

Why do we model infectious diseases?

Policy and practicalities

Chennai, 25/11/15

1. Aims

Aims

- To introduce
 - Concepts of modelling for public health
 - Practical steps in the formulation of a model
 - How to include interventions within a modelling framework
- Using the example of the complexity of TB natural history

Why do we model infectious diseases?

You?

- 1) Interesting
- 2) Understand natural history or epidemiology
 - 1) Outbreak scenario
 - 2) Endemic scenario
- 3) Relative impact of interventions
 - What would happen if we changed current behaviour?
- 4) Predict future

How do we know what to model?

$$\sqrt{16 \cdot x}$$
$$I = \frac{(x+10)^2}{50\pi} = \cancel{\frac{20x}{\pi}}$$
$$\sum_N$$
$$\alpha^2 C_1^3 \quad \pi = 3.14$$
$$(y+A) = \frac{2}{3}A$$
$$m+n \quad E=mc^2 \quad \text{grad } \phi(x,y) M = \sqrt{\frac{3 \cdot 6 \cdot 10^3}{3 \cdot 18 \cdot 10^6}}$$
$$\nabla \phi(x,y,z) = \frac{\partial \phi}{\partial x} i + \frac{\partial \phi}{\partial y} j$$
$$\int \sqrt{a^2 - x^2} dx = \frac{x}{2} \sqrt{a^2 - x^2} + \frac{a^2}{2} \sin^{-1} \frac{x}{a} + C$$
$$46 < X$$
$$c = \pi r^2$$
$$ax + bx + c = 0$$
$$\Delta = b^2 - 4ac$$
$$Y = u \nu$$
$$a \neq 0 \quad f(x) = a(x^2 + \frac{b}{a}x + \frac{c}{a}) \quad \{a \in b\}$$

How do we know what to model?



Campfire effect



2. Interventions

Modelling interventions

- Why?
 - Policymaker needs result for trial / intervention design
 - Estimate population impact of intervention (over time) in different populations
 - Input for costing models
 - Understand most influential aspects of the intervention(s)
 - Speed of roll-out, population targeted, etc
 - Inform estimates of cost-effectiveness, affordability
- Models need a “hook”
→ Support policy decisions, research funding, trial design, product pipeline...

Why is modelling good for assessing interventions?

- Models are flexible
 - Evaluate single or combination of interventions
 - Evaluate alternative roll-out strategies
 - Extrapolate to different epidemiological situations or populations (incidence, existing diagnostic pathway)
- Models capture mechanics of intervention, and can project into future
- Modelling studies are (relatively) cheap and fast

Be aware...

- Like any scientific tool, apply rigour in design, analysis and reporting
 - Use best
 - available empirical data
 - understanding of disease
 - Understanding of intervention processes
 - Capture and clearly present uncertainty
 - Similar to need for 95% confidence interval in statistical analyses
 - Acknowledge that uncertainty increases rapidly when projecting into future
- Designing a good (intervention) model requires a lot of thought!

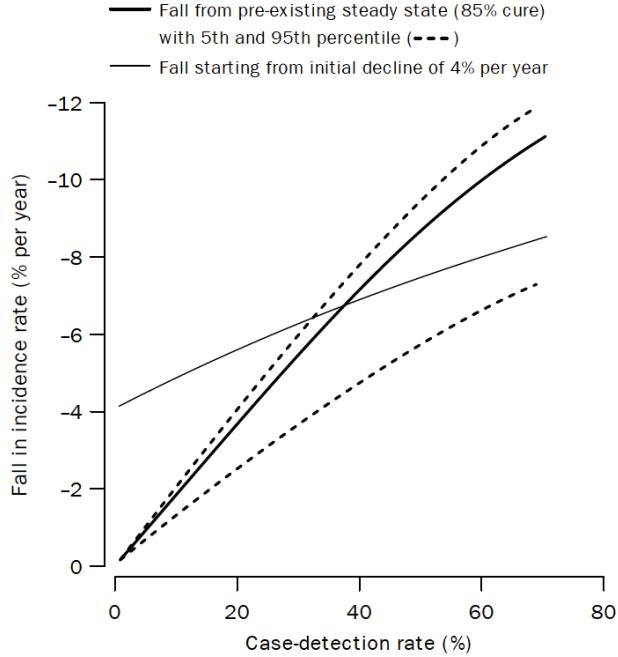


(with thanks to Rein Houben)

3. Impact of models

Examples of impact

- TB global impact of DOTS
 - Dye 1998
- TB vaccine targetting
 - Knight 2014
- Ebola
 - Situation reports CMMID
- HIV control
 - Granich 2009



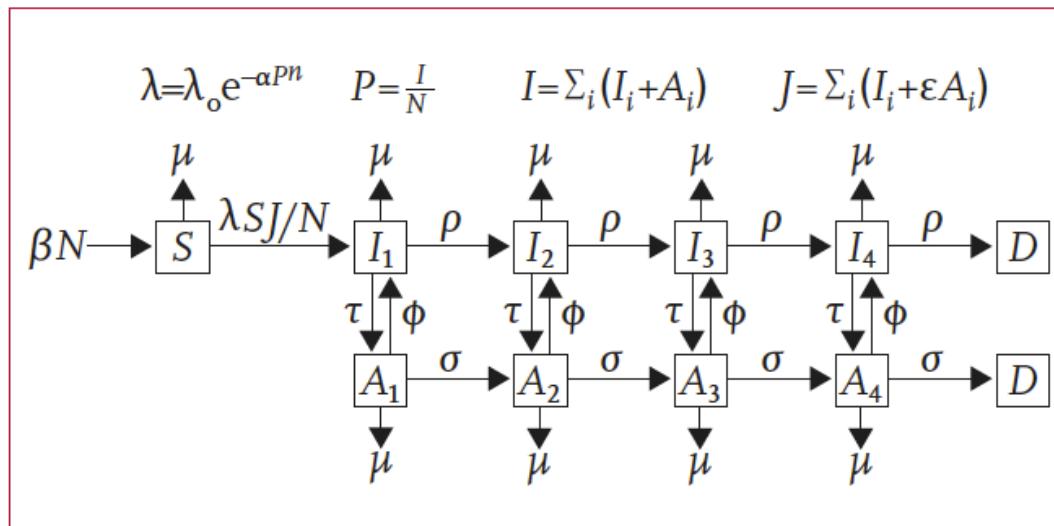
“... We can reverse this trend. Mathematical models show that scaling up combination prevention to realistic levels in high-prevalence countries would drive down the worldwide rate of new infections by at least 40-60%....”

**US Secretary of State,
Nov 8, 2011**

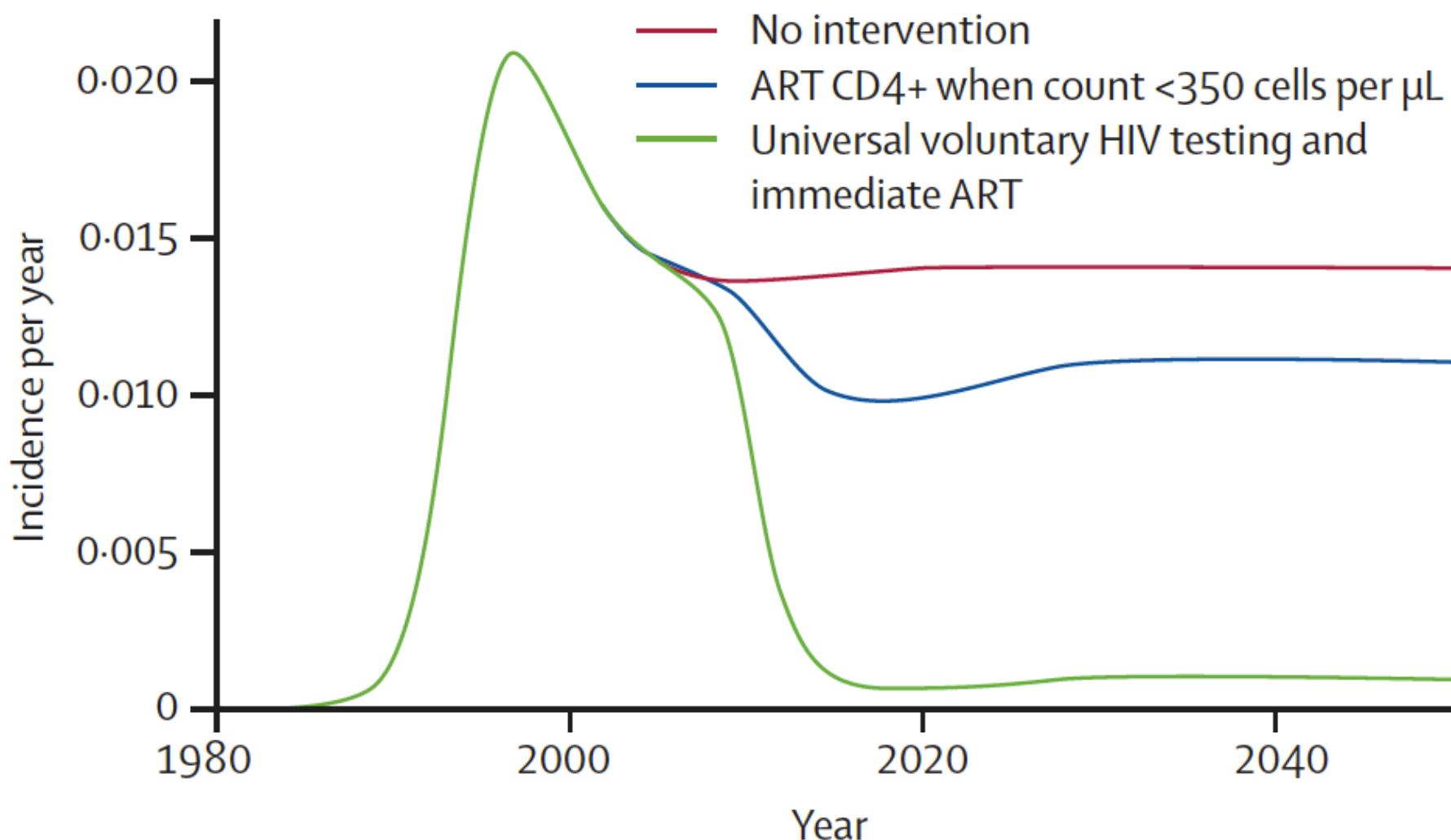
HIV control

Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model

Reuben M Granich, Charles F Gilks, Christopher Dye, Kevin M De Cock, Brian G Williams



A HIV



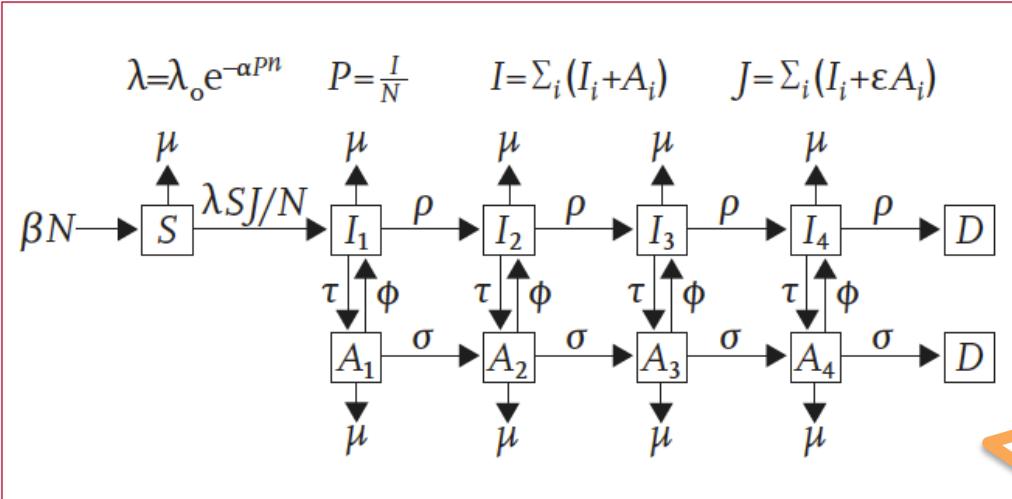


Figure 2: Transmission model for HIV infection and antiretroviral therapy (ART) provision

N represents population aged 15 years and above. People enter into the susceptible class (S) at a rate βN , become infected at a rate $\lambda SJ/N$, progress through four stages of HIV ($I_i, i=1-4$) at a rate μ between each stage, and then die (D). The background mortality rate is μ and people are tested at a rate τ . If they are tested and put onto ART, they move to the corresponding ART box A_i ($i=1-4$), where they progress through four stages at a rate μ and then die. The term governing transmission contains the factor $J \alpha (I_i + \varepsilon A_i)$ where ε allows for the fact that people receiving ART are less infectious than those who are not. They might also stop treatment or the treatment might become ineffective, in which case they return to the corresponding non-ART state at a rate μ . To allow for heterogeneity in sexual behaviour and for the observed steady state prevalence of HIV, we let the transmission decrease with the prevalence, P . If $n=1$, the decrease is exponential; if $n=\infty$, the decrease is a step function. Both have been used in previous models.^{5,29}



Assumed all HIV transmission was heterosexual...

4. Practical steps to model building

Practical steps to a model

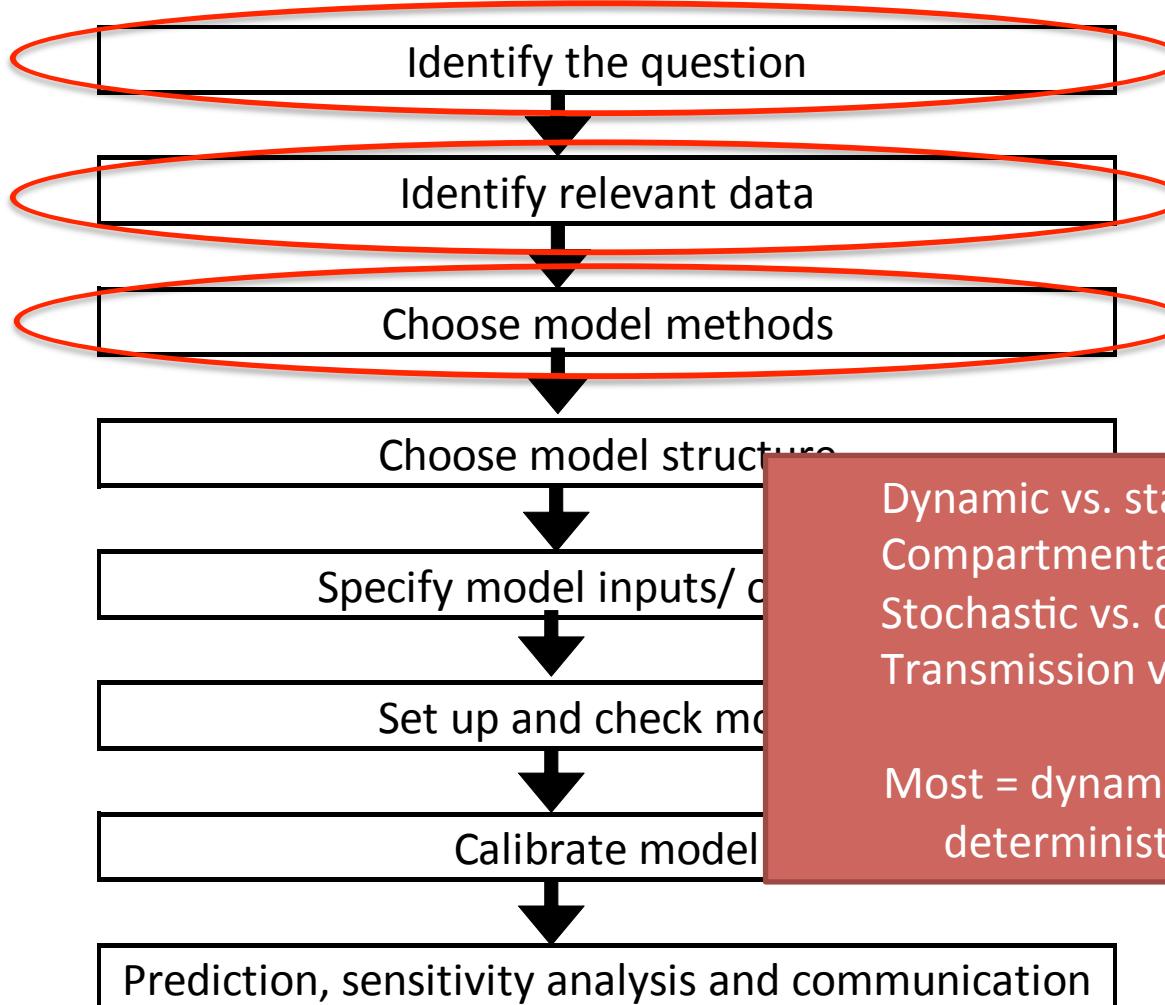
Useful?

Modelling appropriate?

Relevant? for public health?



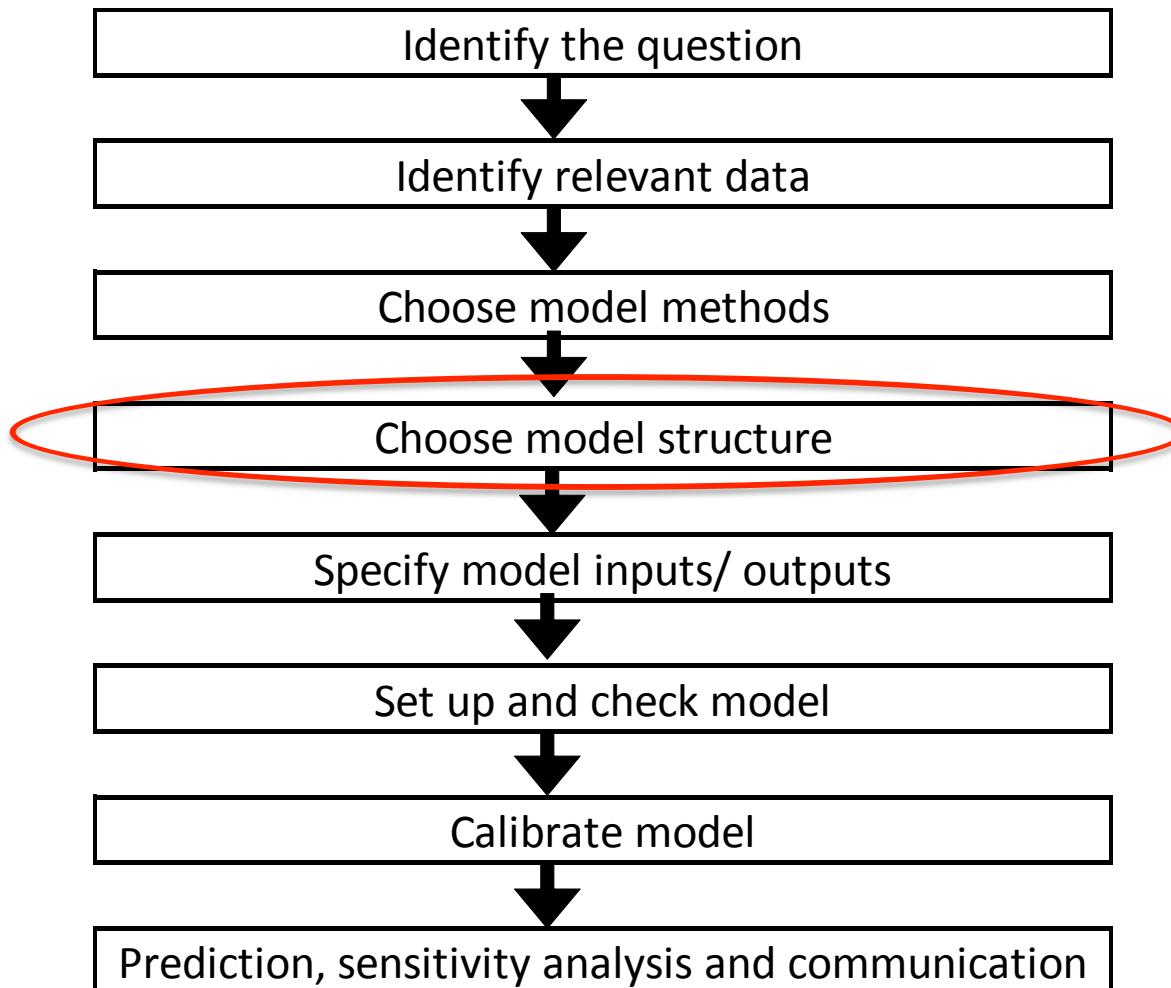
Literature /
WHO / CDC /
Country level
contacts /
Expert opinion



Dynamic vs. static?
Compartmental or individual?
Stochastic vs. deterministic?
Transmission vs. cohort?

Most = dynamic, compartmental,
deterministic, transmission

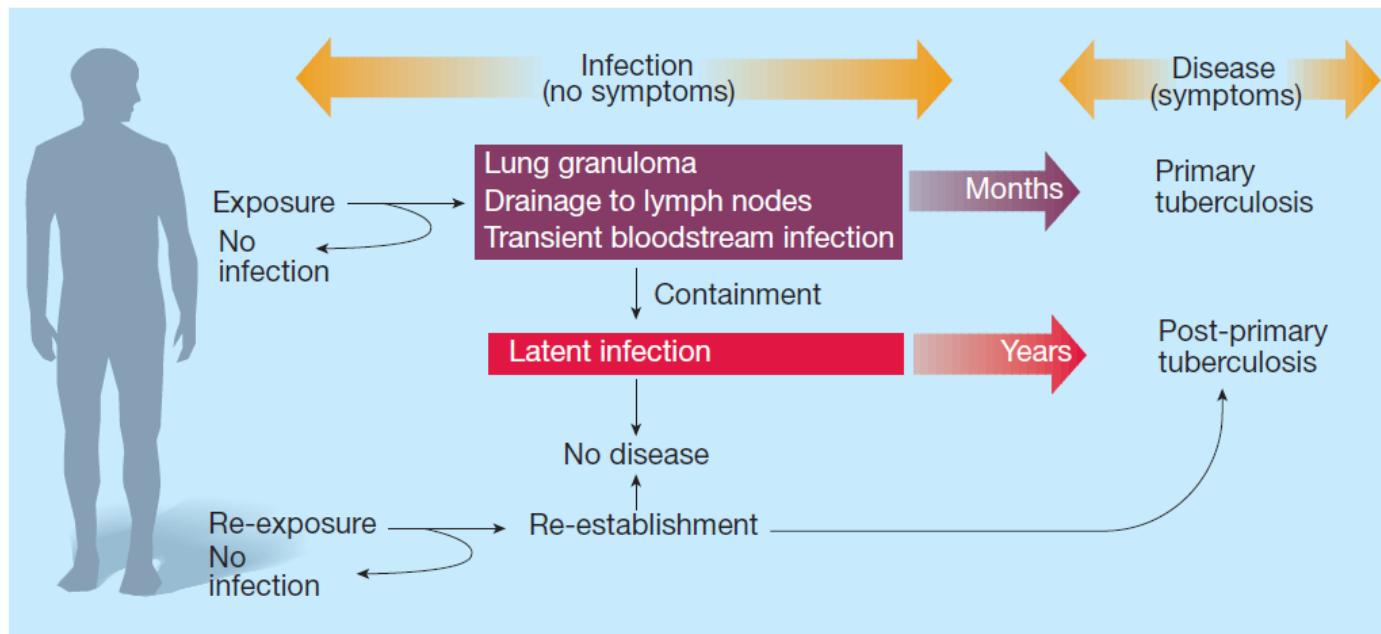
Practical steps to a model



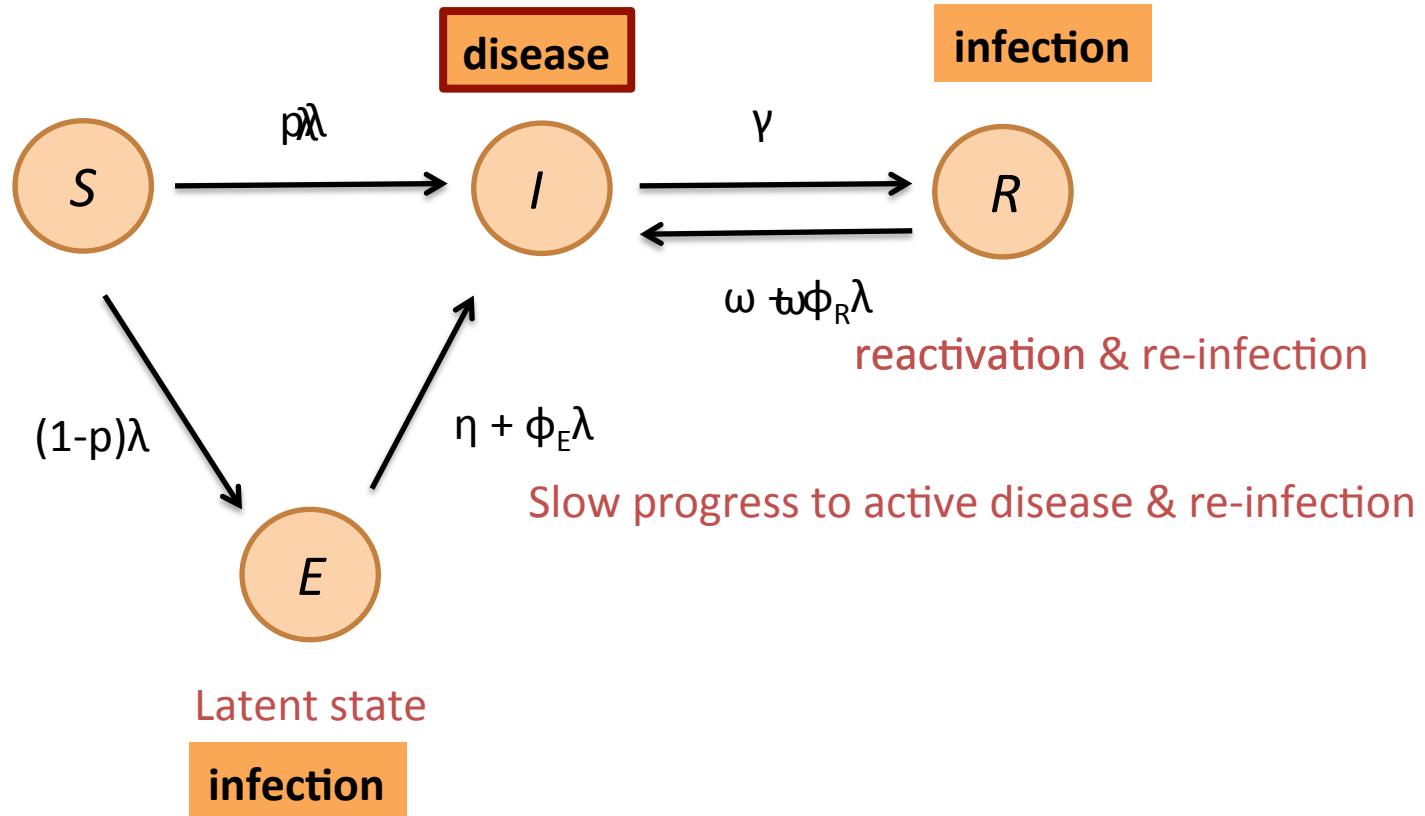
Examples

'models should be as simple as possible and no simpler'
Einstein(?)

- Ebola – new field, Seb & Anton
- HIV – mixing patterns?
- TB – complex natural history and transmission



From an SIR to a TB model



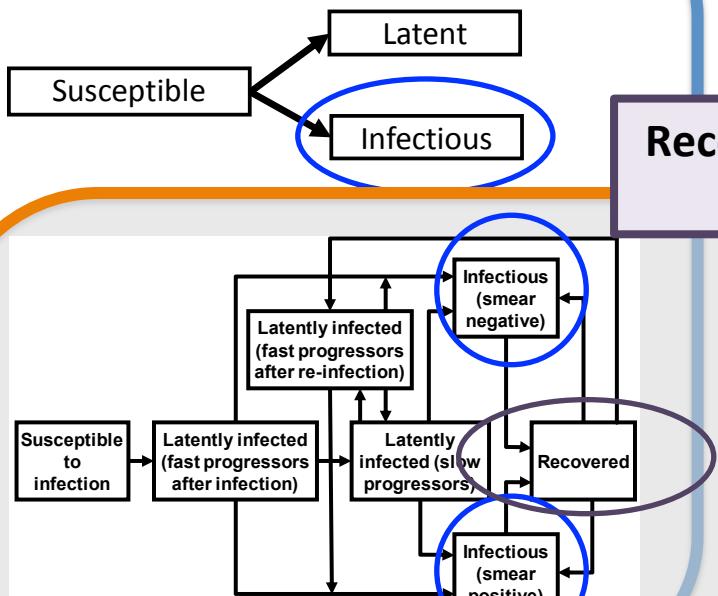
w = reactivation from recovered disease

φ_x = protection from infection to active disease by state x

p = proportion of infections that progress immediately to infectious disease

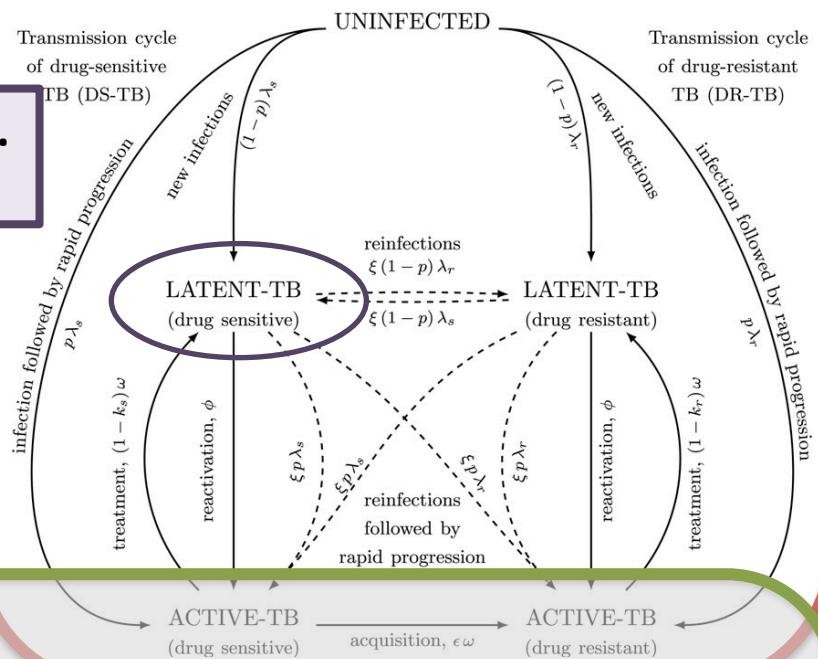
η = slow rate to active disease activation

Disease vs. infection

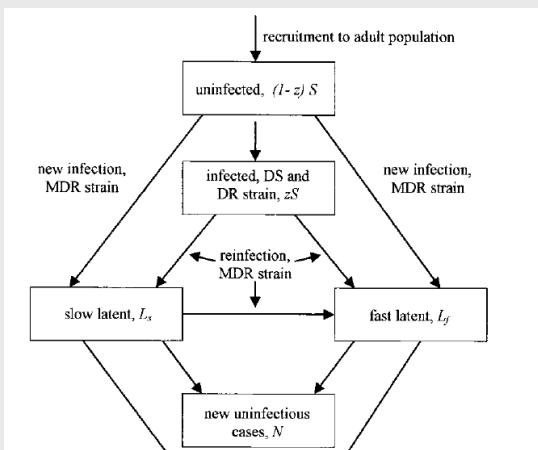


Recovered vs. latent

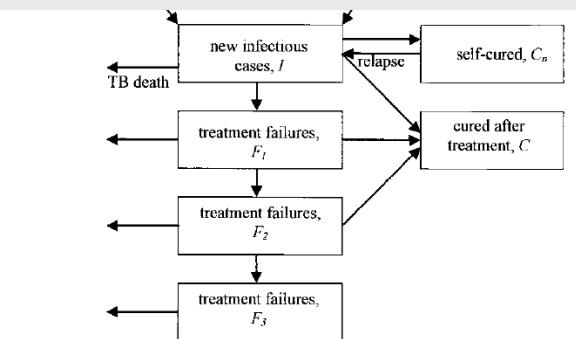
Reinfection

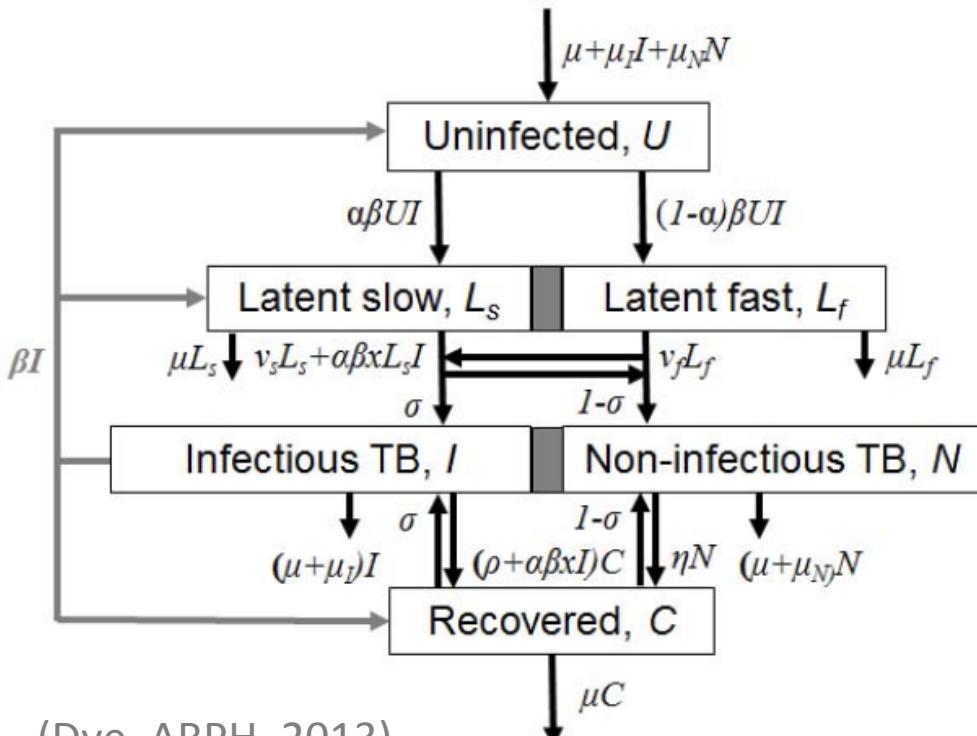


Risk of disease by time since infection

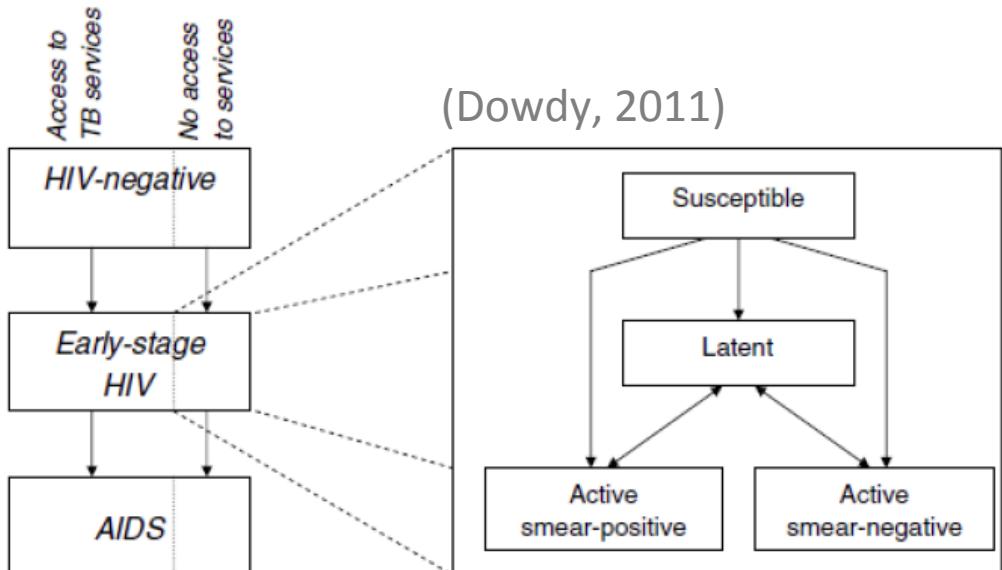


Detection & treatment

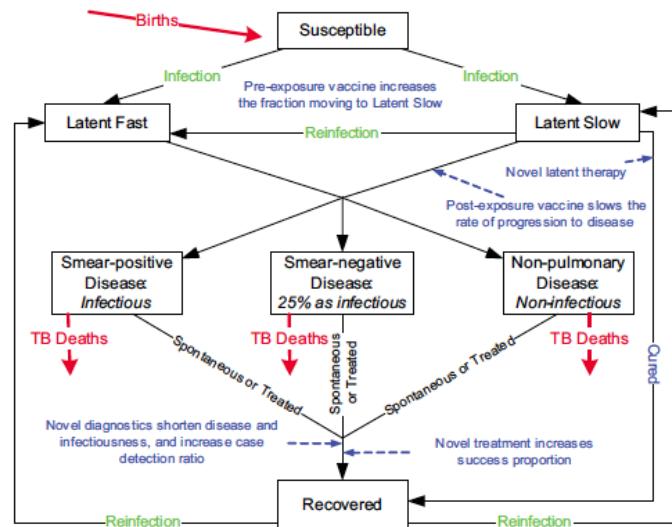




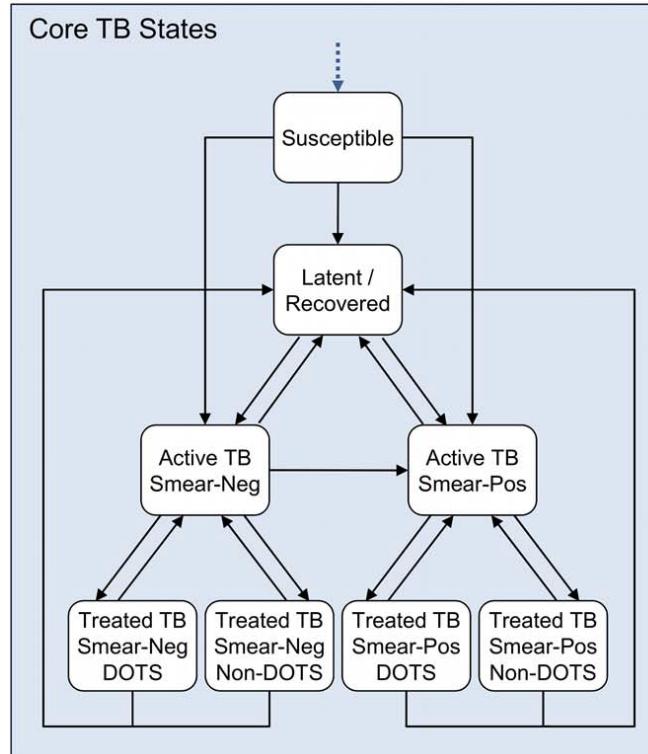
(Dye, ARPH, 2013)



(Dowdy, 2011)

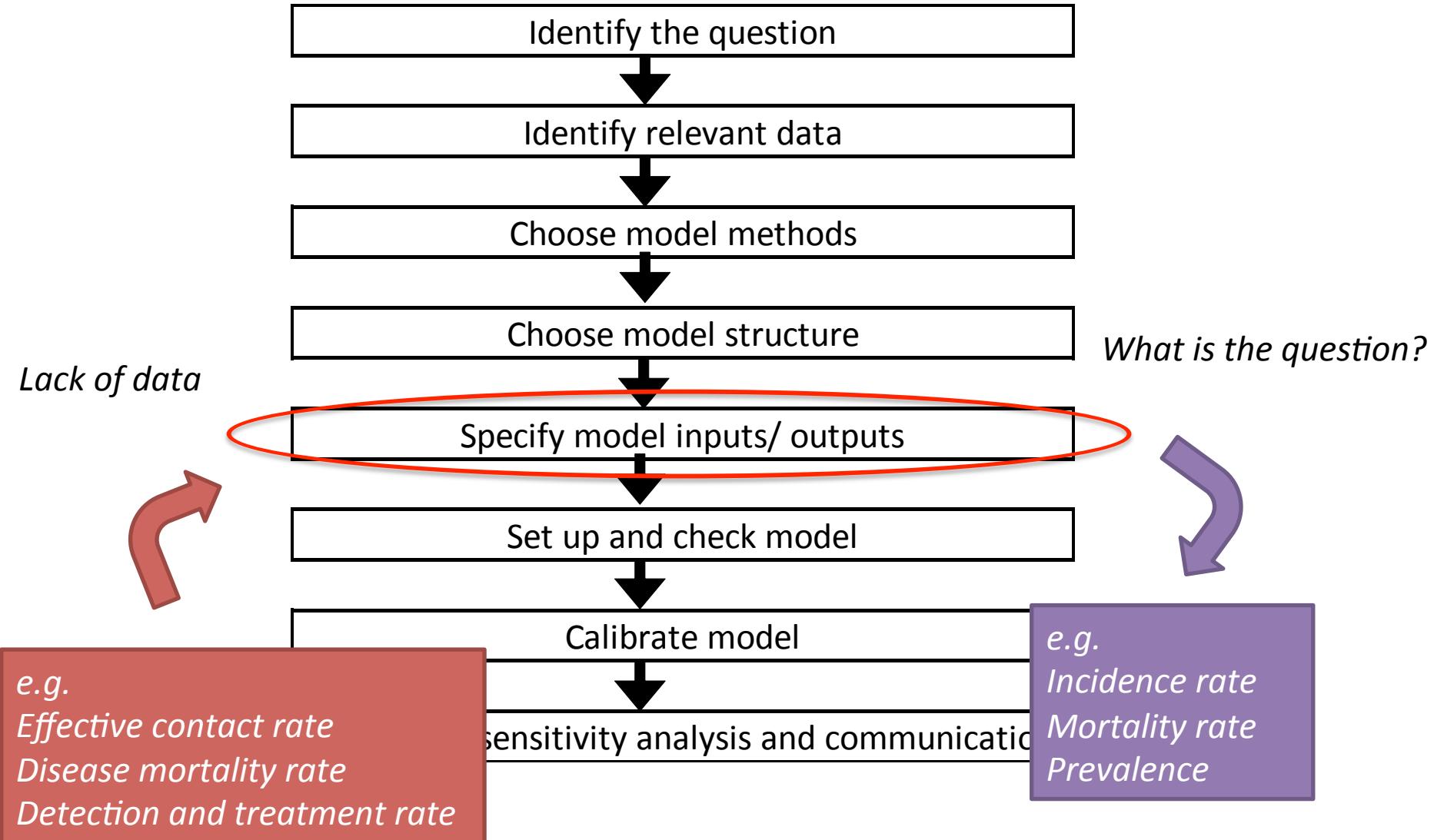


(Abu-Raddad, PNAS, 2009)



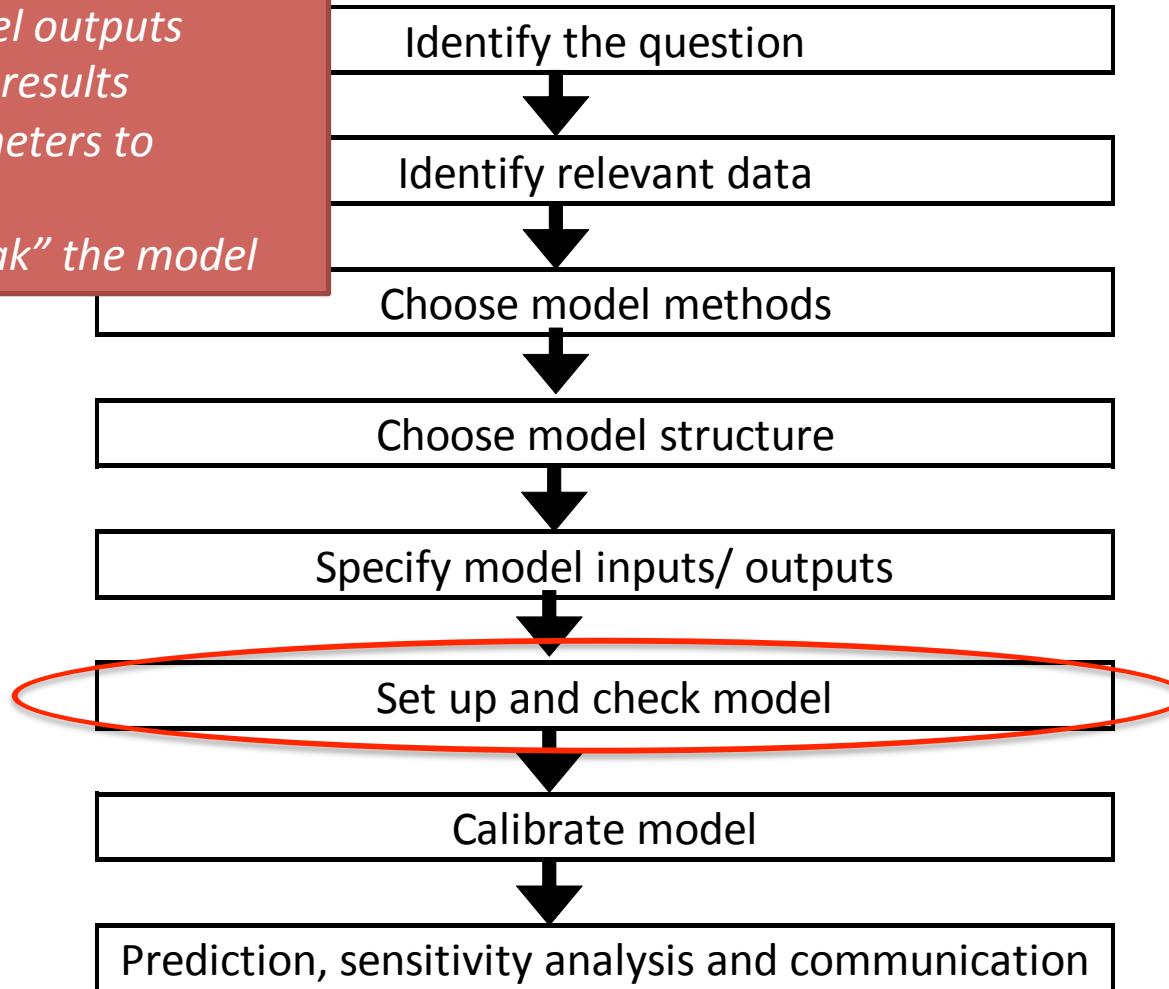
(Menzies, PLoSMed, 2012)

Practical steps to a model



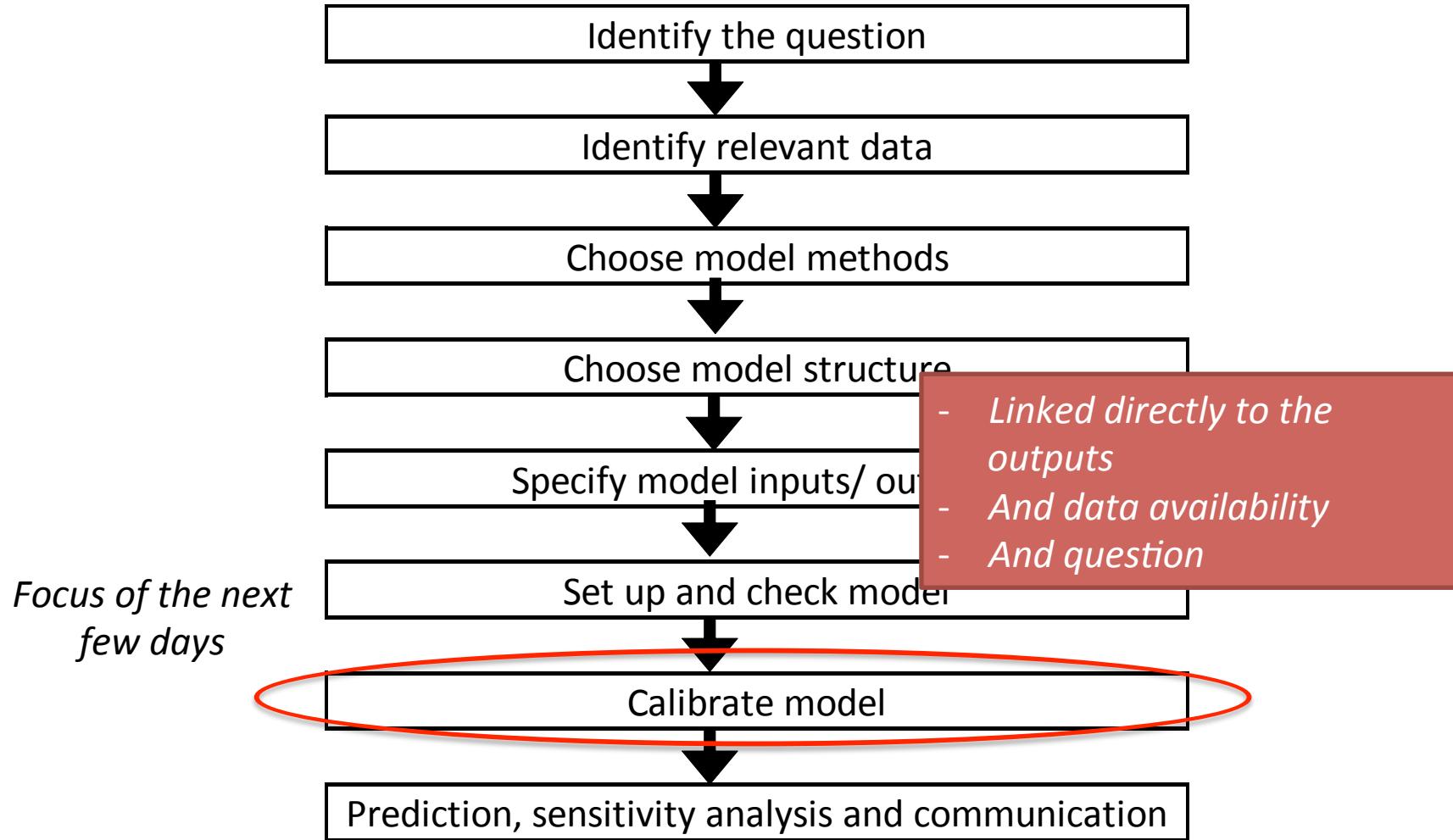
Practical steps to a model

- *Check model outputs “expected” results*
- *Vary parameters to maximum*
- *Try to “break” the model*

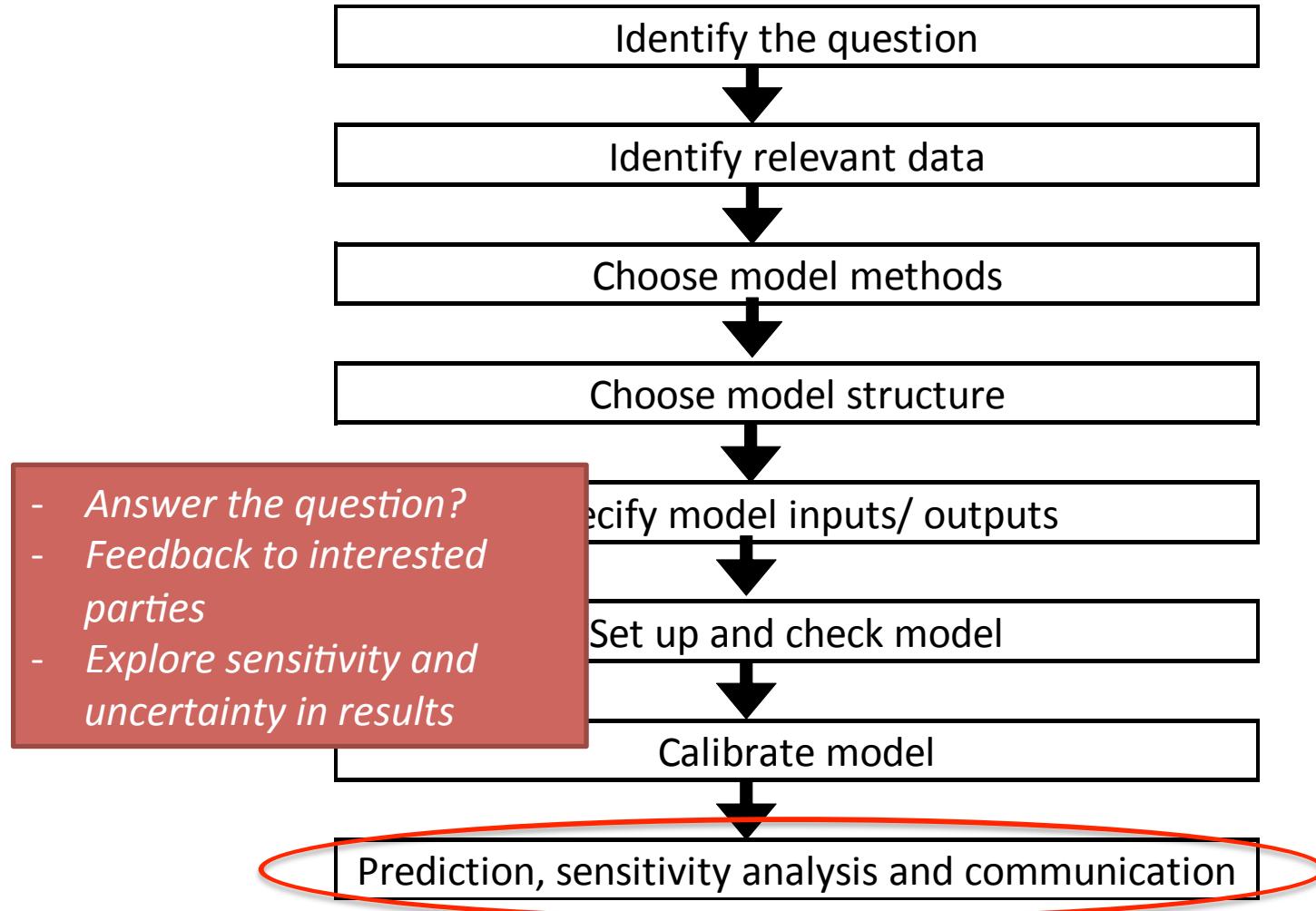


Bug checking...

Practical steps to a model



Practical steps to a model



Interesting part!

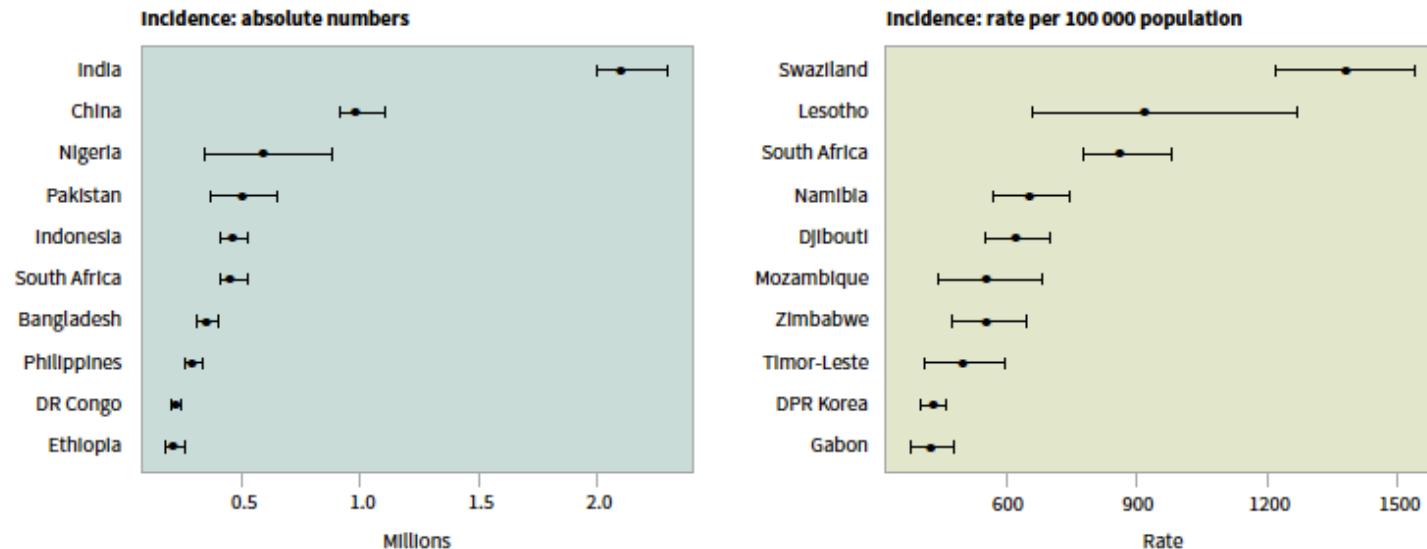
5. An example

Example



- TB global problem:
 - now causes equal number of deaths to HIV: number 1 infectious disease killer
 - 1.5 million deaths in 2014
- Big problem in India
 - 24% of all TB cases in 2013 (2 - 2.3 million)

Estimated TB incidence: top-ten countries, 2013



Example

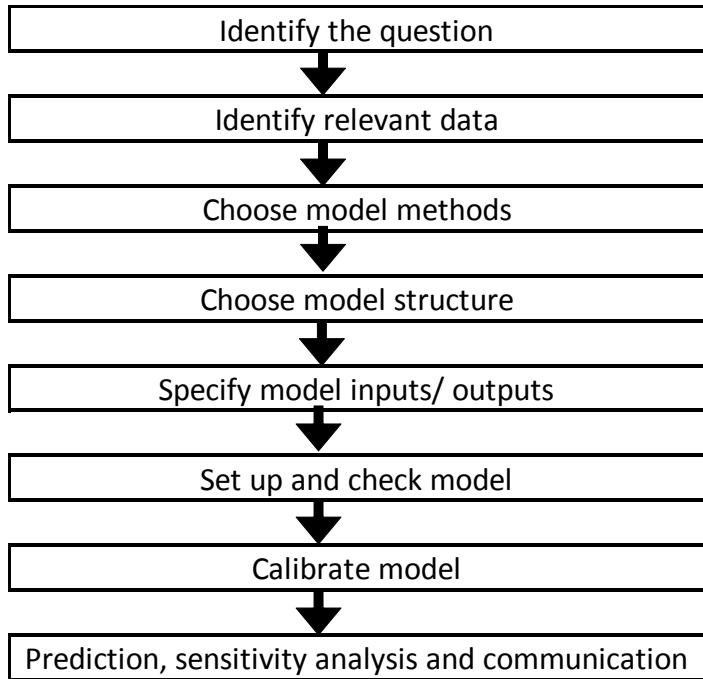


- Investment into TB vaccines expanding
 - Gates Foundation



- Who should these ‘vaccines’ be given to for biggest impact?
 - Traditionally and easiest to give to infants
 - Biggest burden of disease in adolescent/adults
 - Cost-effective?
- BCG - variable efficacy, no additional protection over background mycobacteria exposure
 - Assumed coverage continued at the same level

Practical steps to a model



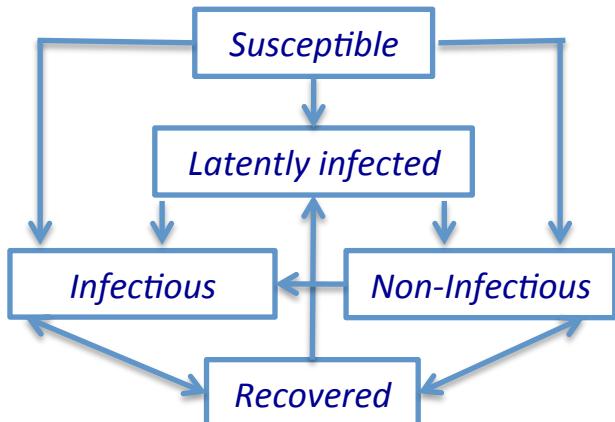
QN: Who should new TB vaccines be given to?

DATA: Demographic (UN), TB (WHO), HIV (UNAIDS), vaccine coverage by country

Country selection: World Bank income group classification

94 countries included, >97% of TB burden in LIC and MIC

MODEL METHODS: Dynamic, transmission, deterministic, compartmental



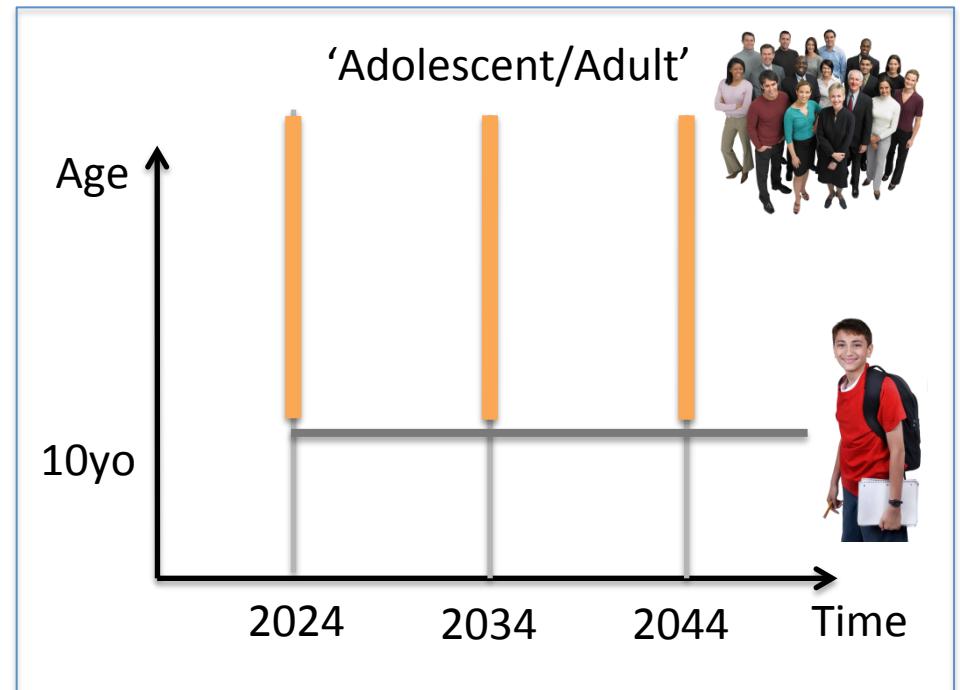
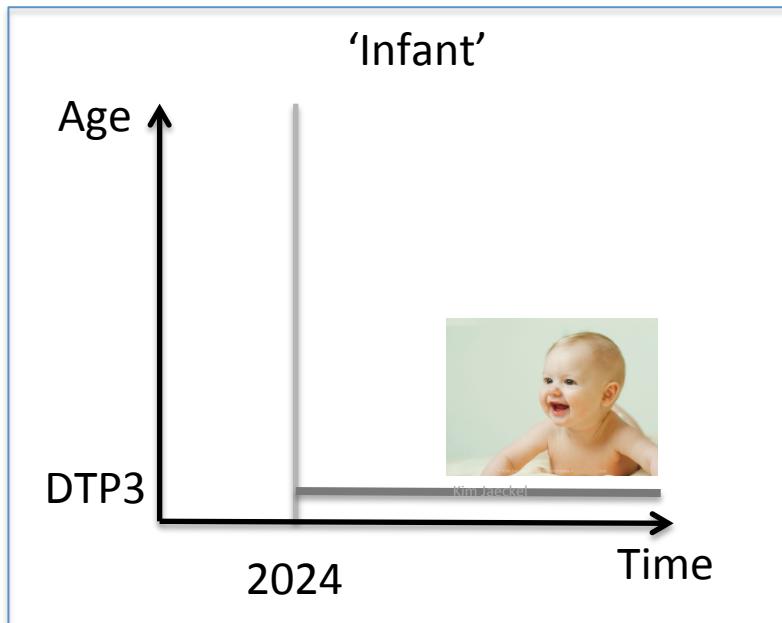
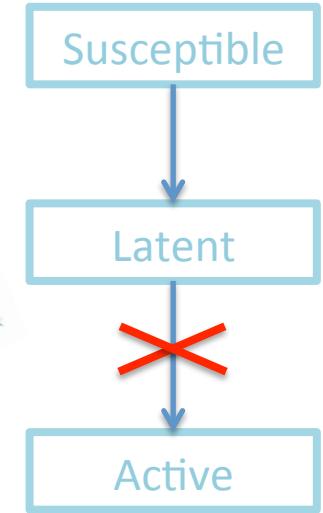
MODEL STRUCTURE: TB/Age/HIV/Vaccine

MODEL INPUTS: TB natural history parameters, HIV incidence, birth/death rate, vaccine coverage

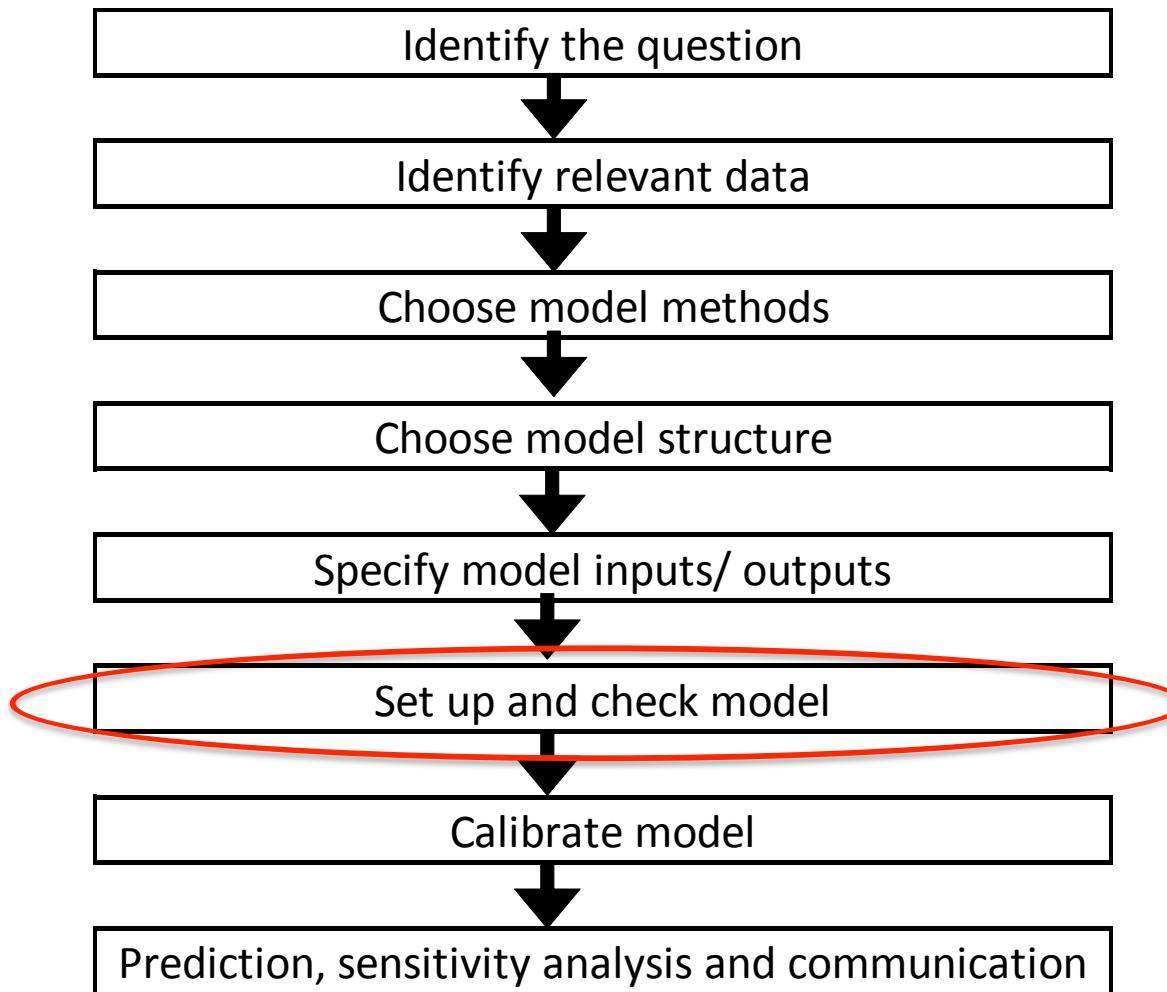
OUTPUTS: TB incidence & mortality, population size, plus number of vaccines given etc

Example

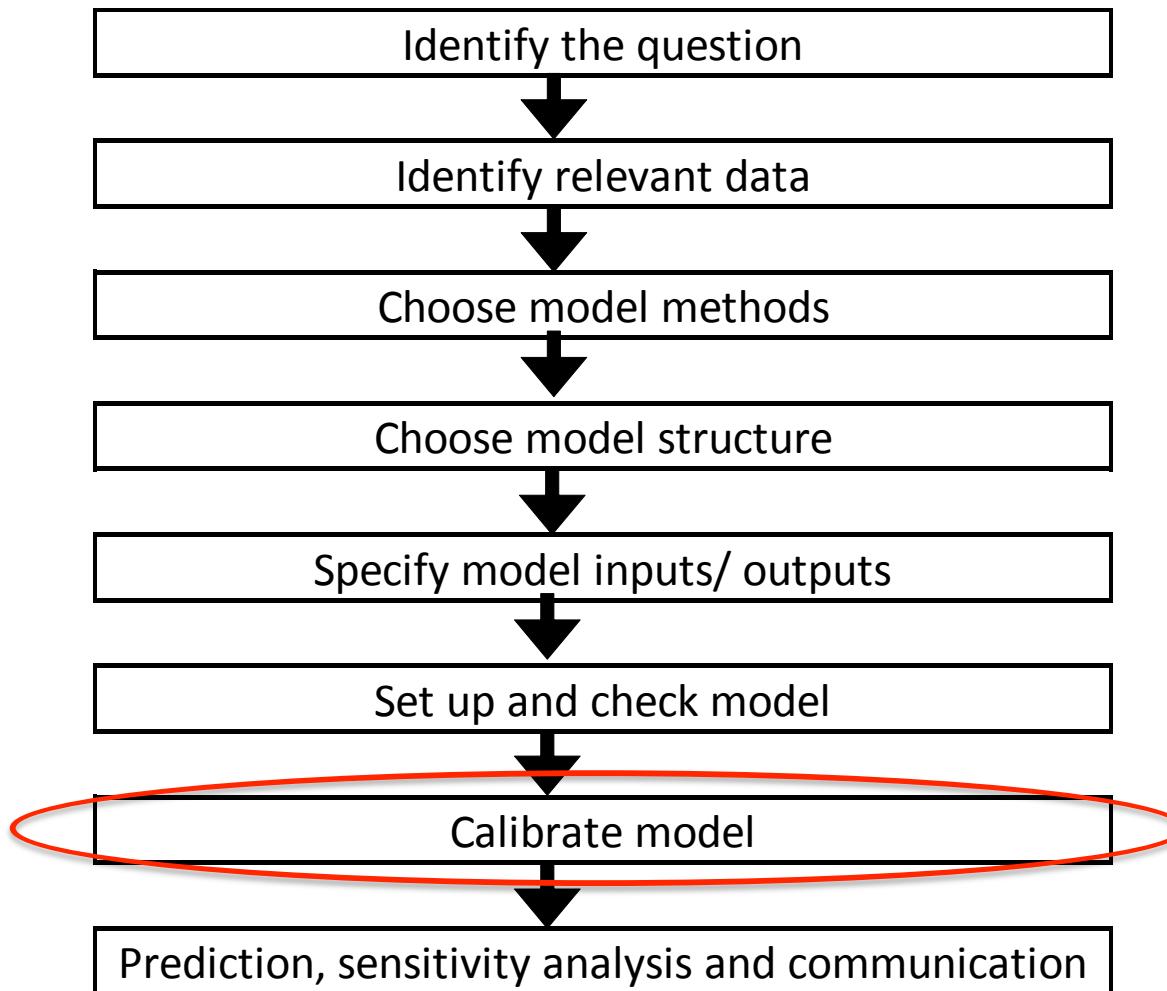
- TB vaccines
 - how might they work?
 - Where is the intervention “hook”?



Practical steps to a model



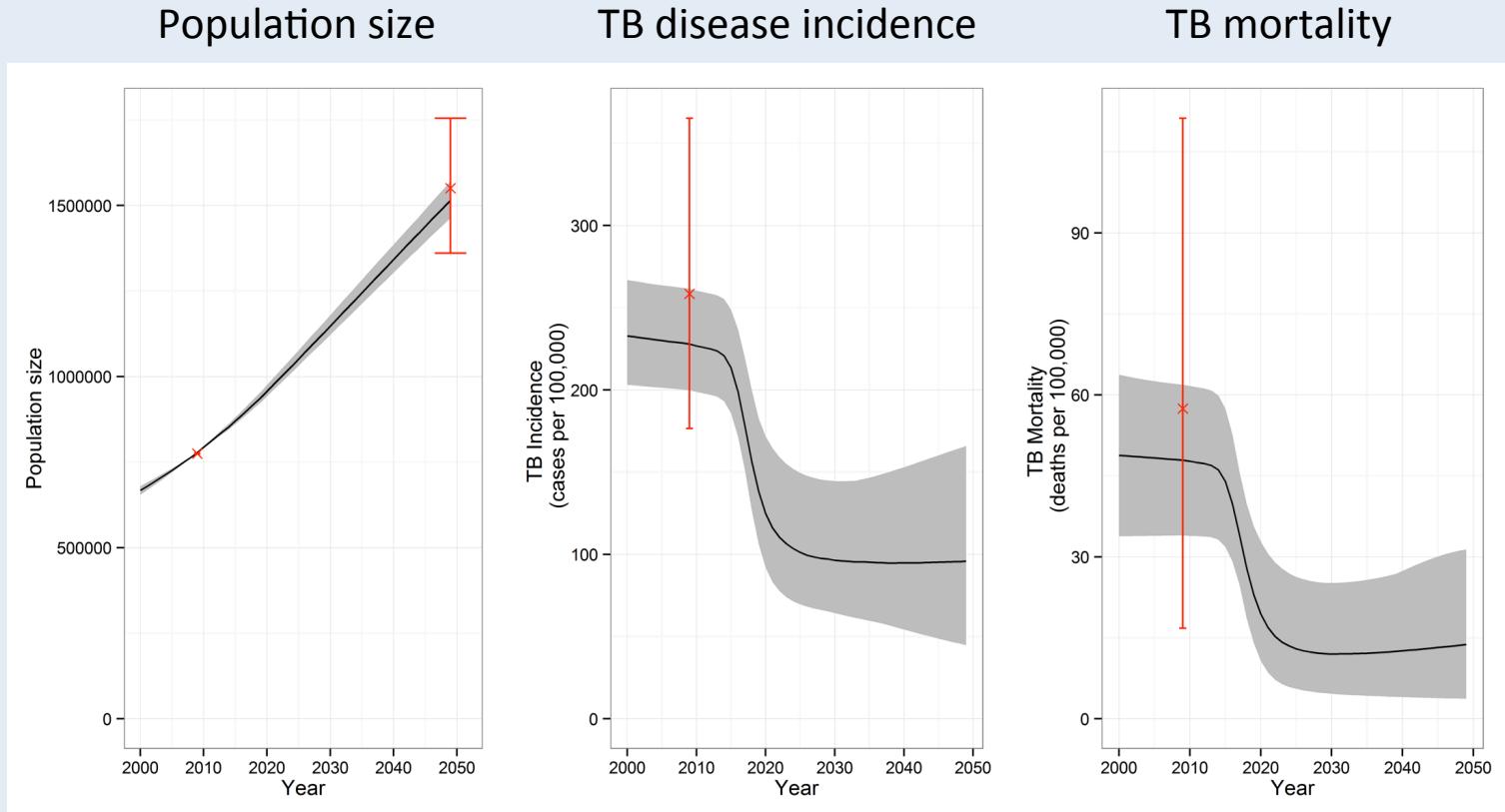
Practical steps to a model



Results

- Model output calibrated by country to:
 - Population size at 2009 and 2050
 - TB incidence and mortality, by HIV status, in 2009

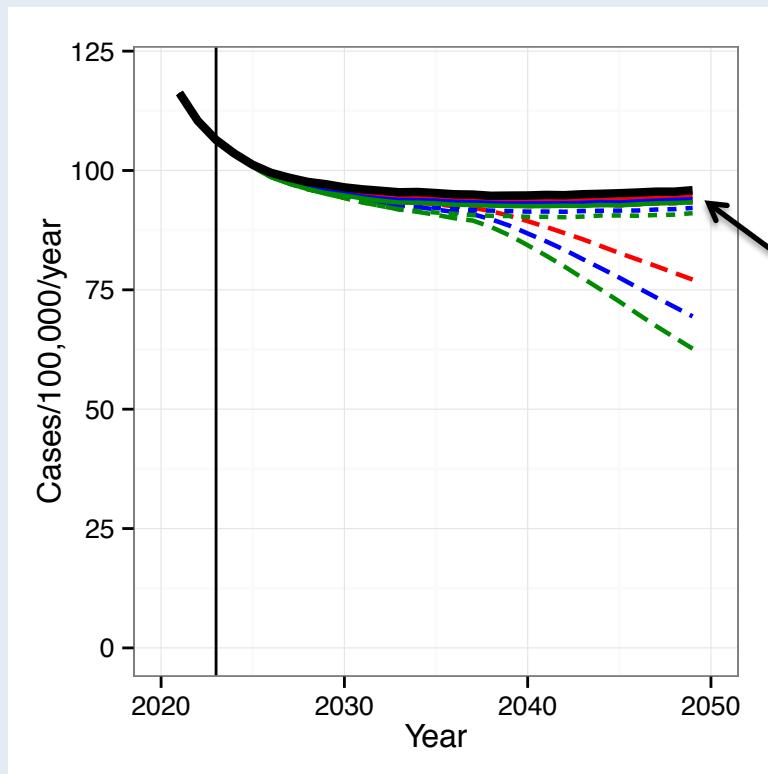
LIC



Impact of vaccine targeted at *infants*

Efficacy =	40%	Duration =	5 years
	60%		--- 10 years
	80%		- - Lifelong

LIC



Vaccine profile:
10yr protection,
40% efficacy

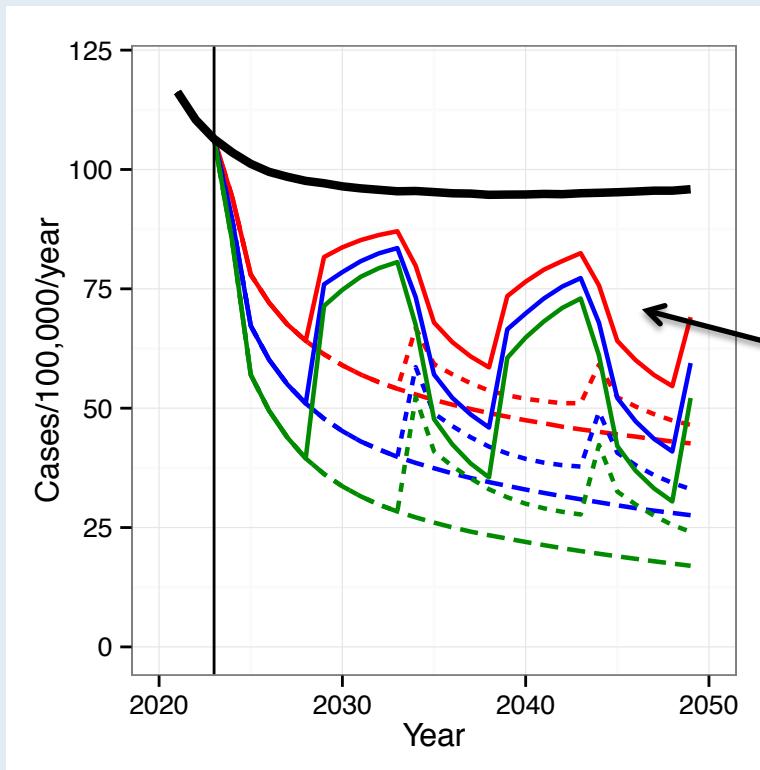
Cases averted:
0.59 (0.25 - 1.18)
million

~ 2% averted

Impact of vaccine targeted at adolescent / adults

Efficacy =	40%	Duration =	5 years
	60%		---
	80%		- - Lifelong

TB disease incidence

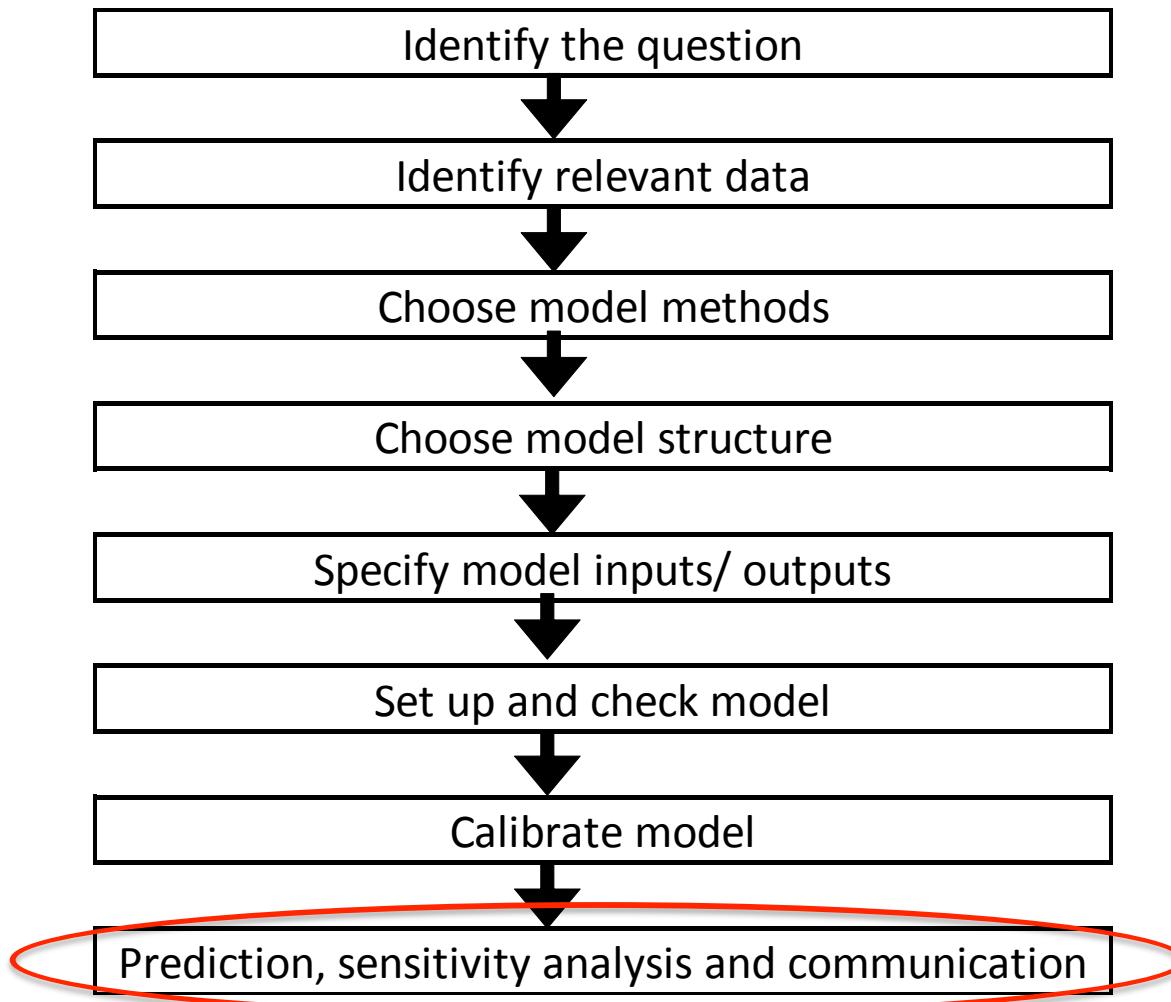


Vaccine profile:
10yr protection,
40% efficacy

Cases averted:
13 (8 – 18)
million

~ 40% averted

Practical steps to a model



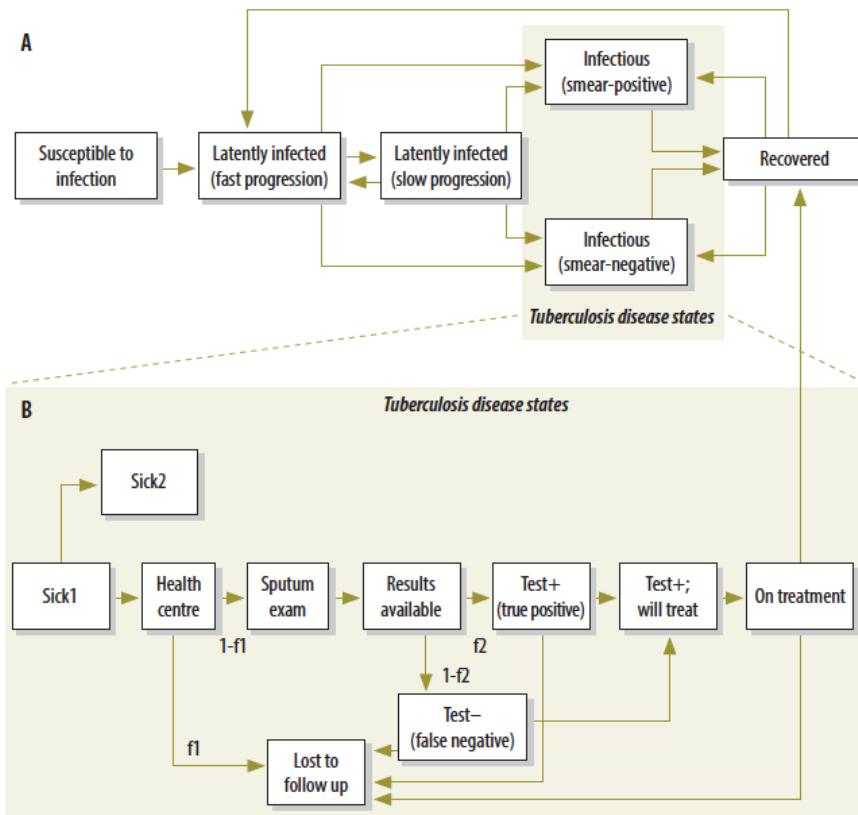
Impact

- Linked to cost-effectiveness work
- Paper (Knight, 2014) and conference presentations
- Presentations to funder (NGO/Gates)
 - Resulted in increased evidence base for targetting TB vaccines at adolescent / adults
 - Research now into how to target this population
 - Trials designed using adolescent / adult populations



Importance of interaction with policymakers

Fig. 1. Graphical representation of the expanded epidemic model used to study the impact of new tuberculosis diagnostics on transmission

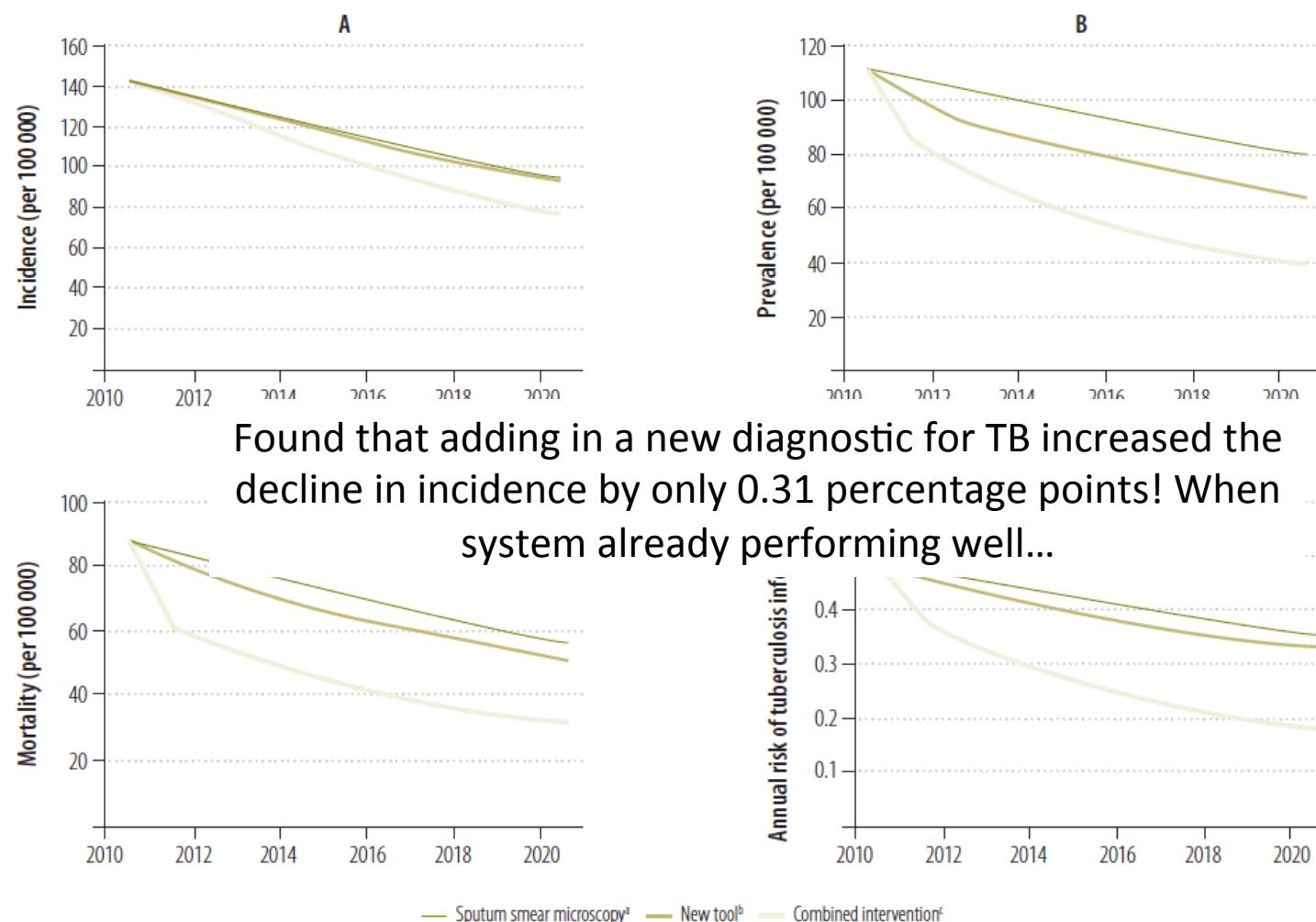


QN: what is the impact of new diagnostics given complex contextual settings?

Basically “how does the existing system affect diagnostic impact?”

MODEL: Deterministic, expanded diagnostics pathway section (“hook” for intervention)
Used data from Tanzania

Fig. 3. Projected incidence, prevalence and mortality trends for pulmonary tuberculosis and annual risk of latent tuberculosis under three diagnostic scenarios^a



^a Scenario I: sputum smear microscopy under the reference case operational context (corresponding to the mode values of operational parameters in Table 2).

^b Scenario II: use of the new tool (with 70% sensitivity for smear-negative disease) to replace sputum smear microscopy in Scenario I.

^c Scenario III: use of the new tool in combination with other interventions that shorten the average patient delay and increase access to care and treatment success rate (with parameter values corresponding to the 90% posterior limits in Table 2).



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Linking to policy

- “New shiny tool” for TB = GeneXpert
- Has been rolled out across South Africa (2013-2014) at great expense with... *little to no impact* on mortality or numbers started on treatment
 - The EXTEND study: Churchyard et al (CROI 2014). Pragmatic, randomized trial. Determined the 6 month mortality risk.
 - Mortality was not reduced by Xpert replacing smear: (Xpert, 3.9%) and control (smear, 5.0%); risk ratio =0.86 ($p=0.42$)
 - Xpert did increase the yield of TB by 49%, but not the proportion treated or reduce LTFU.
 - Therefore diagnosis is just the beginning – need system strengthening for appropriate care.
- Why? Empirical therapy already highly used significantly.
- Modelling could have informed this... beware the policy maker and the shiny new tool....

6. Summary

Practical model building - conclusions

- Why do we model infectious diseases?
 - Argue that key reason is to aid decision-making process of policy makers
 - Models allow us to look beyond status quo, project into future, and explore a variety of scenarios and settings at low costs
 - But requires careful considerations of design, data and presentation of results
- What are the stages in practical model building?
 - Gone through the detailed stages – multiple interlinking levels
 - Complexity of building a model for TB
- How do you model an intervention?
 - Introduce ‘hooks’ that capture impact of intervention
 - Need to consider whether to introduce more model structure
 - Shown you a couple of detailed examples

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