Introduction to Tuberculosis Modelling
48th World Union World Conference on Lung Health, Liverpool
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Practical 1: Setting up a model of *M tuberculosis* transmission: exploring factors influencing tuberculosis incidence

Solutions

PART II: Computer exercise

Factors influencing tuberculosis incidence – contact between individuals

Q1. You would expect that reducing the number of individuals effectively contacted by each smear-positive case would reduce the tuberculosis incidence, tuberculosis mortality and annual risk of infection.

The effective contact rate determines the number of new infections resulting from each infectious case. Therefore if the effective contact rate is reduced, the number of individuals at risk of infection (or reinfection) and subsequent progression to disease will also be reduced. If the number of TB cases is decreased then the number of deaths due to tuberculosis will also be reduced.

Step 1, page 4. The values of the annual tuberculosis incidence, tuberculosis mortality and annual risk of infection for various values of the effective contact rate are given below. The tables show that as the effective contact rate is reduced, all 3 statistics are reduced.

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

Step 2, page 5. The following table summarizes the impact of reducing the effective contact rate on the above statistics.

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. The results that you calculated in step 2 suggest that the effective contact rate is important in determining the tuberculosis incidence and mortality. A 30% reduction in the ecr results in a greater than 70% reduction in the TB incidence.

Q3. **(optional)**. The epidemiology of TB in the population will be influenced by several parameters related to infection and disease. These include: 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.

Q4. **(optional)** a) The values you found in step 1 (page 4) suggest that with an annual risk of infection of ~1% per year (consistent with an effective contact rate of about 12 per year) the overall tuberculosis incidence would be 106 per 100,000 per year. Given that 70% of cases are smear-positive this corresponds to a smear-positive disease incidence of 74 per 100,000. This is inconsistent with the Styblo "thumb" rule.

According to the Styblo thumb rule, the ratio between the annual risk of infection and the incidence of smear-positive TB is constant. For example, using the same units for the annual risk of infection and the incidence of smear-positive TB, dividing the annual risk of infection by 50 per 100,000 (the incidence of smear-positive TB) gives 1000/50 = 20 per year. However, if we divide the annual risk of infection by the incidence of smear-positive TB in the model, we see that the ratio decreases as the annual risk of infection decreases, as shown below:

Effective contact rate (per year)	**Annual TB incidence per 100,000**	**Annual incidence of smear-positive TB per 100,000**	**Annual risk of infection (%)**	**Annual risk of infection (per 100,000) ÷ incidence of smear-positive 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

b) Factors influencing this relationship are the duration of infectiousness (assumed to be 2 years in the Styblo rule) and the infectiousness of smear-negative cases (assumed to be zero). For further discussion of this rule, please read van Leth et al[1].

Factors influencing tuberculosis incidence – duration of infectiousness

Q5. You might expect that reducing the average duration of infectiousness for smear-positive cases would lead to reductions in the tuberculosis incidence, tuberculosis mortality and annual risk of infection.

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

Step 1, page 6. The values of the annual tuberculosis incidence, tuberculosis mortality and annual risk of infection for various values of the average duration of infectiousness of smear-positive cases are given below. The tables show that as the duration of infectiousness is reduced all 3 statistics are reduced.

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

Step 2, page 6. The following table summarizes the impact of reducing the average duration of infectiousness for smear-positive cases on the above statistics:

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 results that you calculated in step 2 suggest that the average duration of infectiousness in smear-positive cases is important in determining the tuberculosis incidence and mortality. A 30% reduction in the average duration of infectiousness results in an approximately 60% reduction in the TB incidence.

Q7. Reducing the average duration of infectiousness in smear-negative cases would have a smaller impact on the epidemiology of TB than reducing the duration of infectiousness in smear-positive cases. This is because smear-negative cases are less infectious than smear-positive cases, so that reducing the duration of infectiousness of smear-negative cases prevents fewer infections than the same reduction in the duration of infectiousness of smear-positive cases. For example, based on Behr et al[2] the infectiousness of smear-negative cases is 22% of that of smear-positive cases, which means that each smear-negative case generates 78% fewer new infections per unit time than does a smear-positive case.

Step 3, page 6 **(optional)** The annual tuberculosis incidence, tuberculosis mortality and annual risk of infection predicted for various values of the average duration of infectiousness of smear-negative cases are given below. The tables show that the reducing the time to detection and treatment in smear negative cases has a minimal impact on the epidemiology of TB.

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

Step 4, page 6/7 **(optional)** The following table summarizes the impact of reducing the average duration of infectiousness for smear-negative cases on the above statistics.

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. **(optional)** Based on the values you calculated in step 4 it is better to reduce the average duration of infectiousness in smear-positive cases than to reduce the duration of infectiousness in smear-negative cases. For example a 10% reduction in the average duration of infectiousness among smear-positive cases leads to a 19% reduction in TB incidence, whereas a 10% reduction in the average duration of infectiousness among smear-negative cases leads to a 3% reduction in TB incidence.

Conclusions (for general discussion)

Q9. Reducing the effective contact rate has a slightly bigger impact on TB incidence than reducing the duration of infectiousness in smear-positive cases. A 10% reduction in the ecr reduces TB incidence by approximately 22%. A 10% reduction in the duration of infectiousness of smear-positive cases reduces TB incidence by approximately 19%. Both changes have a similar effect on the mortality rate.

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	161	39	1.8

Q10. The diagnostic and treatment pathway involves the following steps:

- 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 between accessing care to being tested for tuberculosis and the time between being tested and receiving a diagnosis.
- The time between diagnosis and starting treatment.

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.

Supplementary questions (optional)

Exploring factors influencing the proportion of disease attributable to recent infection, reactivation and reinfection

S1 If a large proportion of disease is attributable to recent transmission, then the 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.

S2. The annual risk of infection that is assumed in the model is fairly high (>1%/year) so you might expect a large proportion of disease to be due to recent transmission. When running the model for an effective contact rate of 15 per year, you will see that approximately 70% of disease in the model population is attributed to recent infection, 24% to reinfection and 6% to reactivation.

S3. As the annual risk of infection increases, you would expect the proportion of disease due to recent infection to decrease and the proportion due to reinfection to increase.

S4. The amount of disease due to recent transmission remains relatively constant. In the low infection risk setting, a large proportion of the disease incidence is attributable to recent infection, but a low proportion is attributable to recent reinfection. In the high infection risk setting, a large proportion of the disease incidence is attributable to recent reinfection, but a low proportion is attributable to recent infection. The net effect is that the sum of the proportion due to recent infection and reinfection are relatively similar in both settings. This is illustrated in the table and figure below:

Effective contact rate (per year)	Annual risk of infection (%)	Proportion of disease due to:			
		Recent infection	Recent reinfection	Reactivation	Recent infection +reinfection
20	5.4	0.57	0.38	0.04	0.95
15	2.4	0.7	0.24	0.06	0.94
13.5	1.7	0.75	0.19	0.07	0.94
12	1	0.8	0.13	0.07	0.93
10.5	0.5	0.86	0.06	0.08	0.92

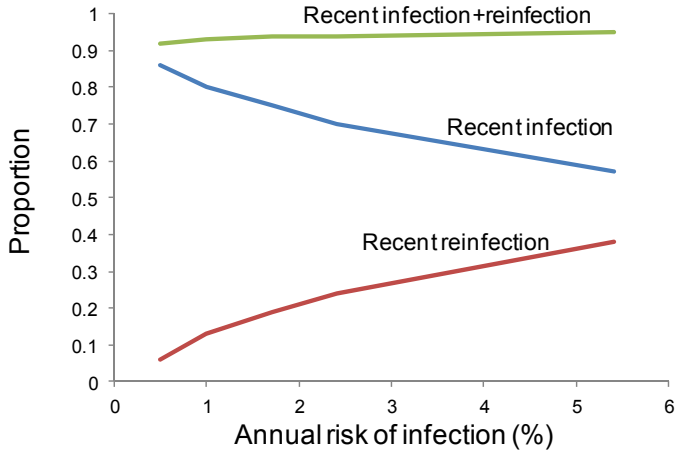

Figure 1: Model predictions of the proportion of disease attributed to recent infection and reinfection in settings in which the ARI has been constant over time at different levels.

S5. When the protection against disease is reduced to 40% the tuberculosis incidence increases to 358 per 100,000. If a previous infection provides an increased level of protection (80%) the incidence is reduced to 141 per 100,000.

S6. If the rate at which individuals experience disease through reactivation is increased, you would expect the total disease incidence to increase and the proportion of disease due to recent transmission to decrease as an increased proportion of cases are due to reactivation of previous infections. A 5-fold increase in the rate of reactivation increases the incidence to 332 per 100,000 from 197 per 100,000 and the proportion of disease due to reactivation to increases from 5% to approximately 20%.

S7. If a low proportion of disease was due to recent transmission, then you would expect any intervention which targeted ongoing transmission to have less impact than in a setting where a large proportion of disease was due to recent transmission.

References

1. van Leth F, van der Werf MJ, Borgdorff MW (2008) Prevalence of tuberculous infection and incidence of tuberculosis: a re-assessment of the Styblo rule. Bull World Health Organ 86: 20-26.
2. Behr MA, Warren SA, Salamon H, Hopewell PC, Ponce de Leon A, et al. (1999) Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. Lancet 353: 444-449.