TB Modelling and Analysis Consortium

Practicals: An introduction to TB modelling

Practical 1

Conflict of interest disclosure

I have **no**, real or perceived, direct or indirect conflicts of interest that relate to this presentation

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Practicals: An introduction to TB modelling

Aims

- To illustrate questions which might be addressed using mathematical models

- To give you insight into what data and assumptions models might need

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Practical 1: Setting up a model of *M tuberculosis* transmission: exploring factors influencing tuberculosis incidence

Objectives

By the end of this practical, you should

- Know the key input parameters which go into a TB model
- Know the key factors which influence the observed TB disease incidence and risk of infection

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Practical 1 – Structure
12.20-14.05

Task 1 – Group discussion (30 mins)

Task 2 – Computer exercise (50-60 mins)

Coffee break – at any time that you need it…

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Task 1 - The problem

- TB incidence in country Z is high (100-200/100,000/ year) and has been stable over the last 10 years
- Two key factors may influence this high incidence:
  - Largely poor population, living in crowded conditions.
  - The time from disease onset until cases are detected and start TB treatment is probably very long but unknown
- Country Z wants to introduce interventions, especially improved diagnostics
- First, it wants to understand how the above factors influence TB incidence

Your task

In small groups, discuss the following questions and summarize your answers on the flipcharts:

1. What would be a simple initial structure for the model which you might use to explore how the factors above influence tuberculosis incidence?
2. What are the limitations of your selected model structure?
3. What model input parameters might you require?
4. What data sources might you use to acquire these input parameters?

1. What would be a simple initial structure for the model?

Considerations:

Largely poor population, living in crowded conditions

- The risk of infection may be high => important to include reinfection

The time from disease onset until cases are detected and start TB treatment is probably very long but unknown

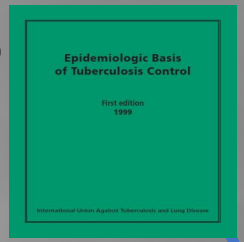
- Need to include undetected cases and those who are no longer infectious (recovered)
- Delays probably depend on smear status – need to stratify infectious people according to smear status (smear-negative cases are typically less infectious than those smear-positive)

3. What input parameters might your model require?

- Effective contact rate (rate at which two specific individuals come into effective contact per unit time)
- Differences in infectiousness between smear-negative and smear-positive TB cases
- Rate of disease onset following new infection, reinfection or through reactivation
- Rate at which smear-positive and smear-negative cases:
  - are detected
  - start treatment
- Proportion of cases who complete treatment
- Mortality rates (general population and TB-related)

4. What data sources might you use to acquire these input parameters?

- Research papers, grey literature, lab reports, existing modelling exercises...
- Organise quantitatively by
  - Transmission
  - Epidemiology
  - Natural history
- Control options
- Discuss review with experts



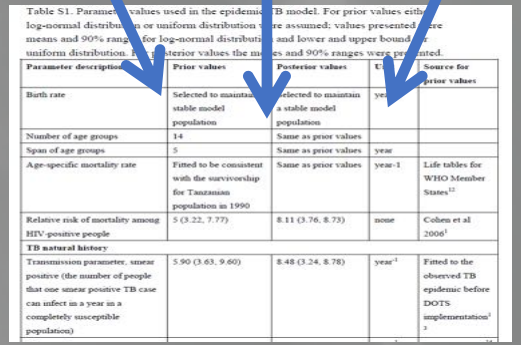


Table S1. Parame values used in the epidemic B model. For prior values either log-normal distribu or uniform distribution were assumed; values presented are means and 90% rang for log-normal distributi and lower and upper bound uniform distribution. Posterior values the me es and 90% ranges were pr nted.

Parameter description	Prior values	Posterior values	U	Source for prior values
Birth rate	Selected to maintain a stable model population	Selected to maintain a stable model population	ye	
Number of age groups	14	Same as prior values		
Span of age groups	5	Same as prior values	year	
Age-specific mortality rate	Fitted to be consistent with the survivorship for Tanzanian population in 1990	Same as prior values	year-1	Life tables for WHO Member States[12]
Relative risk of mortality among HIV-positive people	5 (3.22, 7.77)	8.11 (3.76, 8.73)	none	Cohen et al 2006[1]
TB natural history				
Transmission parameter, smear positive (the number of people that one smear positive TB case can infect in a year in a completely susceptible population)	5.90 (3.63, 9.60)	8.48 (3.24, 8.78)	year-1	Fitted to the observed TB epidemic before DOTS implementation[1 2]

Rieder, H. L. (1999). Epidemiologic basis of tuberculosis control
WHO TB Report 2013 ; Lin, WHO Bull, 2011

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Practical 1 – Structure

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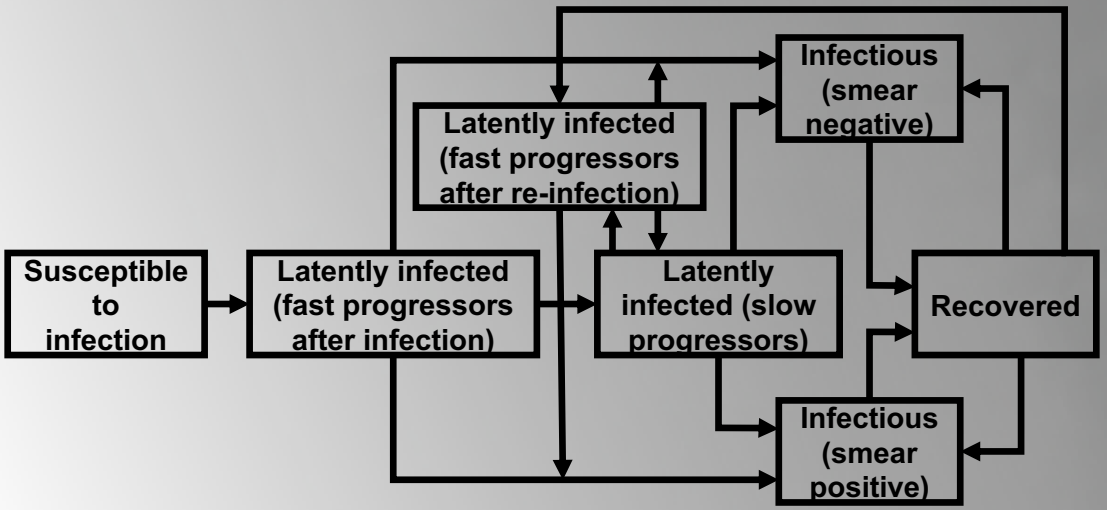
Overview

- Quick introduction to the model
- Exploring factors influencing tuberculosis incidence:
  - Contact between people
  - Duration of infectiousness
- General conclusions
- (Optional) Supplementary questions: factors influencing the amount of disease due to recent infection, reinfection & reactivation

General structure of the model



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Key features of the model

- 7 compartments (“boxes”)
- 100,000 people (“adults”)
- Includes mortality (general population, TB-related) and new entrants to population
- Effective contact rate determines number of people contacted by each case and the risk (force) of infection
- Differences in infectiousness between smear-positive and smear-negative cases
- Fixed duration of infectiousness

What do the (differential) equations mean?

Differential equations describe the rate of change in the number of people, written as:

+ number coming in

- number going out

Number in compartment
×
rate at which they exit compartment
e.g. Number recently infected ("Latent_fast_prog_infn")
×
Rate of (primary) disease onset

Number in compartment
×
rate at which they enter compartment
e.g. Number uninfected
×
Risk ("force") of infection

Answers

Q1 If effective contact rate (ecr) decreases, would expect the TB incidence, mortality and annual risk of infection to decrease.

The effective contact rate determines the number of new infections resulting from each infectious case.

Reduction in the effective contact rate:

=> ↓ in the number of individuals at risk of infection (or reinfection) and subsequent progression to disease

=> ↓ in number of deaths due to TB

Answers

Step 1, page 4

Effective contact rate (per year)	Annual TB incidence per 100,000	Annual TB mortality rate per 100,000	Annual risk of infection (%)
15	197	51	2.4
13.5	153	40	1.7
12	106	28	1.0
10.5	53	14	0.5

Answers

Step 2, page 4

Assumed reduction in the effective contact rate	% reduction:		
	Annual TB incidence per 100,000	Annual TB mortality rate per 100,000	Annual risk of infection (%)
10% (15→13.5 per year)	22%	22%	29%
20% (15→12 per year)	46%	45%	58%
30% (15→10.5 per year)	73%	73%	79%

Q2. Yes, the effective contact rate is important in determining the tuberculosis incidence and mortality.

A 30% reduction in ecr -> a 70% +reduction in TB incidence.

Answers

Q3. Factors influencing TB incidence, mortality and the risk of infection:

- the relative infectiousness of smear-negative cases compared to smear-positive cases;
- the rates of disease onset following initial infection and through reactivation;
- the protection provided by a previous infection against disease following reinfection.

Answers

Q4. From step 1, page 4:

If ARI = 1% per year, TB incidence = 106 per 100,000 per year

If 70% of cases are smear-positive, incidence of smear-positive TB = 0.7×106 = 74 per 100,000 per year

BUT Styblo rule => incidence of 50 per 100,000 corresponds to ARI =1%/year

So…model is inconsistent with rule…

Answers

Q4. Note that the Styblo rule also suggests that ratio between incidence of sm+ TB and ARI is fixed…this doesn't hold

Effective contact rate (per year)	Annual TB incidence per 100,000	Annual incidence of smear-positive TB per 100,000	Annual risk of infection (%)	ARI (per 100,000) ÷ incidence of Sm+TB per 100,000
15	197	138	2.4	17
13.5	153	107	1.7	16
12	106	74	1.1	15
10.5	53	37	0.5	14

Answers

Q4b. Factors influencing relationship between incidence of sm+ TB and ARI:

- duration of infectiousness (assumed to be 2 years in the Styblo rule
- the infectiousness of smear-negative cases (assumed to be zero)

Answers

Q5. If the duration of infectiousness decreases, would expect the TB incidence, mortality and annual risk of infection to decrease.

Reducing the duration of infectiousness means that each smear-positive cases results in fewer new infections than he/she would do previously, which leads to a reduced TB incidence

Answers

Step 1, page 6

Average duration of infectiousness in smear-positives (weeks)	**Annual TB incidence per 100,000**	**Annual TB mortality rate per 100,000**	**Annual risk of infection (%)**
51	197	51	2.4
46	161	39	1.8
41	122	28	1.3
36	80	17	0.7

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Answers

Step 2, page 6

Reduction in the average duration of infectiousness in smear-positives	% reduction:		
	Annual TB incidence per 100,00	Annual TB mortality rate per 100,000	Annual risk of infection (%)
10% (51→46 weeks)	19%	24%	25%
20% (51→41 weeks)	38%	45%	46%
30% (51→36 weeks)	59%	67%	70%

Q6. The average duration of infectiousness in smear-positive cases is important in determining TB incidence and mortality. A 30% reduction in the duration of infectiousness => 60% reduction in TB incidence.

Answers

Q7. ↓ the average duration of infectiousness in smear-negative cases would have a smaller impact than ↓ the duration of infectiousness in smear-positive cases

Smear negative cases are less infectious than smear positive cases, so, ↓ duration of infectiousness of smear-negative cases prevents fewer infections than the same corresponding reduction for smear-positive cases.

If infectiousness of smear-negative cases is 22% of that of smear-positive cases, each smear-negative case generates 78% fewer new infections per unit time than a smear-positive case

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Answers

Step 3, page 6

Average duration of infectiousness in smear-negatives (weeks)	Annual TB incidence per 100,000	Annual TB mortality rate per 100,000	Annual risk of infection (%)
95	197	51	2.4
86	191	48	2.3
76	184	44	2.2
67	178	41	2.1

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Answers

Step 4, page 6/7

Reduction in the average duration of infectiousness in smear-negatives	% reduction:		
	Annual TB incidence per 100,000	Annual TB mortality rate per 100,000	Annual risk of infection (%)
10% (95→86 weeks)	3%	6%	4%
20% (95→76 weeks)	7%	14%	8%
30% (95→67 weeks)	10%	20%	12%

Q8. ↓ average duration of infectiousness in smear-positive cases is better than reducing this for smear-negative cases.
30% ↓ among smear-negative cases=> 10% ↓ in TB incidence,
30% ↓ among smear-positive cases =>60% ↓ in TB incidence

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Conclusions

Q9. For the setting in the model, is it better to ↓ the average duration of infectiousness of smear-positive cases by 10% or to ↓ the number of individuals effectively contacted by each smear-positive case per year (effective contact rate) by 10%?

Scenario	Annual TB incidence per 100,000	Annual TB mortality rate per 100,000	Annual risk of infection (%)
Baseline	197	51	2.4
10% ↓ in effective contact rate	153	40	1.7
10% ↓ in average duration of infectiousness for sm+	161	39	1.8

In this setting, ↓ ecr has a bigger impact on incidence than ↓ the duration of infectiousness among smear-positives

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Conclusions

Q10. What do you think are the key steps in the diagnostic and treatment pathway that determine the average duration of infectiousness?

- The time from onset of disease until an individual accesses care (i.e. attending health services);
- The time between an individual accessing care and being diagnosed with TB. This depends on:
  - the time from accessing care to being tested for tuberculosis
  - the time between being tested and receiving a diagnosis.
- The time between diagnosis and starting treatment.

Conclusions

Q10. What do you think are the key steps in the diagnostic and treatment pathway that determine the average duration of infectiousness?

At each step, some proportion of cases may be lost from the pathway for the following reasons:

- Tuberculosis may not be suspected as a cause.
- Cases may be missed due to the sensitivity of the diagnostic algorithm.
- Diagnosed cases may not start treatment (initial default).
- Cases may stop or fail treatment.

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Supplementary questions - answers

S1 A large proportion of disease is attributable to recent transmission

=> TB incidence could be reduced relatively quickly by interrupting transmission.

Knowing the proportion of disease attributable to recent transmission might help you to anticipate the impact of an intervention.

Supplementary questions - answers

S2. ARI is high (1%/year) in the model, so would expect proportion of disease attributable to recent infection or reinfection to be high. In fact:

Proportion due to: Recent infection = 70%
Recent reinfection = 24%
Reactivation = 6%

S3. As the ARI ↑, you would expect the proportion of disease due to recent infection to decrease and the proportion due to reinfection to increase.

Supplementary questions - answers

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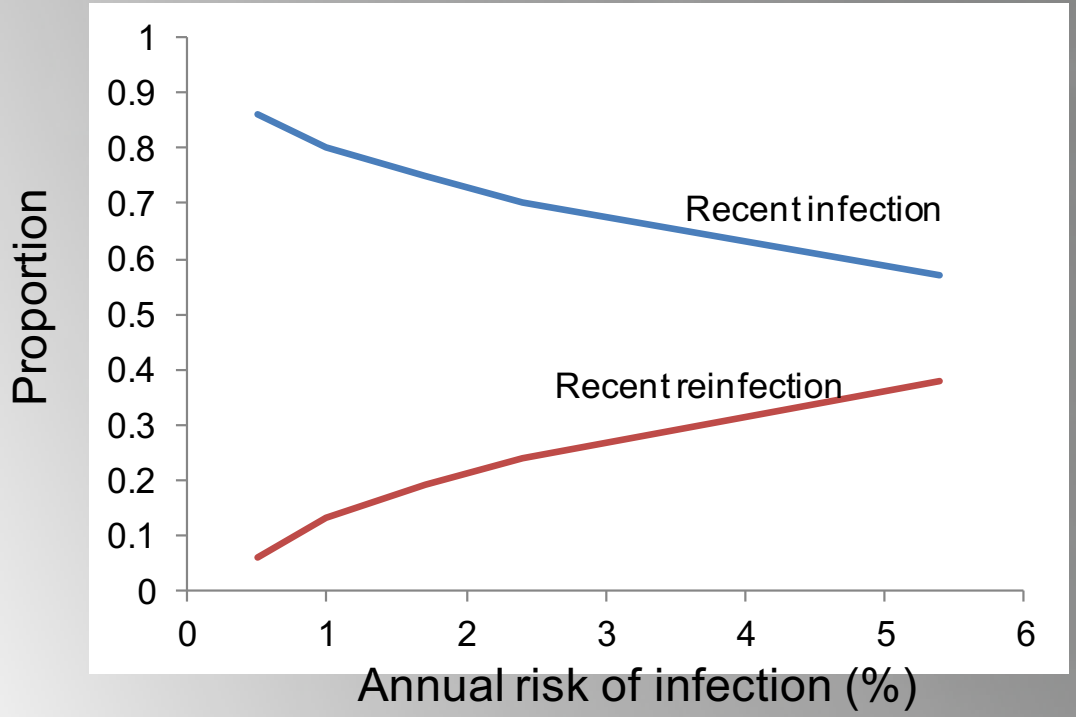

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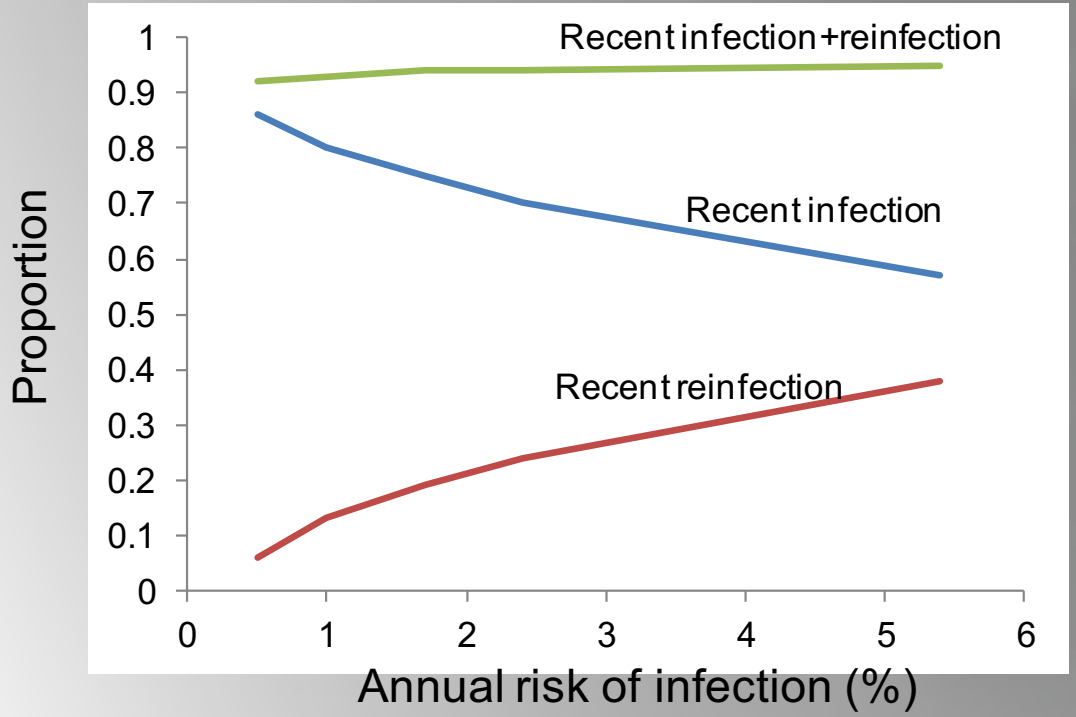
Supplementary questions - answers

S3. As the ARI ↑, you would expect the proportion of disease due to recent infection to decrease and the proportion due to reinfection to increase.



S4. Net effect: overall proportion attributable to recent infection + recent reinfection remains similar as ARI changes

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Supplementary questions - answers

S5. As protection provided against disease following reinfection increases, predicted TB incidence decreases:

Protection (%)	Annual TB incidence per 100,000
40	358
65	197
80	141

S6. As reactivation rate ↑, TB incidence & proportion of disease attributable to reactivation ↑

Reactivation rate	Annual TB incidence per 100,000	Proportion of disease due to reactivation
Baseline	197	5%
5-fold increase	332	20%

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Supplementary questions - answers

S7 A low proportion of disease attributable to recent transmission

=> interventions targetting transmission may have a smaller impact than in settings in which a large proportion of disease is attributable to recent transmission