Intentional infection as a method of population level disease control

Newborn infection

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Motivation

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- This method is out of date, banned in some places, why do we care?
  - In history, the mechanisms and benefits of intentional infection on a population level was not quite understood.
  - New application to immunology, i.e. Transmissible vaccine.

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$$\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= \mu - \beta SI - \mu S\,,\\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta SI - \gamma I - \mu I\,,\\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - \mu R\,.\end{aligned} \tag{1}$$

Where S, I and R represent susceptible, infected and recovered.

μ is birth/death rate, β is the transmission rate, γ is recovery rate.

Method

The following assumptions are made to simplify the model to start with:

- There is no difference between intentionally infected and normally infected individuals.
- There is no disease induced mortality.
- Birth and natural death rate are the same, so the total population remains constant.
- The latent period is short enough to be ignored.
- All susceptible individuals are equally likely to be infected, and all infected individuals are equally infectious.

Method

With intentional infection on newborn, we have,

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \mu(1-p) - \beta SI - \mu S\,, \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta SI + \mu p - \gamma I - \mu I\,, \\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - \mu R\,.
\end{aligned} \tag{2}$$

In addition to the parameters above,

p is the proportion of newborn intentionally infected.

We non-dimensionalize the above system by scaling time, by

$$\tau = (\gamma + \mu)t\,, \tag{3}$$

which yields

$$\frac{\mathrm{d}S}{\mathrm{d}\tau} = \epsilon(1-p) - \mathcal{R}_0 SI - \epsilon S\,, \tag{4a}$$

$$\frac{\mathrm{d}I}{\mathrm{d}\tau} = \mathcal{R}_0 SI + \epsilon p - I\,, \tag{4b}$$

where $\epsilon = \frac{\mu}{\gamma+\mu}$, $\mathcal{R}_0 = \frac{\beta}{\gamma+\mu}$.

Equilibria

Solving equations above to find equilibria, we obtain,

$$\hat{S} = \frac{1}{\mathcal{R}_0} - \frac{2p}{(\mathcal{R}_0 - 1) + \sqrt{(\mathcal{R}_0 - 1)^2 + 4\mathcal{R}_0 p}}, \tag{5a}$$

$$\hat{I} = \frac{\epsilon(\mathcal{R}_0 - 1) + \epsilon\sqrt{(\mathcal{R}_0 - 1)^2 + 4\mathcal{R}_0 p}}{2\mathcal{R}_0}. \tag{5b}$$

Notice, $\hat{I} \neq 0$ for all p between 0 and 1. Meaning there is always infected cases in the population. Therefore, the equilibrium is an Endemic Equilibrium (EE).

Stability of Equilibria

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$$\mathcal{J} = \begin{bmatrix} -\mathcal{R}_0 I - \epsilon & -\mathcal{R}_0 S \\ \mathcal{R}_0 I & \mathcal{R}_0 S - 1 \end{bmatrix}. \tag{6}$$

Stability of Equilibria

Eigenvalues of the Jacobian are,

$$\lambda_{1,2} = \frac{-(\epsilon K^2 + 2\epsilon K + 4p\mathcal{R}_0)}{4K} \pm \frac{\sqrt{(\epsilon K^2 + 2\epsilon K + 4p\mathcal{R}_0)^2 - 4(2\epsilon K^3 + 8\epsilon K p\mathcal{R}_0)}}{4K} \tag{7}$$

Where $K = (\mathcal{R}_0 - 1) + \sqrt{(\mathcal{R}_0 - 1)^2 + 4\mathcal{R}_0 p}$,

We can conclude that $\Re(\lambda_{1,2}) < 0$

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- We are unable to compare the results of this model to others for the purpose of observing any advantages.
- One way of defining "have advantage" is to compare total mortality counts. It describes the total casualty.
- If intentional infected cases have the same mortality rate as normally infected cases, then clearly it is going to be a disaster. Therefore, we need to have separate disease induce mortality rate for each of them.
- We need to divide I into two separate infective classes. V for intentionally infected class, I for normally infected class.

Model with disease induced mortality rate

Therefore, our model becomes,

$$\frac{\mathrm{d}S}{\mathrm{d}\tau} = \epsilon(1-p) - \mathcal{R}_0 S(V+I) - \epsilon S\,, \tag{8a}$$

$$\frac{\mathrm{d}V}{\mathrm{d}\tau} = \mathcal{R}_0 SV + \epsilon p - V\,, \tag{8b}$$

$$\frac{\mathrm{d}I}{\mathrm{d}\tau} = \mathcal{R}_0 SI - I\,, \tag{8c}$$

$$\frac{\mathrm{d}M}{\mathrm{d}\tau} = p_V(1-\epsilon)V + p_I(1-\epsilon)I\,, \tag{8d}$$

$$\frac{\mathrm{d}R}{\mathrm{d}\tau} = (1-p_V)(1-\epsilon)V + (1-p_I)(1-\epsilon)I - \epsilon R\,, \tag{8e}$$

Where p_V and p_I represent the mortality rate for intentionally infected and normally infected cases, respectively.

Equilibria

If $p \neq 0$, the equilibrium is,

$$\hat{S} = \frac{1}{\mathcal{R}_0} - \frac{2p}{(\mathcal{R}_0 - 1) + \sqrt{(\mathcal{R}_0 - 1)^2 + 4\mathcal{R}_0 p}}\,, \tag{9a}$$

$$\hat{V} = \frac{\epsilon(\mathcal{R}_0 - 1) + \epsilon\sqrt{(\mathcal{R}_0 - 1)^2 + 4\mathcal{R}_0 p}}{2\mathcal{R}_0}\,, \tag{9b}$$

$$\hat{I} = 0\,. \tag{9c}$$

It is interesting that, at equilibrium, normally infected cases cease to exist. This may be helpful for eradication of disease.

By using the same method as the previous model, we again showed that the equilibrium is stable.

Effect of intentional infection on total mortality

Smallpox

Table: Model parameters and smallpox values.

Symbol	Meaning	Value
μ	Natural *per capita* death rate	$\frac{1}{50\times365}$ per day
γ	Recovery rate	$\frac{1}{22}$ per day
$\mathcal{R}_0$	Basic reproductive number	4.5
p_V	Intentionally infected cases death rate	0.01
p_I	Normally infected cases death rate	0.3

Effect of intentional infection on total mortality

Mortality rate at EE

$$\left.\frac{\mathrm{d}M}{\mathrm{d}t}\right|_{\mathrm{EE}} = \frac{p_V(1-\epsilon)\epsilon(\mathcal{R}_0-1) + p_V(1-\epsilon)\epsilon\sqrt{(\mathcal{R}_0-1)^2+4\mathcal{R}_0 p}}{2\mathcal{R}_0}, \quad (10)$$

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- Mortality rate increases as p increases.
- In the long run, a larger proportion of intentional infection will lead to more casualties.

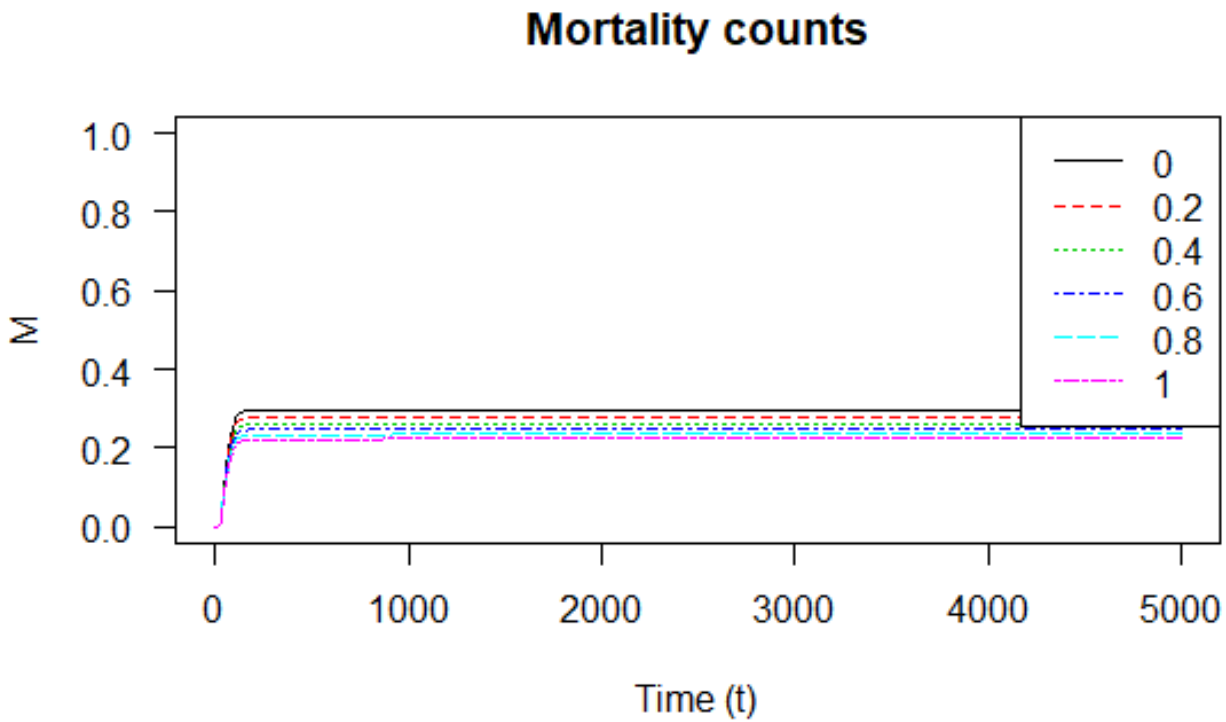
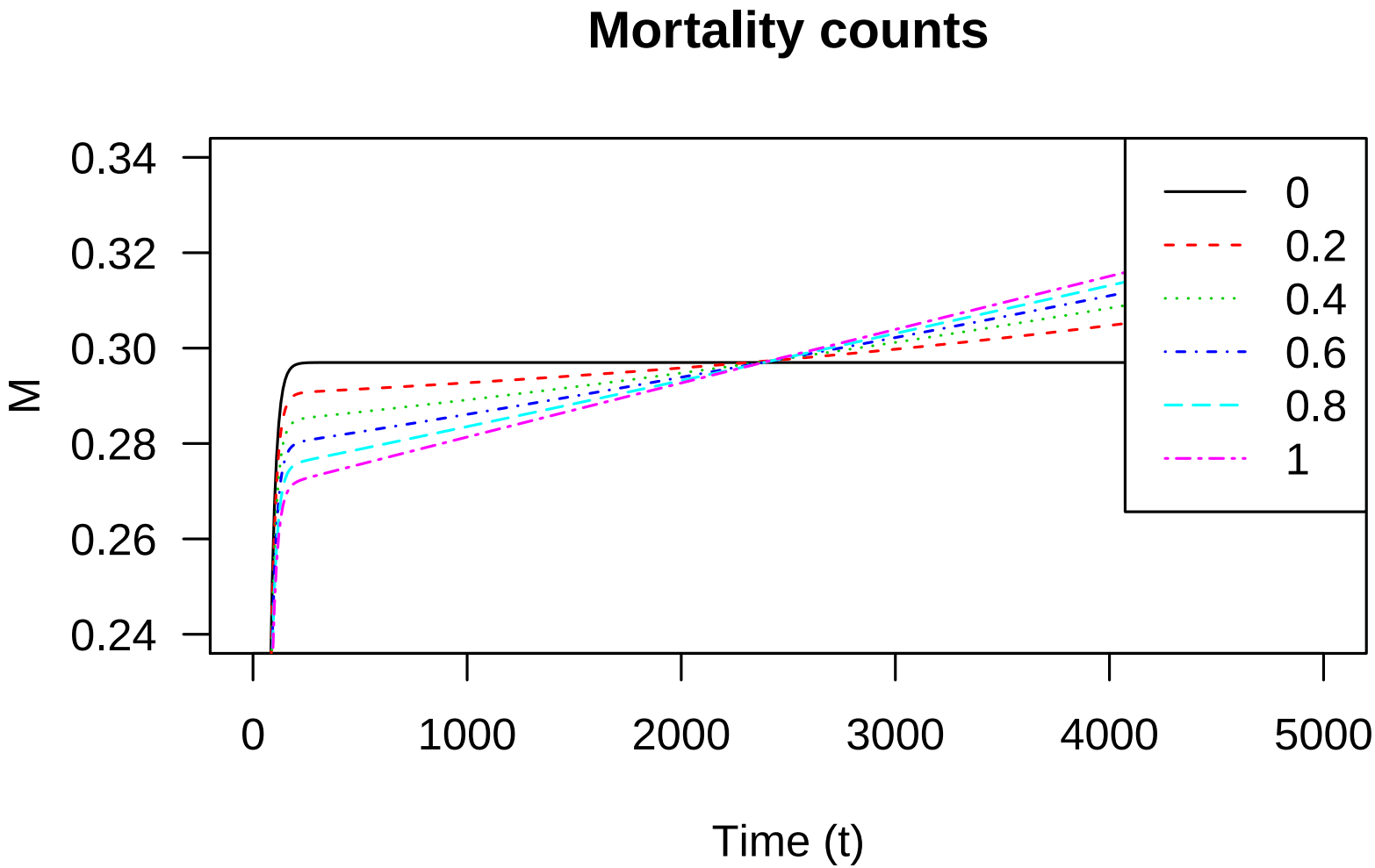


Figure: $\frac{\mathrm{d}M}{\mathrm{d}\tau}$ at EE as a function of p.

Since the magnitude of $\frac{\mathrm{d}M}{\mathrm{d}\tau}$ is too small to be observed, we can hardly the the difference between the lines.

To see the dynamics better, assume $p_V = 0.2$.



Initial state being at equilibrium

In many historical cases, intentional infect is introduced when the population is at equilibrium, which is the equilibrium for $p = 0$.

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$$\hat{S} = \frac{1}{\mathcal{R}_0}\,, \tag{11a}$$

$$\hat{V} = 0\,, \tag{11b}$$

$$\hat{I} = \epsilon(1 - \frac{1}{\mathcal{R}_0}) \tag{11c}$$

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Since the new equilibrium has $\hat{I} = 0$, we define reaching equilibrium $I \leq 1 \times 10^{-6}$ (one in a million).

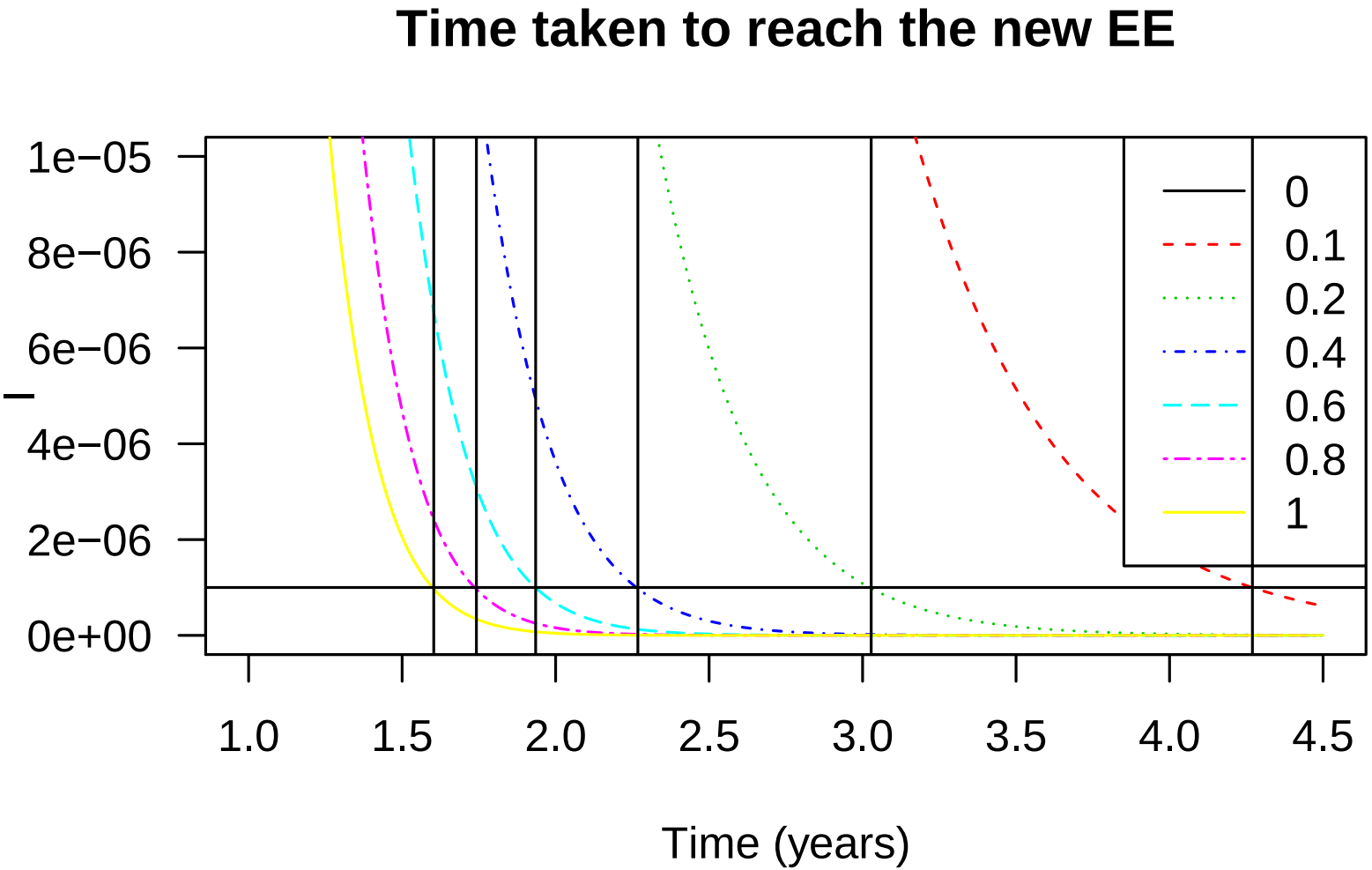

Figure: Determination of time taken to reach equilibrium

Advantages of intentional infection in terms of mortality

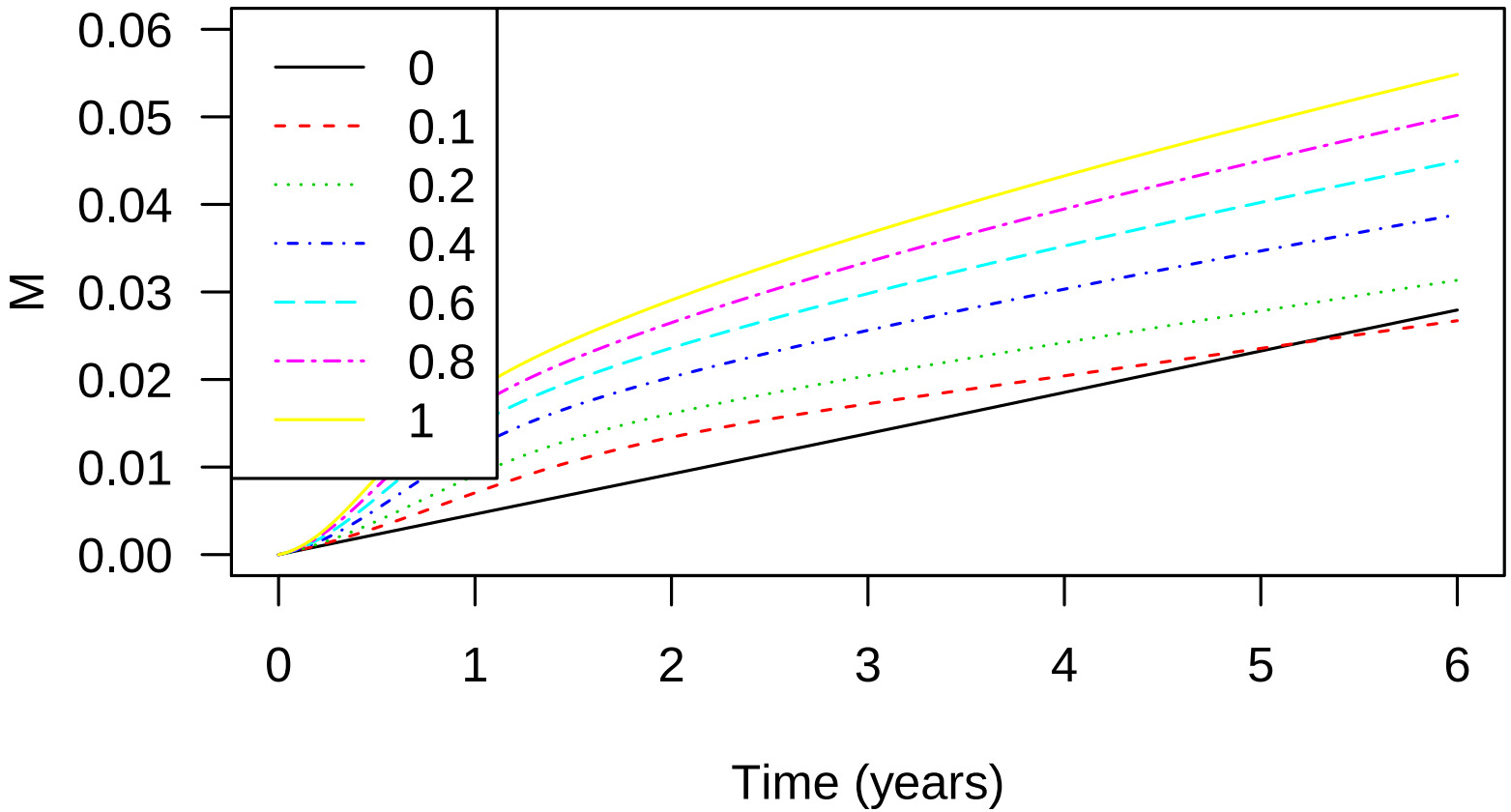

Figure: An illustration of intentional infection have advantages over non-intentional infection

To summarize the figures in the previous two slides,

Table: Time required to reach equilibrium and have advantages over non-intentional infection

p	**Time to EE**	**Time to have advantages**
0.1	4.27 yrs	5.20 yrs
0.2	3.03 yrs	8.81 yrs
0.4	2.27 yrs	17.45 yrs
0.6	1.94 yrs	28.37 yrs
0.8	1.74 yrs	42.43 yrs
1.0	1.60 yrs	61.46 yrs

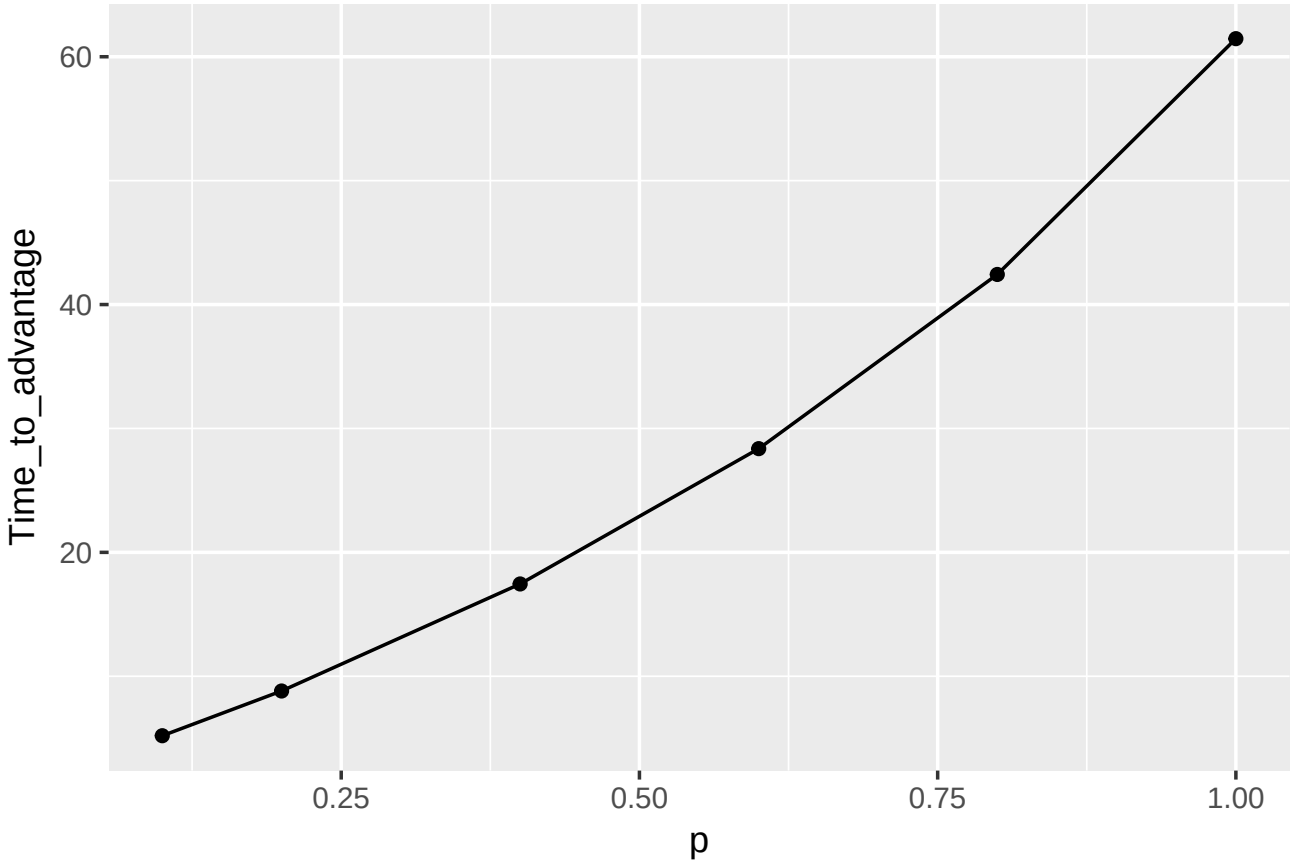

Figure: Time to advantage, as a function of p

It seems like with a lower proportion of intentional infection, we can gain advantages relative faster.

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How about intentionally infected cases? Can they burn out?

Possibility of disease eradication

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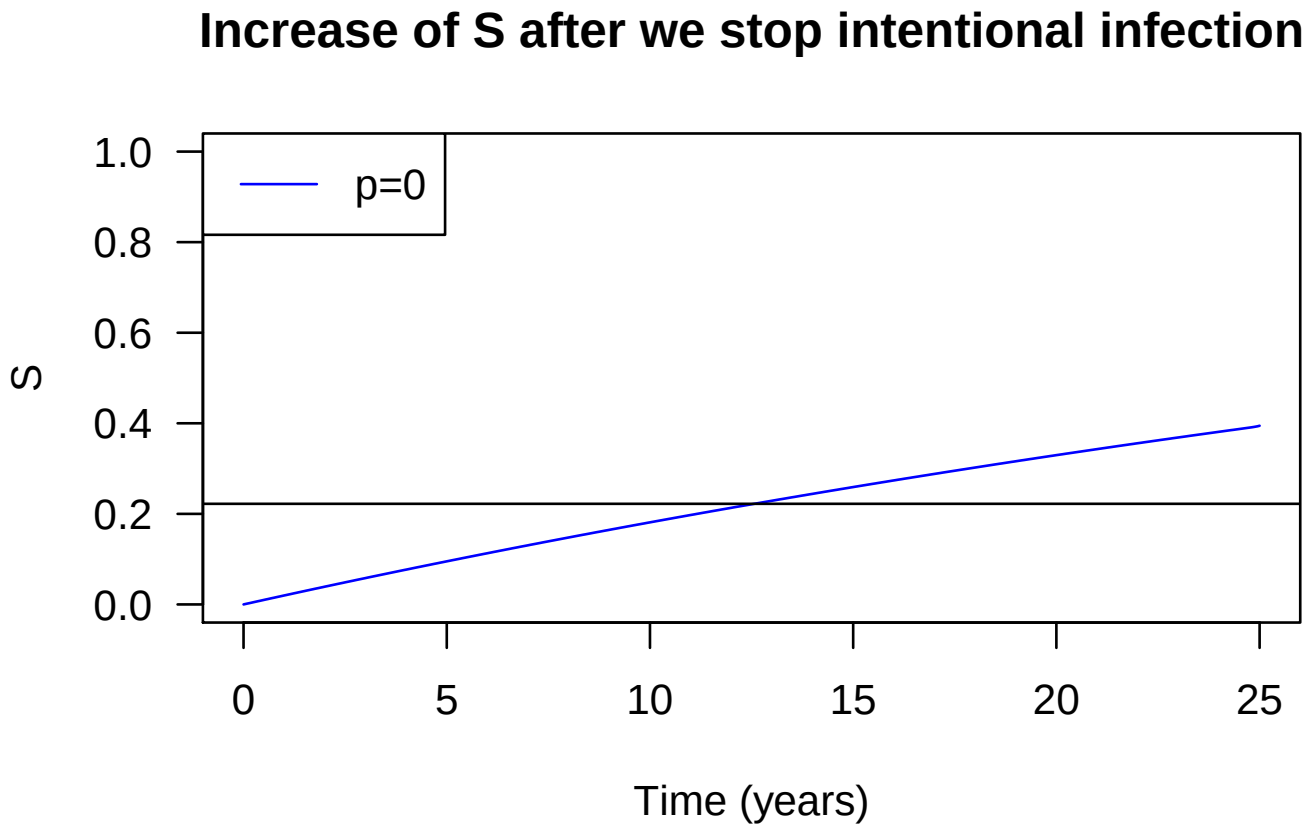
$$S = \frac{1}{\mathcal{R}_0}$$

If S stay below this threshold until V goes extinct, then we can achieve complete eradication of this disease.

Possibility of disease eradication

For example, if our initial intentional infection has a proportion $p = 1$, then



Possibility of disease eradication

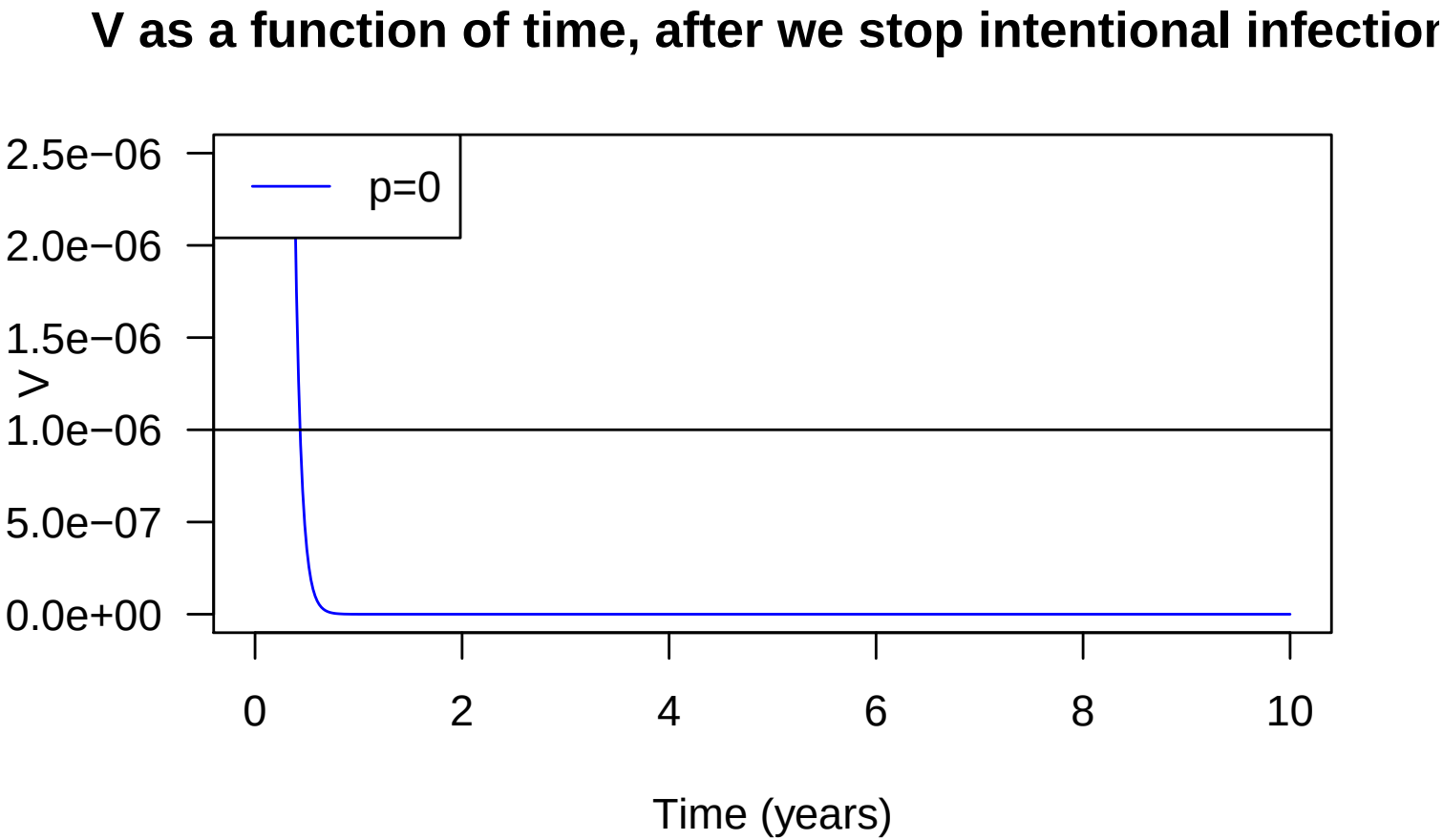


Figure: It takes less than 1 year for V to fall below 1×10^{-6}

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- Other strategies for intentional infection

Other strategies for intentional infection

Another common strategy would be to intentionally infect susceptible individuals, with a certain rate.

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\frac{\mathrm{d}I}{\mathrm{d}t} &= rS + \beta SI - \gamma I - \mu I\,, \\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - \mu R\,,
\end{aligned} \tag{12}$$

Challenges to this method

- Identify susceptible individuals
- Compare with infecting newborn individuals, this method is largely relied on vaccination pattern (If we consider them using the same pattern),