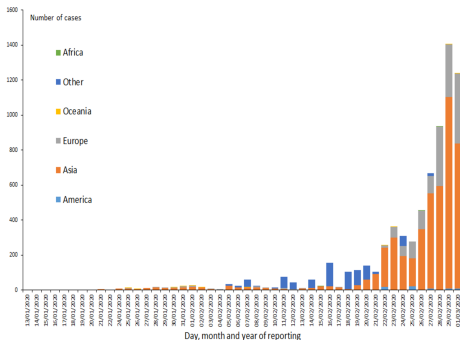


Mathematical models for epidemics like Covid-19

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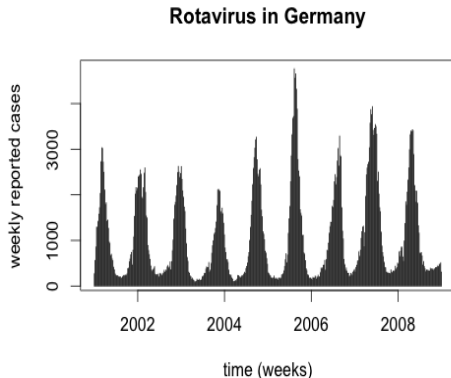
Reality: Ongoing Covid-19 outbreak, outside of China



Reported cases outside China up to mid March, 2020

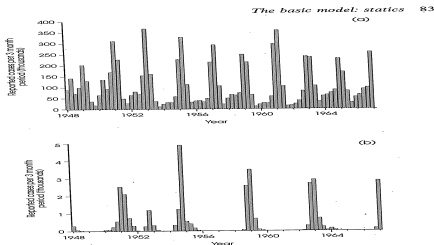
Possible scientific questions: How many will get infected, when is peak, effects of prevention, data collection, ...

Reality: Endemic diseases: Rotavirus in Germany



Possible scientific questions: Average age of infection, critical vaccination coverage, seasonality, under-reporting, ...

Reality: Endemicity or extinction of measles (pre-vac)



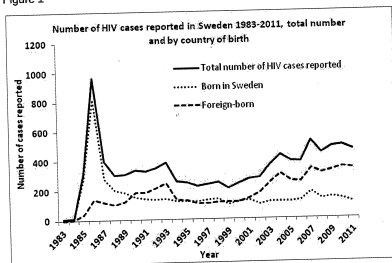
Top: 1948-1968 UK: Endemic

Bottom: 1948-1968 Iceland: outbreaks, extinction, reintroduction

Possible scientific questions: Critical community size, time to extinction, ...

Reality: endemicity in sub-communities of HIV in Sweden

Figure 1



Possible scientific questions: Endemic level, sub-communities and networks, targeted prevention, new data streams (virus sequences), ...

A model for the spread of an infectious disease

Today: simplest model (more advanced/realistic models exist!)

Assumptions:

- No prior immunity
- All individuals are similar (susceptibility and infectivity) and mix uniformly
- An individual who recovers becomes immune (**SIR**: Susceptible - Infectious - Recovered/immune)
- No behavioural changes during course of epidemic!

An epidemic model, cont'd

Model (Reed-Frost, 1929):

- Discrete time (e.g. week by week)
- n = population size (assumed fixed but large)
- Start: $n - 1$ susceptible , 1 infectious , 0 recovered
- An individual who gets infected one week, infects each susceptible individual with probability p (independently) the next week, and then recovers (and remains immune)
- Goes on until no new infected, then epidemic stops

The most important quantity (parameter):

R_0 = average number of new infections caused by a typical infected during early phase of an outbreak ("basic reproduction number")

Question: What is R_0 if $p = 0.0015$ and $n = 1000$?

An epidemic model, cont'd

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Answer: $R_0 = (n - 1)p \approx np = 1000 * 0.0015 = 1.5$.

The final epidemic size

Question: How many will get infected (possible values: $1, \dots, n = 1000$)? How does incidence/prevalence vary over time?

First: Final epidemic size (not time evolution)

On the next two slides I have simulated the epidemic model 10 000 times for a population of size $n = 1000$.

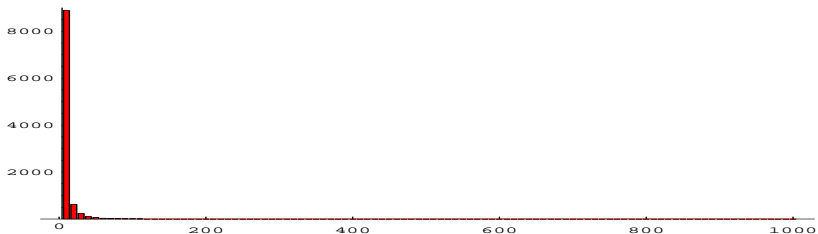
Histograms of final size

x-axis: number of infected

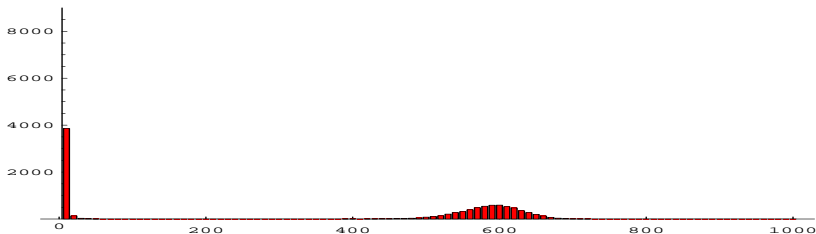
y-axis: frequency of simulations

First figure for $R_0 = 0.8$ and second figure for $R_0 = 1.5$

Histogram: final epidemic size: $R_0 = 0.8$ (Only small outbreaks!)



Histogram: final epidemic size: $R_0 = 1.5$ (Small and major outbreaks)



Mathematical formula for final epidemic size

So either very few get infected, or else a positive fraction τ (if $R_0 > 1$). Minor/major outbreak

It is actually possible to derive an equation for the final size τ .
Remember: $n\tau =$ number infected, and $p = R_0/n =$ transmission probability

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$$\begin{aligned}1 - \tau &= \text{proportion **not** infected} \\ &\approx \text{probability not to get infected} \\ &= \text{probability to avoid infection from all } n\tau \text{ infected} \\ &= (1 - p)^{n\tau} \\ &= \left(1 - \frac{R_0}{n}\right)^{n\tau} \\ &\approx e^{-R_0\tau} \quad (\text{since } (1 - x/n)^n \approx e^{-x}, \text{ for large } n)\end{aligned}$$

Mathematical formula, cont'd

So final epidemic size τ solves equation

$$1 - \tau = e^{-R_0\tau}$$

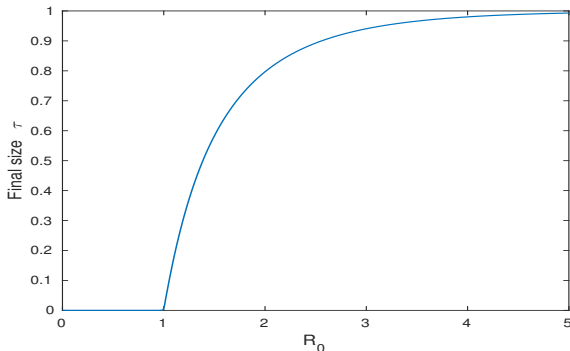
Solution depends on R_0 but is not explicit. Easily solved numerically: $R_0 = 1.5 \implies \tau = 58\%$

Mathematical formula, cont'd

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Our assumptions

Important: If $R_0 \leq 1 \implies$ no major outbreak!

Model/results are based on three assumptions:

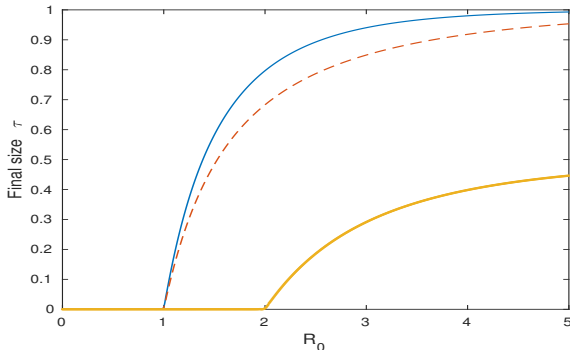
1. No immunity (natural or by vaccination). True for Corona but not for seasonal influenza. If half the community are immune then final epidemic size changes dramatically!
2. A homogeneous community. Not true for Corona or any disease. Which heterogenities are relevant depends on means of spreading (a lot of research in this direction). Often effect is that 10%-20% fewer get infected
3. No changing behaviour during epidemic. Preventive measures during outbreak may give very different outcome

Final epidemic size, different scenarios

Below: Final epidemic size: under model, with heterogeneity, and with 50% initial immunity

Final epidemic size, different scenarios

Below: Final epidemic size: under model, with heterogeneity, and with 50% initial immunity



Characterization of R_0 and prevention

R_0 can be factorized:

$$R_0 = p * c * \ell, \quad \text{where}$$

p = transmission probability for a "contact"

c = number of c "contacts" per day

ℓ = duration of infectious period

All **prevention** aims at decreasing R_0 by decreasing

p : face mask, hand washing, condom, ...

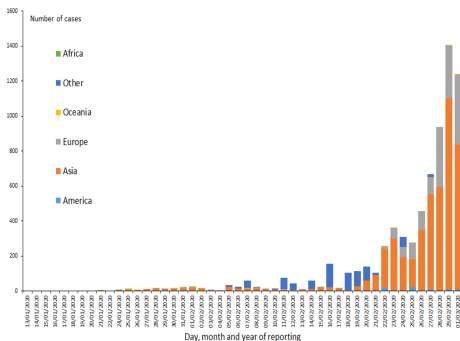
c : quarantine, avoid: public transport, public events, ...

ℓ : quicker diagnosis, isolation, ...

If the combined effect of preventive measures reduces R_0 by factor a , then "effective" reproduction number $R_E = (1 - a)R_0$

\implies No outbreak if $R_E \leq 1$, i.e. if $a \geq 1 - 1/R_0!$

How to estimate R_0 for a new emerging disease?



How to estimate R_0 for a disease?

Unfortunately not possible by only observing incidence curve

Growth rate r of curve depends on two things: R_0 , but also generation time G (typical time between getting infected and infecting others, highly affected by incubation time)

Big R_0 increases r , and *small* G increases r (formulae exist)

Many combinations of R_0 and G give rise to observed growth rate r

But if you also observe generation time G for some cases (e.g. from contact tracing), then it is possible to estimate R_0 !

What happens through time?

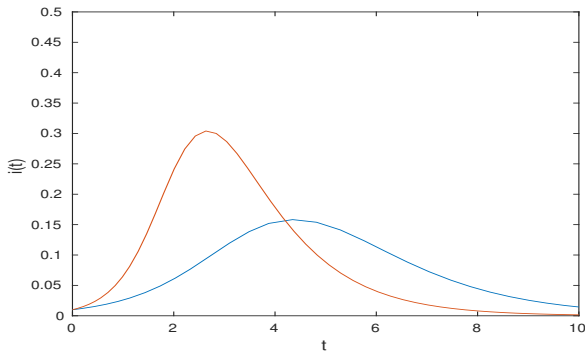
So far: final epidemic size

Now: What happens with outbreak over time?

Next page we plot fraction infectious over time, $i(t)$, for a related but deterministic model. For $R_0 = 3$ but also assuming preventive measures which reduce reproduction number to $R_E = 2$

From above we know that final epidemic sizes approximately equal 92% and 78% respectively. Not a huge difference but ...

Fraction infectives $i(t)$ over time, for $R_0 = 3$ and $R_E = 2$



The peak drops close to 50% and is delayed 70%! Both effects are very important for healthcare system!!

Prevention and vaccine immunity

From before: If overall effect of preventive measures reduce infectious contacts by factor p then reproduction number equals

$$R_E = R_0 * (1 - p)$$

So minimal preventive effect (such that $R_E \leq 1$): $p_{Min} = 1 - 1/R_0$

If additionally a (uniformly distributed) fraction \hat{i} are immune from vaccination, then

$$R_E^{(Vac)} = R_0 * (1 - p) * (1 - \hat{i})$$

and $p_{Min}^{(Vac)} = 1 - 1/(R_0 * (1 - \hat{i}))$

Disease-induced immunity

Based on Britton et al (2020) (*Science + MedRxiv*)

If instead a fraction \hat{i} are immune from disease spreading, then socially active and highly susceptible individuals are over-represented among immune.

\implies immunity is more efficiently distributed

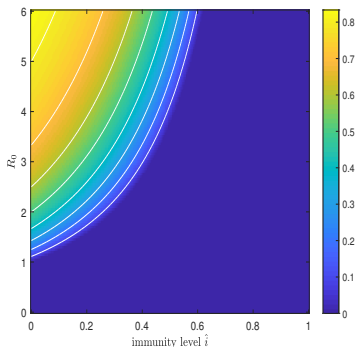
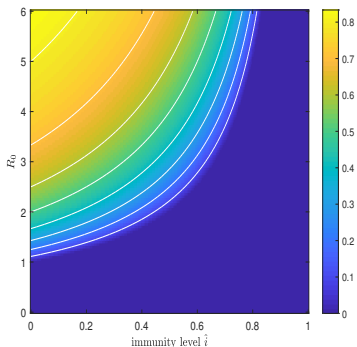
$$\implies R_E^{(Dis)} < R_E^{(Vac)} = R_0 * (1 - p) * (1 - \hat{i})$$

$$\implies p_{(Min)}^{(Dis)} < p_{Min}^{(Vac)} = 1 - 1/(R_0 * (1 - \hat{i}))$$

Heatmap of minimal preventive measures p_{Min}

Left: Vaccine-induced immunity and/or homogeneous model

Right: Disease-induced immunity + heterogeneous model



Example: $R_0 = 2.5$, $\hat{i} = 25\%$: $p_{Min}^{(Vac)} = 47\%$ and $p_{Min}^{(Dis)} = 29\%$

Herd immunity

Herd immunity: $R_E < 1$ without preventive measures (i.e. when $\rho = 0$)

Herd immunity from vaccination: $i_H^{(Vac)} = 1 - 1/R_0$

If vaccine has efficacy E (for example 90%) then critical vaccination coverage v_c given by

$$v_c = \frac{1}{E} \left(1 - \frac{1}{R_0} \right)$$

If $R_0 = 2.5$ and 90% vaccine efficacy, then $v_c = 67\%$

Disease induced Herd immunity is smaller $i_H^{(Dis)} < 1 - 1/R_0$

Global challenges in Infectious disease modelling

Pandemics: Prediction, evaluating effects of preventive measures (including vaccine programs), ...

Endemic diseases (malaria, measles, TB, Polio, ...): effects of different preventive measures, what fraction necessary to vaccinate, ...

HIV and other STI's: risk-groups, targeted preventive measures and treatment, ...

Diseases among domestic animals: stop outbreaks without culling too many animals

Antibiotic resistance: How reduce resistance levels without stopping the *important* use of antibiotics