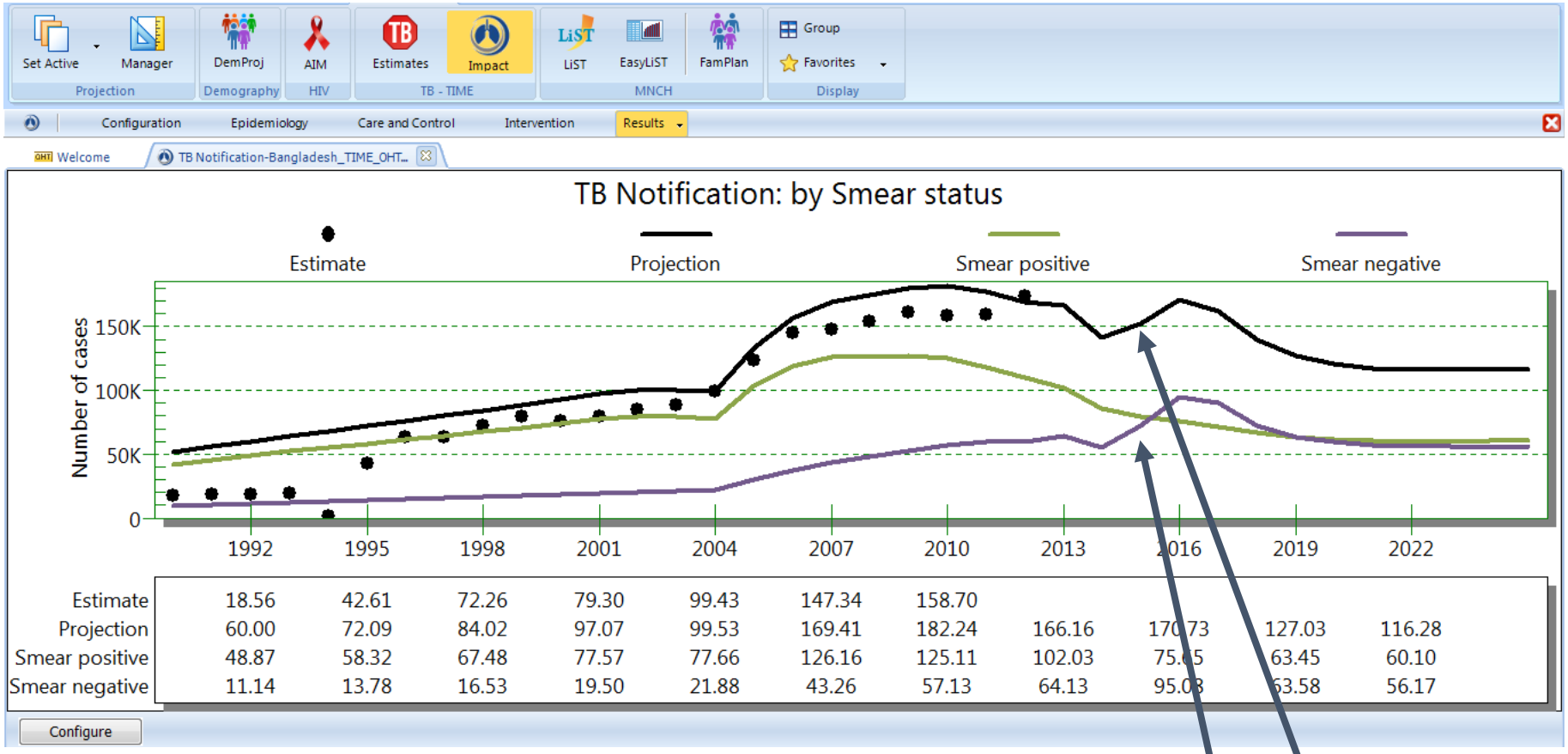
TIME Impact

TIME Impact can handle Pre-specified or user-defined interventions

Data links automated through Spectrum software suite

Model can work on regional (multi-country) or subnational level as long as input data are available

TIME Impact: Results
Bangladesh Pilot work



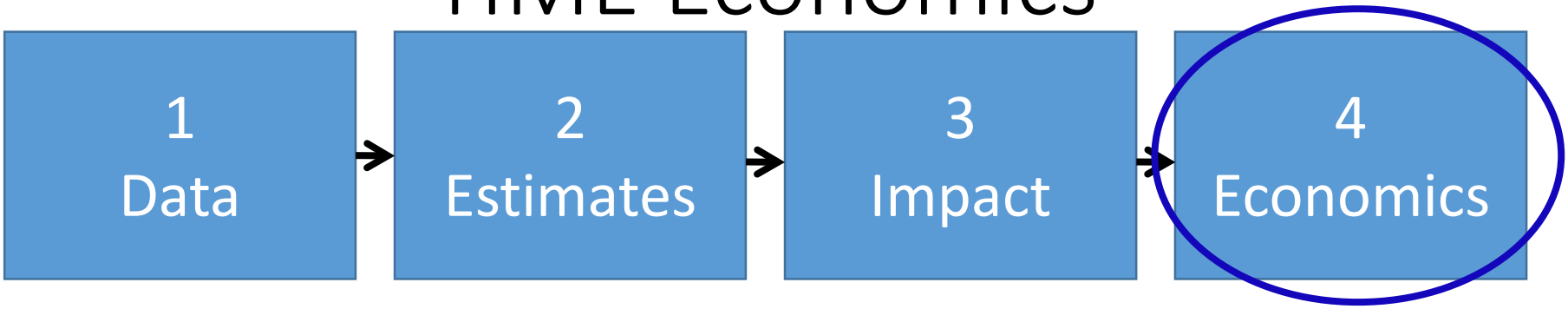
Note: Empirical treatment rates reported to be low

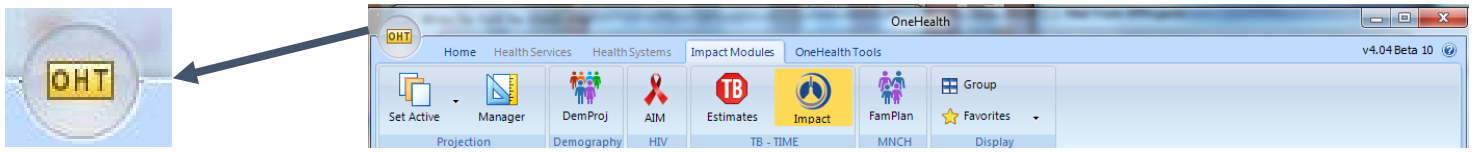
Xpert for smear negative TB

TIME Impact was fit to notification, by smear status (see graph)

Captures impact of roll-out of Xpert for diagnosis of SSneg TB in 2014

TIME Economics





Economics Tool: One Health

- Integrated costing environment for global health areas
- Supported by InterAgency Working Group on Costing
  - UNFPA, UNICEF, UNDP, UNAIDS, WHO, World Bank
- TB costing updated to reflect WHO/GTB budgeting methodology, fully linked to TIME
- Calculate costs per TB case averted, life saved, DALY/QALY, etc…

Acknowledgments

- **Bill and Melinda Gates Foundation**
- **TB Modeling and Analysis Consortium (TB MAC)**
  - Ted Cohen, David Dowdy, Anna Vassall
- **Futures Institute**
  - Carel Pretorius, Rachel Sanders
- **WHO Global TB Program (GTB)**
  - Philippe Glaziou, Babis Sismandis, Ines Garcia-Baena
- **UNAIDS Reference Group for HIV Estimates and Projection**
  - Tim Hallet, Geoff Garnett, Simon Gregson
- **Stop TB Partnership**
  - Lucica Ditiu, Sahu Savenand
- **LSHTM TB Modelling Group**
  - Tom Sumner, Gwen Knight, Emilia Vynnycky and others.

The "Flexible" Approach is Still Limited

- Simplistic model – not enough for full decision-making
- May not speak to the precise questions in-country
  - Which generally are quite detailed and rapidly evolving
- Difficult to appropriately convey uncertainty
  - Some worry about misuse of such models
- Who would be the true user of these models, how would they use it, and can it be done without a big, well-funded team?
- *Panel discussion upcoming…*

The "Top-Down" Option: TB MAC

67th World Health Assembly 2014

World Health Organization

Global strategy and targets for tuberculosis prevention, care and control after 2015

TB Modeling and Analysis Consortium comparative modeling exercise

TB MAC Approach

- 11 different modeling groups
- 3 key countries (South Africa, India, China)
- Model series of pre-determined interventions:
  - Better access to care
  - Improved DOTS
  - Xpert scale-up
  - Active case-finding
  - IPT
  - Combination
- Involve WHO and health economists
- See if models agree or disagree

Challenges with the TB MAC Approach

- Different models treat interventions in different ways
  - Have to specify each intervention in a fashion that is comparable
- WHO wants different outputs than models can provide
  - Example: many models are adult models, but WHO wants all TB
- How to model the scale-up and impact of certain interventions?
  - Example: Xpert, ACF
- Crafting the take-home message
  - “2025 targets are unachievable” is not the message we want to send from this exercise.

Summary

- In theory, models are powerful tools for decision-making, but the practice of bringing model results to decisions is difficult.

- Alternative approaches exist, but none is (close to) perfect.
  - Open-source flexible model designed to be readily accessible
  - More detailed model with country technical missions to support
  - Top-down consortium engaged with global policy

- Is the process of bringing data systematically into the decision-making process impossible?
  - Meaning that we have no choice but to rely on the “mental models” of experts?
  - Time for a panel discussion…

JOHNS HOPKINS
BLOOMBERG
SCHOOL of PUBLIC HEALTH

Modeling and Cost-Effectiveness: Synthesis

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

Modeling: Summary Points

- **1. The purpose of modeling is to inform decision-making, not tell the future.**

- Models serve as the link between epi data (usually individual-level) and population-level decision-making.
  - Without a quantitative structure for this, the process is subjective.

- Projections of future impact are the means, not the end.
  - Decision-makers generally can't process model results without projections.
  - But an appropriate decision-making process involves the modelers discussing strengths and weaknesses of the approach.

Modeling: Summary Points

- **2. Modeling of TB is an uncertain business.**

- Much of our data is weak, and can strongly influence results.
  - For example, we estimate natural history from pre-chemotherapy era.

- Model structure introduces as much uncertainty as the parameters.
  - Example of including a “pre-clinical infectious” stage for diagnostics

- Uncertainty is difficult to convey appropriately.
  - Do you want a confidence interval that includes every possibility?
  - Is the goal to provide precise projections in the first place?

Modeling: Summary Points

- **3. Challenges of Modeling TB Diagnostics**
- Diagnostics are part of a larger **health system**.
- Impact of diagnostics depends on **patient behavior**.
- There are many uncertainties in TB **natural history**.
- **Heterogeneities** in TB transmission are important to consider in designing smart diagnostic strategies.

Cost-Effectiveness: Summary Points

- **1. Basic Economic Concepts**
- Opportunity costs, not financial costs
- Unit costs (fixed & variable) – not straightforward
- Discounting, inflation, currency conversion
  - $1 is not always $1
- Perspective of the analysis
  - Costs from one perspective may not be important from another

Cost-Effectiveness: Summary Points

- **2. Challenges of CEA for TB Diagnostics**

- TB treatment is so effective that even bad diagnostics can look very cost-effective.

- Assumptions that more sensitive diagnosis = more people treated and more lives saved may not be accurate.

- Difficult to incorporate transmission effects and impacts on the health system
  - Though we are improving in this regard

Final Summary Point

Integrating Epidemic-Economic Models into Frameworks for Targeted, Data-Driven Decision Making

- Users want to be able to adapt results to their settings but may not have the expertise to use models appropriately.
- Modeling expertise in TB diagnostics is limited (and largely confined to academia) – must be realistic about how best to use that expertise in practice.
- Decision makers must first understand both the power and limitations of models in order to advance this discussion.