Intentional infection as a method of population level disease control

Newborn infection

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Motivation

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- What are the historical examples?
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- This method is out of date, banned in some places, why do we care?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, e.g. Transmissible vaccine.

Method

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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 transmission rate
- γ is recovery rate

Method

Assumptions:

- No difference between intentionally infected and naturally infected individuals.
- No disease induced mortality.
- Birth and natural death rate are the same, the total population remains constant.
- 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,

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

Where p is the proportion of newborn intentionally infected.

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 obtained only one set of solution,

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

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

- $\hat{I} \neq 0$ for all p between 0 and 1.
- The equilibrium is an Endemic Equilibrium (EE).

Stability of Equilibria

Jacobian Matrix,

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

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  - We need to have separate CFP for each of them.

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- Define " Have advantage" by comparing total number of deaths.
- If intentionally infected cases have the same case fatality proportion (CFP) as naturally infected cases, then it will result in more deaths.
  - We need to have separate CFP for each of them.
- We need to divide I into two separate infective classes. V for intentionally infected class, I for naturally infected class.

Model with disease induced mortality rate

Therefore, our model becomes,

$$\frac{\mathrm{d}S}{\mathrm{d}\tau} = \epsilon(1-p) - \mathcal{R}_0 S(V+I) - \epsilon S\,, \tag{7a}$$

$$\frac{\mathrm{d}V}{\mathrm{d}\tau} = \mathcal{R}_0 SV + \epsilon p - V\,, \tag{7b}$$

$$\frac{\mathrm{d}I}{\mathrm{d}\tau} = \mathcal{R}_0 SI - I\,, \tag{7c}$$

$$\frac{\mathrm{d}M}{\mathrm{d}\tau} = p_V(1-\epsilon)V + p_I(1-\epsilon)I\,, \tag{7d}$$

$$\frac{\mathrm{d}R}{\mathrm{d}\tau} = (1-p_V)(1-\epsilon)V + (1-p_I)(1-\epsilon)I - \epsilon R\,, \tag{7e}$$

Where p_V and p_I represent the CFP for intentionally infected and naturally infected cases, respectively.

Equilibria

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

$$\hat{S} = \frac{1}{\mathcal{R}_0} - \frac{2p}{(\mathcal{R}_0 - 1) + \sqrt{(\mathcal{R}_0 - 1)^2 + 4\mathcal{R}_0 p}}\,, \tag{8a}$$

$$\hat{V} = \frac{\epsilon(\mathcal{R}_0 - 1) + \epsilon\sqrt{(\mathcal{R}_0 - 1)^2 + 4\mathcal{R}_0 p}}{2\mathcal{R}_0}\,, \tag{8b}$$

$$\hat{I} = 0\,. \tag{8c}$$

- Naturally infected cases cease to exist at EE.
  - Helpful for disease eradication.

Effect of intentional infection on total mortality

Smallpox

Table: Model parameters and smallpox values.

Symbol	Meaning	Value
$\frac{1}{\mu}$	Average lifespan	50 years
$\frac{1}{\gamma}$	Mean infectious period	22 days
$\mathcal{R}_0$	Basic reproduction number	4.5
p_V	Intentionally infected CFP	0.01
p_I	Naturally infected CFP	0.3

Effect of intentional infection on total mortality

Mortality rate at EE

$$\left.\frac{\mathrm{d}M}{\mathrm{d}\tau}\right|_{\mathrm{EE}} = \frac{p_V(1-\epsilon)\epsilon(\mathcal{R}_0-1) + p_V(1-\epsilon)\epsilon\sqrt{(\mathcal{R}_0-1)^2+4\mathcal{R}_0 p}}{2\mathcal{R}_0}, \tag{9}$$

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- Mortality rate at EE increases as p increases.

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Mortality rate at EE

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

Initial state being at equilibrium

In history, intentional infection was introduced when the population is at equilibrium, which is the equilibrium for $p = 0$.

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$$\hat{S} = \frac{1}{\mathcal{R}_0}\,, \tag{10a}$$

$$\hat{V} = 0\,, \tag{10b}$$

$$\hat{I} = \epsilon(1 - \frac{1}{\mathcal{R}_0}) \tag{10c}$$

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- What is the time it takes to reach the new EE?
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Since the new equilibrium has $\hat{I} = 0$, define reaching equilibrium by $I \leq 10^{-6}$.

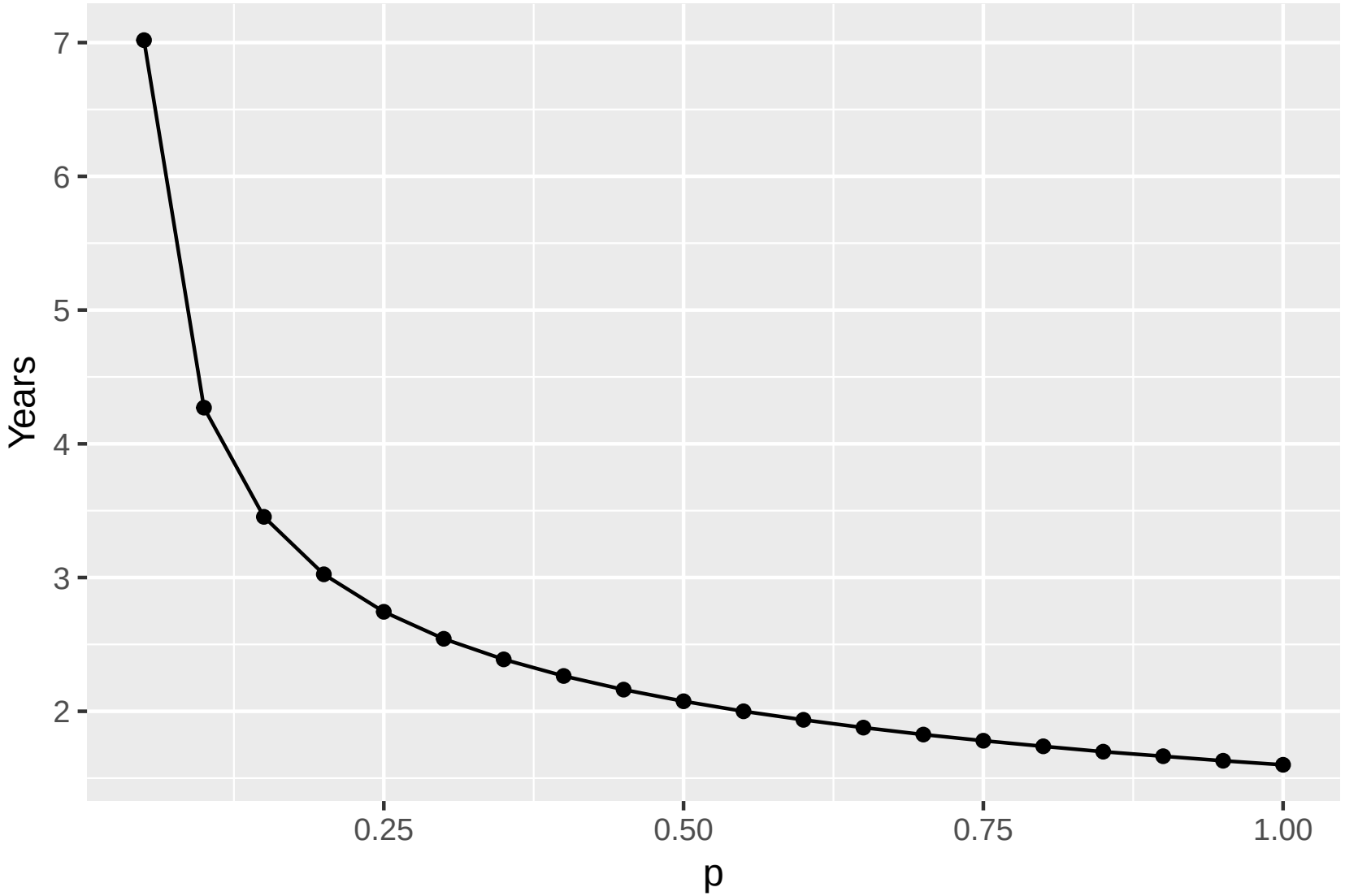

Figure: Determination of time taken to reach equilibrium

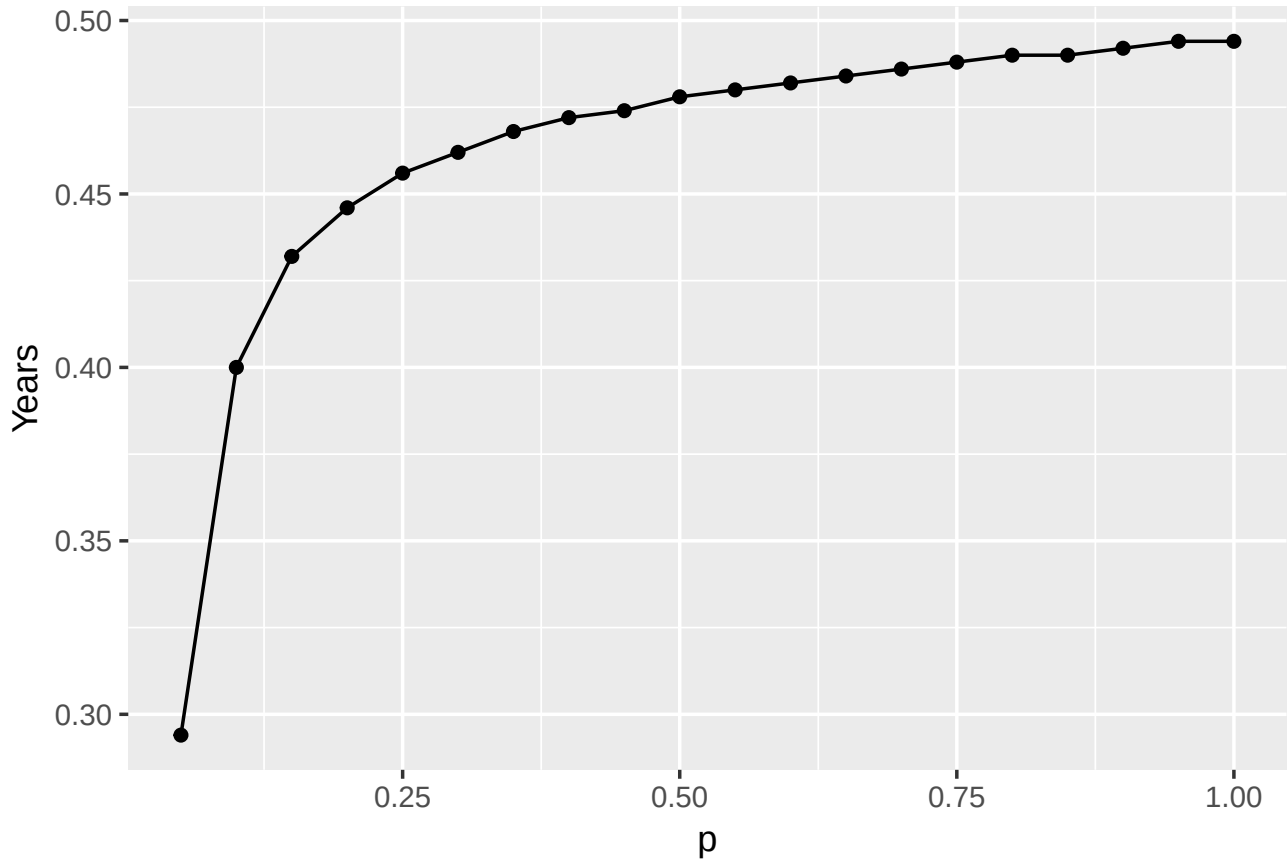

Figure: Time to advantage, as a function of p

With a lower proportion of intentional infection, we can gain advantages relative faster.

Possibility of disease eradication

$\hat{I} = 0$ at EE. We can consider the Naturally infected cases already been eradicated at EE.

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For intentionally infected cases, if we stop intentional infection after we reach EE, can they burn out?

Possibility of disease eradication

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Threshold for susceptible: $S = \frac{1}{\mathcal{R}_0}$

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

Possibility of disease eradication

Example: $p = 1$ initially, stop intentional infection after reaching EE,

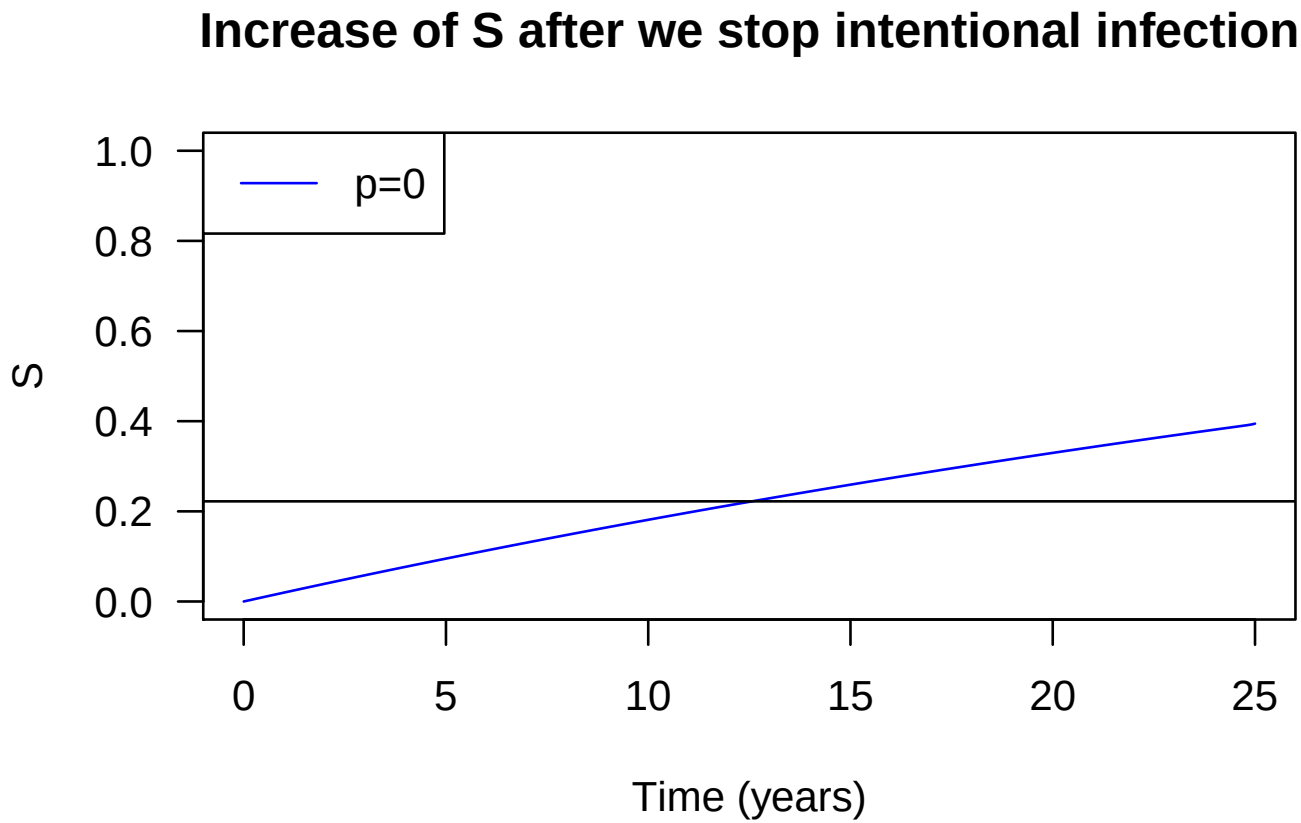

Figure: For more than 10 years after we stop intentional infection, $S < \frac{1}{\mathcal{R}_0}$

Possibility of disease eradication

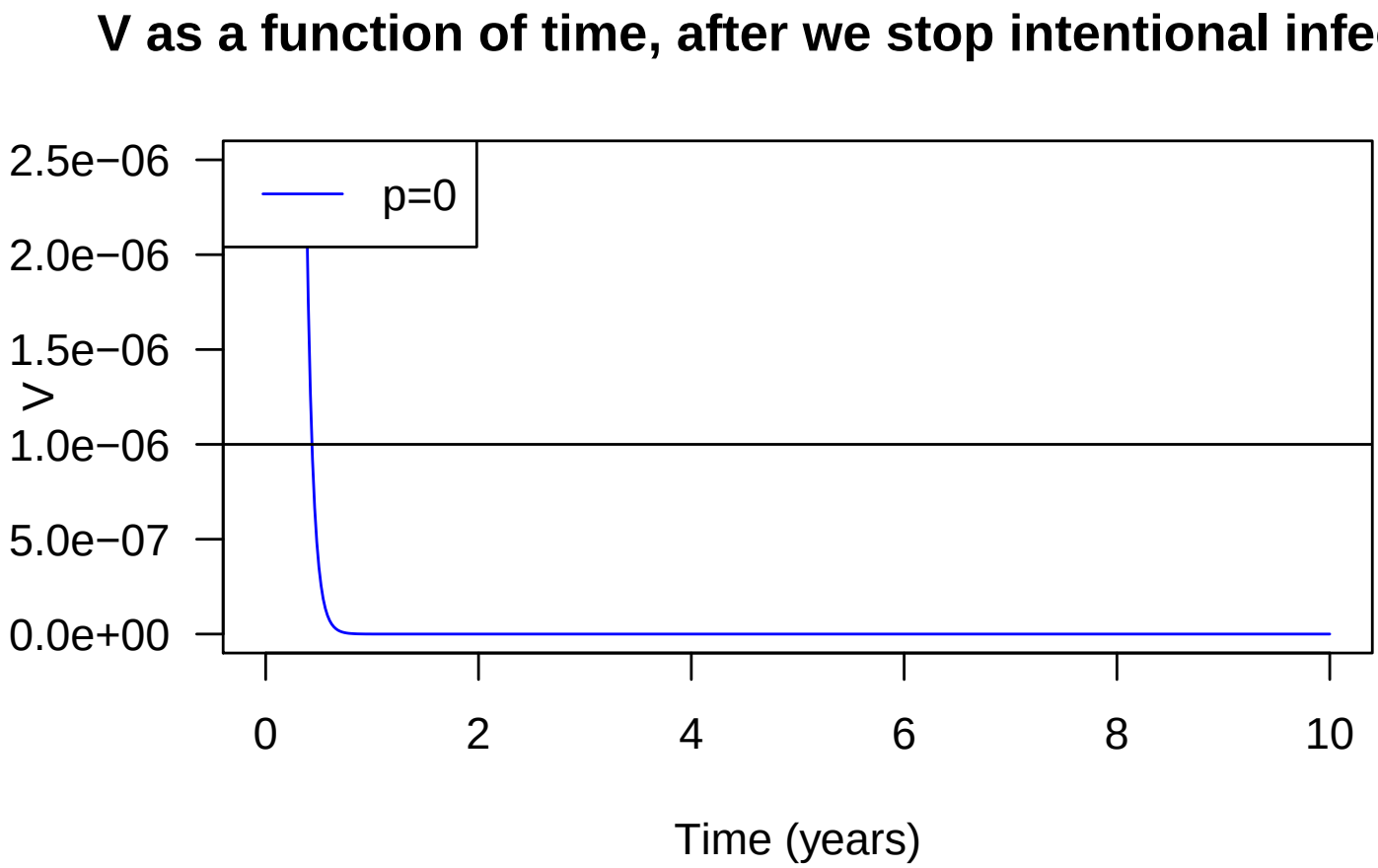

Figure: It takes less than 1 year for V to fall below 1×10^{-6}

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- Other strategies for intentional infection

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Another approach would be to intentionally infect susceptible individuals, with a certain rate r.

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\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - \mu R\,,
\end{aligned} \tag{11}$$

Challenges to this method

- Identify susceptible individuals

Conclusion

- Intentional infection has positive effects on population level disease control.
- Further study is required for determining intentional infection strategies to optimize this method.

References

Paulinevan den Driessche *Reproduction numbers of infectious disease models*, Infectious Disease Modelling, Volume 2, Issue 3, August 2017, Pages 288-303.

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