Areas of Application of TB modeling and case studies

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Objective of session

Last session: discussed how TB can be modeled, and the different modeling approaches to choose from

This session:
- Turn to the literature to look at how TB models have evolved over time
- Outline some key contributions
- Use case studies to illustrate steps involved in generating a modeling study

Turning to the literature...

In general see models with 2 main purposes:

1)   Models that assess population dynamics of epidemic

- Calculate the reproductive number (indicates the severity of the epidemic, and if an epidemic is increasing or decreasing)
- Evaluate the impact of specific parameters or assumptions (ie. role of reactivation vs. re-infection)

2)   Models that evaluate TB interventions

- Assess diagnostic, therapeutic and/or preventative interventions (either separately or in combination)

- When we consult the literature we see that modeling has changed or evolved substantially over the past few decades

Turning to the early literature:

A few key early contributions…

- Styblo 1969
- Waaler 1969
- Blower 1995
- Murray 1998
- Dye 1998

Just to name a very select few from a long list of important contributions!

THE TRANSMISSION OF TUBERCLE BACILLI

ITS TREND IN A HUMAN POPULATION

Tuberculosis Surveillance Research Unit*

The work was carried out and the report prepared by

K. Stýblo, J. Meijer and Ian Sutherland**

- Styblo et al. used prevalence data from the Netherlands (from TST in army recruits in the 1950s) and mathematical equations to derive a series of annual risk of infection estimates for the population

- Estimates derived for different ages and birth years

- Ultimately used model to predict the likely TB-status of the Dutch population between 1910-1965

- Found that the risk of TB infection has been decreasing in the Netherlands from 1910- but became even steeper after 1940

The Use of an Epidemiological Model for Estimating the Effectiveness of Tuberculosis Control Measures

Sensitivity of the Effectiveness of Tuberculosis Control Measures to the Coverage of the Population *

H. T. WAALER [1] & M. A. PIOT [2]

- Waaler and Piot were interested in the "epidemiologic effectiveness" of interventions (ie. "the cumulative effect of measures on the whole community over a period of time")

- Generated hypothetical but "realistic model" of a demographic and epidemiological situation. Reflected the full population of Norway.

- Objective was to quantify the impact of BCG vaccination, chemotherapy and isoniazid prophylaxis

FIG. 5
INCIDENCE OF INFECTIOUS TUBERCULOSIS OVER TIME, ASSOCIATED WITH DIFFERENT BCG VACCINATION COVERAGES OF THE UNINFECTED AT 14 YEARS OF AGE
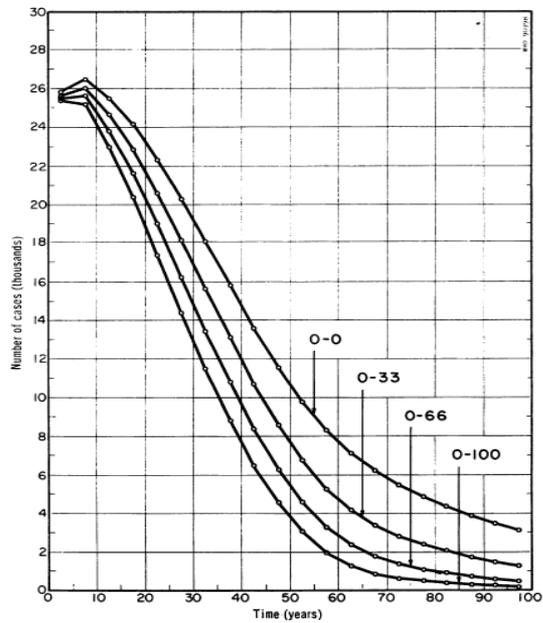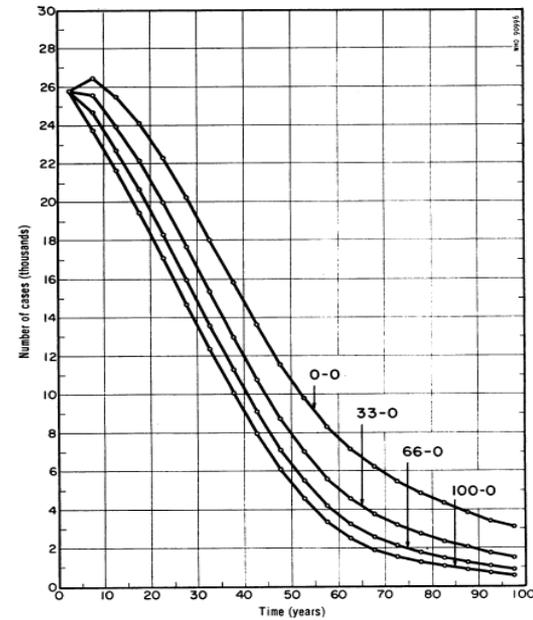
FIG. 7
INCIDENCE OF INFECTIOUS TUBERCULOSIS OVER TIME, ASSOCIATED WITH DIFFERENT TREATMENT COVERAGES OF CASES

In 1969, Waaler noted:

"In recent years, the development of computers with a large core memory has obviated the need for explicit mathematical solution, and thus has allowed for a much higher degree of complexity in the structure of models."

**Tubercle and
Lung Disease**

**An estimate of the future size of the tuberculosis problem in sub-Saharan
Africa resulting from HIV infection**

M. Schulzer[*†], J.M. Fitzgerald[*], D.A. Enarson[‡], S. Grzybowski[*]

- Schulzer et al. developed a model to predict the impact of HIV on the TB epidemic
- Based on the population of Tanzania, 1980-2000
- Considered 4 scenarios with different combinations of TB infection prevalence and HIV prevalence to account for differences in different parts of Sub-Saharan Africa
- Depending on initial HIV / TB infection prevalence, predicted between 50%-1200% increase in smear positive rates in 15-49 yr olds between 1980-2000

The intrinsic transmission dynamics of tuberculosis epidemics

SALLY M. BLOWER[1], ANGELA R. McLEAN[2], TRAVIS C. PORCO[1], PETER M. SMALL[3], PHILIP C. HOPEWELL[4], MELISSA A. SANCHEZ[5] & ANDREW R. MOSS[1]

- Blower et al. (Nature Medicine, 1995) presented a "simple transmission model consisting of 3 ordinary differential equations that represent the current biological understanding of TB"

- Includes primary progression and reactivation from old infection

- Consider the intrinsic transmission dynamic of TB and looks at the length of TB epidemics

- Concluded that epidemics take a very long time to reach stability, and some of decline seen today is due to the natural behavior of the epidemic

Control Strategies for Tuberculosis Epidemics: New Models for Old Problems

S. M. Blower,* P. M. Small, P. C. Hopewell

- In follow up paper in Science in1996, Blower et al. suggest that "control strategies can be designed based on a quantitative understanding of the transmission dynamics of TB"

- Propose a framework for designing effective control strategies and used to determine treatment levels for eradication

- Extended previous model to include chemoprophylaxis and treatment (no mention of diagnostics)

- Considered how suboptimal programs can contribute to the development of drug resistance

Control Strategies for Tuberculosis Epidemics: New Models for Old Problems

S. M. Blower,* P. M. Small, P. C. Hopewell

- Calculated threshold levels of preventive therapy and treatment needed for TB eradication

- Concluded that it is unlikely that eradication can be achieved by reaching WHO's targets for case detection and cure

- And that "any program with a treatment failure rate of greater than 50% should not be operating because it will result in a perverse outcome"

Modeling the impact of global tuberculosis control strategies

CHRISTOPHER J. L. MURRAY AND JOSHUA A. SALOMON*

Center for Population and Development Studies, Harvard School of Public Health, 9 Bow Street, Cambridge, MA 02138

- Murray and Salomon elaborated on Blower model-becomes a more complex model which included a basic HIV model

- Applied model to "real populations" and studied the impact of specific control measures in 5 different regions of the world

- Questioned if enough gains could be made thorough DOTS alone and the focus exclusively on smear positive cases

- Evaluated range of "extension strategies" to improve on accomplishments with DOTS alone

Murray and Salomon 1998

Existing technologies:

- Expanding DOTS for smear negatives,
- Active case finding- screening for respiratory symptoms
- Active case finding- miniature mass radiography (MMR)
- Single cycle active case finding
- Mass preventive therapy
- Preventative therapy for HIV+ population

New Technologies :

- Improved sputum exam
- Nucleic Acid Amplification Tests (NAAT)
- Ultra short chemotherapy
- Vaccines- against reactivation and initial infection

- Also considered Combination strategies

Predicted that active case finding via MMR led to the greatest number of TB cases and deaths averted when compare to the baseline strategy of DOTS

- Murray and Salomon's paper was followed a month later by Dye et al's paper in Lancet…

Prospects for worldwide tuberculosis control under the WHO DOTS strategy

Christopher Dye, Geoffrey P Garnett, Karen Sleeman, Brian G Williams

- Concluded that through DOTS alone substantial reductions TB cases and deaths could be achieved

Dye et al (1998). Lancet 12;352(9144):1886-91.

From this point forward…
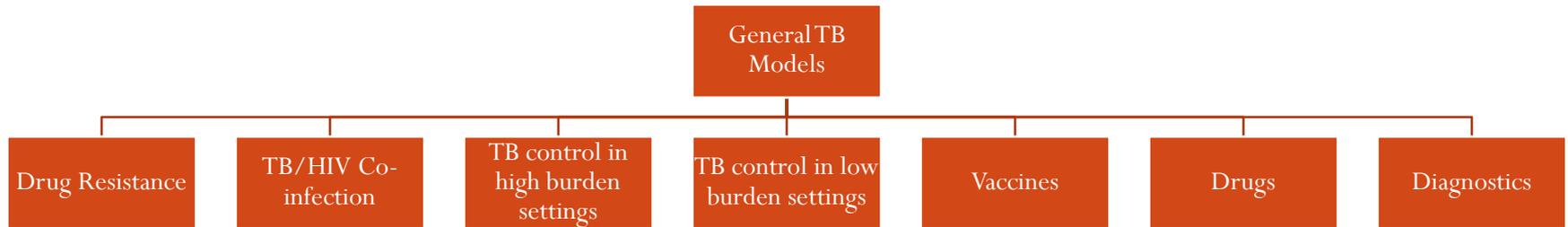
- See a shift from models that characterize the TB epidemic in general and evaluate large categories of interventions
- As the global approach to TB control has become more targeted and nuanced, TB models have become more targeted and nuanced
- Now see more of a focus specific aspects of TB epidemiology and interventions

Case studies- 2 different published TB models

- Use to illustrate key steps in generating a modeling study

1. • Define the study objective
2. • Define the setting/population
3. • Identify outputs of interest
4. • Select modeling approach and start to develop model
5. • Define comparators (baseline and alternatives interventions)
6. • Define key parameters (and ranges)/ assumed impact
7. • Select input data/ enter key transitions
8. • RUN (and re-run) MODEL
9. • Interpret and Summarize outputs/results
10. • Conduct sensitivity analysis
11. • Consider implications/policy recommendations

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Additional note about the work that goes into Step 4: model development

For Some models-

- Calibration and parameterization of model (tweak unknown parameters until model predictions match those of a known data set)
- Validation of model (ensure that model is predicting outcomes correctly using a different known dataset)

For all models-

- Refining parameter estimates
- Debugging models
- Troubleshooting if/and how your model is working

Case Study 1- Reaching DOTS targets:

Prospects for worldwide tuberculosis control under the WHO DOTS strategy

Christopher Dye, Geoffrey P Garnett, Karen Sleeman, Brian G Williams

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Step 1: Define the study objective

- To use a "mathematical model that brings together data from studies of the biology of tuberculosis, and from the history of successful tuberculosis control in industrialised countries, to assess the potential effect of DOTS in those developing countries where the disease is most prevalent"

- More specifically- assess impact of reaching WHO targets: 70% case detection and 85% treatment cure

Step 2: Define the setting/population

- Hypothetical population representing 6 different WHO regions
- Regions could be combined to provide Global totals
- Accounted for HIV

Step 3: Identify the outputs of interest

- incidence over time
- deaths over time

- Under different control strategies
- Under different epidemiologic scenarios
- In 6 different WHO regions

Step 4: Select modeling approach and start to develop model

- "SLT" (susceptible- latent-treatment) compartmental model
- Included infectious (smr+) and non-infectious (smr negative or extra-pulmonary) active cases
- Included rapid progression, reactivation and re-infection
- Included age structure

Step 4: Select modeling approach and start to develop model
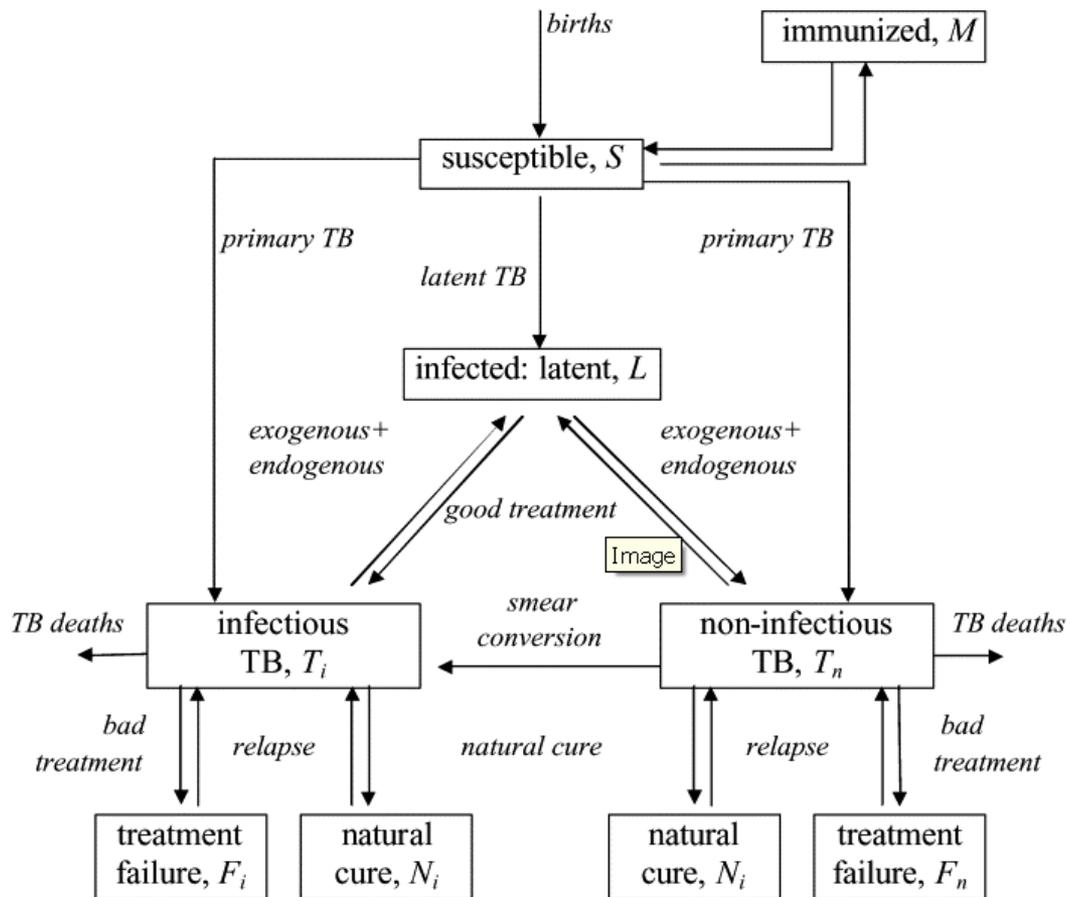
Step 5: Define comparators (baseline and alternatives)

- Baseline:
  - Old program (poor case detection rate, reduced treatment success)

- Alternatives:
  - Improved Case Detection: Maximum case detection rate 70-80%
  - Improved Tx Success: 85%
  - DOTS program: Maximize Case Detection+ treatment success

Step 6: Define key parameters (and ranges)/ assumed impact

Input data (1995 unless indicated)	WHO regions						
	Sub-Saharan Africa	Americas	Eastern Mediterranean	Western Europe	Eastern Europe	Southeast Asia	Western Pacific
Indicators							
Annual risk of infection (ARI %)	2·6	0·6	1·0	0·1	0·5	2·0	0·9
Incidence rates (new cases per 10^5 per year)							
All forms	215	62	102	13	61	188	94
Infectious cases	106	34	55	7	34	102	52
Ratio incidence rate infectious cases/ARI	40	63	57	86	65	49	58
Prevalence rate (infectious cases per 10^5 people)	201	55	101	8	55	184	83
Death rate (all forms per 10^5 people per year)	92	21	40	3	21	73	33
Change in annual risk of infection (% per year)	−0·3	−3·2	−2·9	−5·6	1·3	−0·9	−1·8
Change in incidence rate (% per year)	2·7	−2·5	−2·1	−5·0	1·1	−0·3	−1·2
Change in death rate (% per year)	2·9	−2·7	−2·2	−4·6	0·7	−0·7	−1·6
Change in contact rate (% per (year)	−0·7	−0·8	−1·0	−0·5	−0·9	−0·5	−0·6
HIV-1 infection in tuberculosis cases, 2020 (%)	21	2·5	0·2	0·5	0·5	4·0	1·4
Population growth (% per year)	2·8	1·4	2·7	0·4	0·4	1·7	1·1
Control variables							
Maximum case detection rate, new programme	70	70	70	80	70	70	70
Case detection rate, old programme	50	70	60	80	60	60	60
Relative case detection rate of non-infectious cases	0·5	0·7	0·6	0·8	0·7	0·6	0·7
Fraction cured							
New programme	85	85	85	85	85	85	85
Old programme	40	60	50	75	60	50	60

Step 7: Select input data/ enter key transitions

- Several tables of key parameters and transition parameters listed in Appendix

- Completed a comprehensive review of the published literature

- Some parameters (rates at which people develop primary, exogenous and endogenous disease) derived by fitting to observed data (from the Dutch population between 1951 and 1989)

- Current case-detection and cure rates for different WHO regions were based on published data (& other data available to WHO)

- Estimated rates of HIV from UNAIDS (plus unpublished data)

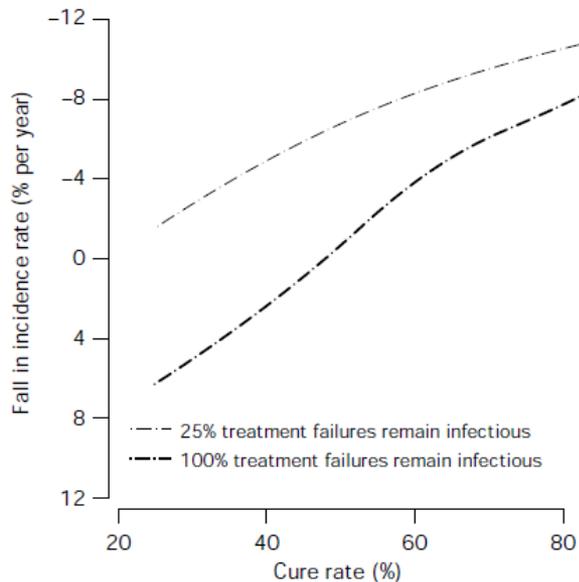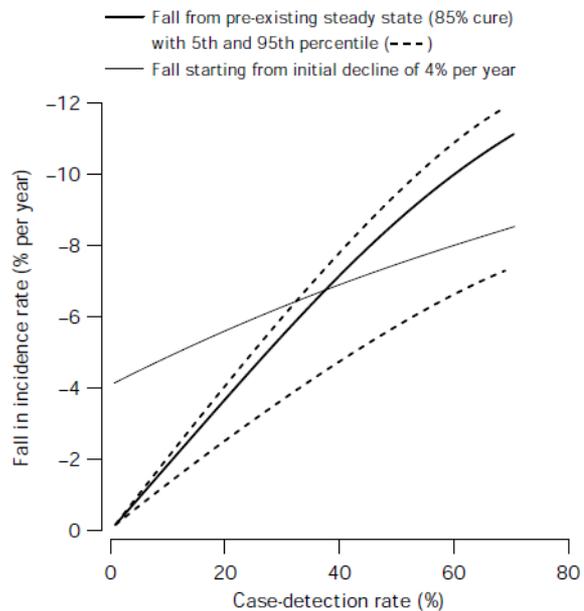- Population age structures and growth rates from United Nations Population Division

Step 8: Run the model!

Step 8: Re-run the model!

Step 9: Summarize outputs/results

Predicted:
- 11% decline in incidence rate
- 12% decline in death rate
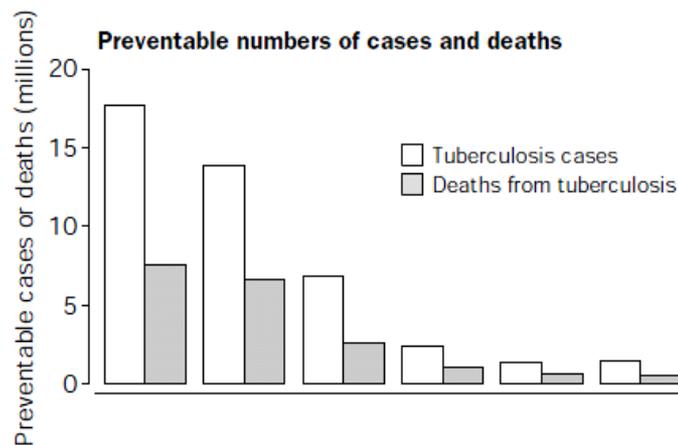
Step 10: Conduct sensitivity analysis

- Used sensitivity analysis to find out which parameters and variables need to be measured with greatest care

- Also to gain some general insights into TB control by DOTS

- All comparisons of absolute numbers were accompanied by multivariate sensitivity analyses, with the objective of singling out variables that most influence the results

- Use Probabilistic Sensitivity Analysis (PSA)- generated 100 sets of parameters selected from between ranges specified in inputs table

- Results of sensitivity analysis were used to attach uncertainty ranges to the main text

Step 11: Implications/policy recommendations

- Concluded that the potential effect of DOTS on TB in many developing countries is even greater than the results achieved in industrialized countries in the 1940s

- Improving case detection should be the focus in endemic areas

A note on impact: this study has been cited over 200 times on Scopus

Case Study 2- IGRA testing

Interferon-gamma release assays and TB screening in high-income countries: a cost-effectiveness analysis

O. Oxlade, K. Schwartzman, D. Menzies

Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, McGill University, Montreal, Canada

1. • Define the study objective
2. • Define the setting/population
3. • Identify outputs of interest
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5. • Define comparators (baseline and alternative interventions)
6. • Define key parameters (and ranges)/ assumed impact
7. • Select input data/ enter key transitions
8. • RUN (and re-run) MODEL
9. • Interpret and Summarize outputs/results
10. • Conduct sensitivity analysis
11. • Consider implications/policy recommendations

Step 1: Define the study objective

- To compare the cost-effectiveness of IFN-gamma release assays (specifically Quantiferon) and TST for TB screening in different high risk settings and populations in Canada

- Note: Cost effectiveness component not discussed in this session- will be covered this afternoon

Step 2: Define the setting/population

- Hypothetical cohorts of various high risk population (legal immigrants at entry to Canada, close or casual contacts)

- Entrants could be from 3 different countries with low, intermediate and high incidence of TB

- Entrants could have varying BCG vaccination status (no BCG, BCG at birth, BCG in childhood)

- No HIV

- Included drug resistance

Step 3:Identify the outputs of interest
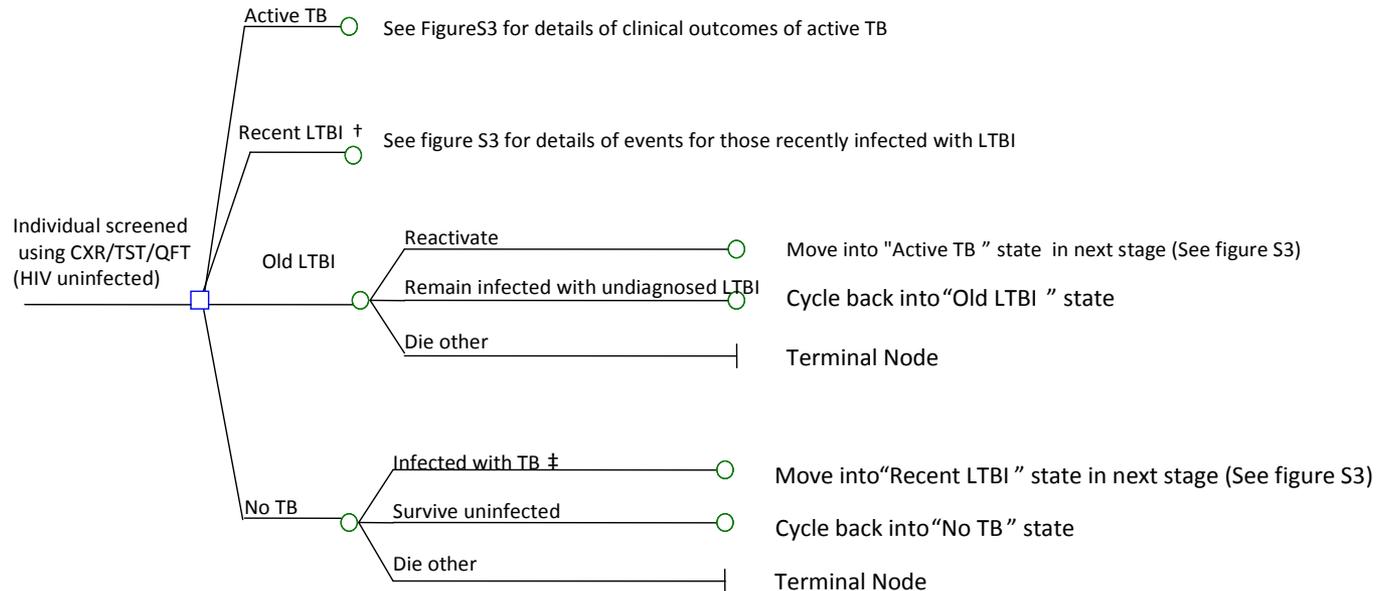
- Incident cases under each strategy
- (Total costs)

Step 4: Select modeling approach and start to develop model

- Decision Analysis (Treeage Software)
- At the beginning the population was divided into one of four underlying TB health states: non-infected, recent LTBI, long-standing LTBI and active TB disease
- No transmission from active cases
- No assumptions about secondary cases

Step 4: Developing the model

Figure S2: Simplified sample decision analysis tree for individual screened - based on underlying TB state in Year 1

Active TB — See FigureS3 for details of clinical outcomes of active TB

Recent LTBI † — See figure S3 for details of events for those recently infected with LTBI

Individual screened using CXR/TST/QFT (HIV uninfected)

Old LTBI
- Reactivate — Move into "Active TB" state in next stage (See figure S3)
- Remain infected with undiagnosed LTBI — Cycle back into "Old LTBI" state
- Die other — Terminal Node

No TB
- Infected with TB ‡ — Move into "Recent LTBI" state in next stage (See figure S3)
- Survive uninfected — Cycle back into "No TB" state
- Die other — Terminal Node

† Person can remain a maximum of 2 years in state of "recent LTBI", then moves to "old LTBI" state.

Depending on test strategy a proportion of active and latent cases would be detected in year 1 and given appropriate therapy- for those missed, model tracks outcomes over subsequent years

For an LTBI case that was missed...

Figure S3: Simplified decision analysis tree for legal immigrant, recently infected with LTBI
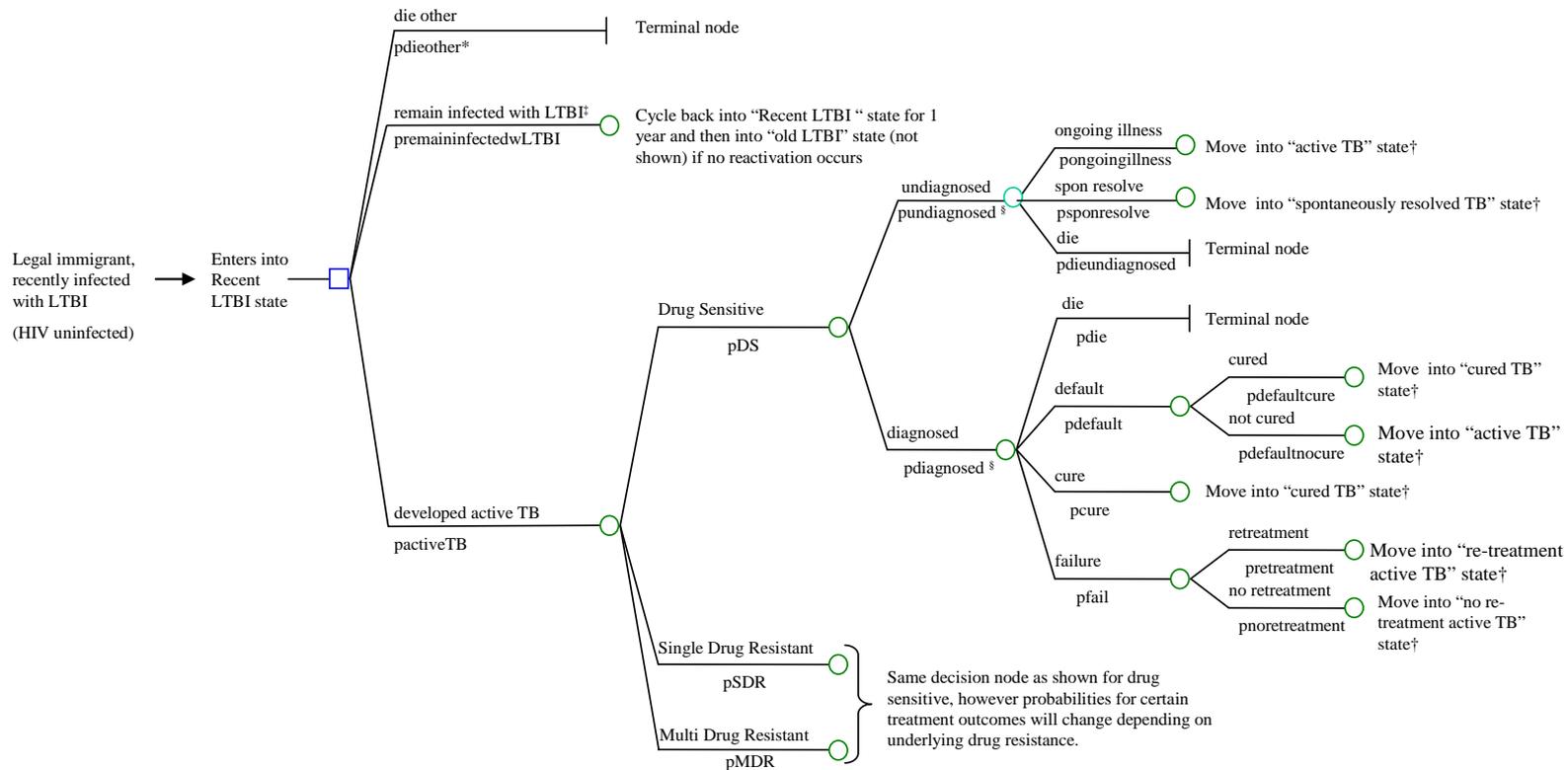
* the letter "p" refers to probability. For example pdieother = probability of dieing from other cause.

‡ decision node is stratified by underlying drug sensitivity in actual model

† states that are entered in subsequent cycles are not shown in figure

Step 5:Define comparators (baseline and alternatives)

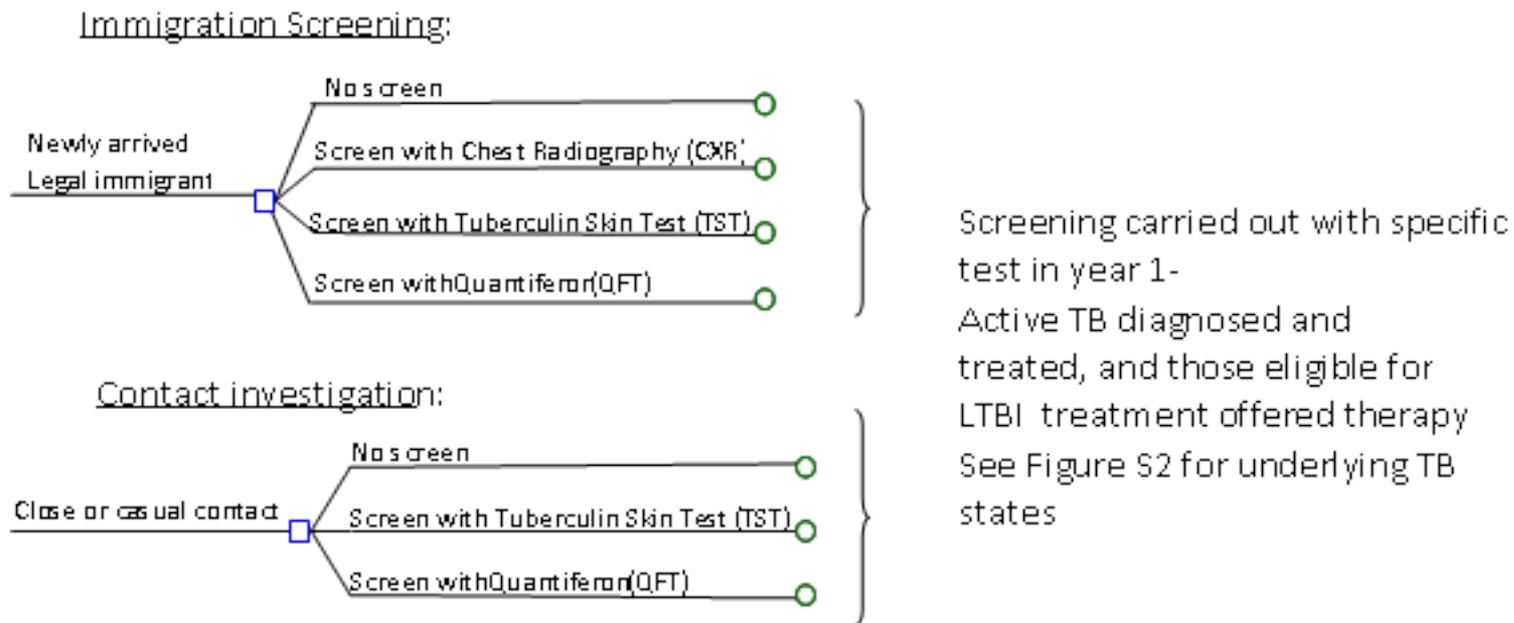- Considered 5 screening strategies for immigrants (no screen, CXR, TST, QFT or TST+QFT) and 3 screening strategies for contacts (no screen, TST or QFT)

- Baseline: No screen

- Alternatives:

  - Immigrants: CXR or TST or QFT or TST+QFT
  - Contacts: TST or QFT

Step 5:Define comparators (baseline and alternatives)

Figure S1: Immigration/ Contact Investigation Screening Scenarios in Year 1

<u>Immigration Screening</u>:

Newly arrived Legal immigrant
- No screen
- Screen with Chest Radiography (CXR)
- Screen with Tuberculin Skin Test (TST)
- Screen with Quantiferon (QFT)

Screening carried out with specific test in year 1-
Active TB diagnosed and treated, and those eligible for LTBI treatment offered therapy
See Figure S2 for underlying TB states

<u>Contact investigation</u>:

Close or casual contact
- No screen
- Screen with Tuberculin Skin Test (TST)
- Screen with Quantiferon (QFT)

Step 6: Define key parameters

Table 1 Modeling inputs and assumptions: characteristics of legal immigrants entering Canada

Hypothetical cohorts of entrants represented by populations from:	Low incidence	Intermediate incidence	High incidence	Reference
Number entering each year	1000	1000	1000	Assumption
Mean age, years	35	35	35	Assumption
Incidence of smear-positive TB/100 000*	2	60	120	[14]
ARI in country of origin	0.04%	1.2%	2.4%	From [14,15]
Prevalence of LTBI				
Legal immigrants entering Canada				
Recent (<2 years)	0.08%	1.6%	2.1%	Calculated
Long standing (2+ years)	1.3%	33.4%	55.9%	
Close contacts (probability of infection = 0.4)				
Recent (<2 years)	39.4%	26%	16.8%	[16–18]
Long standing (2+ years)	1.4%	35.0%	58.0%	[19,20]
Casual contacts (probability of infection = 0.08)				
Recent (<2 years)	7.9%	5.2%	3.4%	
Long standing (2+ years)	1.4%	35.0%	58.0%	
Prevalence of active TB				
Legal immigrants at entry	0.05%	0.2%	0.3%	[21–25]
Close contacts	3%	3%	3%	[25]
Casual contacts	0.6%	0.6%	0.6%	[19,20]
Prevalence of underlying MDR	1.0%	1.0%	1.0%	[26]
Prevalence of underlying INH resistance	10%	10%	10%	[26]

Selected test characteristics		Parameter	Reference
CXR			
Sensitivity	Detection of active TB	100%	Assumption
	Detection of LTBI	11%	[27]
TST			
Sensitivity	Detection of TB disease	82%	[28,29]
	Detection of infection	95%	[30–32]
Specificity	TB infection: not BCG-vaccinated	98%	From [33]
	BCG-vaccinated in infancy	92%	From [33]
	BCG-vaccinated in older childhood/adolescence	60%	From [33]
QFT			
Sensitivity	Detection of TB disease	82%	[34–40]
	Detection of infection	95%	Assumption
Specificity	TB infection: non-vaccinated	98%	
	BCG vaccinated in infancy	98%	For all 3: [34–40]
	BCG vaccinated in older childhood/adolescence		

Step 7: Select input data/ enter key transitions

- Main key inputs summarized in Table 1, additional pathogenetic inputs summarized in appendix

- Active TB treatment outcomes for actively detected case–Public Health Agency of Canada

- LTBI treatment outcomes and pathogenetic parameters-based on data from published cohort studies and randomized controlled trials

- Outcomes of undiagnosed active TB- as reported in the pre-antibiotic era (published literature)

- Average age-specific background mortality rates from Canadian life tables

Step 8: Run the model!

Step 8: Re run the model!

Step 9: Summarize outputs/results

Table 3 Summary of cost-effectiveness of screening strategies in three populations with three BCG vaccination states and in three clinical situations

Clinical situation	Population from country with TB incidence that is	BCG vaccination*	Preferred strategy‡	Cost per incremental case prevented‡ $CDN	Added costs or (savings) per person screened $CDN
				Costs relative to no screening	
Immigration entry screening§	Low	All¶	CXR	2 187 167	43.74
	Intermediate	All	CXR	30 680	15.34
	High	All	CXR	875	0.70
Close contacts‡	Low	None	TST	Savings	(340.84)
		Infancy	TST	Savings	(331.24)
		Older	QFT	Savings	(305.60)
	Intermediate	None	TST	Savings	(297.99)
		Infancy	TST	Savings	(290.68)
		Older	QFT	Savings	(262.20)
	High	None	TST	Savings	(256.35)
		Infancy	TST	Savings	(251.68)
		Older	QFT	Savings	(231.16)
Casual contacts‡	Low	None	TST	Savings	(53.09)
		Infancy	TST	Savings	(43.08)
		Older	QFT	Savings	(18.40)
	Intermediate	None	TST	5 540	11.08
		Infancy	TST	22 530	22.53
		Older	QFT	23 425	46.85
	High	None	TST	28 020	56.04
		Infancy	TST	31 800	63.60
		Older	QFT	45 915	91.03

Step 10: Conduct Sensitivity analysis

Considered parameters where there was felt to be the most uncertainty

- 1 way analysis- Varied key parameters
  - test sensitivity
  - risk of reactivation
  - program performance

- 2 way analysis- Test cost by test sensitivity

- Threshold analysis- Specificity of TST by difference in test cost

Step 11: Consider implications/policy recommendations

- QFT is more cost effective than TST in close/casual contacts who had BCG vaccination after infancy because of reduced TST specificity in this specific group

- All screening strategies would be more cost effective if a higher proportion of those with positive screening tests completed medical evaluation and LTBI therapy

Summary:

- Looked at how TB models have evolved over time
- Outlined some key contributions to the literature
- Use two case studies to illustrate steps involved in creating a modeling study