Key issues and challenges in modeling TB

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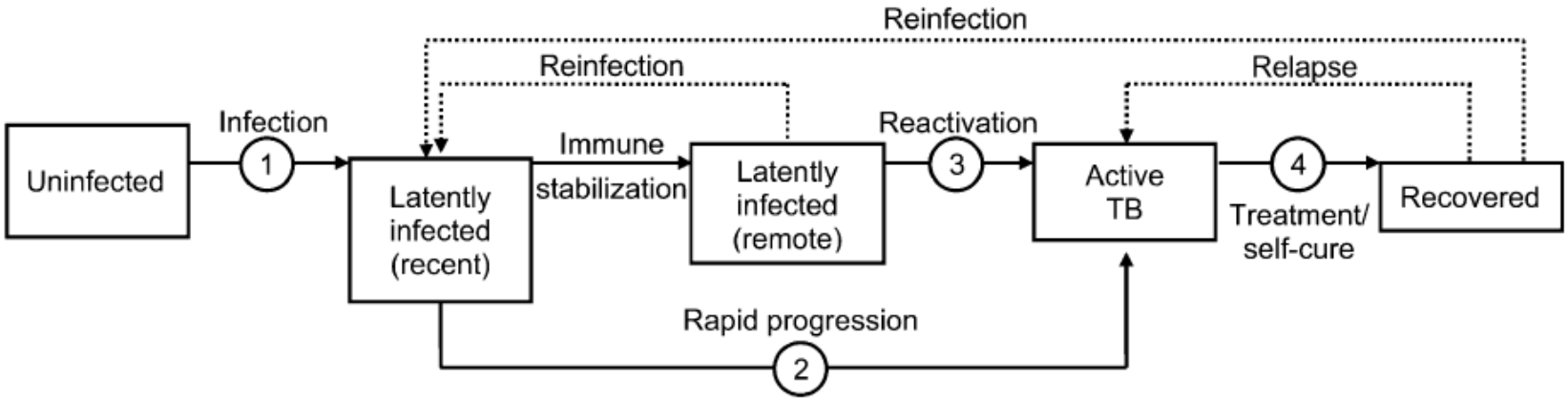

Figure 1 Simplified TB model: the basic structure that is common to many compartmental transmission models of TB. Health states are represented by boxes and transitions are indicated by arrows. We highlight assumptions necessary to estimate rates associated with four basic processes (in circles): infection, rapid progression, reactivation, and treatment/recovery. Mortality (not shown) also occurs from each box. TB = tuberculosis.

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REVIEW ARTICLE

Data needs for evidence-based decisions: a tuberculosis modeler's 'wish list'

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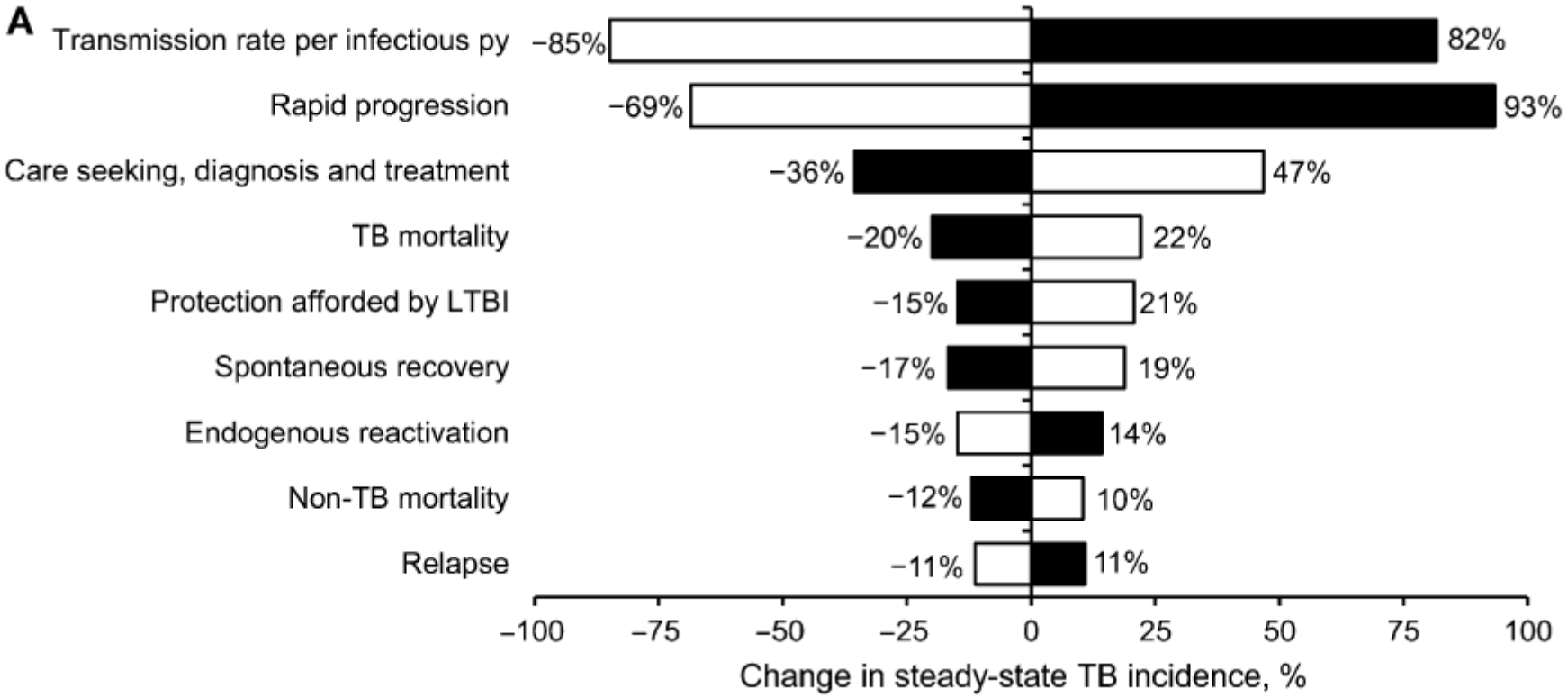
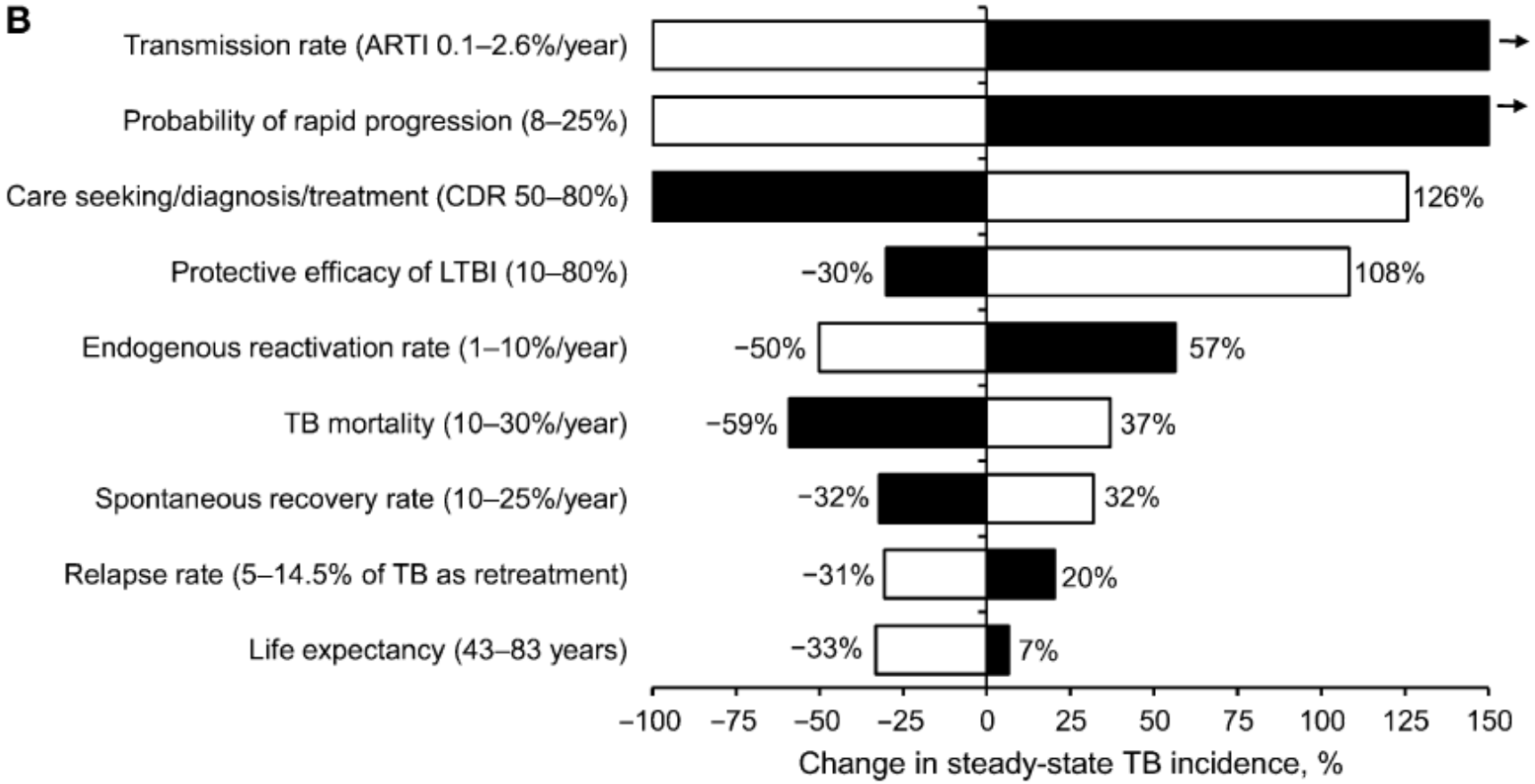
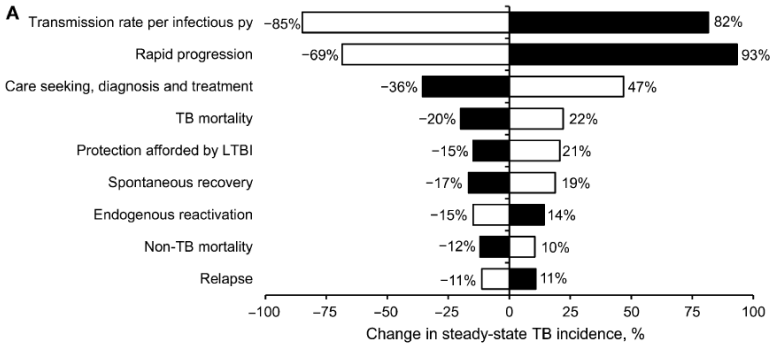
Sensitivity analysis



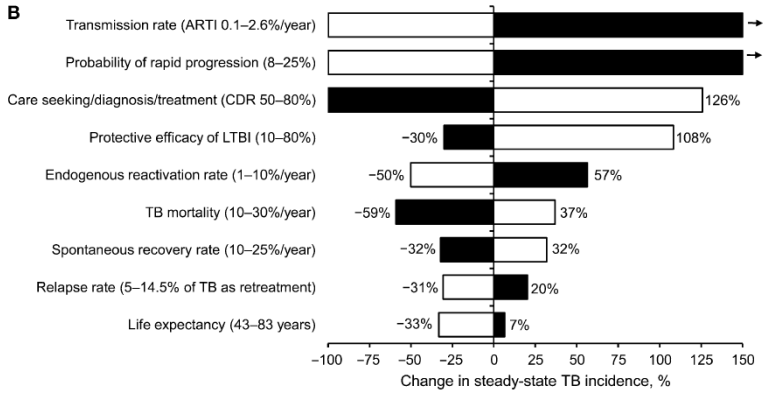
Uncertainty analysis



Sensitivity



Uncertainty



Additional key issues and challenges…and opportunties

- How do "determinants" affect TB at the individual- and population-level?

- How are interventions expected to work and what challenges may limit projected benefits?

Determinants

Who gets TB?

- Even in "high" incidence settings, only a small number of individuals get TB
  - Among those infected, only a minority progress to disease

- We can express the risk that an individual experiences as being dependent on:
  - Risk of exposure
  - Risk of infection after exposure
  - Risk of disease after infection

Individual-level determinants of TB

- There are well known "risk factors" for TB and a growing appreciation that addressing these determinants will be critical for control of TB

Major determinants	Relative risk
HIV	26.7 (20-35) [WHO 2009]
Undernutrition	3.2 (3.1-3.3) [Lonnroth 2010]
Diabetes	3.1 (2.3-4.3) [Jeon 2008]
Alcohol misuse	2.9 (1.9-4.6) [Lonnroth 2008]
Smoking	2.0 (1.6-2.5) [Lin 2007]
Indoor air pollution	1.4 (0.6-3.4) [Lin 2007]

How do these determinants modify the risk of TB for *individuals*?

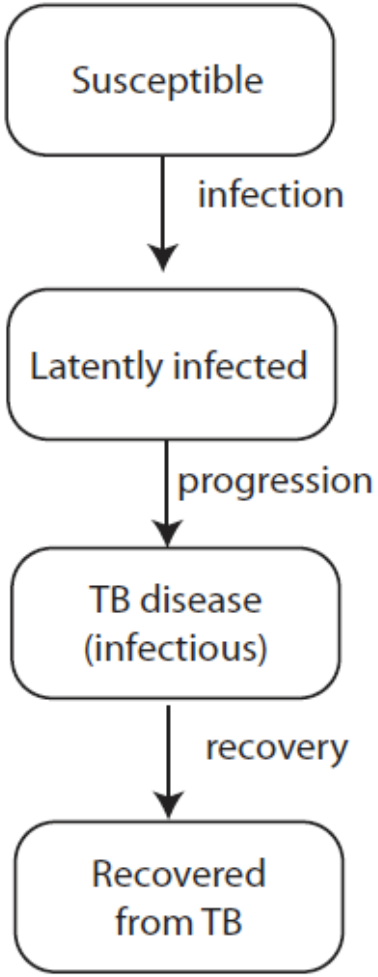
	Risk of exposure	Risk of infection after exposure	Risk of TB after infection
HIV			
Undernutrition			
Diabetes			
Alcohol misuse			
Smoking			
Indoor air pollution			

What are the appropriate study designs to link determinants with these risks?

What do these individual-level effects mean for *populations* at risk of TB?

- How does an changing frequency of a determinant effect the burden of TB in a community?
- What impact on TB can we expect by intervening on determinants?
- What tools to we have to begin to address such questions?

A simple TB model



Understanding the overall impact of TB determinants

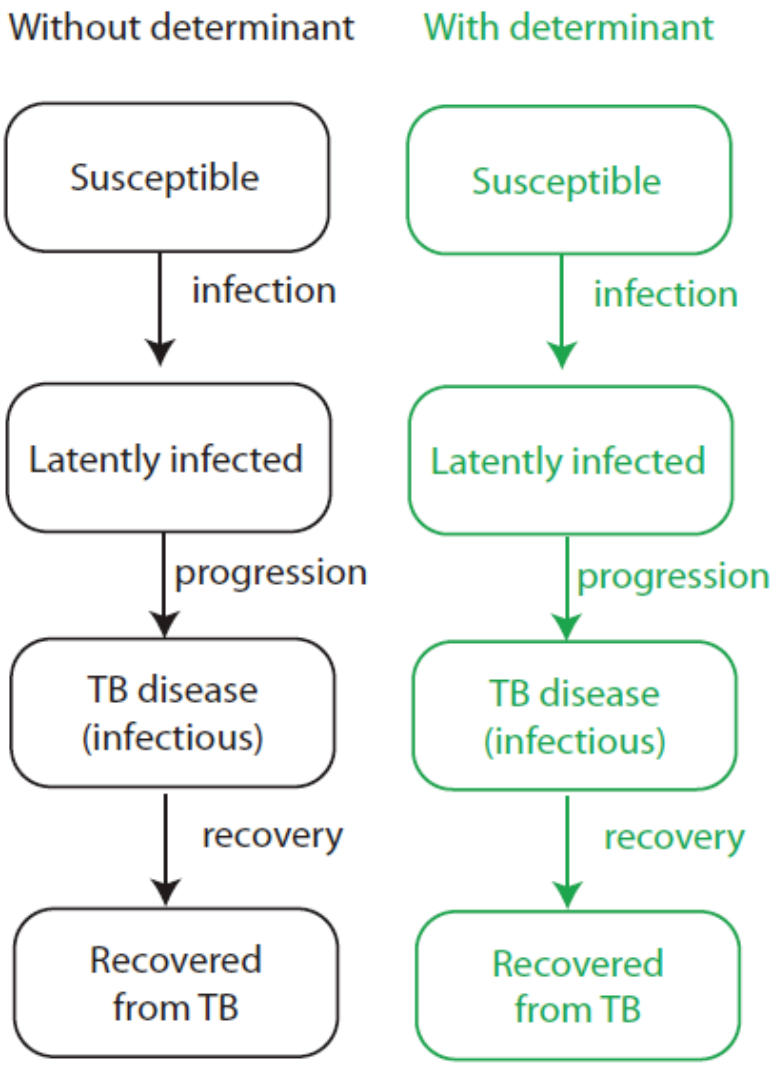
- Impact of determinants occurs at multiple scales
  - Individual-level effects
    - How does the determinant affect an individual's risk of exposure? Of infection? Of disease?
  - Population-level effects
    - How does the presence of the determinant affect the dynamics of disease in the community?
- There is interaction between these scales

Interaction between individual- and population-scales

- The impact of a determinant on the incidence of new infections in the community depends on:
  - Direct effect of the determinant
    - Prevalence of determinant
    - Degree and mechanism of risk conferred by the determinant
  - Indirect effect of the determinant:
    - How "infectious" individuals with the determinant are
    - Their duration of infectiousness
    - Their contact patterns
- The direct and indirect effects do not always work in the same direction

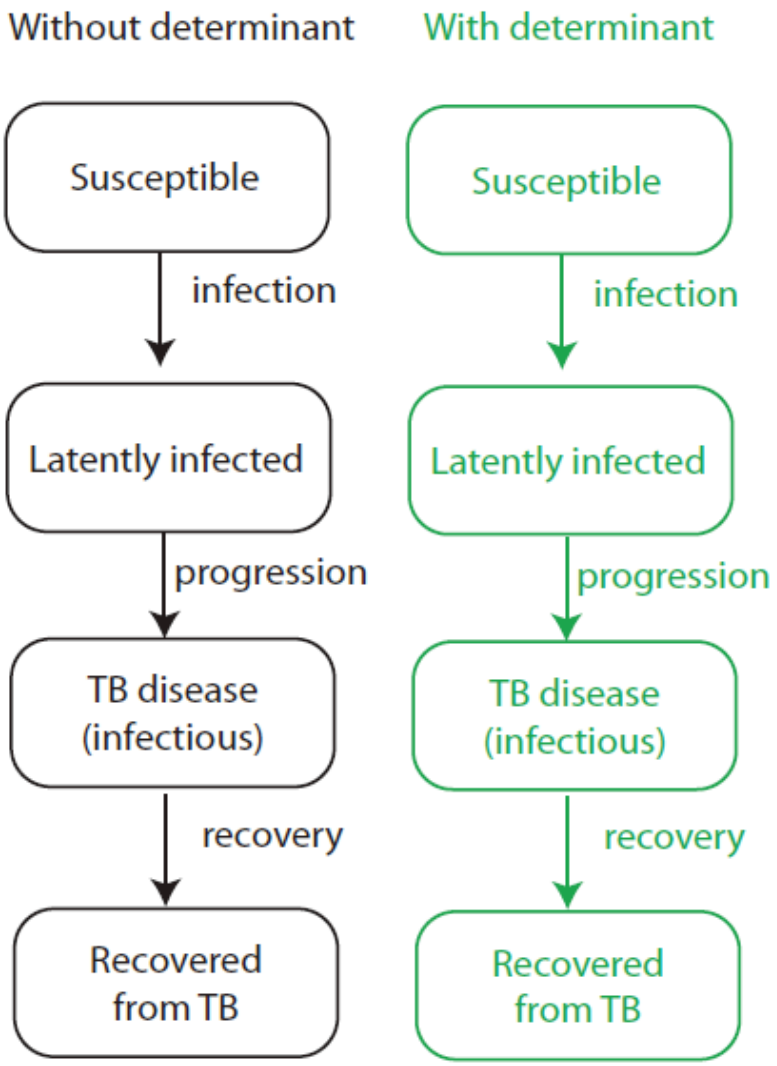
How might we encode this in a model?

- The direct effect of the determinant
  - Prevalence of determinant
  - Degree and mechanism of risk conferred by the determinant
- The indirect effect of the determinant:
  - How "infectious" they are
  - Their duration of infectiousness
  - Their contact patterns
- Overall effect?



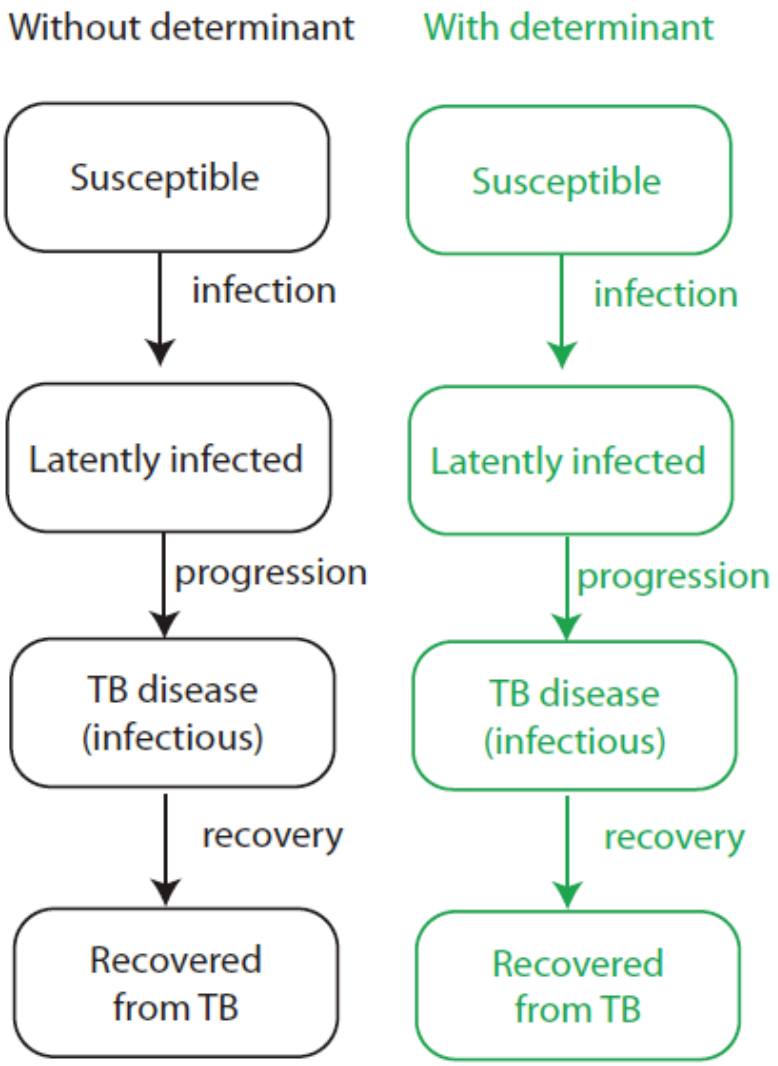
Smoking

- The direct effect of the determinant
  - Prevalence of determinant
  - Degree and mechanism of risk conferred by the determinant
- The indirect effect of the determinant:
  - How "infectious" they are
  - Their duration of infectiousness
  - Their contact patterns
- Overall effect?



HIV

- The direct effect of the determinant
  - Prevalence of determinant
  - Degree and mechanism of risk conferred by the determinant
- The indirect effect of the determinant:
  - How "infectious" they are
  - Their duration of infectiousness
  - Their contact patterns
- Overall effect?



HIV and infectious TB duration

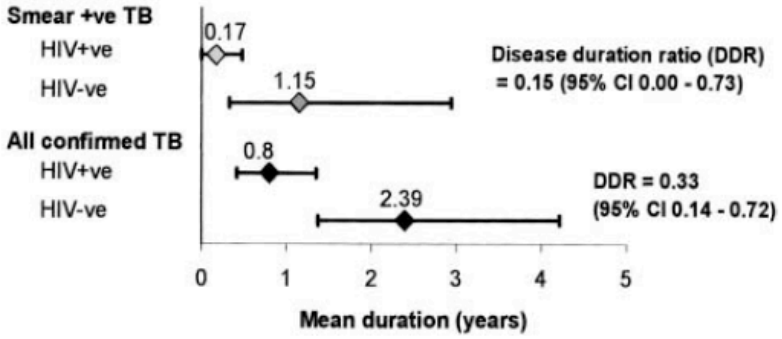


Figure 3. Mean TB disease duration before diagnosis by human immunodeficiency virus (HIV) and smear status. The *diamonds* indicate the duration before diagnosis, in years, of smear positivity (*gray*) and overall TB disease activity (*black*) in miners who were HIV-positive and HIV-negative; 95% confidence intervals are represented by the *horizontal lines*. The difference between patients who are HIV-positive and HIV-negative in estimated disease duration was significant for both smear-positive and all confirmed TB disease, as indicated by disease duration ratios (DDRs) that are significantly less than one for both comparisons.

Corbett et al AJRCCM 2004

TABLE 4. PREVALENCE PER 100,000 OF NOTIFIED, TREATED ADULT CASES WITH PULMONARY TUBERCULOSIS AND UNTREATED CASES WITH PULMONARY TUBERCULOSIS IN THE COMMUNITY, WITH ESTIMATED CASE-FINDING PROPORTION AND TIME IN YEARS BEFORE INITIATION OF TREATMENT

	Total Population HIV Positive (*95% CI*)	Total Population HIV Negative (*95% CI*)
Prevalence of treated PTB	2,508 (1,924–3,210)	464 (327–639)
Prevalence of total (treated and untreated) PTB	7,648 (6,623–8,777)	978 (774–1,219)
Case-finding proportion*	0.34 (0.26–0.46)	0.48 (0.32–0.70)
Estimated mean time (yr) of TB patients before treatment†	1.19	1.02

Definition of abbreviations: CI = confidence interval: PTB = pulmonary tuberculosis.

* Prevalence of treated PTB/prevalence of treated and untreated PTB.

† Mean time untreated = PTB prevalence/(PTB incidence + HIV mortality rate), where the HIV mortality rate is the excess mortality associated with HIV infection in individuals notified with PTB 2002–2004.

Wood et al AJRCCM 2007

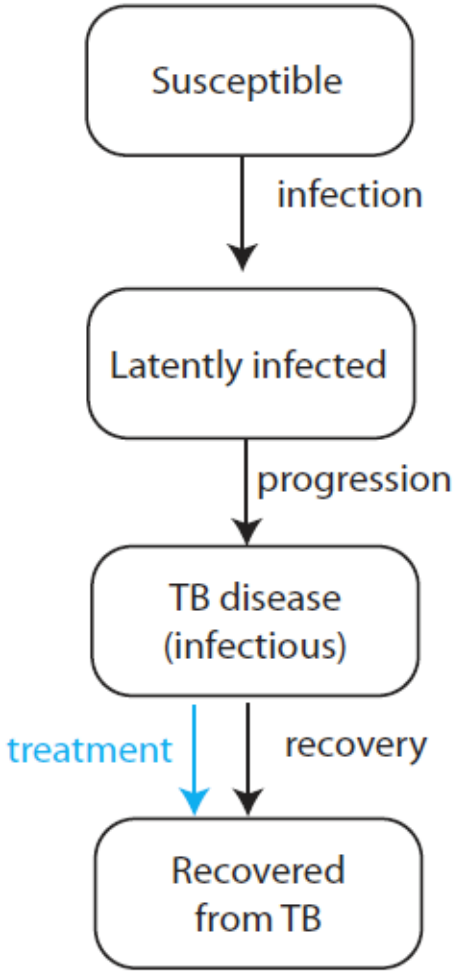
Interventions

Effects of interventions

- TB antibiotics
  - Treatment of disease
    - Drug resistance?
  - Treatment of infection (IPT)
    - Re-infection?
- New vaccines
    - Strain differences?
- New diagnostic tools
    - Diagnostic pathways/health systems considerations?

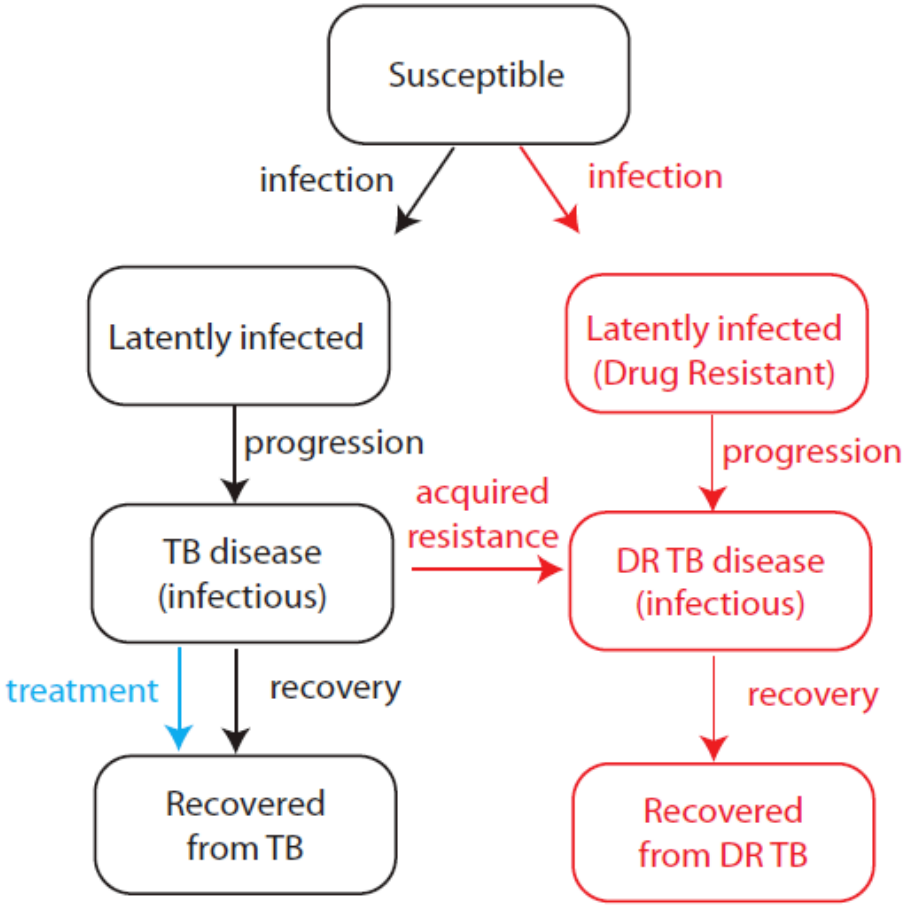
TB antibiotics

- What determines the direct effect for individuals receiving treatment for TB?
- What determines the indirect effect for the community?
- How might antibiotic resistance pose a threat?



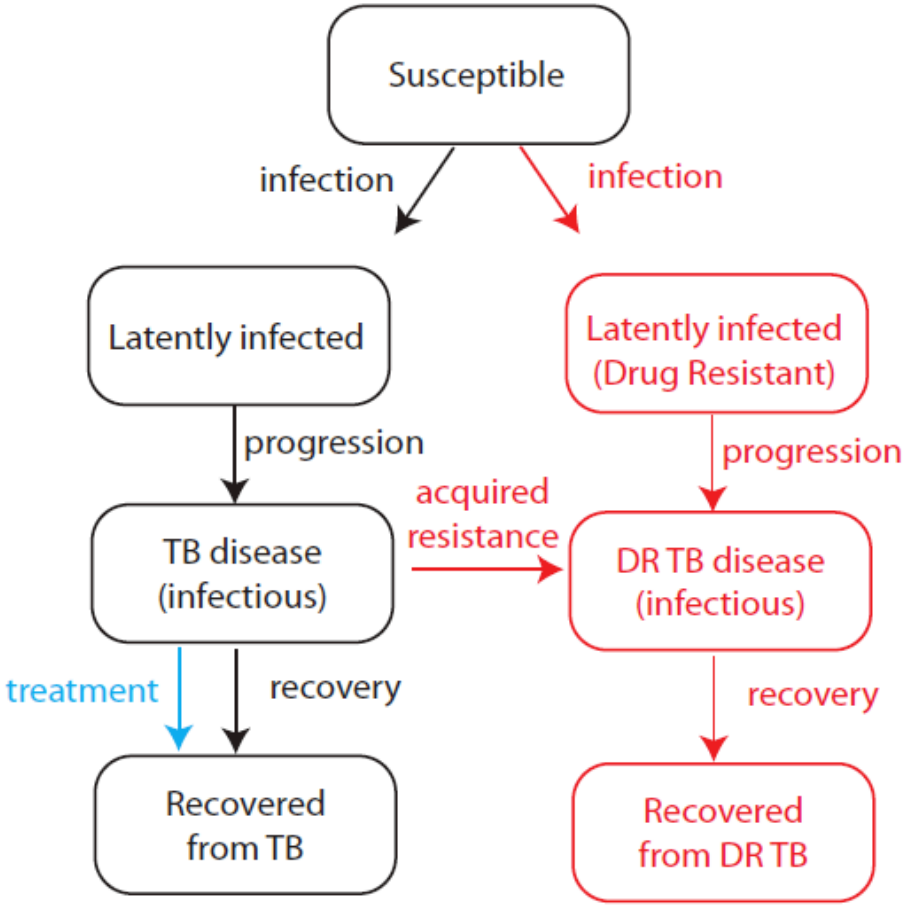
TB antibiotics: Drug-resistance

- Can a model help to clarify the questions must be answered to better understand the threat of antibiotic resistance for individuals and their communities?



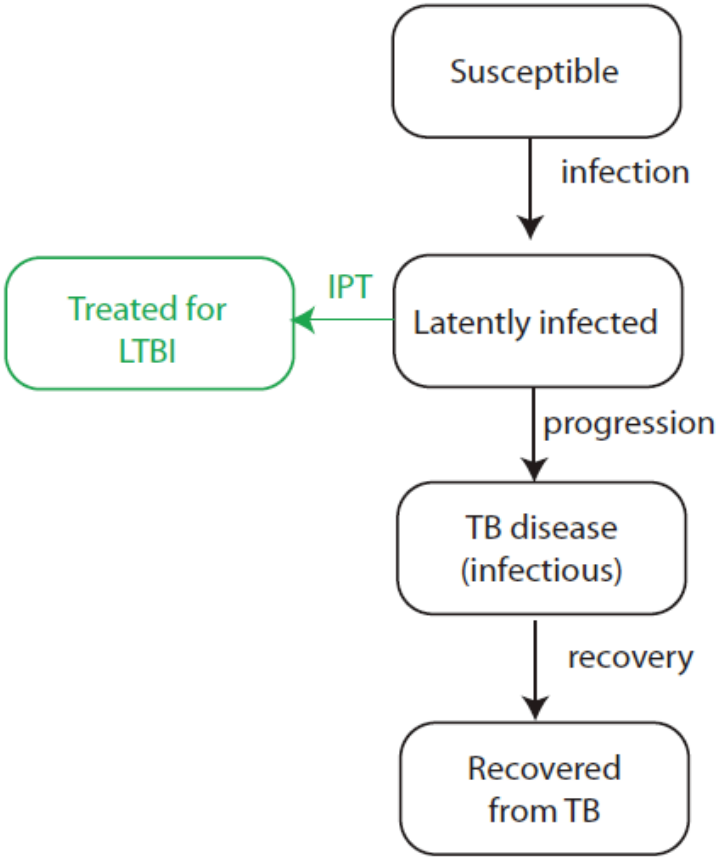
Drug-resistance: questions

- Risk of acquired resistance?
- Risk of transmitted resistance?
  - Relative transmissibility of resistant strains?
  - Relative duration of drug resistant and drug sensitive TB?



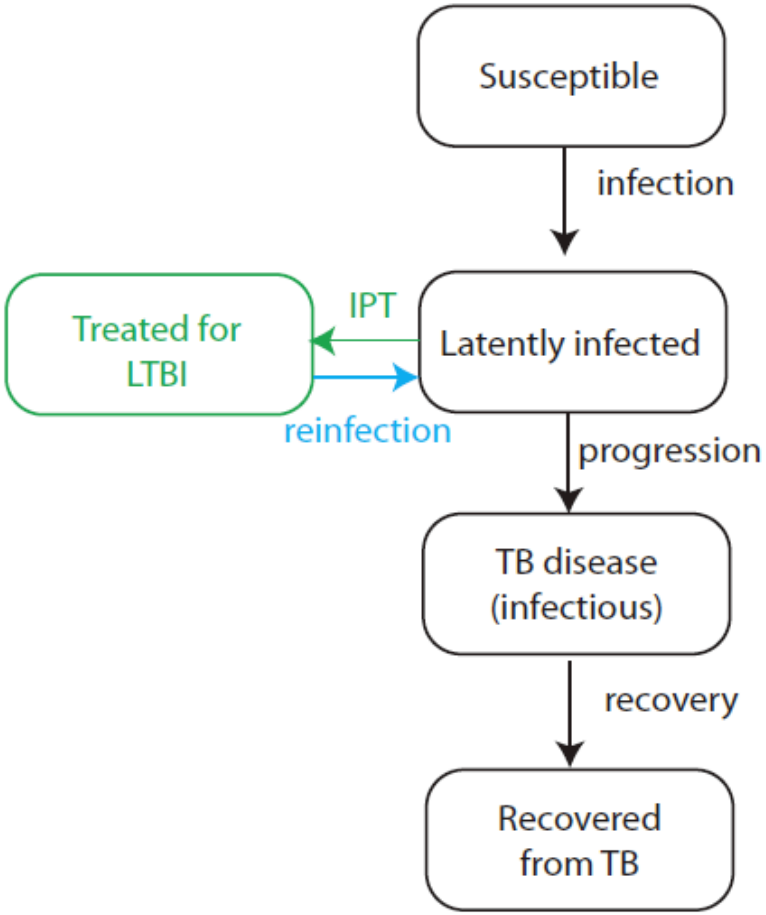
Preventive therapy

- What determines effect of isoniazid preventive therapy for individuals?
- What determines the indirect effect for the community?
- How might re-infection pose a threat to the success of IPT?



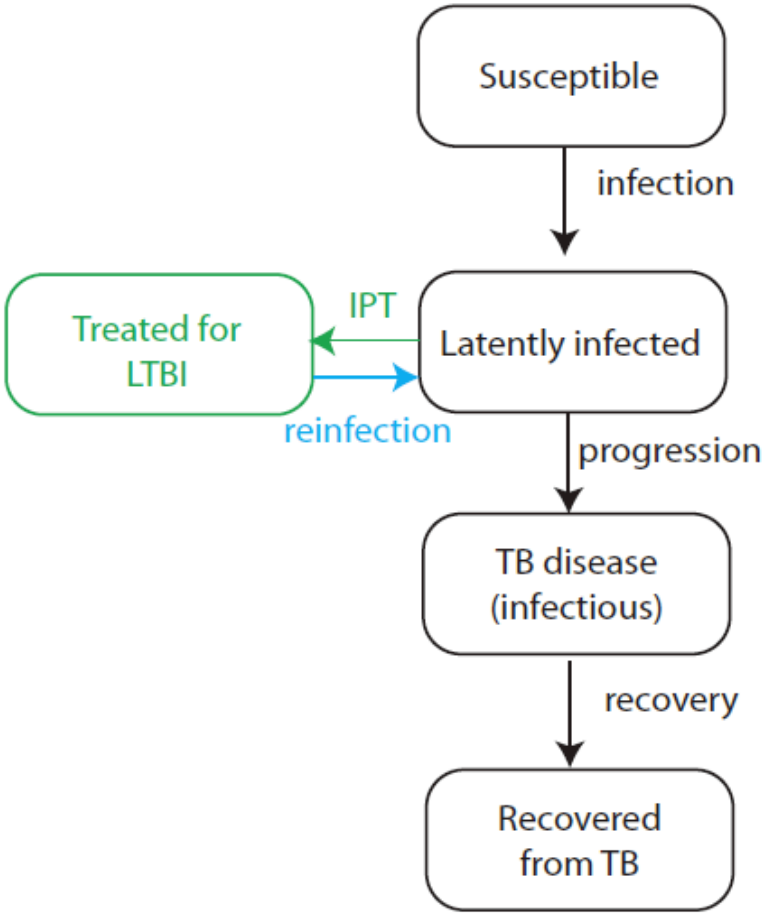
IPT: re-infection

- Can a model help to clarify the questions must be answered to better understand the threat of re-infection for the success of IPT?



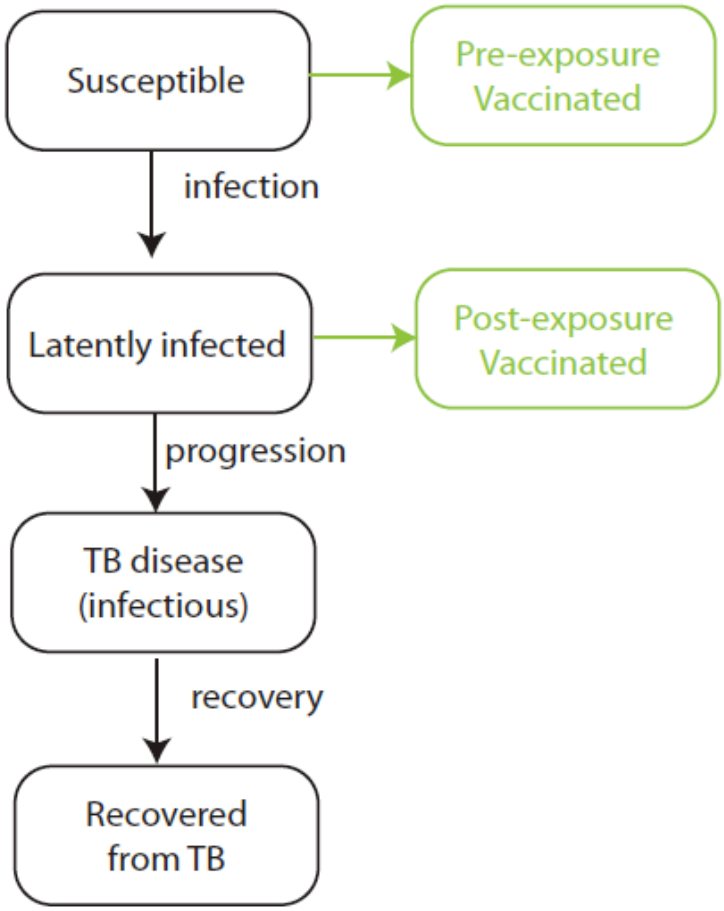
IPT/re-infection: questions

- What determines risk posed by re-infection?
  - Immunity?
  - Risk of exposure/re-exposure?
- Is everyone at equal risk of TB infection?
  - Are those who have previously been exposed more likely to be exposed again?
- Aside: How might you consider differential risk of exposure in a model?



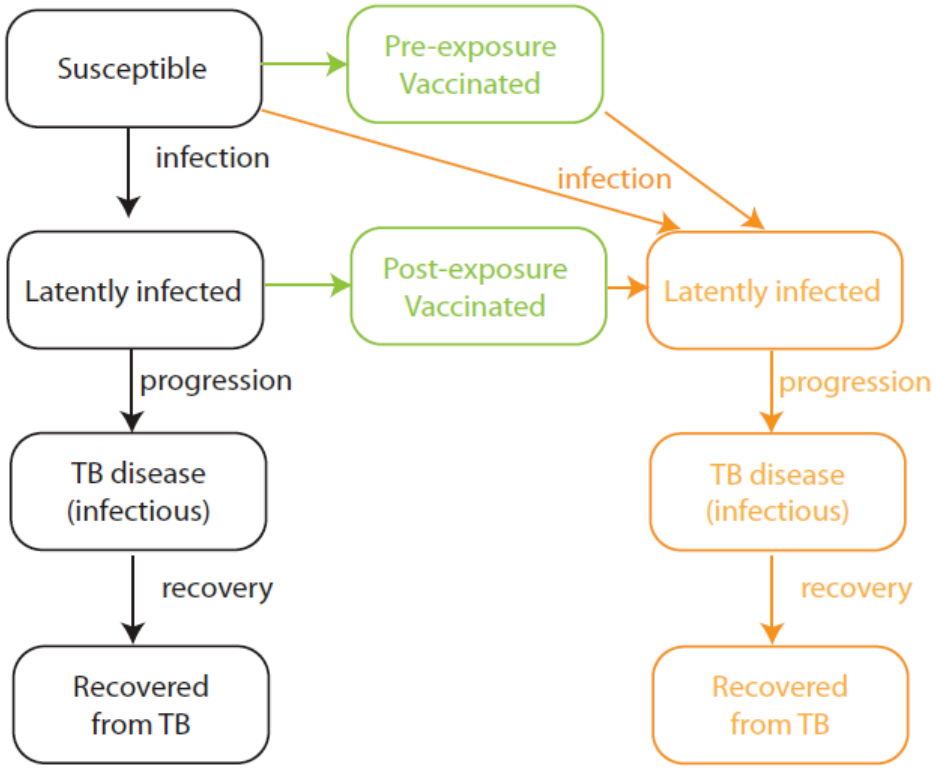
TB vaccines

- What determines the direct effect for individuals receiving TB vaccine?
- What determines the indirect effect for the community?
- How might strain heterogeneity pose a threat?



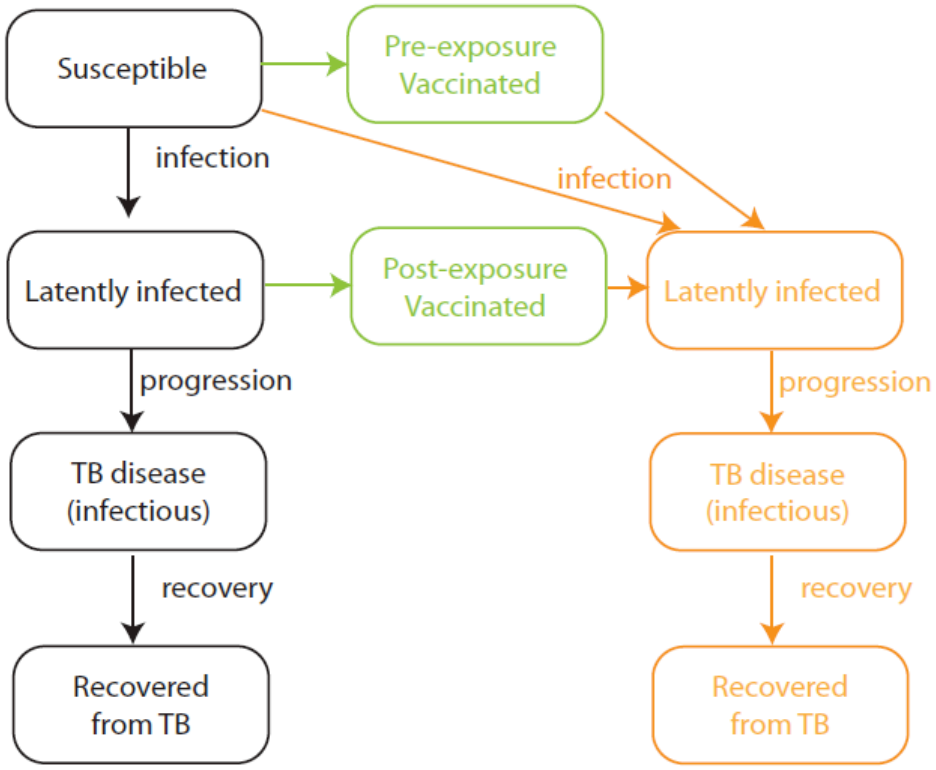
TB vaccines: strain heterogeneity

- Can a model help to clarify the questions must be answered to better understand the threat of strain heterogeneity for the success of new TB vaccines?



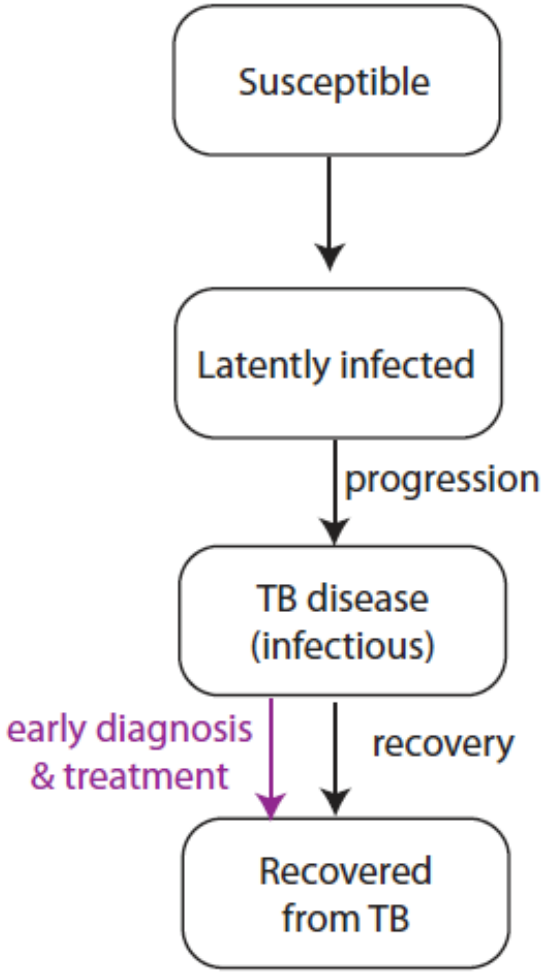
Vaccines/strain heterogeneity: questions

- Are vaccines strain-specific?
- Differences between strains:
  - Transmissibility?
  - Progression rates?
  - Stimulation of immune response?
  - Association with drug resistance?
- Possibility for post-vaccine strain replacement?



TB diagnostic tools

- What determines the direct effect for individuals receiving early diagnosis?
- What determines the indirect effect for the community?
- Does this look like another intervention we've modeled?
- How are more sensitive diagnostics different than better treatment regimens?
  - How to account for health systems effects in models?



Summary

- Determinants affect individual risk of TB through multiple mechanisms; these manner in which individual risks translate into population effects may be complicated
- Interventions against TB target different steps in the pathway to disease; obstacles to these interventions are diverse
- Models can be helpful if they can help us to
  - Simplify the complexity
  - Identify critical unanswered questions
  - Communicate our (internal) models
  - Make projections