Mathematical modelling of infectious disease transmission

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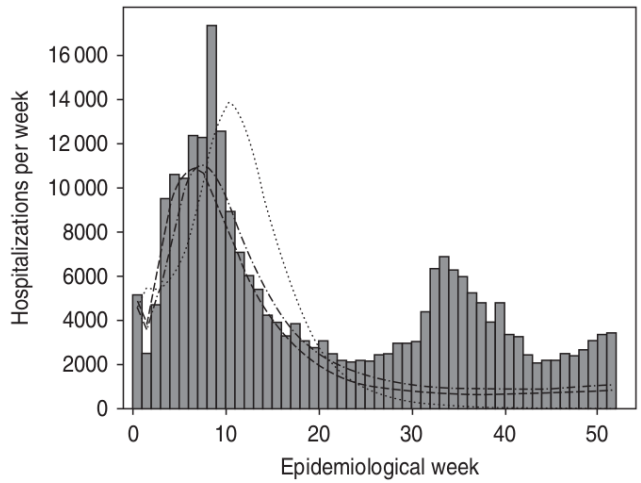
Role of models in epidemiology

Mathematical models can help epidemiologists:

- How fast will an epidemic spread?
- How severe will an epidemic be?
- How effective would an intervention strategy be?
- Testing hypotheses about disease transmission.

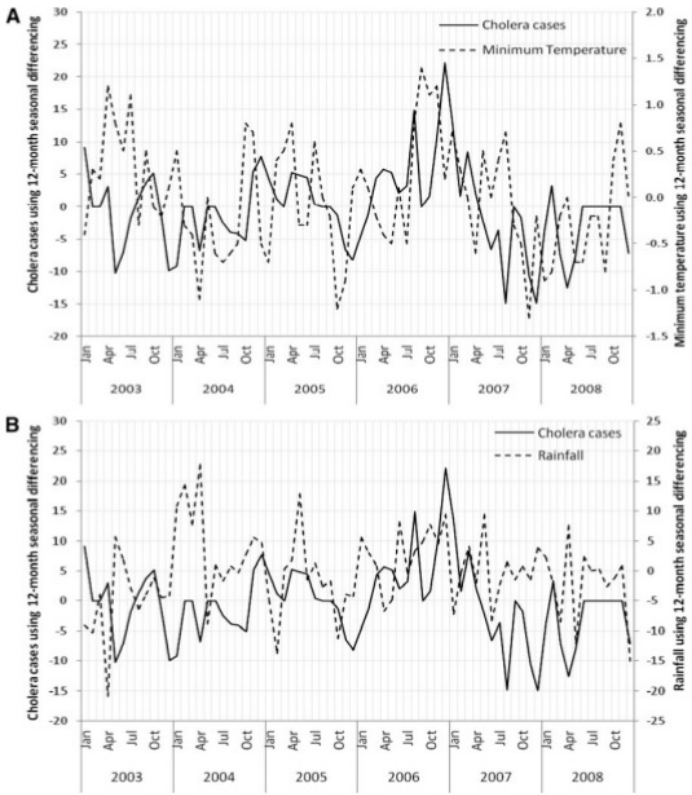


Abrams, Copeland, Tauxe, Date, Belay, Mody, Mintz. Real-time modelling used for outbreak management during a cholera epidemic, Haiti, 2010–2011. Epidemiol Infect 141(6):1276–85. 2013.

Kinds of models

Statistical

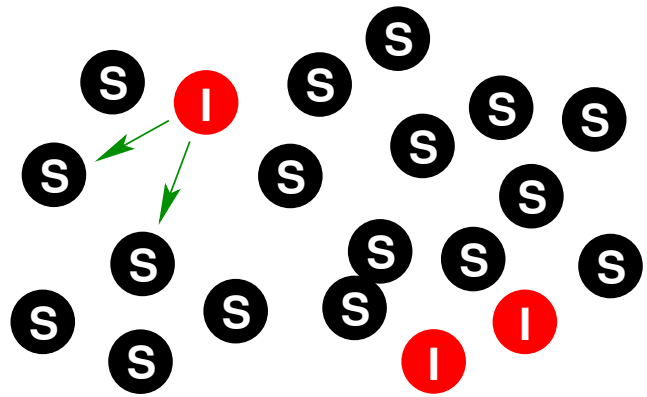
Discover correlations and patterns (e.g., regressions, time series analyses)



Reyburn, Kim, Emch, Khatib, von Seidlein, Ali. Climate variability and the outbreaks of cholera in Zanzibar, East Africa: a time series analysis. *Am J Trop Med Hyg* 84(6):862–9. 2011.

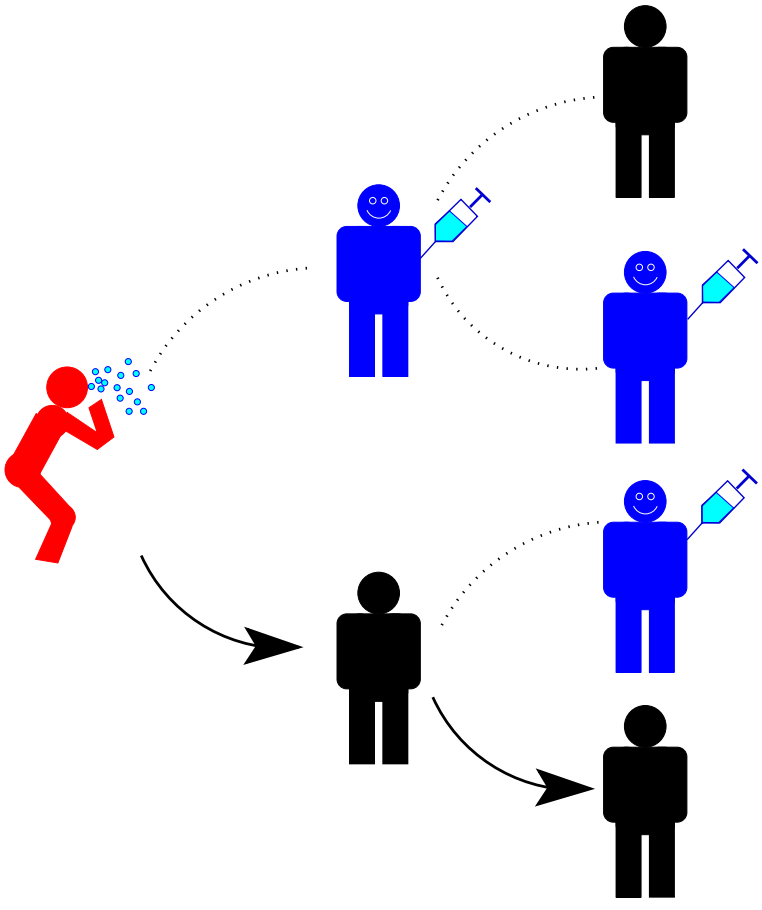
Mechanistic

Simulate processes, dynamics (e.g., differential equations, agent-based models)



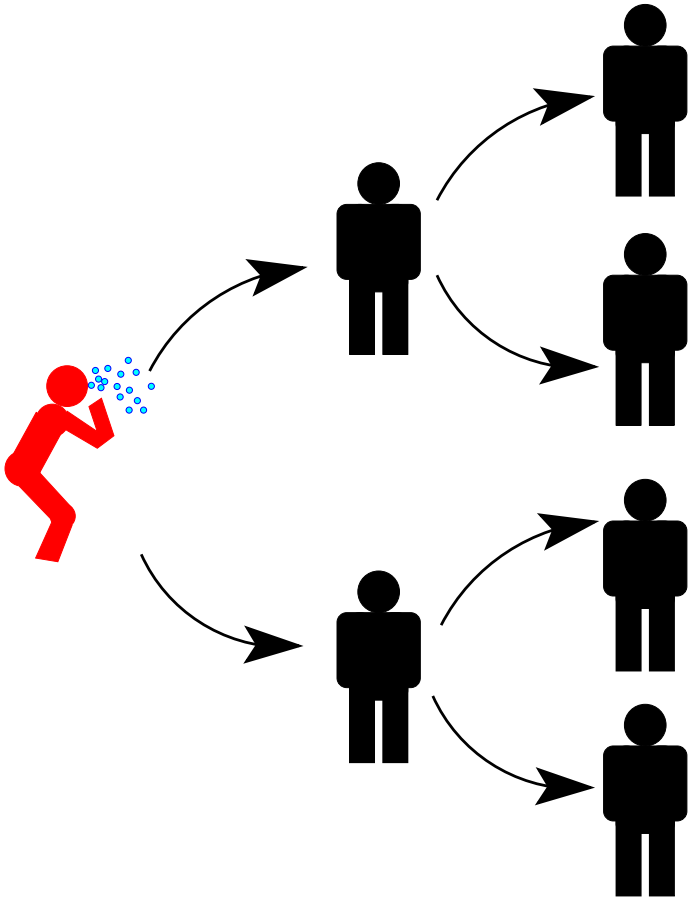
Mechanistic (or "mathematical") models can be used to test interventions.

How does vaccination reduce transmission?



- **Individual-level benefit:**
  Vaccination reduces the chance of infection. *(VE)*
- **Population-level benefit:**
  Vaccination reduces the number of people a person can infect.

Transmissibility and R_0

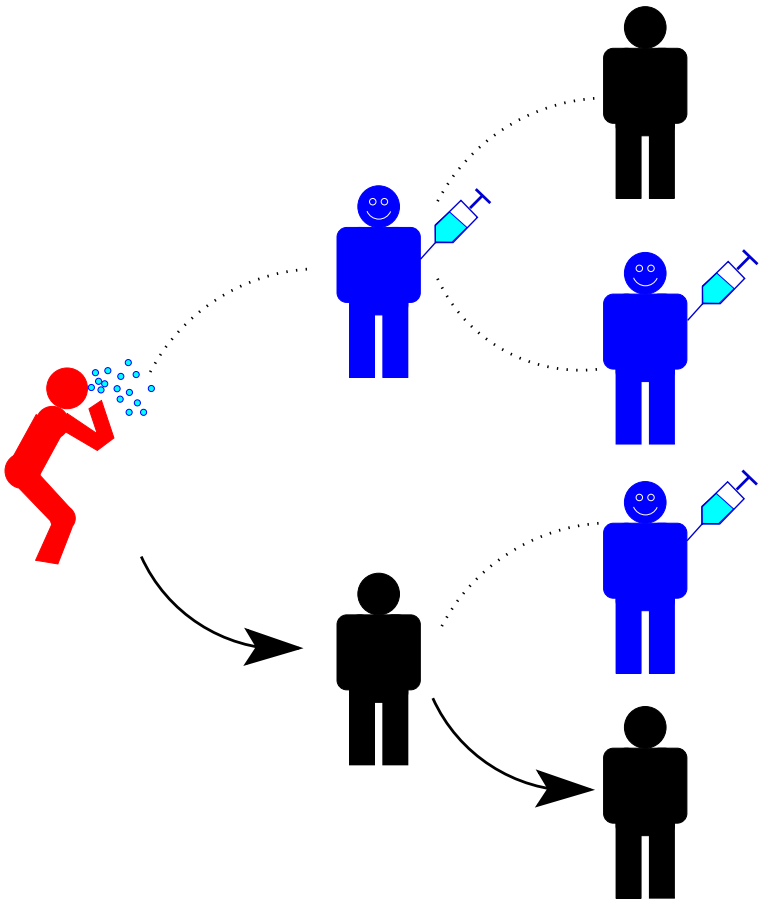


$R_0 = 2.0$

- R_0 is the number of people that a typical infected person infects in a fully susceptible population.
- R_0 must be greater than 1.0 for an outbreak to occur.
- Epidemics initially grow *exponentially*.

pathogen	R_0 *or* R
Influenza	1.1–1.5
SARS	2.7
Smallpox	3
Rubella	6–7
Measles	7.7

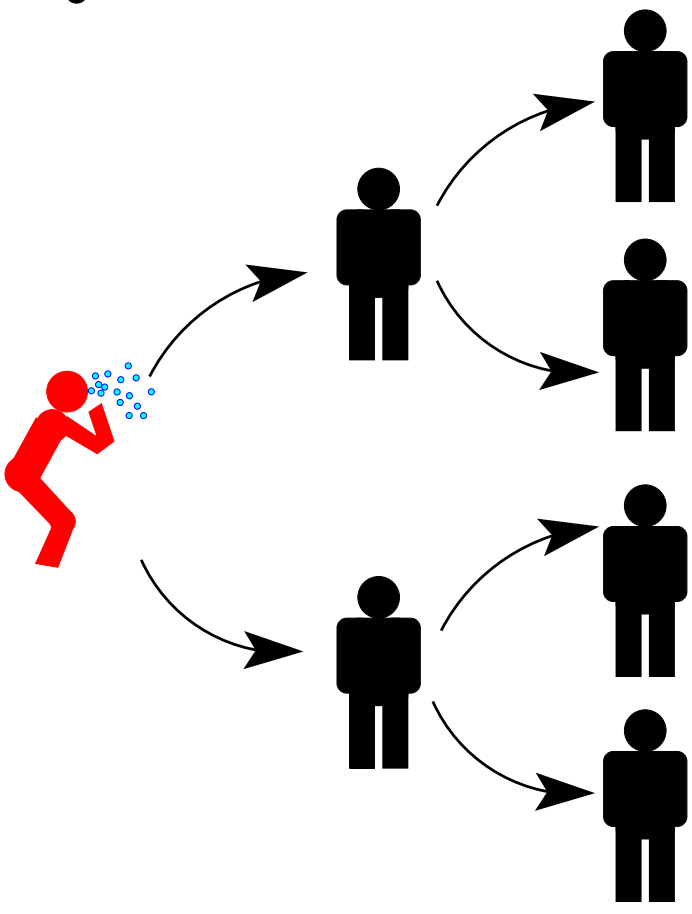
How does vaccination reduce transmission?



- If infected people infect less than **1** other on average, outbreaks should not occur.

How many people do we need to vaccinate?

R_0=2.0



pathogen	*R or* R_0
Influenza	1.1–1.5
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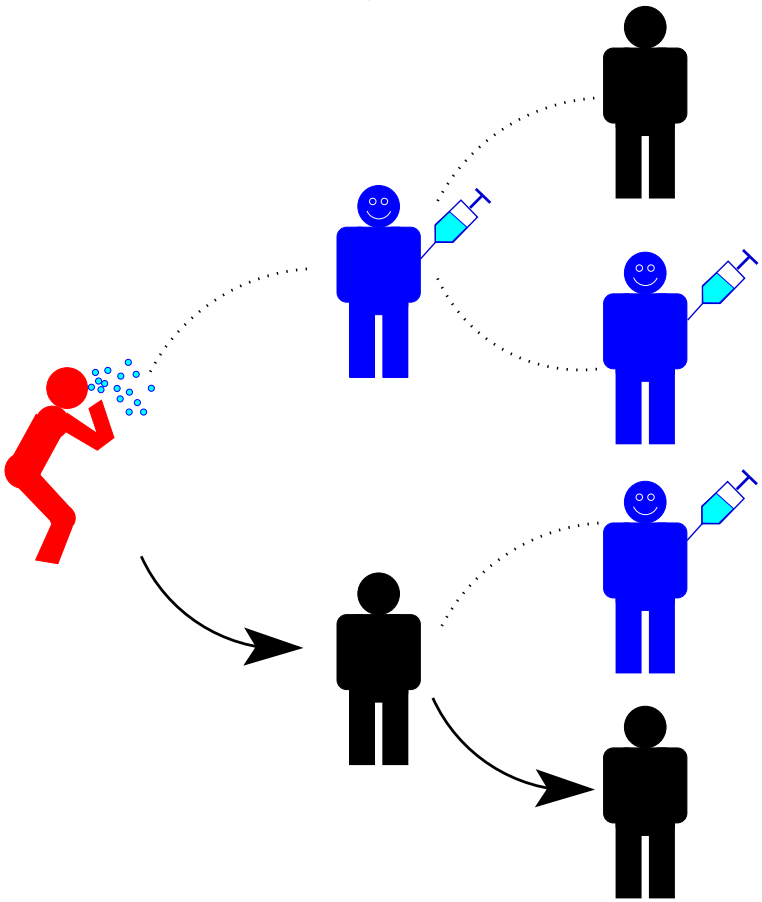
How many people do we need to vaccinate?

50% for R_0=2.0



pathogen	*R or R_0*
Influenza	1.1–1.5
SARS	2.7
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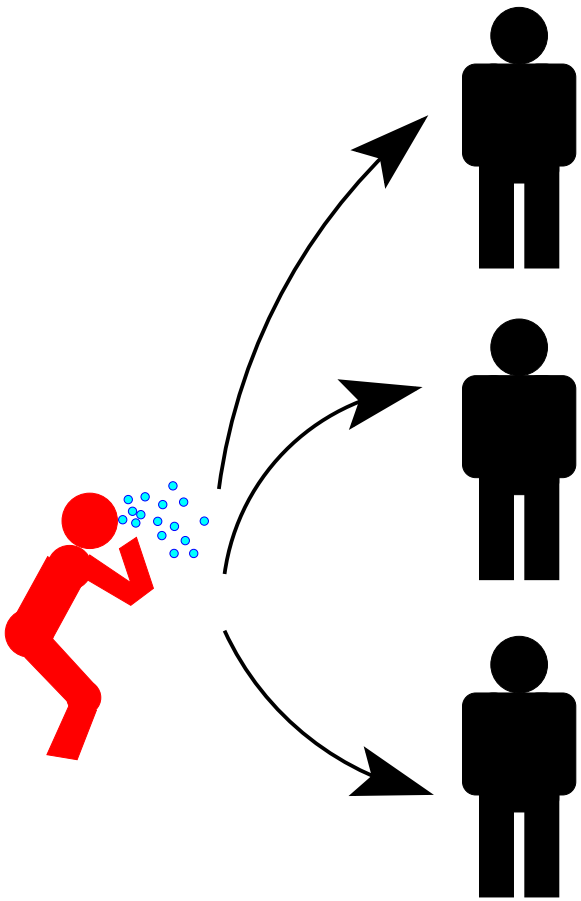
Measles	7.7

Vaccinating 50% for R_0=2.0 results in an *effective* R_0 of 1.0 (assuming a perfect vaccine).

How many people do we need to vaccinate?

R_0=3.0



pathogen	*R or* R_0
Influenza	1.1–1.5
SARS	2.7
Smallpox	3
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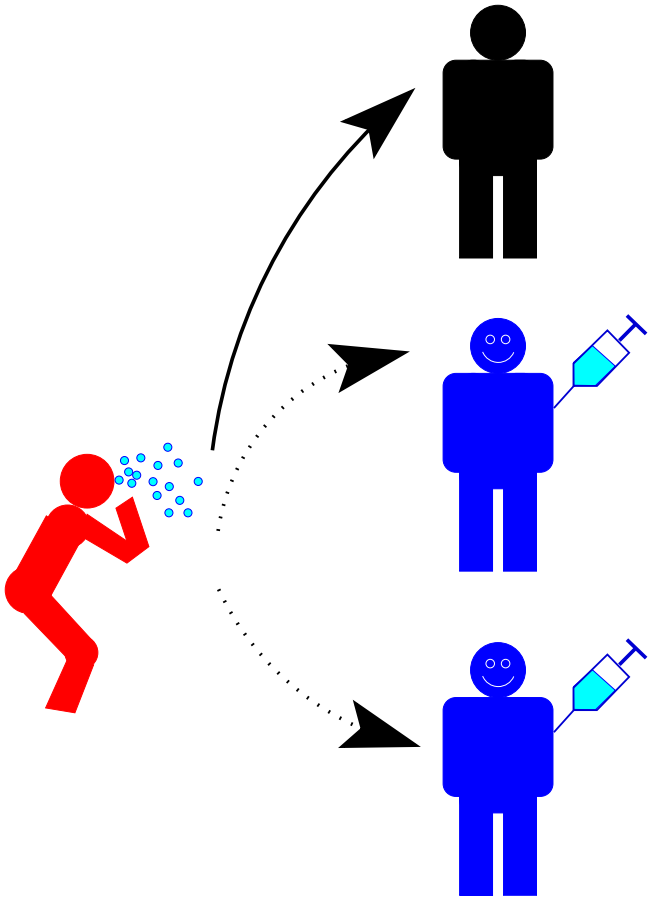
Measles	7.7

How many people do we need to vaccinate?

67% for R_0=3.0



pathogen	*R or* R_0
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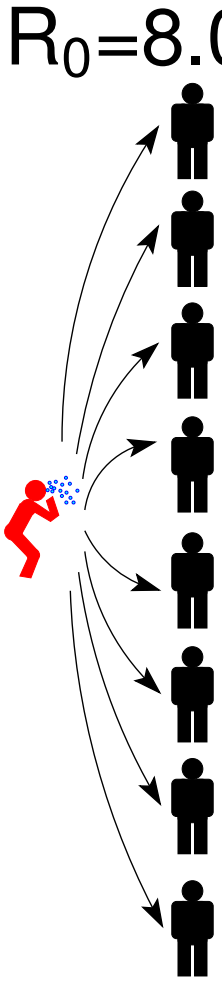
(assuming a perfect vaccine)

How many people do we need to vaccinate?



pathogen	*R or* R_0
Influenza	1.1–1.5
SARS	2.7
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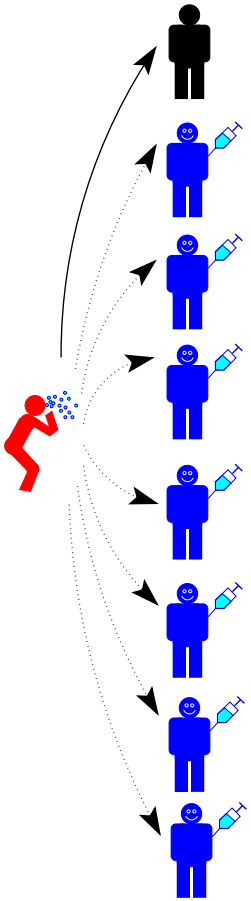
How many people do we need to vaccinate?

87.5% for R_0=8.0



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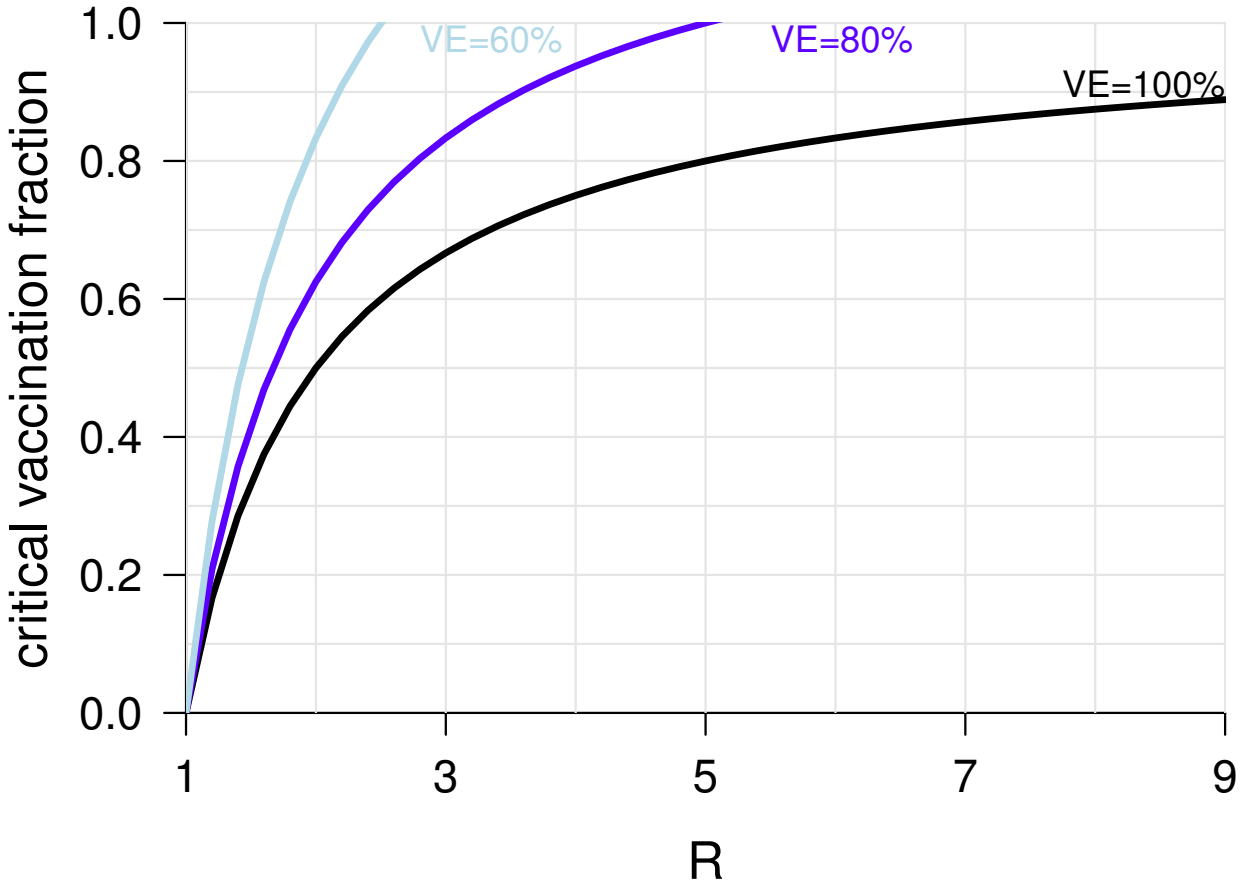
(assuming a perfect vaccine)

Critical vaccination fraction



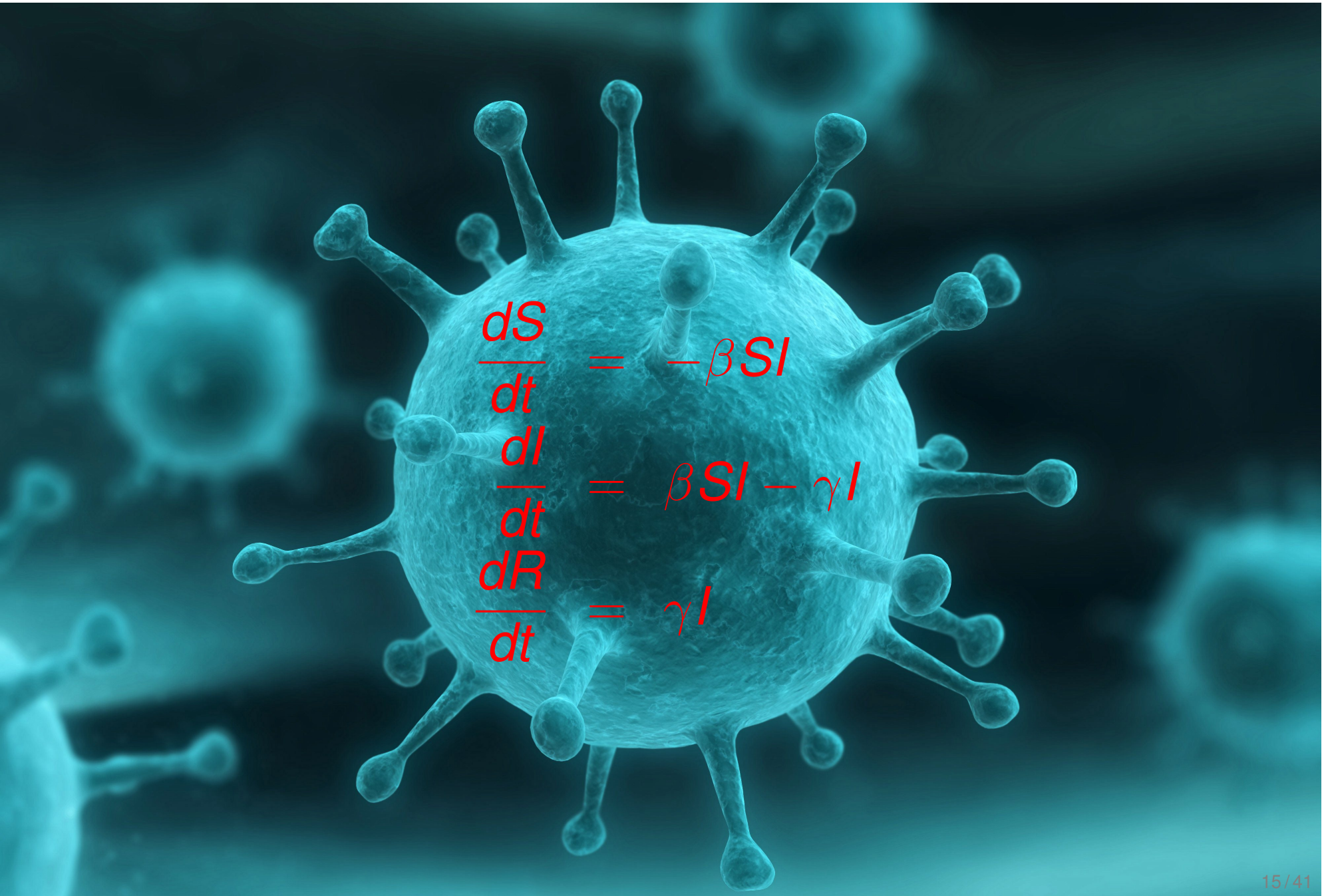
- The *critical vaccination fraction* is the proportion of the population that needs to be vaccinated to prevent outbreaks.
- Basically, vaccinate enough to drive R_0 below 1.
- The critical vaccination fraction depends on R_0 and the vaccine efficacy, VE: $\frac{1-1/R_0}{\mathrm{VE}}$

Unanswered questions

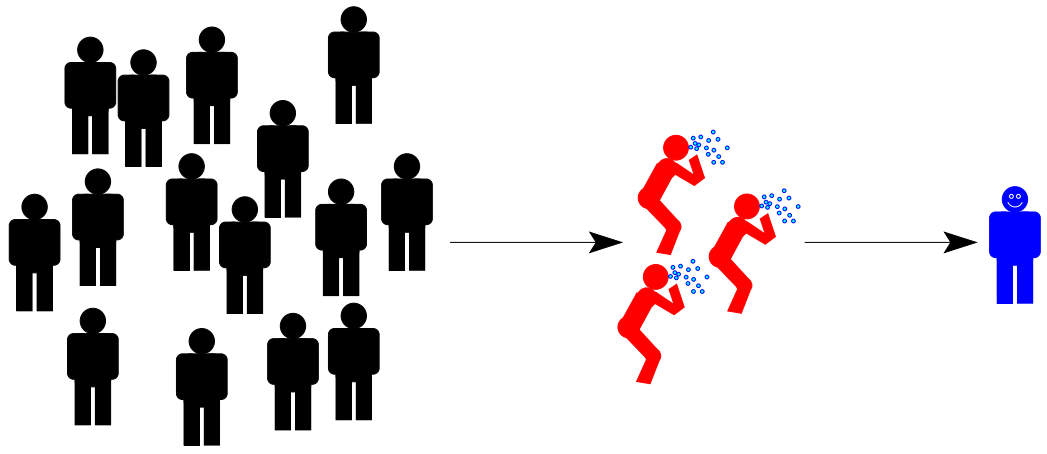
- What if we don't vaccinate enough people to prevent outbreaks?
- How many people will an epidemic infect?
- How fast will an epidemic spread?
- What if we vaccinate *during* an outbreak?

***Dynamic* modeling can help answer these questions.**

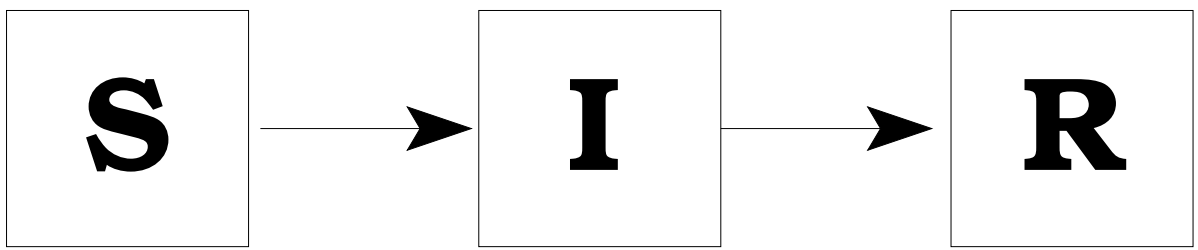
Modeling infectious disease transmission



Creating compartments for a mathematical model

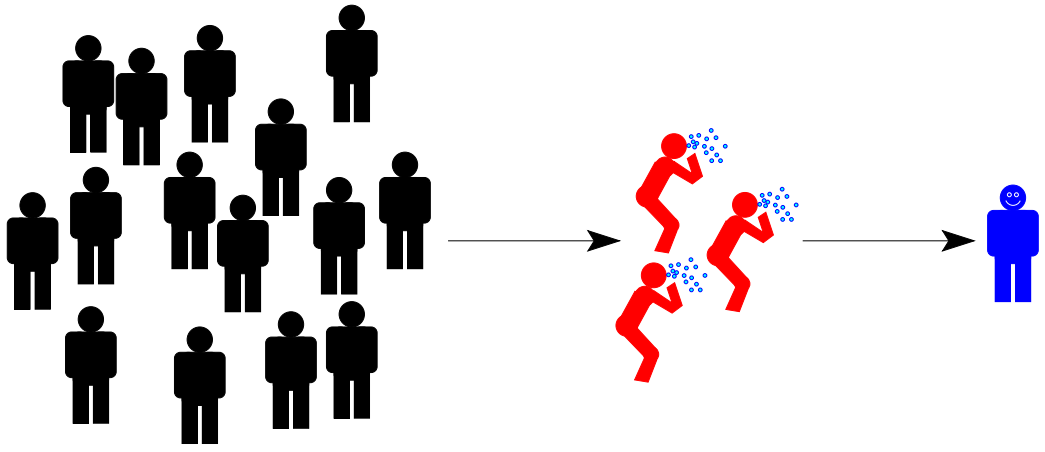


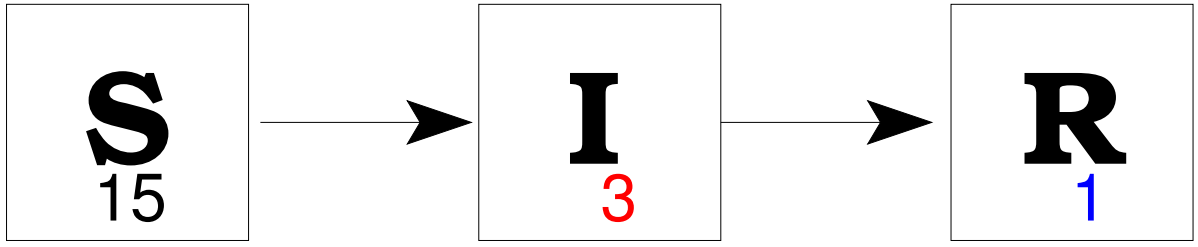
Susceptible Infected Recovered



Math models consider a small number of essential disease states (“compartments”).

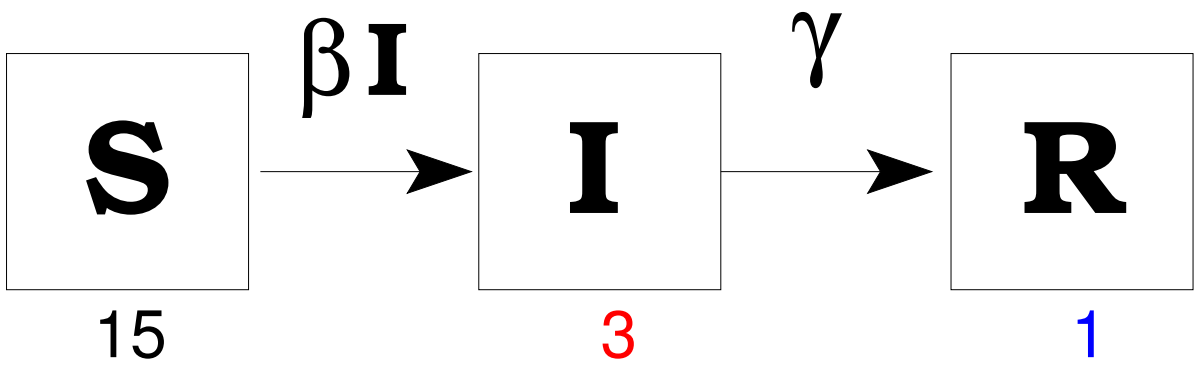
Putting people in the compartments





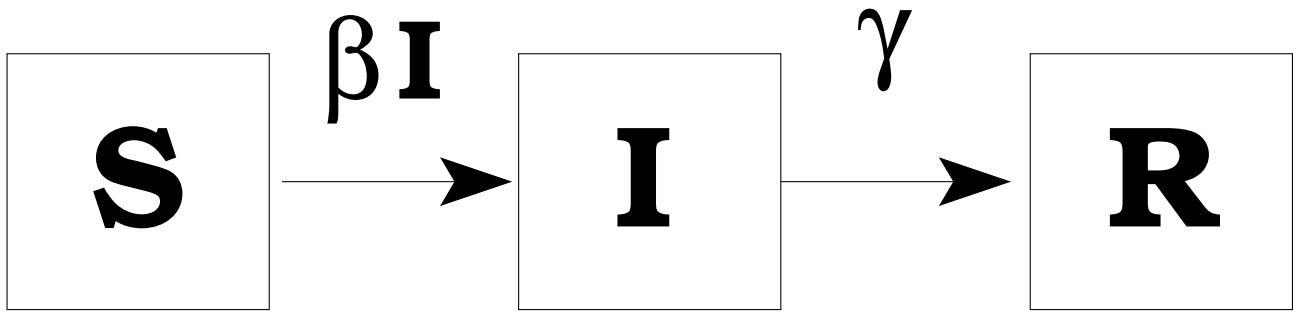
How many people are in each disease state (“compartment”)?

Transitioning between compartments

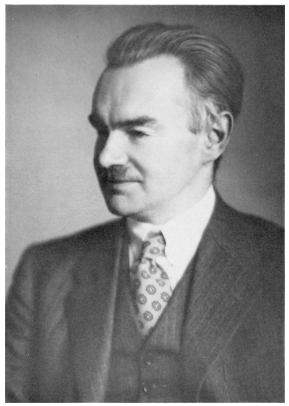


- **Susceptible** population is exposed to pathogen and become **Infected**.
- **Infected** people **Recover** and become immune to infection.
- Add rates of transition between compartments (disease states):
  - βI: Force of infection is proportional to the number of Infected people.
  - γ: Recovery rate is the inverse of the serial interval. For influenza, the serial interval is about 3.4 days, so $\gamma = 1/3.4$.

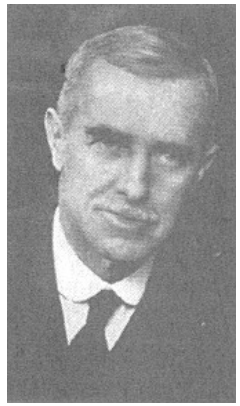
Classic SIR model



$$\frac{dS}{dt} = -\beta SI$$
$$\frac{dI}{dt} = \beta SI - \gamma I$$
$$\frac{dR}{dt} = \gamma I$$



William Kermack
1898–1970

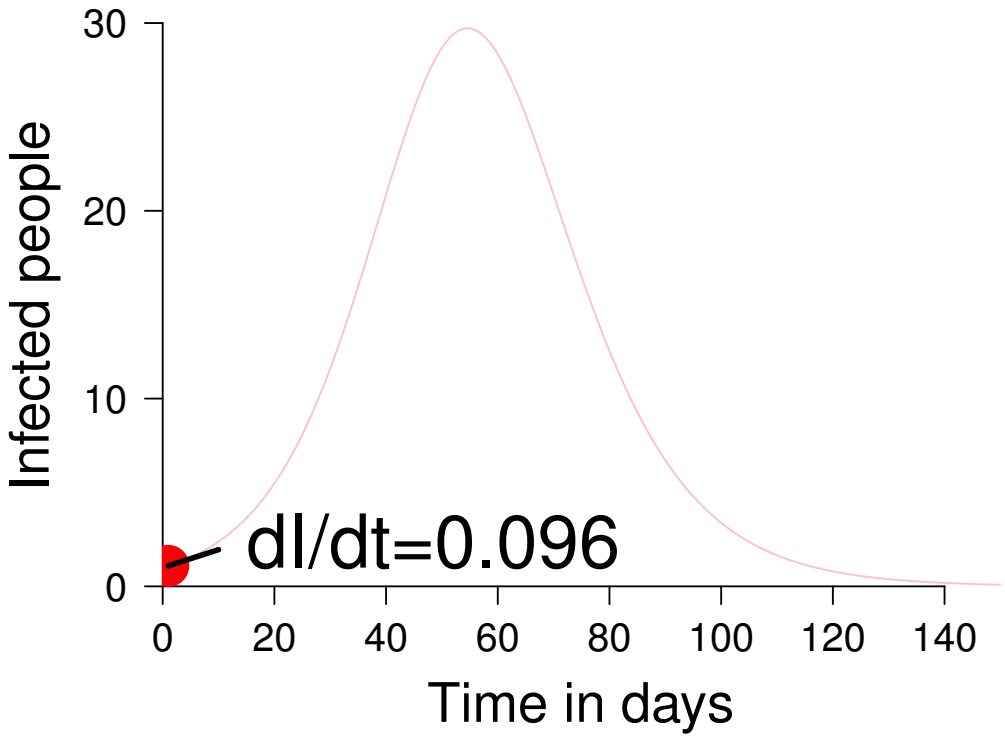


Anderson McKendrick
1876–1943

Ordinary differential equations (ODEs) are used to model the flow of people between compartments.

Modeling an influenza epidemic

- We can solve the SIR equations for how many Infected people there will be at any time.
- Starting with a population of 1000 people: 999 Susceptible and 1 Infected. . .



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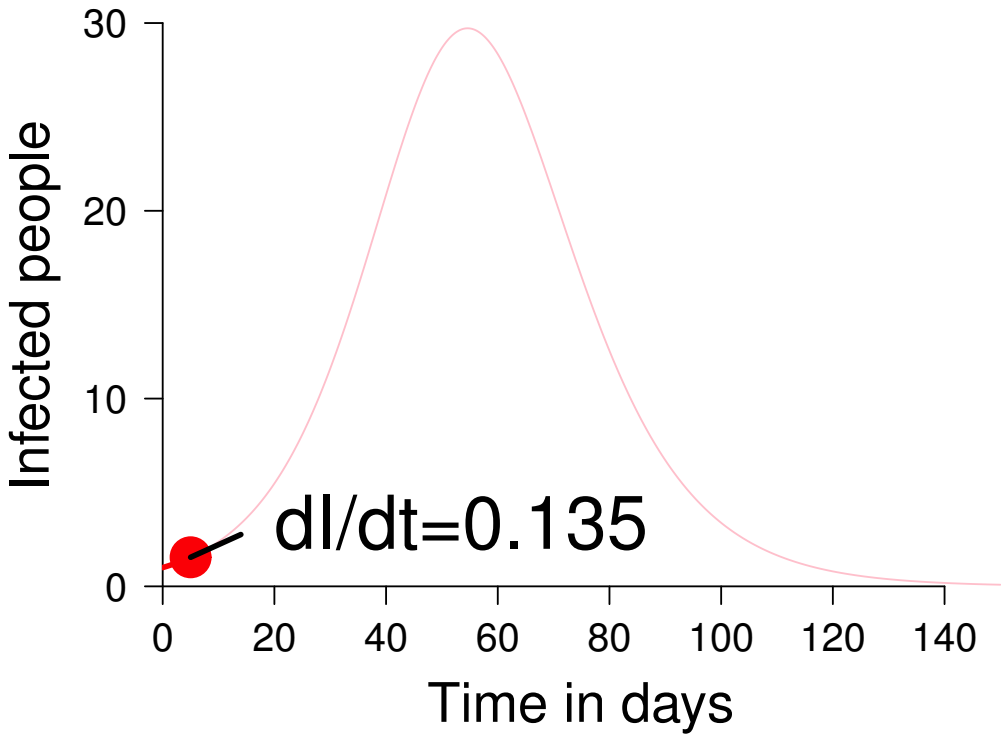

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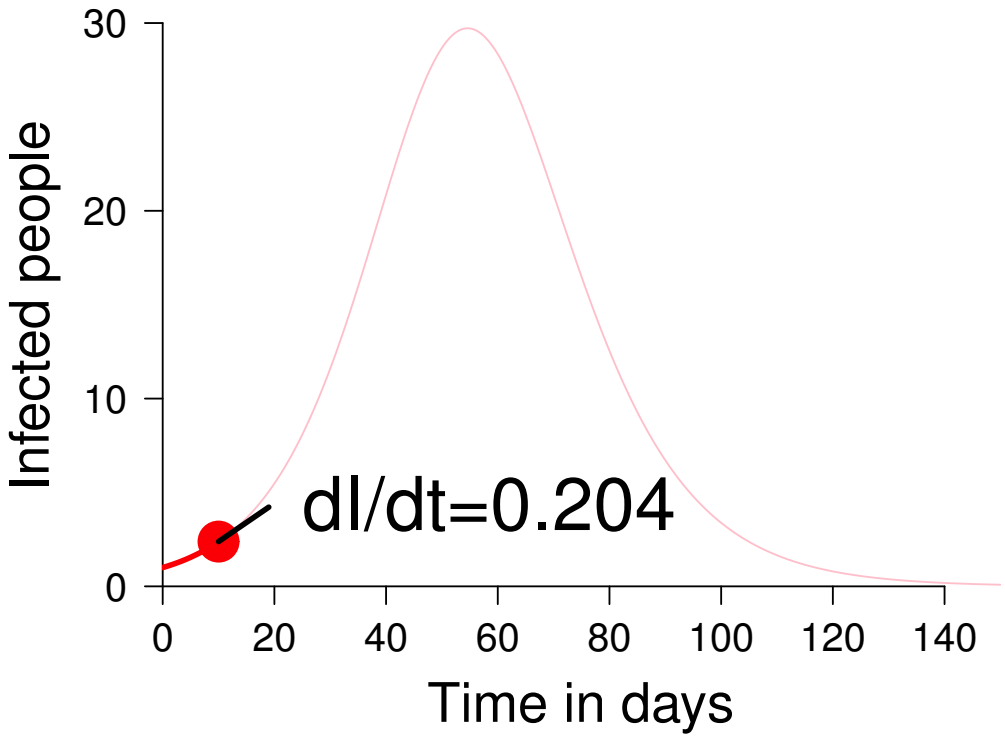

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Modeling an influenza epidemic

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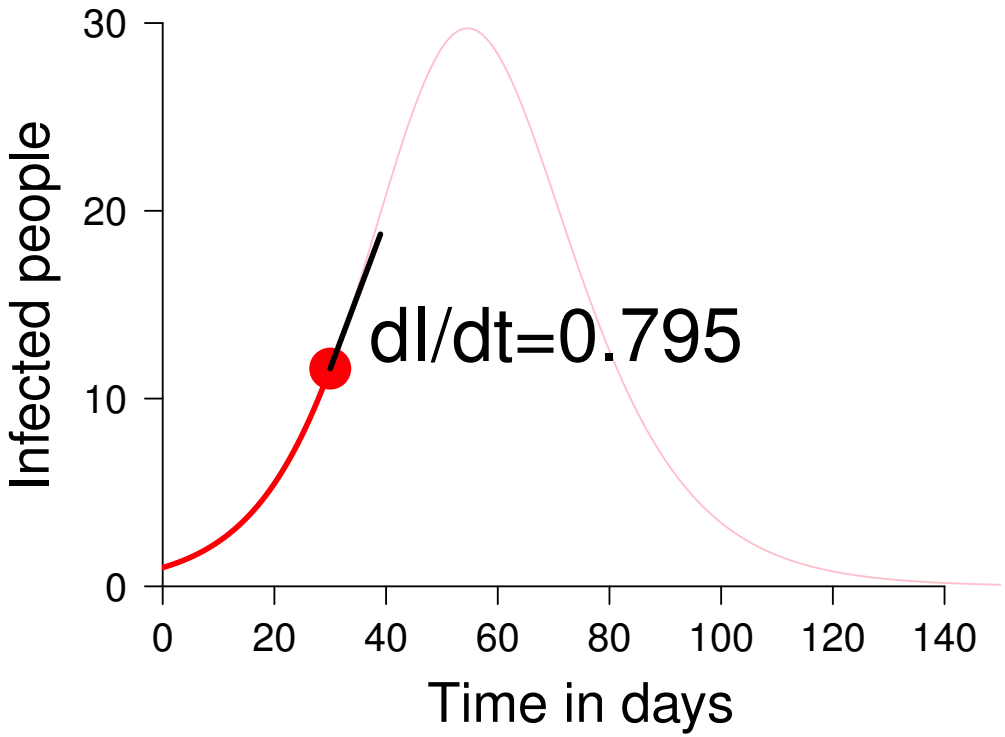
- Starting with a population of 1000 people: 999 Susceptible and 1 Infected...



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Modeling an influenza epidemic

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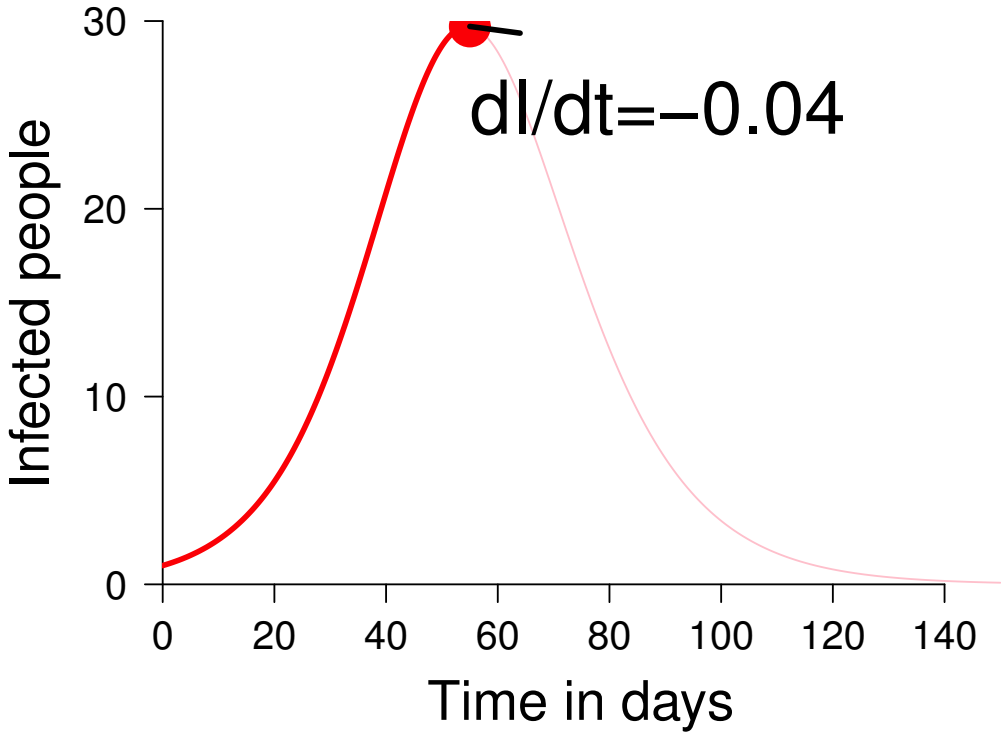

$$\frac{dS}{dt} = -\beta SI$$
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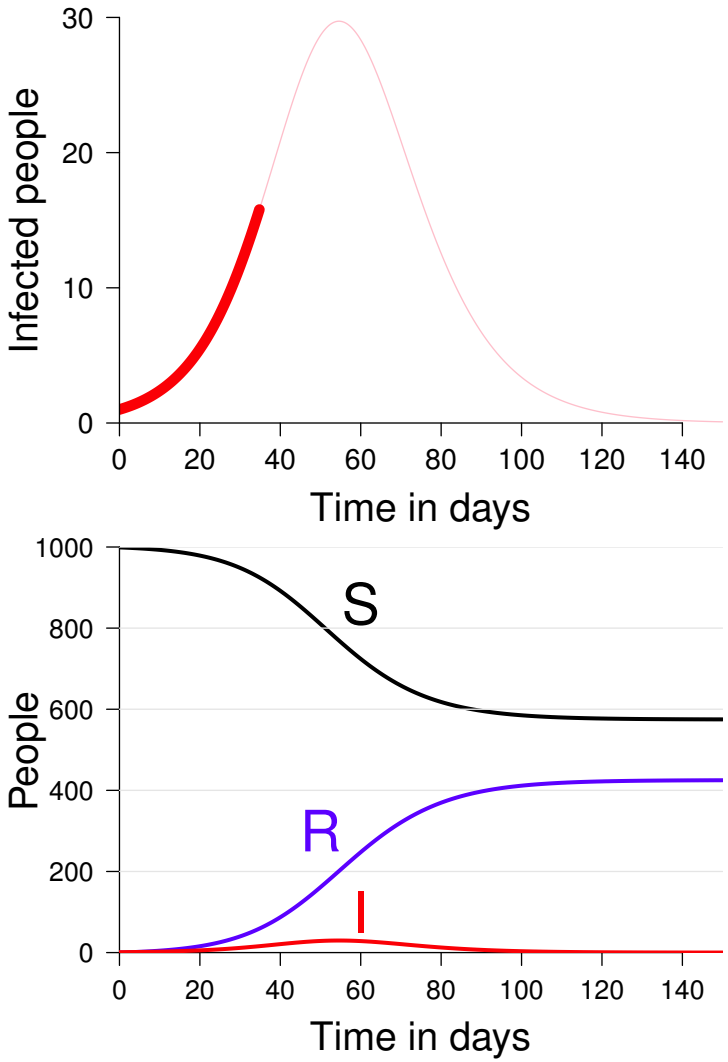
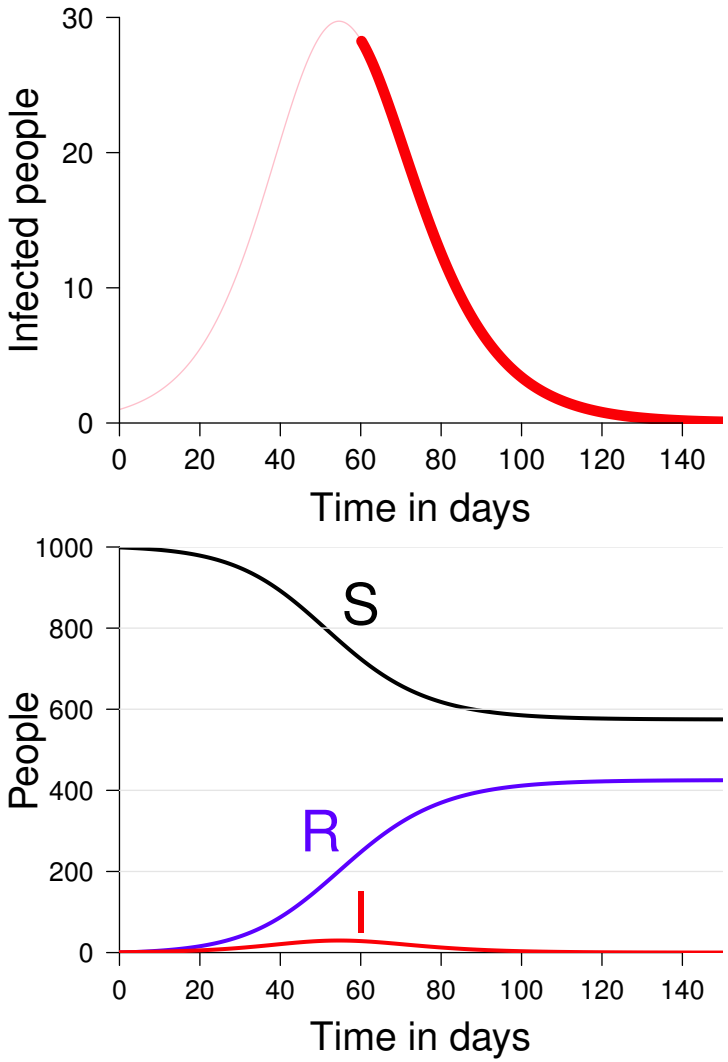
Why does the epidemic peak then decline?



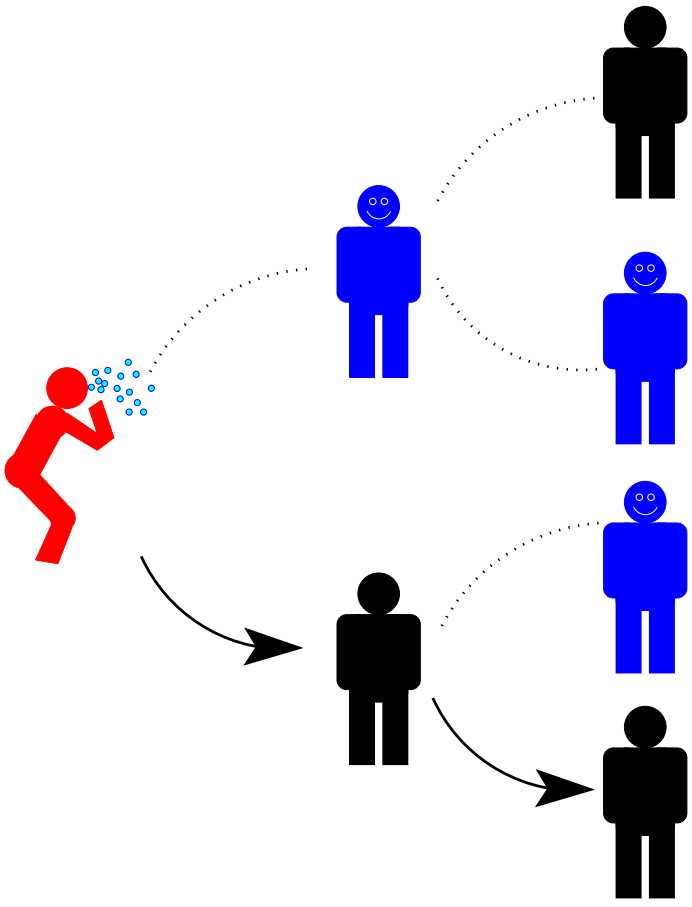
- $\frac{dI}{dt} = \beta SI - \gamma I$
- In the beginning, the population is fully susceptible and S is large.
- The epidemic grows exponentially.

What happens as the outbreak progresses?



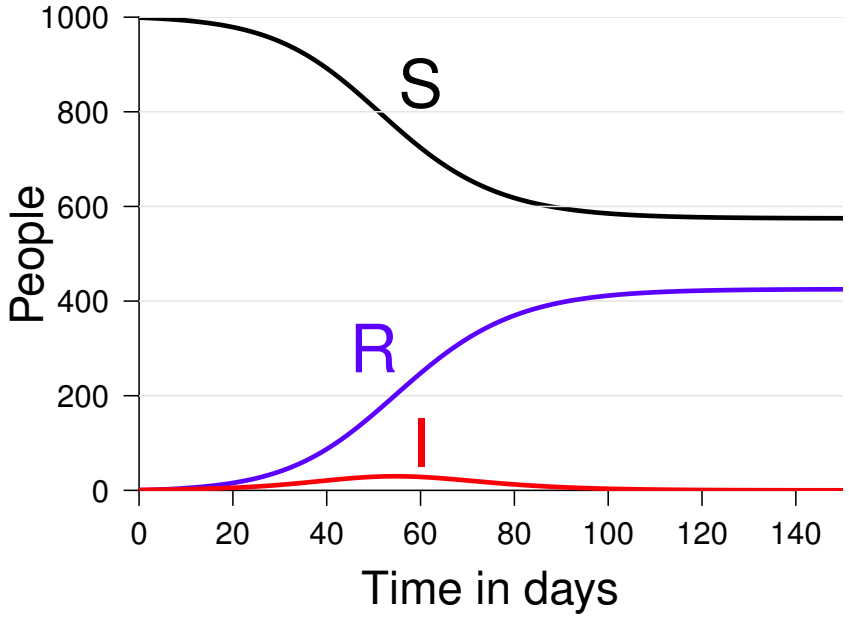
- $\frac{dI}{dt} = \beta SI - \gamma I$
- As people are infected then recover, the pool of susceptible people shrinks.
- Growth slows as susceptibles are consumed.
- The epidemic declines when the infected population becomes smaller and smaller.

When does the epidemic stop?

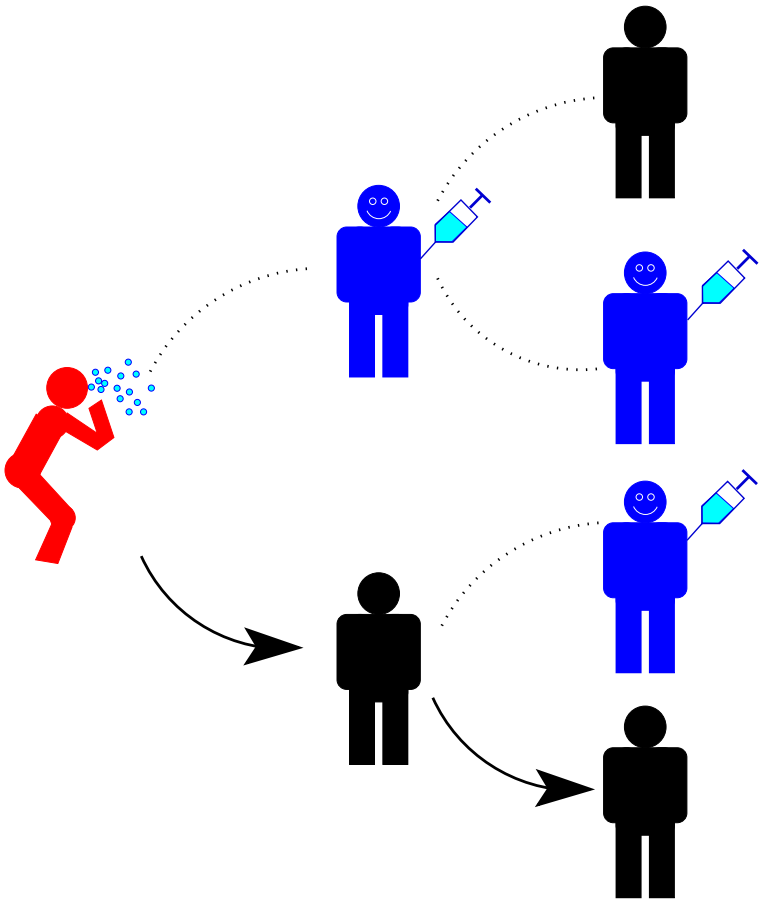


$R_0 = 2.0$,
"effective" R = 1.0

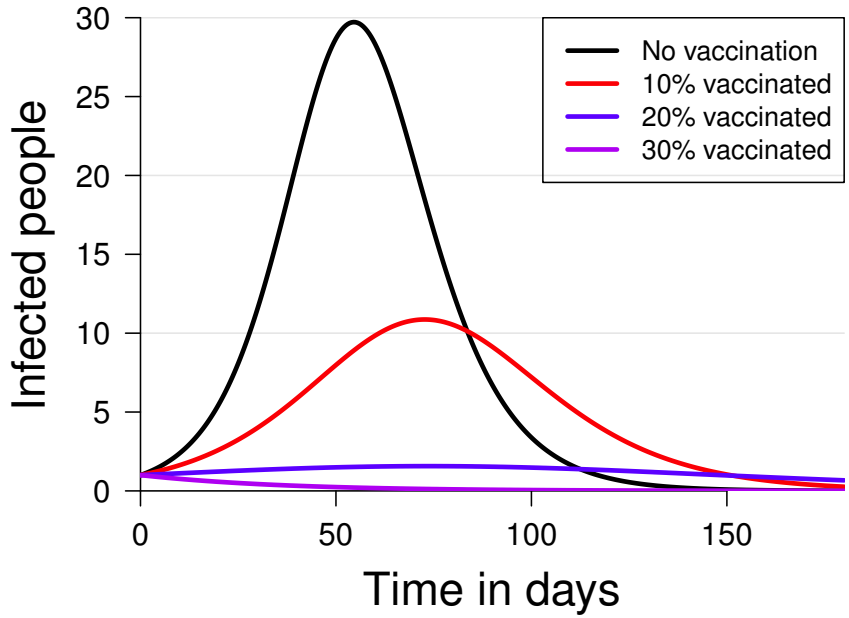
- When a infected person can not infect more than one other, the epidemic will shrink.
- The epidemic stops before all Susceptibles are infected.
- The epidemic can not resume unless immunity wanes or more susceptibles are added (e.g., birth or immigration).



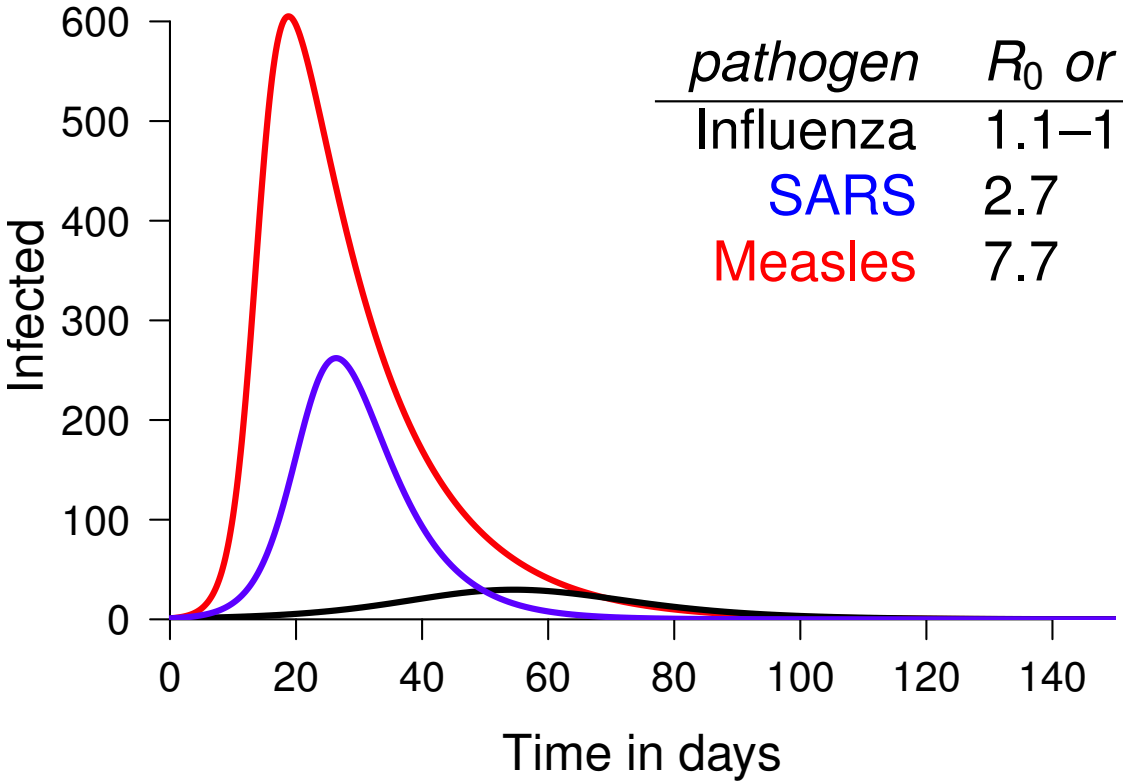
Both mass vaccination and large epidemics deplete susceptible individuals



- **Vaccination** reduces the susceptible population.



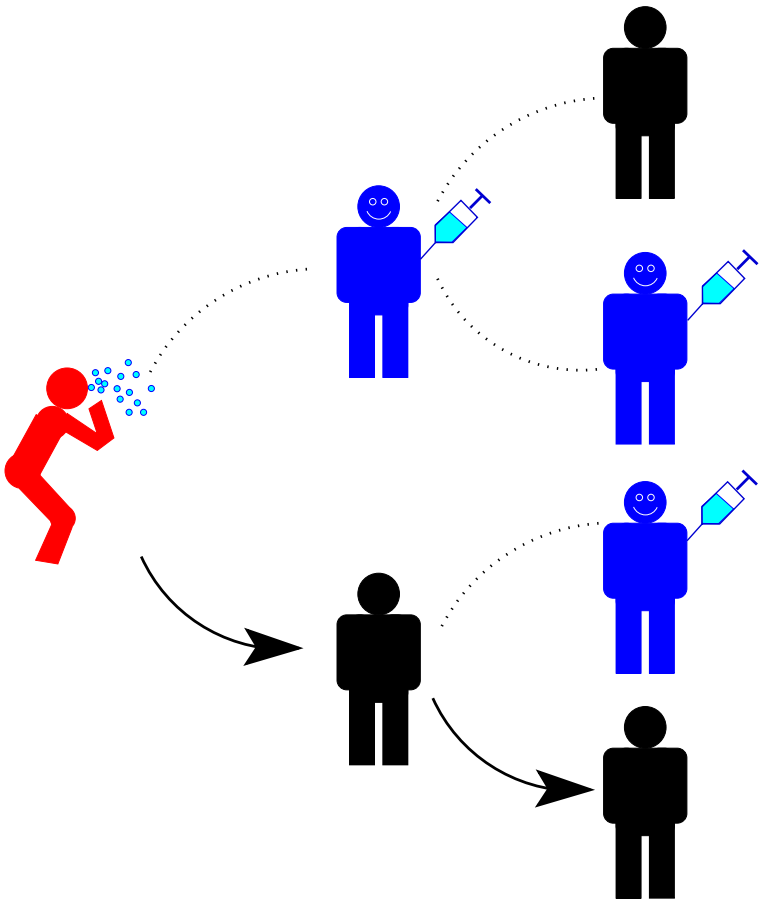
R_0 for different pathogens



pathogen	R_0 *or* R	*serial interval*
Influenza	1.1–1.5	3.4 days
SARS	2.7	6 days
Measles	7.7	14 days

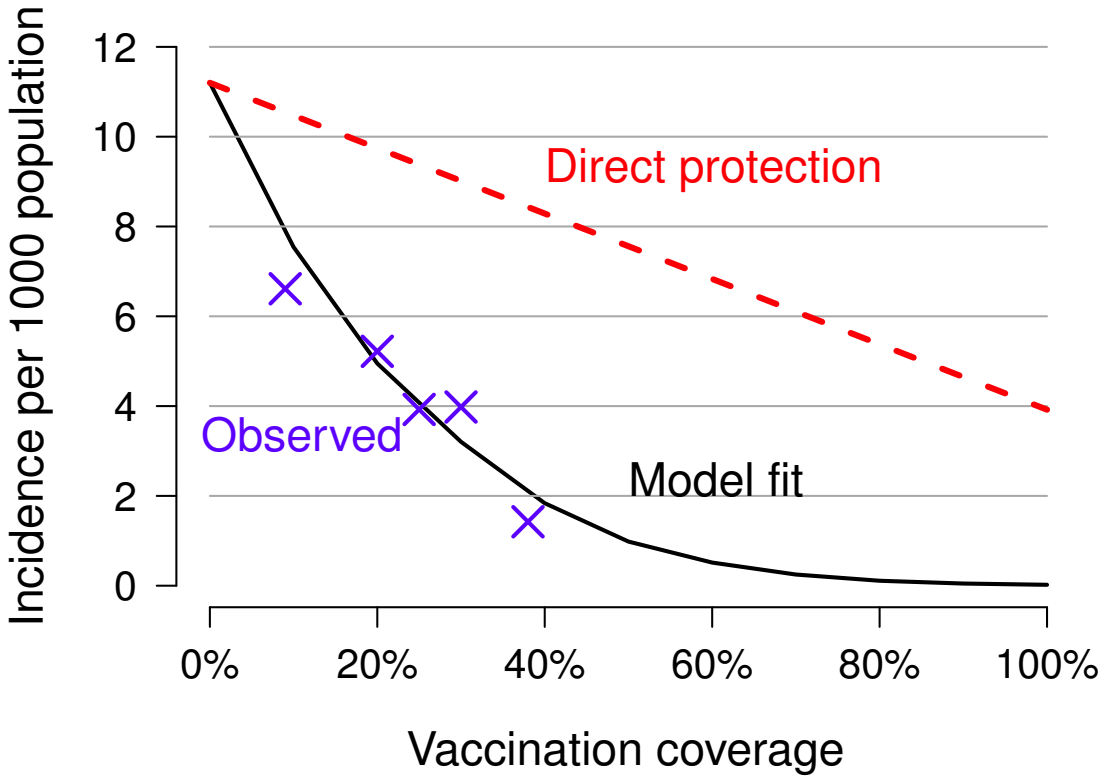
- If we know R_0 for a pathogen, we can set β in an SIR model using: $\beta = R_0\gamma/N$
- If part of the population is not susceptible, then we might use the term "R" instead of R_0.
- The epidemic peak time is determined by both transmissibility (β) and the serial interval ($1/\gamma$).

“Indirect protection” or “Herd immunity”



- There is both **direct** and **indirect** protection from vaccination.
- **Vaccinated people** are less likely to become infected *and* less likely to infect others. Therefore, vaccines can protect vaccinated *and* unvaccinated people.
- If some people are vaccinated, epidemics may be smaller.
- If enough people are vaccinated, epidemics should not spread and there is “**herd immunity**”.

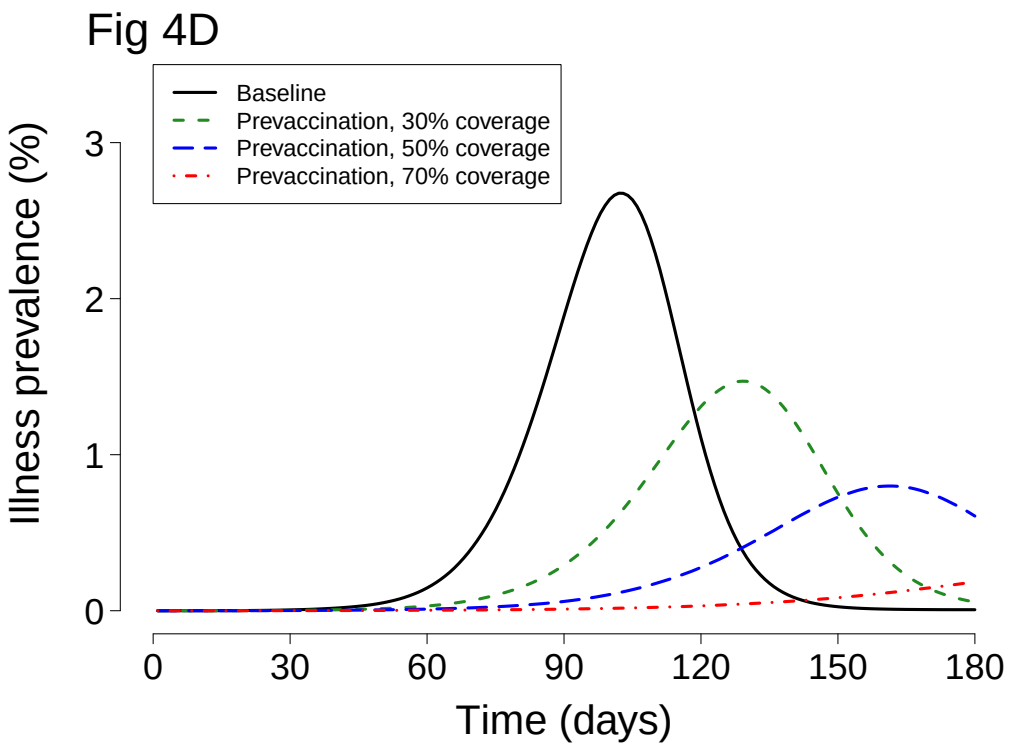
Evidence of indirect protection from mass cholera vaccination



- If a vaccine is 65% effective, then one should avert at least 65% of cases.
- The observed reduction in a large-scale trial was greater.
- Indirect protection can be important for cost-effectiveness studies.

Mathematical modeling was used to understand the relationship between coverage and incidence.

Other benefits from mass cholera vaccination

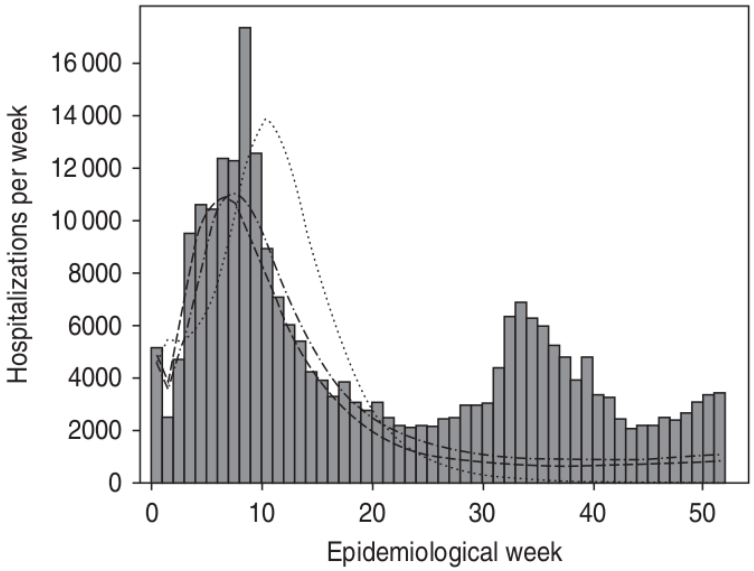


- Mass vaccination can *reduce* and *delay* the epidemic peak.
- The size of the peak may be important for hospital capacity planning.
- Delaying the peak might give officials time to implement other interventions.

Yang, Sugimoto, Halloran, Basta, Chao, Matrajt, Potter, Kenah, and Longini. The transmissibility and control of pandemic influenza A (H1N1) virus. *Science* 326:729-733. 2009.

Mathematical modeling can be used to predict how mass vaccination (or other interventions) could slow down an epidemic.

Some practical applications of SIR models



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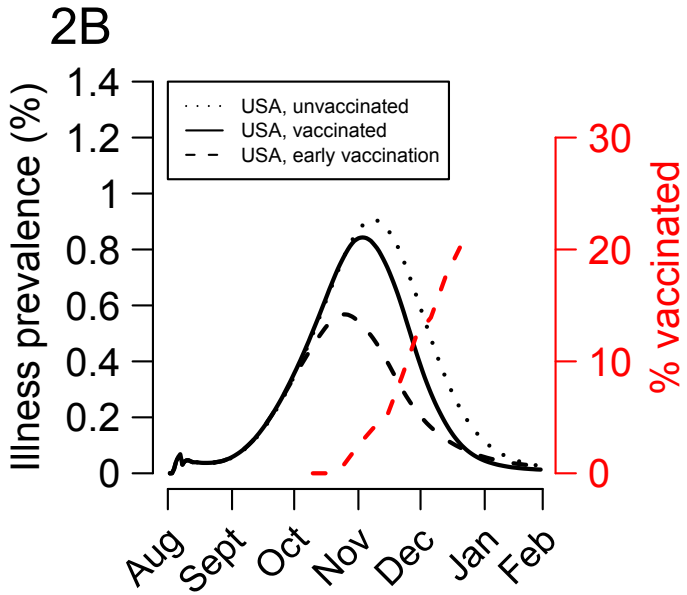
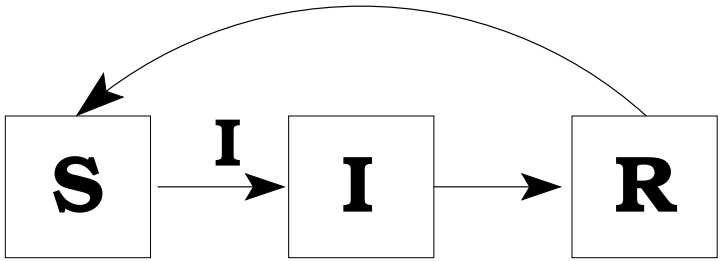


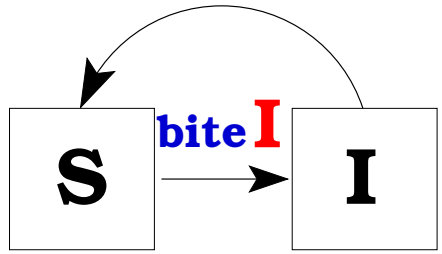
Chao, Matrajt, Basta, Sugimoto, Dean, Bagwell, Oiulfstad, Halloran, and Longini Jr. *Planning for the control of pandemic influenza H1N1 in Los Angeles County and the United States*. Am J Epidemiol. 173(10):1121–30. 2011.

- Epidemic peak timing and height (e.g., for emerging diseases)
- Final attack rate
- Predicting effectiveness of mass vaccination
  - Understanding “indirect protection”, “herd immunity”, or “population” immunity
  - Computing the vaccination coverage needed to prevent outbreaks

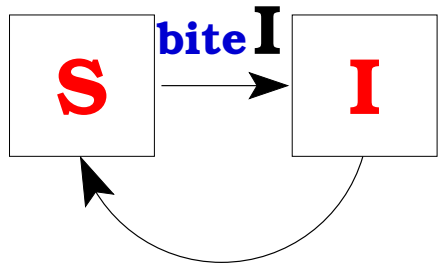
Related models



SIRS model

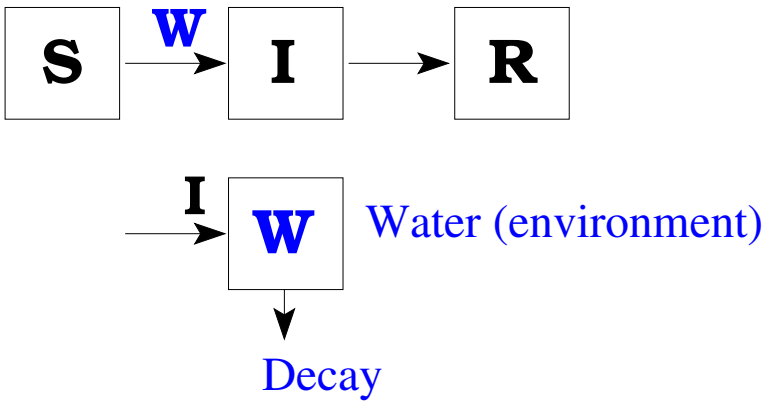


People



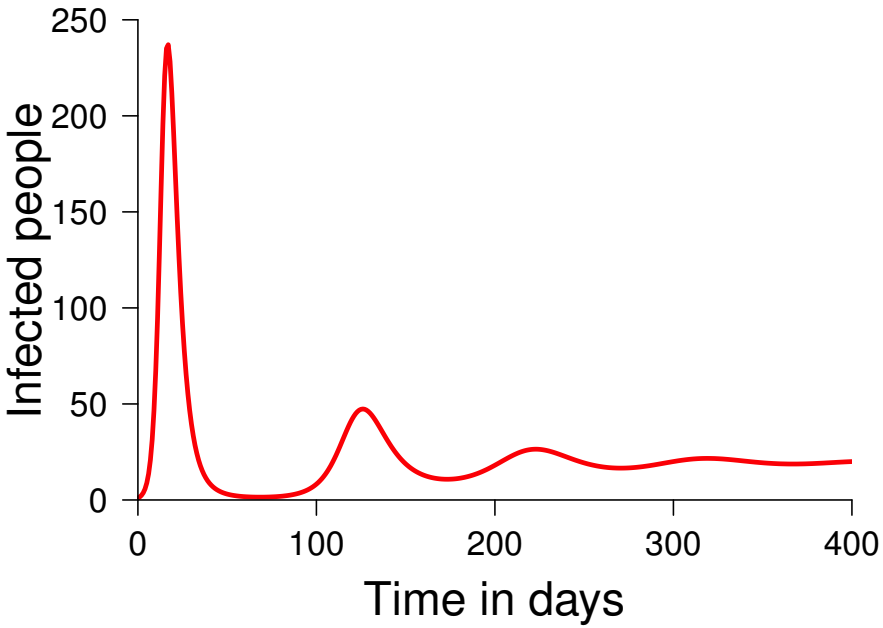
Mosquitoes

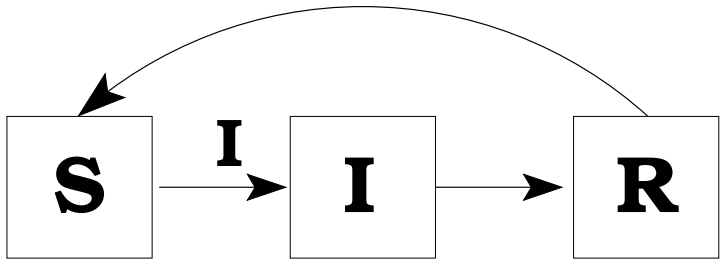
Ross-Macdonald model



Waterborne

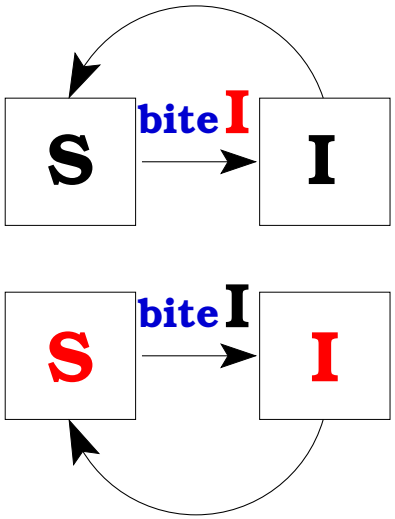
SIRS model when immunity is not lifelong

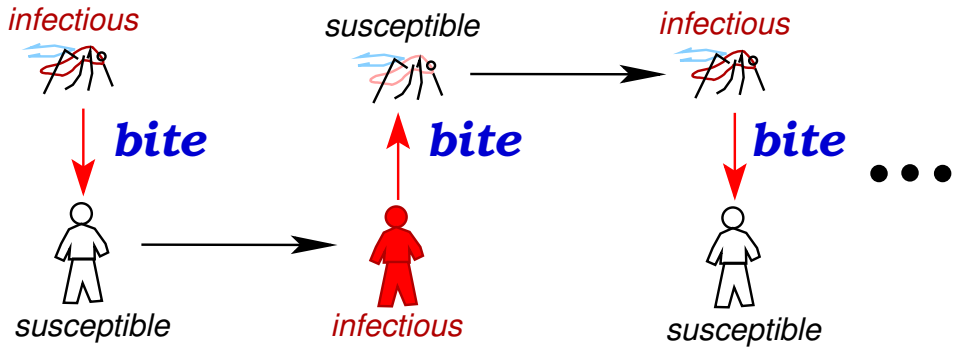




- When Recovered people can become Susceptible again, the epidemic can persist.

Ross–Macdonald model for vectorborne disease

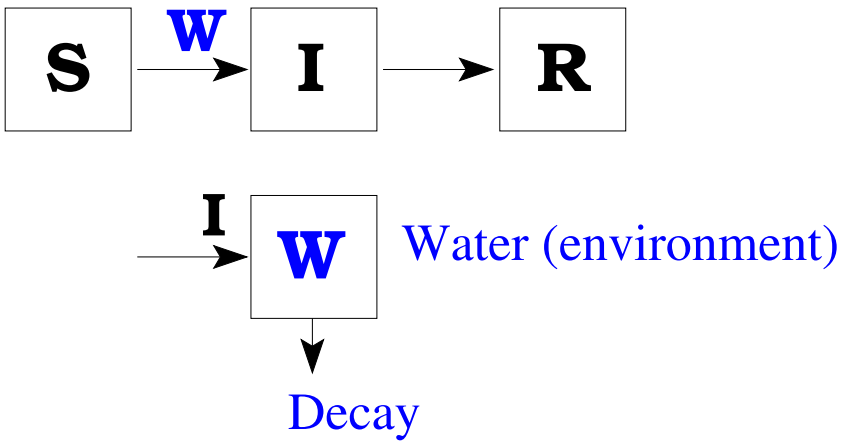




- An early (and still used) malaria model.
- Two populations: People and Mosquitoes.
- Infected Mosquitoes bite Susceptible humans.
- Infected humans are bitten by Susceptible Mosquitoes.
- Because both infection rates depend on the biting rate, transmissibility is a function of the biting rate squared.

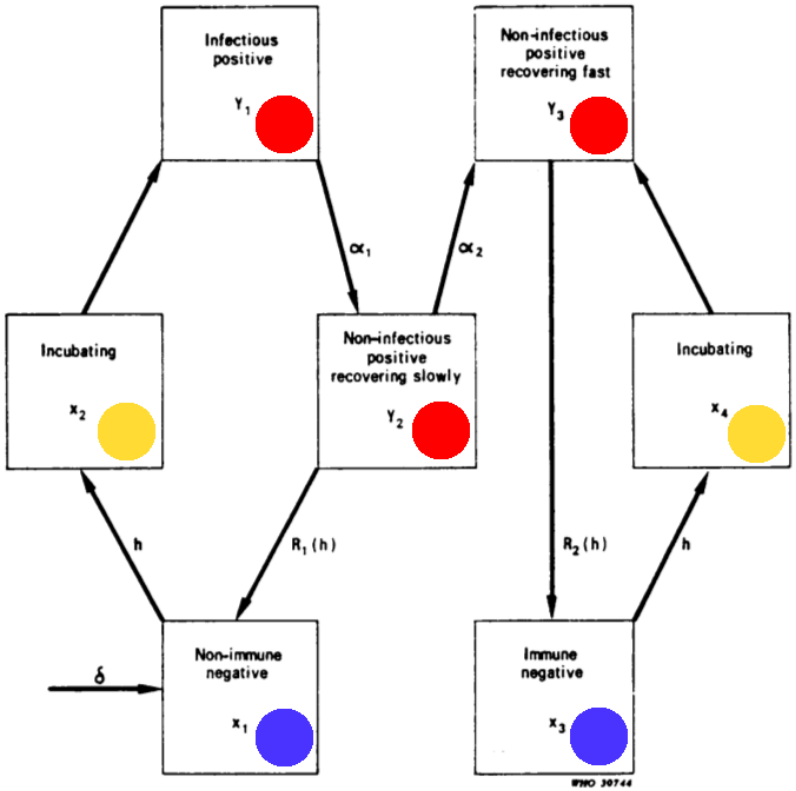
Ronald Ross
1857–1932

Waterborne disease model



- People are infected by contaminated Water.
- Infected people contaminate Water.
- The pathogen in the Water declines over time.
- If the decay rate of pathogen in the Water is slow (i.e., the water remains contaminated for a long time), the epidemic can be prolonged.

More complex models (malaria)



$$
\begin{aligned}
\Delta x_1 &= \delta + R_1(h)y_2 - (h+\delta)x_1 \\
\Delta x_2 &= hx_1 - (1-\delta)^N h(t-N)x_1(t-N) - \delta x_2 \\
\Delta x_3 &= R_2(h)y_3 - (h+\delta)x_3 \\
\Delta x_4 &= hx_3 - (1-\delta)^N h(t-N)x_3(t-N) - \delta x_4 \\
\Delta y_1 &= (1-\delta)^N h(t-N)x_1(t-N) - (a_1+\delta)y_1 \\
\Delta y_2 &= a_1 y_1 - [a_2 + R_1(h) + \delta]y_2 \\
\Delta y_3 &= a_2 y_2 + (1-\delta)^N h(t-N)x_3(t-N) - [R_2(h)+\delta]y_3
\end{aligned}
$$

Dietz, Molineaux, Thomas. A malaria model tested in the African savannah. Bull World Health Organ 50(3–4):347–57. 1974.

- System of 7 difference equations.
- States: Negatives (no parasites), have liver parasites, have blood parasites

More complex models (typhoid)

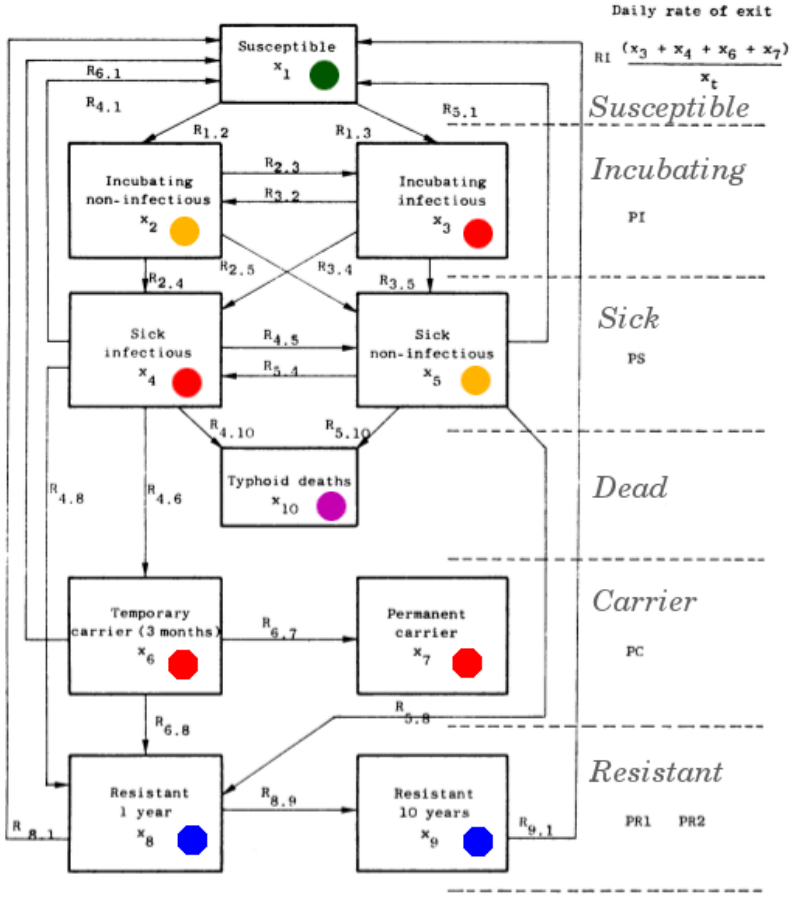


Fig. 1. Flow chart for epidemiological model of the natural course of typhoid fever.

$$
\begin{aligned}
dx_1 &= -(x_3 + x_4 + x_6 + x_7)(x_1/x_t)RI + (x_4R_{4.1} + x_5R_{5.1})PS + x_6R_{6.1}PC + x_8R_{8.1}PR_1 + x_9R_{9.1}PR_2 + \\
&\quad x_tPB - x_1(PD - dx_{10}/x_t) \\
dx_2 &= R_{1.2}(x_3 + x_4 + x_6 + x_7)(x_1/x_t)RI + x_3R_{3.2}PI - x_2(PI + PD - dx_{10}/x_t) \\
dx_3 &= R_{1.3}(x_3 + x_4 + x_6 + x_7)(x_1/x_t)RI + x_2R_{2.3}PI - x_3(PI + PD - dx_{10}/x_t) \\
dx_4 &= (x_2R_{2.4} + x_3R_{3.4})PI + x_5R_{5.4}PS - x_4(PS + PD - dx_{10}/x_t) \\
dx_5 &= (x_2R_{2.5} + x_3R_{3.5})PI + x_4R_{4.5}PS - x_5(PS + PD - dx_{10}/x_t) \\
dx_6 &= x_4R_{4.6}PS - x_6(PC + PD - dx_{10}/x_t) \\
dx_7 &= x_6R_{6.7}PC - x_7(PD - dx_{10}/x_t) \\
dx_8 &= (x_4R_{4.8} + x_5R_{5.8})PS + x_6R_{6.8}PC - x_8(PR_1 + PD - dx_{10}/x_t) \\
dx_9 &= x_8R_{8.9}PR_1 - x_9(PR_2 + PD - dx_{10}/x_t) \\
dx_{10} &= (x_4R_{4.10} + x_5R_{5.10})PS
\end{aligned}
$$

where $x_t = \sum_{1}^{9} x_i$

Cvjetanović, Grab, Uemura. Epidemiological model of typhoid fever and its use in the planning and evaluation of antityphoid immunization and sanitation programmes. *Bull World Health Organ* 45(1):53-75. 1971.

- System of 10 difference equations.
- States: Susceptible, exposed (asymptomatic or symptomatic), infectious (latent, sick, or carrier), resistant, dead
- Each compartment needs an equation.
- Each relationship between compartments needs a parameter.

Summary and conclusions

- Mathematical modeling is a quantitative tool based on our understanding of disease transmission.
- Simple mathematical models can be useful and general, and more complex models can be developed when needed.
- Mathematical modeling can be used to predict the speed and size of an outbreak.
- Modeling can be used to test hypotheses about disease transmission.
- For vaccines, models have been used to:
  - Predict the effectiveness of mass vaccination.
  - Predict the effectiveness of vaccinating different subpopulations (e.g., children).
  - Quantify the benefits of “indirect protection”, “herd immunity”, or “population” immunity.
  - Establishing thresholds for vaccine coverage to eliminate a disease.

Thank you!

Boukan Kare, Haiti.
Photo by D. Chao

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