Chapter 5 (Solutions)

# Age patterns

**5.1** Adapting expression 5.25 in the book, the number of new infections per person among individuals in age group *a* can be calculated using the expression:

$$\lambda s_a$$

where $s_a$ is the proportion of individuals in age group *a* who were seronegative. The values obtained for the average number of new infections per 100 population are as follows:

| | **Average number of infections per year per 100 population (calculated using $\lambda s_a \times 100$)** | | |
|---|---|---|---|
| **Age group (years)** | **China λ=20%/yr** | **Fiji λ=4%/yr** | **UK λ=12%/yr** |
| 15-19 | **0.80** (=0.2×0.04×100) | **1.74** (=0.04×0.435×100) | **1.54** (=0.12×0.128×100) |
| 20-29 | **0.86** (=0.2×0.043×100) | **1.15** (=0.04×0.288×100) | **1.04** (=0.12×0.087×100) |
| 30-39 | **1.08** (=0.2×0.054×100) | **0.77** (=0.04×0.193×100) | **0.85** (=0.12×0.071×100) |

We could have also used the expression $s_a$×risk of infection, which, using the relationship risk =1-e$^{-rate}$ (Panel 2.2), leads to the expression $s_a(1-e^{-\lambda})$ for the number of new infections per person. This expression leads to the following values for the average infection incidence:

| | **Average number of infections per year per 100 population (calculated using $s_a(1-e^{-\lambda})\times 100$)** | | |
|---|---|---|---|
| **Age group (years)** | **China λ=20%/yr** | **Fiji λ=4%/yr** | **UK λ=12%/yr** |
| 15-19 | 0.73 | 1.71 | 1.45 |
| 20-29 | 0.78 | 1.13 | 0.98 |
| 30-39 | 0.98 | 0.76 | 0.80 |

Note that the greatest discrepancy between the values obtained using the expressions $\lambda s_a$ and $s_a(1-e^{-\lambda})$ occurs for the estimates for China. This follows from the facts that the force of infection is higher for China that it is for the UK and Fiji, and the difference between the value for the risk $(1-e^{-\lambda})$ and the rate ($\lambda$) is greatest for large values of the rate (see Figure 2.5).

The estimates suggest that the highest number of new infections per 100 population would have been seen among 15-19 year olds in Fiji, followed closely by that for 15-19 year olds in the UK. Therefore, based on these estimates, we would expect the incidence of CRS to have been greater among babies born to women in these age groups in these countries, than for babies born to women in other age groups in the same countries.

However, the overall burden of CRS depends both on the infection incidence and number of livebirths among women in different age groups. Therefore, to infer the setting in which the burden of CRS is likely to be the greatest, we would need to combine the above estimates with the age-specific fertility rate.

**5.2** a) Figure S5.1 plots the observed proportion seronegative. The median age at infection is the point at which the vertical dotted line in this figure crosses the x-axis, which occurs at about 6 years. This estimate suggests that the average force of infection is about 100×1/6≈17% per year.

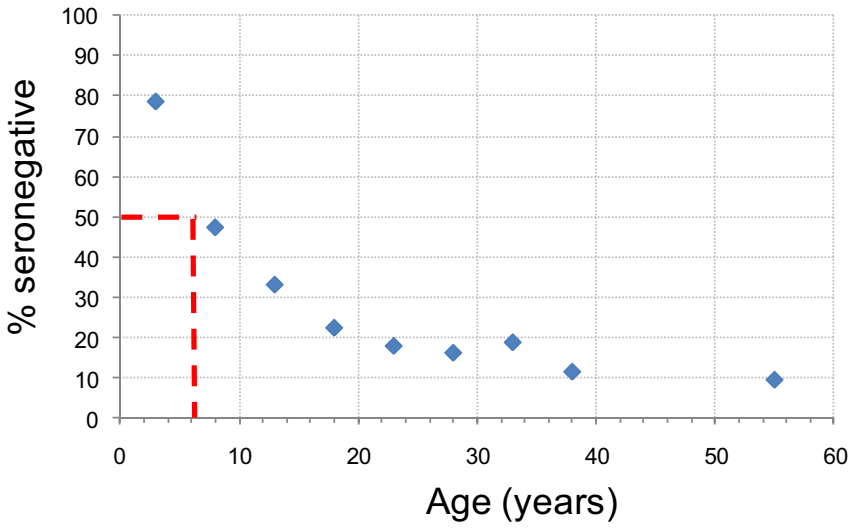



**Figure S5.1:** Observed proportion of individuals who did not have antibodies to rubella during 2004-5 in Bangladesh[1]

b) i)The overall proportion susceptible is calculated using equation 5.17 as the sum of the proportion susceptible in each age group, weighted by the proportion of the population that is in that age group ($p_a \times S_a/N_a$). The final column in the following table gives the values for $p_a \times S_a/N_a$ in each age group.

| Age group (years) | Number tested | Number negative | % negative | Proportion of the population that is in the given age range ($p_a$) | $p_a \times S_a/N_a$ |
|---|---|---|---|---|---|
| 1-5 | 61 | 48 | 78.7 | 0.1139 | 0.08964 |
| 6-10 | 61 | 29 | 47.5 | 0.1135 | 0.05391 |
| 11-15 | 63 | 21 | 33.3 | 0.1109 | 0.03693 |
| 16-20 | 62 | 14 | 22.6 | 0.1087 | 0.02457 |
| 21-25 | 83 | 15 | 18.1 | 0.104 | 0.01882 |
| 26-30 | 67 | 11 | 16.4 | 0.0923 | 0.01514 |
| 31-35 | 63 | 12 | 19.0 | 0.0775 | 0.01473 |
| 36-40 | 60 | 7 | 11.7 | 0.0641 | 0.0075 |
| ≥41 | 62 | 6 | 9.7 | 0.2151 | 0.02086 |

The overall proportion susceptible is therefore given by the sum of the values in the final column, i.e. 0.2821.

ii) The basic reproduction number can be estimated using the expression $1/s$ (equation 5.20), where $s$ is the proportion of the population that is susceptible. Using the value for $s$ obtained in part i) implies that $R_0=1/0.2821\approx3.5$.

iii) We can obtain an expression for the force of infection in terms of $R_0$ after rearranging either the expression $R_0=1+\lambda L$ or $R_0=\lambda L$, depending on whether the age distribution of the population is exponential or rectangular respectively. Figure S5.2, which plots the values for $p_a$ for 5 year age groups in Bangladesh in 2005[2] suggests that the age distribution was closer to being exponential than to being rectangular.

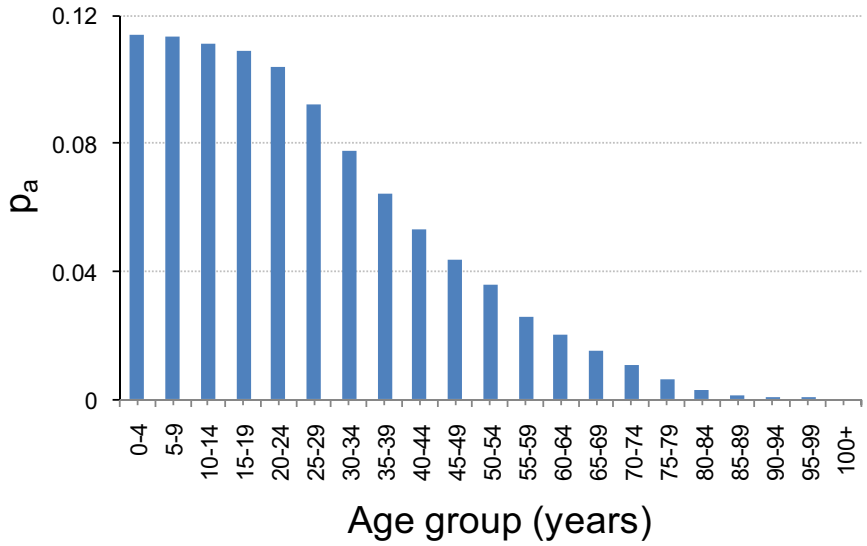



**Figure S5.2:** Proportion of individuals in different age groups in Bangladesh in 2005 ($p_a$).

Rearranging the expression $R_0=1+\lambda L$ gives the following expression for $\lambda$:

$$\lambda = \frac{R_0 - 1}{L}$$

Substituting for $L$=65 years and the value for $R_0$ obtained in part ii) implies that the force of infection equals:

$$\lambda \approx \frac{3.5-1}{65} \approx 4\% \text{ per year}$$

iv) Using the relationship $A = \frac{1}{\lambda + 1/L}$ (equation 5.10) and substituting for $L$=65 years and the value for $\lambda$ obtained in part iii) implies that the average age at infection is approximately:

$$A = \frac{1}{0.04 + 1/65} \approx 18 \text{ years}$$

Note that the values for $A$ and $\lambda$ are much smaller than those obtained in part a). This follows largely from the fact that estimates in part a) did not account for the age distribution of the population.

c) The following table summarizes the estimates for the average annual risk of infection calculated using the expression $\lambda = 1 - s_a^{1/a}$, where $a$ was taken as the midpoint of the age group for the corresponding data point. The force of infection was calculated using the result *rate≈-ln(*1*-risk)* (see page 111).

| **Age group (years)** | **% negative** | **Average annual risk of infection, calculated using $\lambda = 1 - s_a^{1/a}$** | **Average annual force of infection** |
|---|---|---|---|
| 1-5 | 78.7 | 0.0767 | 0.0798 |
| 6-10 | 47.5 | 0.0889 | 0.0931 |
| 11-15 | 33.3 | 0.0811 | 0.0846 |
| 16-20 | 22.6 | 0.0793 | 0.0826 |
| 21-25 | 18.1 | 0.0716 | 0.0743 |
| 26-30 | 16.4 | 0.0625 | 0.0646 |
| 31-35 | 19.0 | 0.0491 | 0.0503 |
| 36-40 | 11.7 | 0.0549 | 0.0565 |
| ≥41 | 9.7 | 0.0415 | 0.0424 |

We can also use the equation $\lambda_a = 1 - \frac{s_{a+1}}{s_a}$. However, when substituting $s_a$ and $s_{a+1}$ into this equation, we obtain the risk of infection between age band $a$ and age band $a$+1. Since each age band is of width 5 years, this infection risk is equivalent to a five year risk. We can convert this five year risk into an annual risk by adapting the logic described in section 5.2.2.1.4, which leads to the following equation for the average annual risk in age group $a$:

$$\lambda = 1 - (1 - \lambda_a)^{1/5}$$

The force of infection is then calculated using the result *rate≈-ln(1-risk)* (see page 111).

The following table summarizes the estimates obtained using this approach:

| Age group (years) | % negative | 5 year risk of infection, calculated using: $\lambda_a = 1 - \frac{s_{a+1}}{s_a}$ | Average annual risk of infection, calculated using: $\lambda = 1-(1-\lambda_a)^{1/a}$ | Average annual force of infection |
|---|---|---|---|---|
| 1-5 | 78.7 | 0.3964 | 0.0961 | 0.0798 |
| 6-10 | 47.5 | 0.2989 | 0.0686 | 0.0931 |
| 11-15 | 33.3 | 0.3213 | 0.0746 | 0.0846 |
| 16-20 | 22.6 | 0.1991 | 0.0434 | 0.0826 |
| 21-25 | 18.1 | 0.0939 | 0.0195 | 0.0743 |
| 26-30 | 16.4 | -0.1585 | -0.0299 | 0.0646 |
| 31-35 | 19.0 | 0.3842 | 0.0924 | 0.0503 |
| 36-40 | 11.7 | 0.1709 | 0.0368 | 0.0565 |
| ≥41 | 9.7 | - | - | 0.0424 |

The estimates obtained using both approaches suggest that the force of infection for adults is lower than that for children, e.g. >8% per year for those aged <20 years and <8% per year for those aged >20 years. However, the estimates for adults that are based on the equation $\lambda = 1-\lambda_a^{1/a}$ are difficult to interpret, since the proportion of 31-35 year olds who are seronegative is smaller than that for 26-30 year olds, which leads to the (unrealistic) estimate that the risk of infection was negative between the ages 21-25 and 26-30 year olds.

d) Figure S5.3 shows a plot of –ln(observed proportion seronegative) against the age midpoints for the data from Bangladesh. These figures also clearly highlight the fact that the datapoint for individuals aged 31-35 years is an outlier.

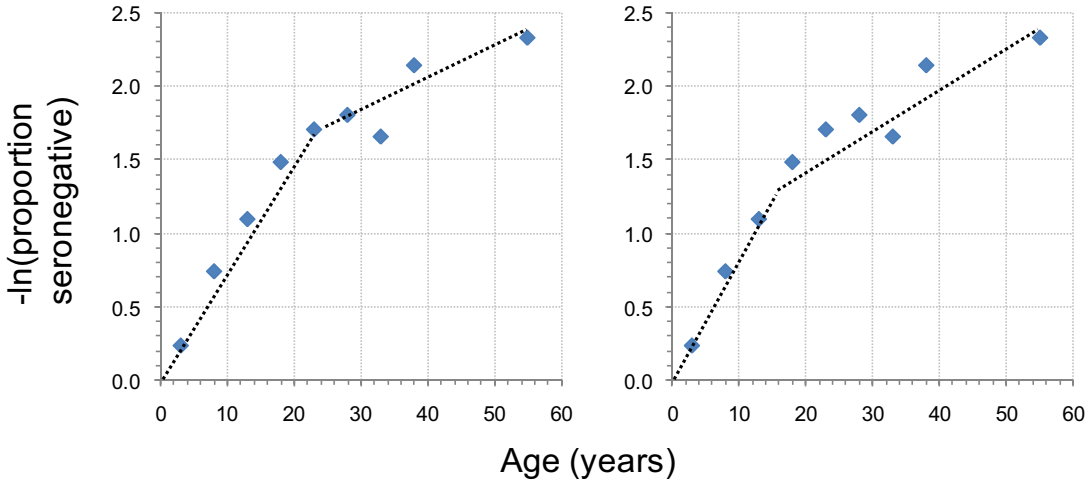



**Figure S5.3:** Plot –ln(observed proportion seronegative) against the age midpoints for the data from Bangladesh in Nessa *et al*[1], with different lines drawn by eye through the data points for individuals aged <20years (left-hand figure) and for those aged <15 years (right-hand figure).

As shown in the left-hand figure, the gradient of the line through the points for individuals aged <20 years is steeper than that through the points for individuals aged >20 years, suggesting that the force of infection is greater for those aged <20 years than for those aged >20 years.

However, based on these plots, we cannot conclude that the force of infection changes at age 20 years, since, as shown in the right-hand figure, we can also draw a straight line through the points for individuals aged over 15 years, which would imply that the force of infection changes at about this age. Ultimately, the age at which the force of infection is assumed to change needs to be biologically plausible, e.g. consistent with changes in behaviour, possible exposure to the infection, contact patterns etc at ages 15 or 20 years.

The gradient of the line through the points for individuals aged <15 years is about 1.6/15≈0.11 per year, suggesting that the force of infection in this age group is about 11% per year. The gradient of the line through the points for individuals aged >15 years is about 0.7/35≈0.02 per year, suggesting that the force of infection in this age group is about 2% per year.

**5.3** The following figure shows a plot of –ln(observed proportion seropositive) for the mumps data in section 5.2.3.2.2. The gradient of the line through the points for individuals aged <13 years is steeper than that through the points for individuals aged >13 years (3/13≈0.23 per year vs 1/35≈0.03 per year). This suggests that the force of infection is also greater for those aged <13 years than for those aged >13 years (23% vs 3% per year respectively).

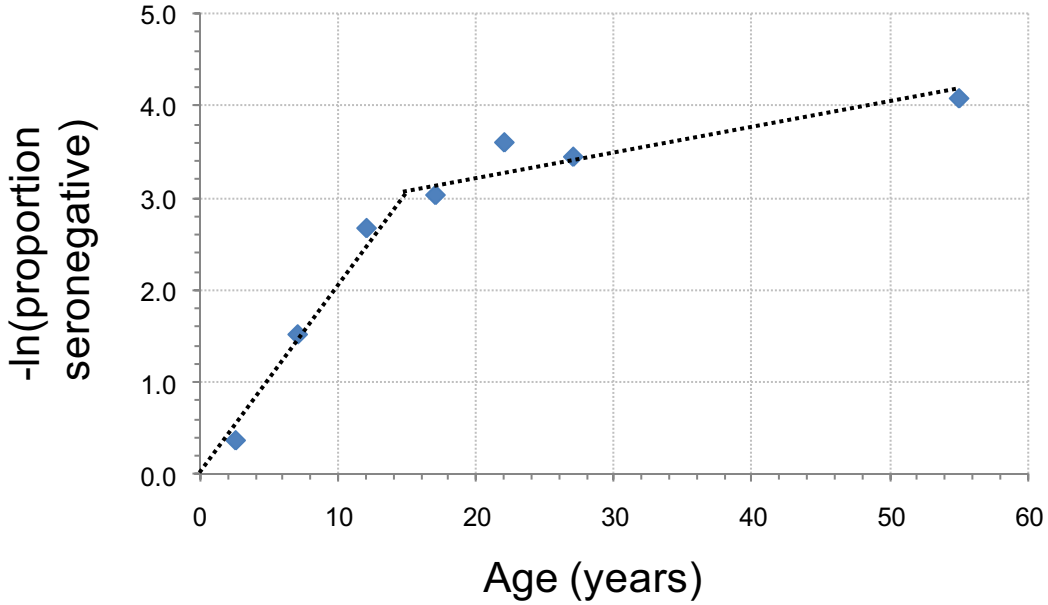



**Figure S5.4:** Plot of –ln(observed proportion seronegative) for the mumps data in section 5.2.3.2.2.

**5.4** i) One informal argument that is sometimes used to obtain this result is that, for realistic values of $L$, $1/L$ is small, in comparison with $\lambda$, and therefore $\frac{1}{\lambda + 1/L}$ must be approximately equal to $\frac{1}{\lambda}$.

We can also apply a formal mathematical argument, which uses the result that, for small values of $x$ (i.e. values that are close to zero), the expression $\frac{1}{1+x}$ is approximately equal to $1-x$ (see proof at the end of the solution to this question).

This argument is as follows:

We begin by noting that the equation $A = \frac{1}{\lambda + 1/L}$ can be rewritten in the form $\frac{1}{1+x}$ as follows:

$$A = \frac{1}{\lambda}\left(\frac{1}{1+\frac{1}{\lambda L}}\right) \qquad \text{S5.1}$$

For realistic values of the average life expectancy and for large values of the force of infection, $\frac{1}{\lambda L}$ is close to zero, and so, according to the result $\frac{1}{1+x} \approx 1-x$, the term in brackets in equation S5.1 is approximately equal to $1-\frac{1}{\lambda L}$. Substituting this approximation into equation S5.1 leads to the following:

$$A \approx \frac{1}{\lambda}\left(1-\frac{1}{\lambda L}\right) = \frac{1}{\lambda} - \frac{1}{\lambda^2 L}$$

If both the force of infection and the life expectancy are sufficiently large, then the second term in this equation is negligible (i.e. $\frac{1}{\lambda^2 L} \approx 0$) and so $A \approx \frac{1}{\lambda}$.

ii) To show that the expression $A = \frac{1}{\lambda}\left(\frac{1-(1+\lambda L)e^{-\lambda L}}{1-e^{-\lambda L}}\right)$ approximates to $1/\lambda$, we begin by observing that, for sufficiently large values for the life expectancy and the force of infection, $e^{-\lambda L}$ is close to zero. Using the result that for small values of $x$ (i.e. values that are close to zero), $\frac{1}{1-x} \approx 1+x$, we see that $\frac{1}{1-e^{-\lambda L}} \approx 1+e^{-\lambda L}$. Substituting this approximation into the equation for $A$, we obtain the following result:

$$A = \frac{1}{\lambda}\left(\frac{1-(1+\lambda L)e^{-\lambda L}}{1-e^{-\lambda L}}\right) \approx \frac{(1-(1+\lambda L)e^{-\lambda L})(1+e^{-\lambda L})}{\lambda}$$

This equation simplifies to the following:

$$A \approx \frac{1-e^{-2\lambda L}(1+\lambda L)-\lambda L e^{-\lambda L}}{\lambda}$$

If the force of infection is sufficiently large and for realistic values for the life expectancy, both $e^{-2\lambda L}(1+\lambda L) \approx 0$ and $\lambda L e^{-\lambda L} \approx 0$, which implies that $A \approx \frac{1}{\lambda}$

***Proof of the result*** $\frac{1}{1+x} \approx 1-x$ ***for small values of x***

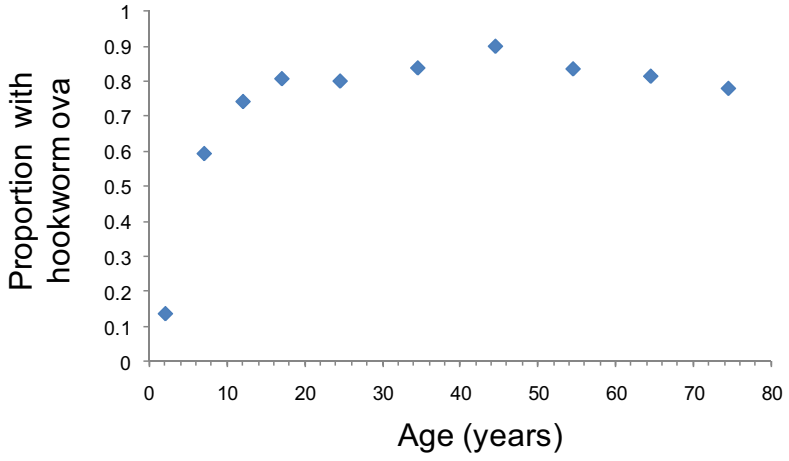
This result can be derived by using the fact that an expression of the form $\frac{1}{1+x}$ can be written using the following Binomial expansion:

$$\begin{aligned}\frac{1}{1+x} = (1+x)^{-1} &= 1-x+\frac{(-1)(-1-1)x^2}{2!}+\frac{(-1)(-1-1)(-1-2)x^3}{3!}+\ldots \\ &\quad +\frac{(-1)(-1-1)(-1-2)..(-1-n)x^{n-1}}{(n-1)!}+\ldots \\ &= 1-x+x^2-x^3+\ldots+(-1)^{n-1}x^{n-1}+\ldots\end{aligned}$$

For small values of $x$, terms in $x^2$, $x^3$ etc (known as "higher order terms") are small and can be ignored. Consequently $\frac{1}{1+x} \approx 1-x$.

The result that $\frac{1}{1-x} \approx 1+x$ follows after repeating the above argument but replacing $-x$ for x.

**5.5** The following figure shows that the proportion of individuals who had hookworm ova in their stools ($S_a/N_a$) increases with age and then reaches a plateau or (plausibly) decreases with increasing age.



We might therefore use a reversible model to describe the data, which assumes that the age-specific proportion infected eventually reaches a plateau with increasing age. Alternatively, a 2-stage model or a compound catalytic model might be appropriate, since these assume that the proportion positive peaks before subsequently decreasing with increasing age. In fact, the authors of [3] used a compound model to analyse the data.

**5.6** a) Assuming that maternal immunity is lost at a constant rate, $\mu$, the rate of change in the proportion of individuals who have maternal immunity ($m(a)$) and the proportion who are susceptible ($s(a)$) are given by the following equations:

$$\frac{dm(a)}{da} = -\mu m(a)$$

$$\frac{ds(a)}{da} = \mu m(a) - \lambda s(a)$$

The differential equation for $m(a)$ is of the form $\frac{dQ(t)}{dt} = -kQ(t)$ and can be solved to give the following (see section 3.5.1):

$$m(a) = m(0)e^{-\mu a}$$

where $m(0)$ is the proportion of inewborns who have maternal immunity. Since all individuals are assumed to be born with maternal immunity, $m(0)$=1, and so, substituting for $m(0)$=1 into the above equation gives $m(a)=e^{-\mu a}$.

Substituting for $m(a)=e^{-\mu a}$ into the differential equation for $s(a)$, we obtain the following equation:

$$\frac{ds(a)}{da} = \mu e^{-\mu a} - \lambda s(a)$$

which can be rewritten as follows:

$$\frac{ds(a)}{da} + \lambda s(a) = \mu e^{-\mu a}$$

This equation can be solved using the technique of "integrating factors" by following the steps below:

*Step 1.* Multiply both sides of the equation by $e^{\lambda a}$, to obtain the following:

$$\frac{ds(a)}{da}e^{\lambda a} + \lambda s(a)e^{\lambda a} = \mu e^{-\mu a}e^{\lambda a}$$

Note that, according to the rules of differentiation (section B.5), the left-hand side of this equation is equivalent to the derivative of $s(a)e^{\lambda a}$ with respect to $a$, and so the equation can be rewritten as follows:

$$\frac{d}{da}(s(a)e^{\lambda a}) = \mu e^{-\mu a}e^{\lambda a} \qquad \text{S5.2}$$

*Step 2.* We now integrate both sides of equation S5.2 between 0 and *a* to obtain the following:

$$\int_0^a \frac{d}{da}(s(a)e^{\lambda a})da = \int_0^a \mu e^{-\mu a} e^{\lambda a} da \qquad \text{S5.3}$$

Since integration is the converse of differentiation, the left-hand side equation S5.3 simplifies to:

$$s(a)e^{\lambda a}\Big|_0^a = s(a)e^{\lambda a} - s(0)$$

However, *s(0)*=0 (since no individuals are assumed to be susceptible at birth) and therefore the left-hand side of equation S5.3 simplifies to $s(a)e^{\lambda a}$.

By the rules of integration (section B.6) the right-hand side of equation S5.3 simplifies to the following:

$$\left[\frac{\mu}{\lambda-\mu}e^{(\lambda-\mu)a}\right]_0^a = \frac{\mu}{\lambda-\mu}e^{(\lambda-\mu)a} - \frac{\mu}{\lambda-\mu}$$

*Step 3*. Equating the expressions obtained from integrating the left-hand and right-hand sides of equation S5.3 leads to the following:

$$s(a)e^{\lambda a} = \frac{\mu}{\lambda-\mu}e^{(\lambda-\mu)a} - \frac{\mu}{\lambda-\mu}$$

Dividing both sides of this equation by $e^{\lambda a}$ leads to the intended result:

$$s(a) = \frac{\mu(e^{-\mu a} - e^{-\lambda a})}{\lambda-\mu}$$

b) Note that when *s(a)* is at a minimum, $\frac{ds(a)}{da} = 0$. We can therefore obtain the age at which the proportion of the population that is susceptible is at a minimum by identifying the values for *a* for which $\frac{ds(a)}{da} = 0$.

Differentiating the equation for *s(a)* that is discussed in part a), we obtain the following:

$$\frac{ds(a)}{da} = \frac{\mu(-\mu e^{-\mu a} + \lambda e^{-\lambda a})}{\lambda-\mu}$$

Setting this equation to zero, we see that the following must be satisfied for the proportion susceptible to be at a minimum:

$$-\mu e^{-\mu a} + \lambda e^{-\lambda a} = 0$$

Multiplying both sides of this equation by $e^{-\lambda a}$ and rearranging the resulting equation, implies that the following must hold:

$$e^{(\lambda-\mu)a} = \frac{\lambda}{\mu}$$

Taking the natural logs of both sides of this equation and then dividing by $\lambda$-$\mu$ leads to the intended result that the minimum in the proportion susceptible occurs when

$$a = \frac{\ln(\lambda/\mu)}{\lambda-\mu}$$

**5.7 a) *Proof of the result that $A = \frac{1}{\lambda+m}$, or equivalently, $A = \frac{1}{\lambda+1/L}$ for populations with an exponential age distribution, where m=1/L is the average mortality rate.***

Suppose that $N_0$ individuals are born each year. Assuming a constant mortality rate of $m$, the number of individuals of age $a$ is given by the equation (see section 3.5.1):

$$N(a) = N_0 e^{-ma}$$

Assuming a constant force of infection, $\lambda$, a proportion $e^{-\lambda a}$ of these individuals will be susceptible, and so the number of susceptible individuals of age $a$ ($S(a)$) is obtained by multiplying $N(a)$ by $e^{-\lambda a}$ , i.e.

$$S(a) = N(a)e^{-\lambda a} = N_0 e^{-(\lambda+m)a}$$

After substituting this expression into equation 5.9, we obtain the following equation:

$$A = \frac{\int_0^\infty a\lambda(a)S(a)da}{\int_0^\infty \lambda(a)S(a)da} = \frac{\int_0^\infty a\lambda N_0 e^{-(\lambda+m)a}da}{\int_0^\infty \lambda N_0 e^{-(\lambda+m)a}da} \qquad \text{S5.4}$$

Using the techniques discussed in section B.6, the numerator of this equation simplifies to the following:

$$\int_0^\infty a\lambda N_0 e^{-(\lambda+m)a}da = \lambda N_0\left[\frac{ae^{-(\lambda+m)a}}{-(\lambda+m)} - \frac{e^{-(\lambda+m)a}}{(\lambda+m)^2}\right]_0^\infty = \frac{\lambda N_0}{(\lambda+m)^2} \qquad \text{S5.5}$$

Similarly, the denominator in equation S5.5 simplifies to the following:

$$\int_0^\infty \lambda N_0 e^{-(\lambda+m)a}da = \lambda N_0\left[\frac{e^{-(\lambda+m)a}}{-(\lambda+m)}\right]_0^\infty = \frac{\lambda N_0}{\lambda+m} \qquad \text{S5.6}$$

Substituting the right-hand sides of equations S5.5 and S5.6 into the numerator and denominator of equation S5.4, and cancelling common terms from the numerator and denominator leads to our intended expression for $A$:

$$A = \frac{\frac{\lambda N_0}{(\lambda+m)^2}}{\frac{\lambda N_0}{\lambda+m}} = \frac{1}{\lambda+m}$$

***b) Proof of the result that, for populations with a rectangular age distribution, with a life expectancy of L, and assuming random mixing,*** $A = \frac{1}{\lambda}\left(\frac{1-(1+\lambda L)e^{-\lambda L}}{1-e^{-\lambda L}}\right)$

Suppose that $N_0$ individuals are born into the population each year. If the population has a rectangular age distribution in which no individuals die until age $L$, then the number of individuals of age $a$ also equals $N_0$.

A proportion $e^{-\lambda a}$ of these individuals will be susceptible, and so the number of susceptible individuals of age $a$ ($S(a)$) is obtained by multiplying $N_0$ by $e^{-\lambda a}$ , i.e.

$$S(a) = N_0 e^{-\lambda a}$$

After substituting this expression into equation 5.9, we obtain the following equation:

$$A = \frac{\int_0^\infty a\lambda(a)S(a)da}{\int_0^\infty \lambda(a)S(a)da} = \frac{\int_0^L a\lambda N_0 e^{-\lambda a}da}{\int_0^L \lambda N_0 e^{-\lambda a}da} \qquad \text{S5.7}$$

Using the techniques discussed in section B.5, the numerator of this expression simplifies to the following:

$$\int_0^L a\lambda N_0 e^{-\lambda a}da = \lambda N_0\left[\frac{ae^{-\lambda a}}{-\lambda} - \frac{e^{-\lambda a}}{\lambda^2}\right]_0^L = \lambda N_0\left(\frac{Le^{-\lambda L}}{-\lambda} - \frac{e^{-\lambda L}}{\lambda^2} + \frac{1}{\lambda^2}\right)$$
$$= \frac{N_0(1-(1+\lambda L)e^{-\lambda L})}{\lambda} \qquad \text{S5.8}$$

Similarly, the denominator in equation 5.7 simplifies to the following:

$$\int_0^L \lambda N_0 e^{-\lambda a}da = \lambda N_0\left[\frac{e^{-\lambda a}}{-\lambda}\right]_0^L = \frac{\lambda N_0(1-e^{-\lambda L})}{\lambda}$$
$$= N_0(1-e^{-\lambda L}) \qquad \text{S5.9}$$

Substituting the right-hand sides of equations S5.8 and S5.9 into the numerator and denominator respectively of equation S5.7, and cancelling out the common term $N_0$ leads to the intended result:

$$A = \frac{N_0(1-(1+\lambda L)e^{-\lambda L})}{\lambda N_0(1-e^{-\lambda L})} = \frac{1-(1+\lambda L)e^{-\lambda L}}{\lambda(1-e^{-\lambda L})}$$

**5.8** For a reversible catalytic model, the differential equations for the rate of change in the proportion susceptible and proportion currently infected is given by the following:

$$\frac{ds(a)}{da} = -\lambda s(a) + r_s z(a)$$
$$\frac{dz(a)}{da} = \lambda s(a) - r_s z(a)$$

In this model, the proportion of individuals of age *a* that are currently susceptible is given by 1-proportion currently infected, i.e. *s(a) = 1-z(a).*

Substituting this expression for *s(a)* into the differential equation for *z(a)* leads to the following equation:

$$\begin{aligned}\frac{dz(a)}{da} &= \lambda(1 - z(a)) - r_s z(a) \\ &= \lambda - (\lambda + r_s)z(a)\end{aligned} \qquad \text{S5.10}$$

At a given point on the plateau, $\frac{dz(a)}{da} = 0$. Equating equation S5.10 to zero, leads to the following result:

$$\lambda - (\lambda + r_s)z(a) = 0$$

After rearranging this equation, we obtain our intended result, i.e. $z(a) = \frac{\lambda}{\lambda + r_s}$

**5.9** a i) With the information provided, we can use the equation $A' = \frac{A}{(1-v)}$ (equation 5.34) to work out the long-term average age at infection for mumps following the introduction of vaccination. Substituting for *A*=4 years and *v*=0.6 into this equation (assuming for now, that the vaccine efficacy is 100%), the long-term average age at infection is given by $A' = \frac{4}{(1-0.6)} = 10$ years.

Given the debate about the efficacy of the mumps component of the MMR vaccine [4-6], it would be sensible to assume a vaccine efficacy of <100%. Assuming a vaccine efficacy of 85%, the long-term average age at infection equals:

$$A' = \frac{4}{(1 - 0.85 \times 0.6)} = \frac{4}{(1 - 0.51)} \approx 8.2 \text{ years}$$

a ii) The long-term average force of infection *λ'* can be obtained after rearranging the expression $A' = \frac{1}{\lambda' + m}$ (equation 5.33) and substituting our estimate of *A'* that we obtained in part i) into the resulting expression.

For example, the expression $A' = \frac{1}{\lambda' + m}$ can be rearranged to give the following expression for *λ'*:

$$\lambda' = \frac{1}{A'} - m$$

Substituting for $A'$ = 10 years (based on a vaccine efficacy of 100%), and $m$=1/60 per year into this equation leads to the following value for $\lambda'$:

$$\lambda' = \frac{1}{10} - \frac{1}{60} = \frac{5}{60} = 0.0833 \text{ per year}\cdot$$

Substituting for $A'$ = 8.2 years (based on a vaccine efficacy of 85%) leads to an estimate for the average force of infection of :

$$\lambda' = \frac{1}{8.2} - \frac{1}{60} = 0.106 \text{ per year.}$$

a iii) and a iv) The proportion susceptible and the infection incidence in the long-term can be calculated using equations 5.31 and 5.36, leading to the following values:

| | **100% vaccine efficacy** | | **85% vaccine efficacy** | |
|---|---|---|---|---|
| **Age (years)** | **Proportion susceptible (s(a)')=** $(1-v)e^{-\lambda' a}$ | **Average annual number of new infections per 100,000** $(\lambda' s(a)' \times 100{,}000)$ | **Proportion susceptible (s(a)')=** $(1-v)e^{-\lambda' a}$ | **Average annual number of new infections per 100,000** $(\lambda' s(a)' \times 100{,}000)$ |
| **15** | 0.115 | 955 | 0.1 | 1060 |
| **25** | 0.05 | 415 | 0.035 | 368 |
| **35** | 0.022 | 180 | 0.012 | 128 |

b) As shown by the calculations below, the average annual number of mumps infections per 100,000 population among 15-35 year olds in the long-term following the introduction of vaccination is somewhat higher than that before the introduction of vaccination. You might therefore advise the government to aim to attain a coverage which is much higher than 60% (e.g. 95%) and to proceed with caution when introducing MMR vaccination if it thinks that a coverage of only 60% can be achieved.

It might want to consider having a catch-up campaign covering the birth cohorts at greatest risk, and monitor the age-specific proportion susceptible in the population through seroprevalence surveys. Most importantly, before proceeding, it should also consider the effect that 60% coverage of MMR vaccination would have on the burden of measles, rubella and Congenital Rubella Syndrome.

***Calculations of the number of mumps infections per 100,000 population before the introduction of vaccination:***

For these calculations, we first need to estimate the force of infection that is predicted in the absence of vaccination. Rearranging the equation $A = \frac{1}{\lambda + m}$ (equation 5.10) we

obtain the following equation for the force of infection in the absence of vaccination: $\lambda = \frac{1}{A} - m$. Substituting for $A$=4 years (the average age at infection before the introduction of vaccination) and $m$=1/60 per year into this equation, we obtain the following for $\lambda$:

$$\lambda = \frac{1}{4} - \frac{1}{60} = 0.233 \text{ per year.}$$

Using this estimate for the force of infection, we obtain the following values for the proportion susceptible and the average annual numbers of infections per 100,000 population in different age groups before the introduction of vaccination:

| **Age (years)** | **Proportion susceptible (s(a)=$e^{-\lambda a}$)** | **Average annual number of new infections per 100,000 ($\lambda s(a) \times 100000$)** |
|---|---|---|
| **15** | 0.03 | 705 |
| **25** | 0.003 | 68 |
| **35** | (0) | 7 |

c) If the herd immunity effects of vaccination are not accounted for, the proportion susceptible and the number of infections per 100,000 population in the long-term following the introduction of vaccination would be given by the values calculated in part b) but multiplied by (1-$v$), where $v$ is the proportion of individuals that are effectively vaccinated. $v$ is given by the expression vaccine coverage×vaccine efficacy. The values obtained assuming that the vaccine efficacy is 100% and 85% are provided below. These show that the static model greatly underestimates the long-term numbers of mumps infections per 100,000 population in 15-35 year olds following the introduction of vaccination.

| | **100% vaccine efficacy** | | **85% vaccine efficacy** | |
|---|---|---|---|---|
| **Age (years)** | **Proportion susceptible** | **Average annual number of new infections per 100,000** | **Proportion susceptible** | **Average annual number of new infections per 100,000** |
| **15** | 0.012 | 282 | 0.015 | 345 |
| **25** | 0.001 | 27 | 0.001 | 33 |
| **35** | 0 | 3 | 0 | 3 |

**5.10** a) Multiplying both sides of equation 5.29 by (1-$v$), we obtain the following:

$$R_0(1-v) = \lambda' L + 1$$

Subtracting both sides of this equation by 1 and dividing by L, we obtain the following equation:

$$\frac{R_0(1-v)-1}{L} = \lambda' \qquad \text{S5.11}$$

b) and d) Figure S5.5 compares the plot of $\lambda' = \frac{R_0(1-v)-1}{L}$ against that of $\lambda' = \lambda(1-v)$.

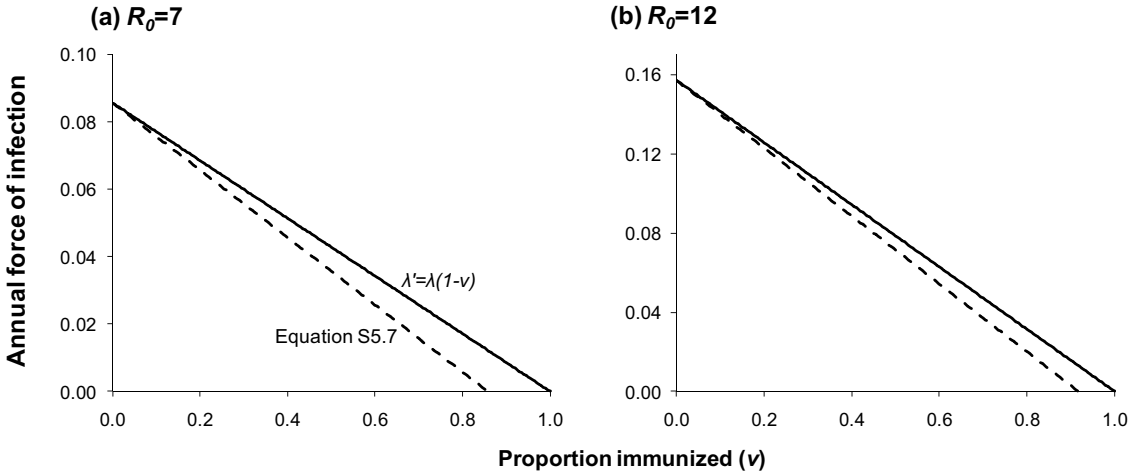



**Figure S5.5:** Predictions of the average annual long-term force of infection following the introduction of vaccination, calculated using $\lambda' = \frac{R_0(1-v)-1}{L}$ (dotted line) for different levels of the immunization coverage among newborns, in a A. low transmission ($R_0$=7) and B. a high transmission setting ($R_0$=12). The solid line shows the annual force of infection which would be seen if the force of infection was directly proportional to the proportion of individuals that are protected by vaccination($v$), i.e. if $\lambda' = \lambda(1-v)$.

c) You might have expected the force of infection as predicted by the equation $\lambda' = \lambda(1-v)$ to decrease more slowly with increased vaccination coverage than that predicted by the line $\frac{R_0(1-v)-1}{L} = \lambda'$, since the gradient of the latter line is steeper than that for $\lambda' = \lambda(1-v)$.

For example, recall that the gradient of the line $\frac{R_0(1-v)-1}{L} = \lambda'$ is the factor by which we multiply "$v$" (i.e. the "coefficient" of $v$). The coefficient of $v$ in this equation, and therefore the gradient of the line is $-R_0/L$. Substituting for $R_0 = 1+\lambda L$ (equation 5.21) into this equation, we see that the coefficient is equal to:

$$-\frac{R_0}{L} = -\frac{1+\lambda L}{L}$$

The expression for the gradient simplifies to the following:

$$-\left(\lambda + \frac{1}{L}\right)$$

In contrast, the gradient of the line $\lambda' = \lambda(1-v)$ is just $-\lambda$.

Since $\lambda + \frac{1}{L}$ is bigger than λ, we can conclude that the gradient of the line $\lambda' = \lambda(1-v)$ will be steeper than that given by equation 5.11.

e) You should find that it is not possible to rearrange the equation to obtain an explicit expression for $\lambda'$ in terms of $R_0$, $L$ and $v$, since the numerator has a term $\lambda'$ and the denominator has a term $e^{-\lambda' L}$.

Instead, we need to use iterative techniques to obtain the value for $\lambda'$ which results from a given value for $R_0$, $v$ and $L$, as follows:

We first rearrange the equation $R_0 = \frac{\lambda' L}{(1-v)(1-e^{-\lambda' L})}$ so that we have an expression for $\lambda'$ in terms of all the other terms in the equation. For example, we could rearrange the equation to obtain the following:

$$\lambda' = \frac{R_0(1-v)(1-e^{-\lambda' L})}{L} \qquad \text{S5.12}$$

If we substitute some value for $\lambda'$ (denoted by $\lambda'_0$) into the right-hand side of this equation, then for given values for $R_0$, $L$ and $v$, we will obtain another value for $\lambda'$ (we shall denote it by $\lambda'_1$). If we then substitute $\lambda'_1$ into the right-hand side of equation 5.12, we obtain another value for $\lambda'$ (we shall denote it by $\lambda'_2$). Repeating this process several times, we eventually obtain a series of values, $\lambda'_0, \lambda'_1, \lambda'_2, \lambda'_3, \ldots$, and we find that the difference between successive values of $\lambda'_i$ becomes progressively smaller, until the value obtained satisfies equation S5.12 (see Table S5.1). These iterations can be set up in a spreadsheet.

**Table S5.1**: Illustration of how the post-vaccination force of infection at equilibrium, $\lambda'$, which satisfies the equation $R_0 = \frac{\lambda' L}{(1-v)(1-e^{-\lambda' L})}$ may be calculated iteratively from the equation $\lambda'_{i+1} = \frac{R_0(1-v)(1-e^{-\lambda'_i L})}{L}$, assuming that $R_0$=7, $L$=70 years and $v$=0.1. In this instance, the average force of infection which might be expected if the vaccination coverage among newborns is 10% is 0.090 per year.

| **Iteration number** | $\lambda'_i$ (per year) | **Value for** $\frac{R_0(1-v)(1-e^{-\lambda'_i L})}{L}$ |
|---|---|---|
| 0 | $\lambda'_0 = 0.05$ | $\frac{7(1-0.1)(1-e^{-0.05\times 70})}{70} = 0.2$ per year. |
| 1 | $\lambda'_1 = 0.2$ | $\frac{7(1-0.1)(1-e^{-0.2\times 70})}{70} = 0.0899999$ per year |
| 2 | $\lambda'_2 = 0.0899999$ | $\frac{7(1-0.1)(1-e^{-0.0899999\times 70})}{70} = 0.0898347$ per year |
| 3 | $\lambda'_3 = 0.0898328$ | $\frac{7(1-0.1)(1-e^{-0.0898328\times 70})}{70} = 0.0898328$ per year |

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