Imperial College London – Zambart

Workshop on *Analysing and modelling epidemic data*

Practical: Modelling vaccination.

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Adapted using materials from Prof Nim Arinaminpathy

The aims of the practical are:

- To introduce yourselves to the modelling of public health interventions in a compartmental model.
- To explore the concepts of perfect, all-or-nothing and leaky vaccines in a transmission model, and understand their utility and limitations in the control of infectious diseases.

In this hand-out, generally:

▶ Indicates an instruction.

▶ Indicates a useful tip or note.

▶ Indicates a question.

Example 1: Vaccination at birth

► *Navigate to the odin interface* https://shiny.dide.ic.ac.uk/infectiousdiseasemodels-lusaka-2022/ *in Chrome or Safari.*

► *In the Friday section, "Modelling vaccination", click on "Vaccine at birth".*

This is a simple simulation of a vaccine that is introduced at or soon after birth. Think back to your open SIR model. The aim of vaccinating at birth is to effectively remove new-born individuals from the $Susceptible$ population before they encounter $Infected$ individuals, so you do not really need any new compartments to 'track' the vaccinated population.

Instead, the ODEs will be

$$\frac{dS}{dt} = (1-p)bN - \beta\frac{SI}{N} - \mu S$$

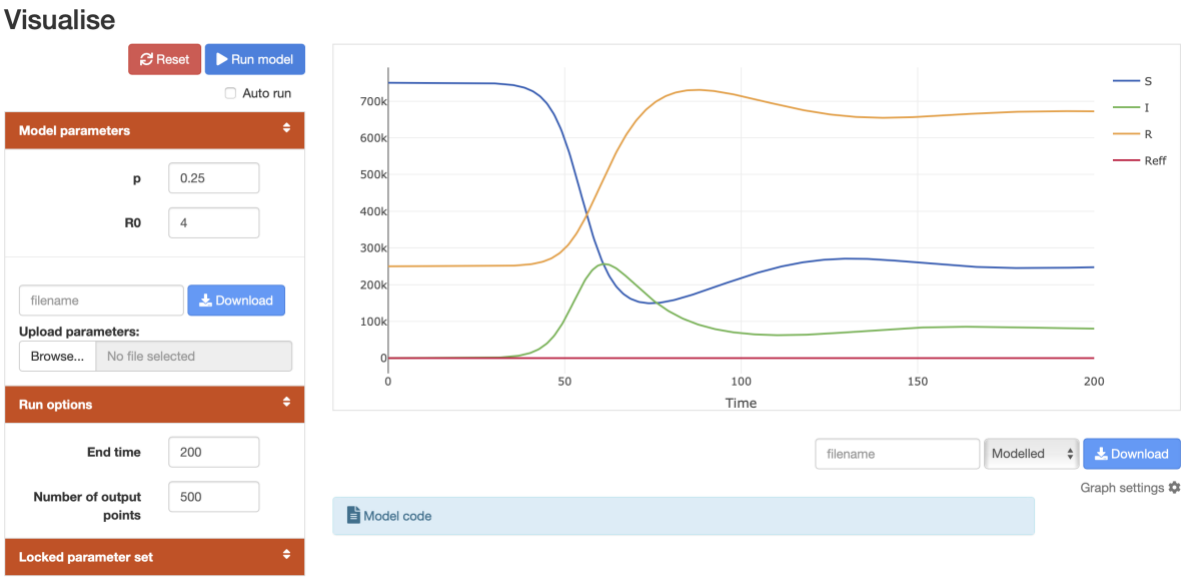
$$\frac{dI}{dt} = \beta\frac{SI}{N} - \gamma I - \mu I$$

$$\frac{dR}{dt} = pbN + \gamma I - \mu R$$

where *p* equals the proportion vaccinated at birth. Note that in the first equation we are not subtracting *p,* but rather calculating *1 – p*.

► *Code in the above ODEs into the* **Editor tab** *and compile your code with the parameters and initial conditions provided.*

► *Once you are happy with your code, go to the* **Visualise tab** *and run the model for 200 days. Your result should look like this:*



► **Question 1:** what is the value of β for this disease? How does the value of R_0 compare with the value for R_{eff} at the start of the outbreak? Why are they different?

► Remember that in an SIR model, R_0 is calculated as the rate of movement into the *I* compartment divided by the rate(s) of movement out of *I*.
► You can remove variables from the graph by clicking on their letter (name) on the top-right of the plot area.

```
# Your code should look like this
deriv(S) <- (1 - p) * b * N - beta * S * I / N - mu * S
deriv(I) <- beta * S * I / N - gamma * I - mu * I
deriv(R) <- p * b * N + gamma * I - mu * R
```

The code already gives you the calculation, which is $\beta = R_0 (\gamma + \mu) = 4 \cdot (0.1 + 0.019) = 0.48$
In this case, the outbreak does not start with the value of R_{eff} being equal to R_0, given the population is NOT completely susceptible. Rather, at the start of the simulation 25% of the population is assumed to be 'vaccinated', as it is the 25% of all those being born at every time-step in the model. This would be similar to saying that a neonatal vaccination campaign has a 25% coverage in the population being vaccinated, which reduces the 'baseline' susceptibility of the population.

► *Now use* Graph settings *to plot R_{eff} on a secondary y axis.*

► **Question 2:** How is the R_{eff} changing over the course of the outbreak? On which day does the outbreak peak (i.e. max. number of individuals in *I*)? How does this relate with the number of individuals in *S* and *R*?

It can be seen that the outbreak peaks around the 62nd day. This is roughly the same time-step in the model as when the value of R_{eff} is equal to 1. That is, from this point onward, the epidemic starts to decline. Interestingly, a few days prior to this point, the number of individuals in the *S* and *R* compartments was the same. That is, the pool of susceptible individuals was matched by the number of individuals who had recovered (and therefore were immune).

In this example, you can see how the reduction in the pool of susceptible brings about a decrease in the force of infection, despite the proportion of infected in the population continued to increase for 6 more days. This can be better visualised by setting the y axis to the log scale. At the point in which the *S* and *R* trajectory lines cross, there is a deceleration in the growth trajectory of the *I* line, which was previously increasing exponentially.

► **Question 3:** What proportion of the population would have to be vaccinated at birth to prevent an outbreak?

► This is known as the *heard immunity threshold* (HIT) and is closely related to R_0. You can corroborate your estimate by varying the value of *p* in the **Sensitivity tab** and plotting *I*.

For the simple case of a vaccine that offers perfect protection against infection with homogeneous coverage in the population

$$HIT = 1 - \frac{1}{R_0} = 1 - \frac{1}{4} = 0.75$$

Please let the class demonstrator know you are finished.

Example 2: Perfect vaccine

► *Navigate back to the odin interface* https://shiny.dide.ic.ac.uk/infectiousdiseasemodels-lusaka-2022/ *and, in the Friday section, now click on "Perfect vaccine".*

We are now going to model a 'perfect' vaccine that is introduced before the onset of an outbreak. In this case, we are also aiming to remove individuals from the $Susceptible$ population before they come in contact with $Infected$ individuals.

We are going to move them into an absorbing state, $Vaccinated$. This is called an absorbing state, because there are no further movements out of it, only in, so they are assumed to remain there throughout the duration of the model run. Whilst this is not dissimilar from what we did in ***Example 1***, it will serve as a good cornerstone for building more complex vaccinations models!

p_vacc is our vaccination parameter, representing the proportion of $Susceptible$ being vaccinated at the start of the model simulation.

► Compile and run the model for 200 days with p_vacc set to its default value of 0.

► **Question 1:** from the model parameters, what is the value of R_0 for this disease? Given this value, what is the HIT? Corroborate your estimate by varying the value of p_vacc in the **Sensitivity tab** and plotting *I*.

► Note we are assuming a closed population where everyone mixes homogeneously.

$$R_0 = \frac{\beta}{\gamma} = \frac{1/5}{1/7} = \frac{0.25}{0.14} = 1.75$$

$$HIT = 1 - \frac{1}{R_0} = 1 - \frac{1}{1.75} = 0.43$$

► *In groups of 4, discuss an example of an infectious disease with similar characteristics to the one being modelled here.*

► **Question 2:** What potential dynamics would you incorporate in this model to make it useful for informing discussions around vaccination strategies to prevent an outbreak of this disease? What vaccine characteristics would you model to make it more "realistic"?

This example is similar to what would be experienced during a flu outbreak in a confined population. For example, in army barracks or boarding schools.

We have thus assumed a homogenous population with equally homogenous mixing. However, other populations do not follow these dynamics. For a heterogenous population (e.g. general population), it would be important to consider factors such as age distribution and age-specific mixing in the population.

Similarly, for the case of the vaccine being simulated, protection conferred is in reality not perfect. We would need to consider that vaccines have varying degrees of *efficacy* against different aspects of the natural history of disease.

Please let the class demonstrator know you are finished.

Example 3: 'Imperfect' vaccines

► *Navigate back to the odin interface* https://shiny.dide.ic.ac.uk/infectiousdiseasemodels-lusaka-2022/ *and, in the Friday section, now click on "Leaky vaccine".*

Vaccination efficacy in the real world is not perfect. We are now going to look at some approaches to model 'imperfect' vaccines; that is, more realistic vaccines! 'Imperfect' properties of a vaccine reflect the actual *vaccine efficacy*.

Broadly, we can think of vaccine efficacy as an 'all-or-nothing' type of protection, or as a 'leaky' protection. For instance, if what we are intending to represent is a vaccine that protects against infection, an 'all-or-nothing' vaccine will be one where a proportion of those vaccinated are assumed to become fully immune against infection, whereas the rest are assumed to have no protection at all and remain fully susceptible.

Most commonly, though, vaccine efficacy will be 'leaky', meaning all individuals vaccinated receive some level of protection. However, they will also be susceptible to infection, yet at a lower rate than those not vaccinated (i.e. those in the $Susceptible$ population).

► **Let's start simple!**

► Go to the **Editor tab** and observe the model provided. This is a model for an 'all-or-nothing' vaccine that provides 70% protection against infection. Compile and run the model for 200 days with p_vacc set to its default value of 0.

► **Question 3:** With p_vacc set to its default value of 0, how do the outbreak dynamics compare to those in the previous example with a "perfect" vaccine? As in the previous example, calculate the value of R_0 and the ***critical vaccination coverage*** for this disease. Corroborate your estimate by varying the value of p_vacc in the **Sensitivity tab** and plotting *I*. How does your new R_0 and HIT vary from the previous example?

At a coverage of 0%, the outbreak dynamics are identical to the previous example with a perfect vaccine. Again, the aim is to build in complexity little by little. Outbreak dynamics will be, however, different once we increase vaccination coverage.

For example, we can see that at a coverage of 43%, there is still an outbreak starting towards the end of the simulated period. That is, the HIT has increased now we assume the vaccine is not perfect, but rather that only a proportion of those vaccinated acquire (perfect) immunity!

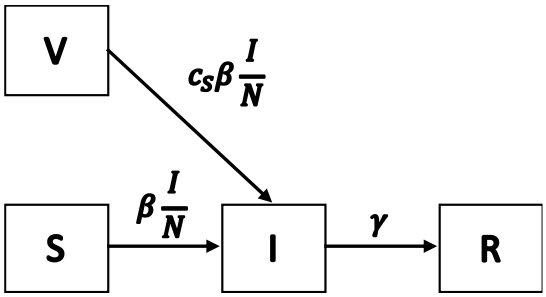
In this case, rather than the HIT we need to calculate the critical vaccination coverage, p_c, as follows

$$p_c = \frac{HIT}{ve} = \frac{0.43}{0.7} = 0.61$$

You can corroborate that a *p_vacc* of 0.61 is indeed enough to stop an epidemic from taking off. Use the sensitivity tab to set 10 model runs using an arithmetic range from 0.5 to 0.7, with a central value of 0.61.

► **Let's build in complexity!**

We are now going to modify our code to simulate a 'leaky' vaccine. In this case, we are accounting for the fact that all those vaccinated will be subject to the force of infection too, albeit lower than those unvaccinated (i.e. fully susceptible), given vaccine efficacy against infection, c_S. So, the model diagram looks like this



We can denote vaccine efficacy as a reduced susceptibility to infection

$$c_s = (1 - ve)$$

where ve is the vaccine efficacy parameter, and thus c_s is a multiplier reducing the force of infection acting on those in the *Vaccinated* compartment.

► Use the box below to write down the ODEs for this model with a 'leaky' vaccine.
► Once you have your new equations, go back to the **Editor tab** and modify the code accordingly.

► You may find the following steps helpful:

1. c_s is a new parameter we need to define.
2. Write down the new model equation of $^{dV}/_{dt}$ accounting for the reduced susceptibility c_s to infection.
3. Note we are implying they leave the *Vaccinated* compartment because they are becoming infected, so you would also need to account for this movement in $^{dI}/_{dt}$.
4. In your initial conditions, we are no longer assuming that only a proportion receive the protective effect of the vaccine, so your will need to modify initial(S) and initial(V) too.
5. The rest of your code will remain unchanged.

```
# modified bits of code should look like this, the rest should remain the same
deriv(I) <- beta * S * I / N + c_s * beta * V * I / N - gamma * I
deriv(V) <- -c_s * beta * V * I / N
initial(S) <- pop * (1 - p_vacc) - I0
initial(V) <- pop * p_vacc
c_s <- 1 - ve
```

$$\frac{dS}{dt} = -\beta\frac{I}{N}S$$

$$\frac{dI}{dt} = \beta\frac{I}{N}S + c_s\beta\frac{I}{N}V - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

$$\frac{dV}{dt} = -c_s\beta\frac{I}{N}V$$

► Compile and run the model for 365 days, and **plot only *I and V*** (use secondary axis for *V*) with p_vacc set to:

1. Its default value of 0.
2. The HIT you calculated in ***Example 1*** for a perfect vaccine.
3. The HIT you calculated in ***Example 2*** for an "all-or-nothing" vaccine.

► **Question 4:** What is your new critical vaccination coverage with a 'leaky' vaccine that is 70% effective at preventing infection? What would this mean for a vaccination campaign against this disease?

We need to calculate the **critical vaccination coverage, p_c;** that is, the coverage needed to interrupt transmission (i.e. $R_{eff} < 1$). So firstly

$$R_{eff} = (1-p) * R_0 + pc_s * R_0$$

where p is the proportion of the population vaccinated and c_s the reduction in susceptibility given the vaccine. Setting $p = p_c$ when $R_{eff} = 1$, and solving for p_c we find that

$$p_c = \frac{1 - \frac{1}{R_0}}{1 - c_s} = \frac{1 - \frac{1}{1.75}}{1 - 0.3} = 0.61$$

The value for p_c has not changed compared to that calculated for an "all-or-nothing" vaccine. However, given vaccine-induced immunity is leaky, a subsequent seeding of the infection in the population could trigger an outbreak.

Indeed, you can corroborate this would be the case when vaccinating 61% of the population and plotting only the model trajectory for *V*. We can see that the number of individuals in *V* over time decreases, whereas in the previous example with "all-or-nothing" vaccine it remained constant over time.

► Just another notch more complex!

So far, we have only considered vaccine efficacy against infection. However, we know vaccines against infectious diseases can have an impact in different aspects of the natural history of disease.

For example, vaccines may be effective in reducing the severity of symptoms if people get infected, but not in preventing infection in the first place. Conversely, vaccines can reduce susceptibility, just as we have modelled them thus far, and have an additional effect in reducing *infectivity* (i.e. the probability a vaccinated individual will transmit the disease onward if infected).

► Use the box below to draw a model diagram and its equations, for a vaccine with both efficacy in reducing *susceptibility*, c_S, and *infectivity,* c_I.

► You may find the following steps helpful:

1. Build on your last model, which already accounts for a reduced force of infection given c_s for those in the $Vaccinated$ compartment.
2. We can pre-define the force of infection, λ, as the joint effect of individuals who are infected, but unvaccinated, I, and those that are infected and vaccinated, I_v:

$$\lambda = \beta \frac{I}{N} + c_I \beta \frac{I_v}{N}$$

This new model requires an additional compartment I_v to represent those who move on from vaccinated to infected. This is because they will be intrinsically different to those moving from susceptible to infected, given they have a reduced effect on the force of infection given the new vaccine efficacy parameter, c_I.

Given the added layer of complexity, we are pre-defining the force of infection as λ, which is already accounting for the different infectivity of those in the new different infectious compartments. So, the model diagram and equations should look like this

$$\lambda = \beta \frac{I}{N} + c_I \beta \frac{I_v}{N}$$

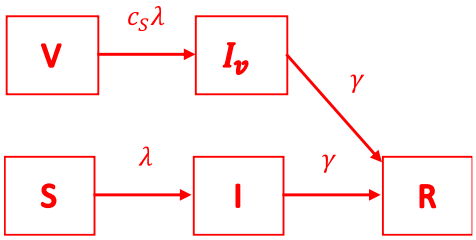
$$\frac{dS}{dt} = -\lambda S$$

$$\frac{dI}{dt} = \lambda S - \gamma I$$

$$\frac{dV}{dt} = -c_S \lambda V$$

$$\frac{dI_v}{dt} = c_S \lambda V - \gamma I_v$$

$$\frac{dR}{dt} = \gamma I + \gamma I_v$$



This is the end of the practical!