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L7, Vaccination, other preventive measures and uncertainties

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Modelling vaccination

Why is modelling of disease spread important?

Modelling vaccination

Why is modelling of disease spread important?

Increase understanding and *prevention* (e.g. **vaccination**)

Suppose that a fraction v are vaccinated **prior** to outbreak

Assume first a perfect vaccine (100% immunity)

$\Longrightarrow$ a fraction v are initially immune (discussed in previous lecture)

R_v is the reproduction number after a fraction v has been vaccinated

$\Longrightarrow R_v = R_0(1-v)$

$R_v < 1$ equivalent to $R_0(1-v) < 1$ equivalent to $v > 1 - 1/R_0$

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Modelling vaccination cont'd

So, if $v > 1 - 1/R_0$ there will be no major outbreak: "Herd immunity"

$v_c = 1 - 1/R_0$ is called the *critical vaccination coverage* (or critical immunity coverage)

Exercise 7.1: Compute v_c for a disease having $R_0 = 1.5$, 3 and 6

On next page are estimates of v_c for some diseases

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v_c for some diseases (Anderson & May, 1991)

Fig. 5.1. The dependence of the critical level of vaccination coverage required to halt transmission, p_c, on the basic reproductive rate R_0, or, equivalently, on the average age at infection, A (see eqns (5.2) and (5.3)).

Table 5.1 Approximate estimates of the vaccination coverage (the degree of herd immunity) required to eradicate a variety of viral, bacterial, and protozoan infections in developed and developing countries (eqn (5.2) in the main text)

Infectious disease	Critical proportions (p_c) of the population to be immunized for eradication
Malaria (*P. falciparum* in a hyperendemic region)	99%
Measles	90–95%
Whooping cough (pertussis)	90–95%
Fifths disease (human parvovirus infection)	90–95%
Chicken pox	85–90%
Mumps	85–90%
Rubella	82–87%
Poliomyelitis	82–87%
Diphtheria	82–87%
Scarlet fever	82–87%
Smallpox	70–80%

Modelling vaccination cont'd

If vaccine is not perfect but relative risk of getting infected from an infectious contact for vaccinees is $1 - E$, $0 < E \leq 1$ (E for "efficacy", later to be called VE_S), then

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

For a highly infectious disease (R_0 large) and a not so effective vaccine (E not too close to 1) v_c might exceed 1. This means vaccination alone cannot prevent an outbreak!

Estimation of v_c from one large outbreak

It was shown earlier that: $\hat{R}_0 = -\ln(1-\tilde{\tau})/\tilde{\tau}$
By observing an outbreak we can hence also estimate v_c (for the same or similar community but not for any community!):

$$\hat{v}_c = 1 - \frac{1}{\hat{R}_0} = 1 - \frac{\tilde{\tau}}{-\ln(1-\tilde{\tau})}$$

If a fraction r was immune in the observed outbreak and $\tilde{\tau}$ of the initially susceptibles were infected this changes to

$$\hat{v}_c = 1 - \frac{1}{\hat{R}_0} = 1 - \frac{(1-r)\tilde{\tau}}{-\ln(1-\tilde{\tau})}$$

Estimation of v_c from one large outbreak

If vaccine not perfect but efficacy E known v_c estimated by

$$\hat{v}_c = \frac{1}{E}\left(1 - \frac{1}{\hat{R}_0}\right) = \frac{1}{E}\left(1 - \frac{(1-r)\tilde{\tau}}{-\ln(1-\tilde{\tau})}\right)$$

Exercise 7.2. Suppose that 20% of the community got infected but the initial fraction susceptible was 50% (so 40% of these susceptibles were infected). Estimate the critical vaccination coverage for a vaccine having 90% efficacy.

Endemic diseases: estimation of v_c

Same data: $\tilde{s}$ = average age of infection divided by average life-length (= average fraction susceptible in community)

Earlier we showed that $\hat{R}_0 = 1/\tilde{s}$

We know that $v_c = 1 - 1/R_0$ (or $v_c = E^{-1}(1 - 1/R_0)$ if vaccine has known efficacy E)

$$\Longrightarrow \hat{v}_c = \frac{1}{E}(1 - \tilde{s})$$

Exercise 7.3 Suppose (as with measles) average age of infection is 5 years and average life-length is 75 years. Estimate R_0 and v_c assuming a vaccine having efficacy $E = 0.95$. (How about if $E = 0.90$?)

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Repetition: Inference from large outbreaks

The basic reproduction number R_0 and critical vaccination coverage v_c were estimated by:

$$\hat{R}_0 = -\ln(1-\tilde{\tau})/\tilde{\tau}$$

$$\hat{v}_c = 1 - \frac{\tilde{\tau}}{-\ln(1-\tilde{\tau})}$$

if outbreak takes place in a fully susceptible homogeneous community, resulting in a fraction $\tilde{\tau}$ getting infected during the outbreak

How about uncertainty?

Uncertainty of previous estimate

Intuition: The larger community (and more getting infected) the less uncertainty

It was mentioned that final number infected $n\tilde{\tau} = Z$ in case of a major outbreak is normally distributed with mean $n\tau^*$ and standard deviation $\sqrt{n\sigma^2}$ where σ^2 depends on model parameters and shown two slides ahead

This result can be used to show that $\hat{R}_0$ and $\hat{v}_c$ are normally distributed with correct means (i.e. R_0 and v_c respectively) and standard errors to be derived using δ-method

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The δ-method

Suppose random variable X has mean $\mu = E(X)$ and (small) variance $V(X)$

Then the δ-method gives the following approximation for the mean and variance of $f(X)$, where $f(x)$ is a "nice function":

$$E(f(X)) \approx f(\mu) \qquad V(f(X)) \approx (f'(\mu))^2 V(X)$$

The approximation holds better the smaller variance X has (i.e. smaller $V(X)$)

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The δ-method for $V(\hat{R}_0)$

Probabilists have proven that the asymptotic variance of $\tilde{\tau}$ equals (see e.g. Andersson and Britton):

$$V(\tilde{\tau}) \approx \frac{1}{n} \frac{\tau(1-\tau)}{(1-(1-\tau)R_0)^2} \left(1 + c_v^2(1-\tau)R_0^2\right)$$

where τ and R_0 are the true parameter values related by $R_0 = -\ln(1-\tau)/\tau$, and c_v is the coefficient of variation of the infectious period ($c_v = 0$ for Reed-Frost and $c_v = 1$ for General stochastic epidemic).

We now apply the δ-method on $\hat{R}_0 = -\ln(1-\tilde{\tau})/\tilde{\tau}$. We hence have the function $f(x) = -\ln(1-x)/x$

After some algebra we get $V(\hat{R}_0) \approx \frac{1}{n\tau(1-\tau)} \left(1 + c_v^2(1-\tau)R_0^2\right)$

Uncertainty of previous estimate

For a standard error estimate we take square roots and replace unknown quantities with there estimates/observed values. The result, also for $\hat{v}_c$, is given by:

$$s.e.(\hat{R}_0) = \sqrt{\frac{1 + c_v^2(1-\tilde{\tau})\hat{R}_0^2}{\tilde{\tau}(1-\tilde{\tau})}/n}$$

$$s.e.(\hat{v}_c) = \sqrt{\frac{1 + c_v^2(1-\tilde{\tau})\hat{R}_0^2}{\hat{R}_0^4\tilde{\tau}(1-\tilde{\tau})}/n}$$

$c_v^2 = V(I)/(E(I))^2$= squared coefficient of variation of infectious period of individuals (variance divided by the squared mean)

Larger n gives smaller standard deviation (as expected)!

Uncertainty of previous estimate

c_v^2 cannot be estimated from final outbreak size – possibly known from before

If not one has to insert a "conservative" bound. E.g. $c_v^2 = 1$: very rarely is standard deviation larger than mean

Exercise 7.4 Do the details showing the expressions for $s.e.(\hat{R}_0)$ and $s.e.(\hat{v}_c)$

Exercise 7.5 Suppose that 239 out of 651 individuals in an isolated village were infected during an outbreak. Estimate R_0 and v_c and give 95% confidence interval for the estimates. Consider both the case when all individuals have the same length of infectious period (so no variation) and the case where its standard deviation is equal to the mean.

Exercise 7.6 Repeat, now assuming 2390 out of 6510 got infected.

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Leaky and All-or-Nothing vaccines

Recall from before that

Leaky vaccines: each vaccinee has risk of transmission at each contact (as long as the person is not yet infected) reduced from p to $p\theta$

All-or-nothing vaccines: each vaccinee has probability $1-\theta$ of being fully immune and probability θ of not having any reduced susceptibility at all

Both vaccines have $VE_S = 1-\theta$ and $v_c = \frac{1}{1-\theta}(1-1/R_0)$

Are they equally good vaccines (for same θ)?

Leaky and All-or-Nothing vaccines

It can be shown that $P(\text{to get infected within } k \text{ contacts})$ is equal for $k = 1$ but for $k > 1$ probability is always larger for leaky vaccine

$\Longrightarrow$ distribution of final size Z satisfies $Z^{(no)} \geq Z^{(leaky)} \geq Z^{(AoN)}$

So, if a community is vaccinated, but not enough for herd immunity, then All-or-nothing vaccine reduces transmission the most (and is hence superior)

If vaccine effect is unknown leaky is worst case scenario

So, an estimate of VE_S is larger if vaccine is assumed to be leaky

Consequence: if VE_S estimated assuming AoN when it really is leaky, the estimate is *under-estimated*

General preventive measures

Common way of expressing R_0 (Anderson & May, 1991):

$$R_0 = p * k * \ell$$

p is probability of transmission given a "contact" by an infective

k is the rate of "contacts" per unit of time

ℓ is average duration of infectious period

Suppose **preventive measures** (put in place very early) reduce $p * k * \ell$ by a factor c ($c(t)$ if time-varying)

$\Longrightarrow$ new *effective* reproduction number equals $R_E = (1 - c)R_0$

No outbreak possible if $R_E \leq 1$ which is equivalent to $c \geq 1 - 1/R_0$

General preventive measures, cont'd

Once the epidemic has got going and a positive fraction has become infected, the effective (or current) reproduction number reduces to

$$R_E(t) = (1 - c(t))s(t)R_0$$

A common goal is to keep $R_E(t) \leq 1$, which is equivalent to

$$c(t) \geq 1 - 1/(s(t)R_0)$$

Topic for break-out-rooms: Discuss different preventive measures for different diseases (Covid-19, HIV, measles, ...), and which of p, k and ℓ each of them aim to reduce