Disease control

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Outline

Approaches to disease control

Theoretical results

- Threshold levels for eradication
- Heterogeneity (Cities and villages)
- Individual vs population-wide control
- Targeted control

Success stories

Dynamical impacts of vaccination

Challenges to control

Infectious disease control

Goal: Reduce morbidity and mortality due to disease.

Sometimes control measures are focused on protecting vulnerable populations (e.g. elderly people for influenza, or endangered populations of wildlife)

…but usually the aim is to reduce disease burden in the whole population, by reducing transmission of the infection.

From earlier lectures, we know that the effective reproductive rate for transmission within a population can be expressed:

$$R_{\text{eff}} = c\ p\ D\ (S/N)$$

where

- c = contact rate
- p = probability of transmission given contact
- D = duration of infectiousness
- S/N = proportion of the population that is susceptible

Overall disease spread can also be reduced by measures to limiting transmission among populations or among regions.

Measures to reduce the contact rate, *c*

Quarantine: reduce contacts of possible latent cases (*E*)

Case isolation: reduce contacts of known infected indiv's (*I*)

ABC: 'Abstinence' & 'Be faithful'

Reducing mass gatherings: school closures etc

Culling (killing of hosts): reducing population density will reduce contact rate (if it's density dependent)

Measures to reduce the probability of transmission, *p*

Barrier precautions (masks, gloves, gowns etc.)

ABC: 'Condomize'

Male circumcision
(now known to reduce f→m transmission of HIV)

Imperfect vaccines

Prophylactic treatment

Measures to reduce the duration of infectiousness, *D*

Treatment

Case isolation

Contact tracing

Improved diagnostics

Culling of infected hosts

Measures to reduce the proportion susceptible, *S/N*

Vaccination

'Ring' vaccination Contacts of suspect smallpox cases are traced and vaccinated when found. Can be coupled with policy of isolation of identified contacts.	Minimizes use of vaccine, and hence morbidity and mortality caused by adverse reactions to vaccination.
Targeted vaccination For example, vaccination of whole population in affected neighbourhood or city.	Highly effective during eradication campaign at containing transmission localized to a single geographic area or subpopulation. Reduced vaccine related mortality. Not dependent on contact tracing.
Mass vaccination Vaccination of whole population of a country experiencing or threatened by an outbreak.	Effective at stopping widespread dissemination of the virus across large areas and protecting individuals from infection. Not dependent on contact tracing.
Prophylactic vaccination Vaccination before a smallpox release.	Useful for protecting essential "first-responder" personnel. If used for entire population, very effective at stopping widespread dissemination of virus. Does not have to be implemented quickly. Not dependent on contact tracing.

Measures to reduce transmission between populations

Ring vaccination

Ring culling

Movement restrictions (cordon sanitaire)

Fencing

Measures to reduce vector-borne diseases

Bednets and insect repellents

Vector population reduction
- larvicides
- removal of standing water

Biological control of vectors
- e.g. fungal pathogens of mosquitoes

Treatment of human cases

Vaccination of humans (e.g. yellow fever, malaria?)

Basic theory of disease control

People in Niger awaiting a smallpox and measles vaccination, 1969.

How many to vaccinate? (*the return of R_0*)

Population threshold for disease invasion

Recall: Under any form of transmission, $R_{effective} = R_0 \times S/N$.

→ For $R_{effective} > 1$, must have $S/N > 1/R_0$.

The next step is simple:

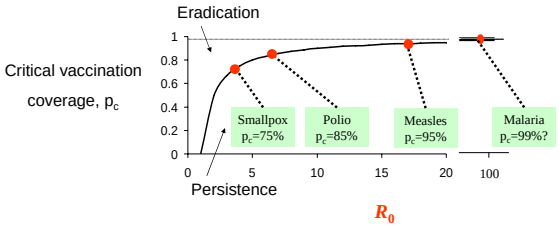
→ For $R_{effective} < 1$, must have $S/N < 1/R_0$.

Therefore, the critical vaccination coverage to eradicate a disease is

$$p_c = 1 - 1/R_0$$

Note that this calculation assumes mass, untargeted vaccination in a randomly mixing, homogeneous population, and that vaccination occurs at birth and is 100% protective.

Eradication through mass-vaccination depends on R_0



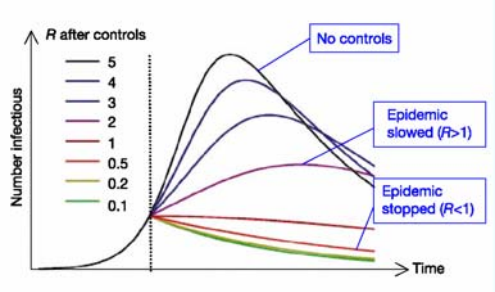
- Herd immunity → don't need to vaccinate everyone.
- As R_0 increases, eradication by vaccination becomes very challenging due to logistical problems in achieving high coverage levels.

Table 5.1 Approximate estimates of the vaccination coverage (the degree herd immunity) required to eradicate a variety of viral, bacterial, and proto 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%

Anderson & May (1991)

Good news: R_{eff} >1 but <R_0 still reduces disease!



Generalizing the result

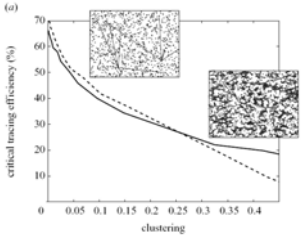
Any control method that reduces R_0 by proportion k, so that

$$R_{control} = (1-k)\, R_0$$

will have a critical level $k_{crit} = 1-1/R_0$ in a randomly mixed situation.

What about non-random mixing?

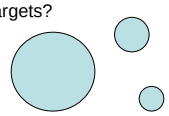
Eames & Keeling studied the efficacy of contact tracing in a network epidemic model, and found that the critical tracing efficacy was ~$1-1/R_0$ *unless* the network was clustered.



Eames & Keeling (2003) Proc Roy Soc B 270: 2565-2571

Spatial heterogeneity

How does simple population structure influence vaccination targets?



$$R_{ij} = D_i\beta_{ij} \quad \text{with}$$
$$\beta_{ij} = \beta \quad \text{if } i = j$$
$$= \varepsilon\beta \quad \text{if } i \neq j$$
$$\text{where } \varepsilon < 1.$$

Patches have different population sizes.

If the same fraction is vaccinated in each group, regardless of group size, then the critical vaccination coverage for the whole population is once again $p_c = 1-1/R_0$, where R_0 is the dominant eigenvalue of the matrix $\boldsymbol{R}$.

If $\hat{p}_c$ is the critical vaccination coverage calculated for a homogeneous population, then $p_c \geq \hat{p}_c$.

May & Anderson (1984); Hethcote & Van Ark (1986)

Spatial heterogeneity

However, if the fraction vaccinated in each group is allowed to vary, then there exists an optimal vaccination strategy requiring total coverage p_{opt}, where $p_c \geq \hat{p}_c \geq p_{opt}$

So spatial heterogeneity

→ increased vaccination required if applied uniformly

→ decreased vaccination required if applied optimally in space

Under mass-action transmission, the optimal vaccination program is that which leaves the same number of susceptibles in each population group.

If density dependence is weaker, the quantitative effect is diminished but the general inequality holds.

May & Anderson (1984); Hethcote & Van Ark (1986)

Another theoretical approach

Population-wide control:
reduce ν by a fraction *c* for all individuals.

$R_c=(1–c)R_0$

Reduces individual variation.

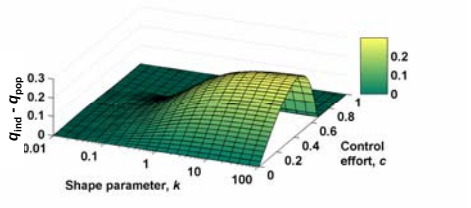
Individual-specific control:
reduce ν to 0 for a fraction *c* of individuals, chosen at random.

$R_c=(1–c)R_0$

Increases individual variation.

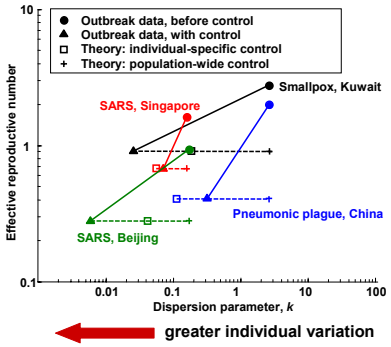
Analysis of branching process models shows that, for a given reduction in R_0, individual-specific control is always more likely to cause disease extinction than population-wide control.

Population-wide vs individual-specific control



q_{ind} = prob. of disease extinction under individual-specific control
q_{pop} = prob. of disease extinction under population-wide control

For a given reduction in R_0 (represented by control effort *c*), individual-specific control is always more effective than population-wide control.

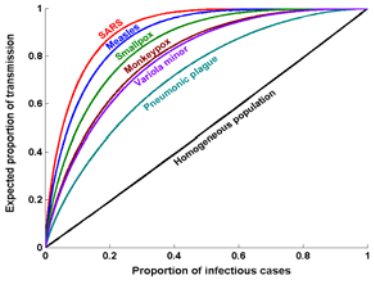


Data: Control appears to increase variation in infectiousness, as in individual-specific model.

Probably due to mixed success in identifying cases.

Heterogeneity and targeted control

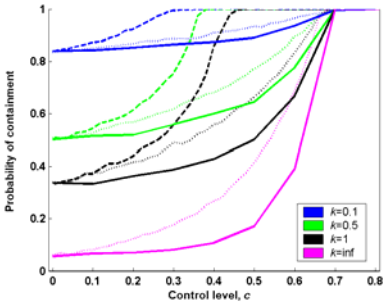
Measures targeting more infectious cases are always more effective for a given control effort. Again, this can be proven in a branching process framework. (See Lloyd-Smith et al 2005)



Targeted control – results of stochastic simulations

R_0 = 3

Lines
Solid: Population-wide
Dotted: Random individual-specific
Dashed: Targeted individual-specific



Measures targeting the most infectious individuals are always more likely to contain an outbreak.

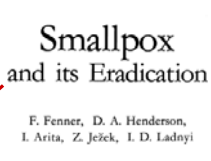
Success stories: smallpox eradication

Smallpox virus

Incubation period 1-2 weeks
Infectious period = 3 wks

R_0 = 4-6 p_c=70-80%

Major vaccination effort led by WHO led to global eradication of smallpox. The last naturally occurring case in the world was in Somalia in 1977.



Whole book available for download at
whqlibdoc.who.int/**smallpox**/9241561106.pdf

Test of simple theory: two major differences

1. Eradication depended on both vaccination coverage and population density.

Table 5.2 Estimates of population densities, densities of susceptibles, and reported cases of smallpox in countries in Africa and the Indian subcontinent, around 1968–73 (condensed from Arita *et al.* 1986)

Country	Population* (thousands)	Area ($km^2 \times 10^{-3}$)	Population density (km^{-2})	Vaccination coverage* (per cent)	Density of susceptibles* (km^{-2})	Reported cases of smallpox per km^2 ($\times 10^5$) 1973
Bangladesh	72 000	143	502	80	100	22 875
India	574 000	3280	175	80	35	2686
Pakistan	67 000	304	83	80	17	3045
						1967 1969 1970
Nigeria	53 730	924	58	77	13.4	514 22 7
Sierra Leone	2510	72	35	84	5.6	2357 111 0
Ghana	8440	239	35	93	2.5	48 0 0
Togo	1900	56	34	88	4.1	593 148 0
Benin	2650	113	23	80	4.7	721 51 0
Guinea	3840	246	16	90	1.6	622 7 0
Liberia	1490	111	13	83	2.3	5 0 0
Mali	4930	1240	4.0	95	0.2	24 0.1 0
Niger	3910	1267	3.1	79	0.6	94 2 0
Chad	3570	1284	2.8	78	0.6	7 0 0

* Population in 1973 for Asian countries, in 1969 for African.
* Vaccination coverage and density of susceptibles in 1973 for Asian countries, and around 1969 for African.

2. Final eradication or "end-game" required intensive contact tracing and ring vaccination.

Smallpox vaccination policy is still an important applied problem because of concerns of bioterrorism.

- need to balance protection vs risk of side effects
- also logistics of vaccinating many people in a short time
- Big question: mass vaccination vs contact tracing?

Kaplan et al (PNAS 2002) presented a model that argued for mass vaccination of entire cities in the event of a smallpox release.

This finding was controversial, and criticism focused on the assumption of random mixing across a city of 10M people.

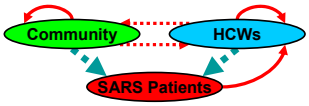
Other models (e.g. Halloran et al, Porco et al) used refined contact structure and reached different conclusions.

Lesson: Watch your assumptions!!

Success stories: SARS eradication

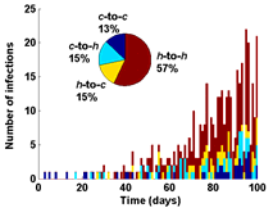
Health care workers (HCWs) comprised 18-63% of SARS cases.

Infected cases were concentrated in hospitals.



Analyzed role of community and hospital in SARS spread:

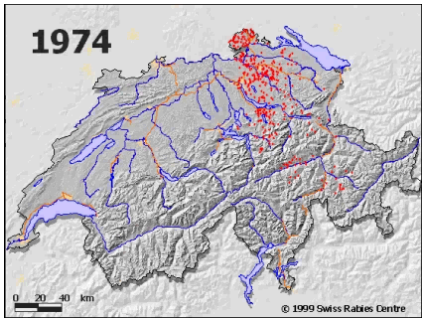
- effect of hospital-based control measures
- tradeoffs among control measures and impact of delays



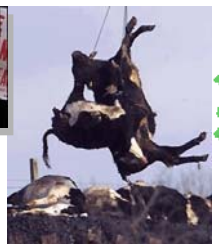
Lloyd-Smith *et al.* (2003) *Proc. Royal Soc. B* **270**: 1979-1989

Success stories: rabies in Switzerland

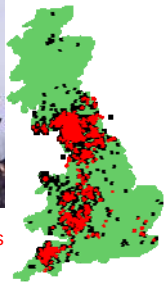
Spatial vaccination campaign

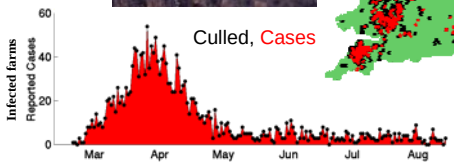


Success story? Foot and mouth disease in the UK, 2001



Major FMD outbreak was contained by massive targeted culling program.

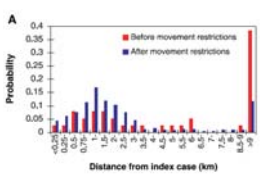




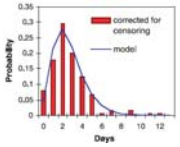
Success story? FMD in UK

Models played a central role in deciding control policy:

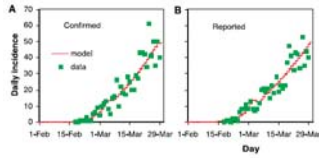
Ferguson et al (2001) Science 292: 1156-1160

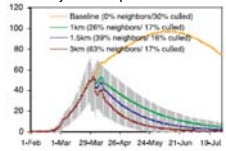


Report-to-slaughter delay



Projected impact of control





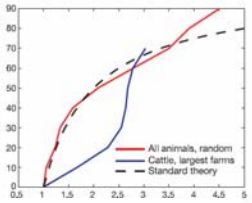
Success story? FMD in UK

But the decision to cull instead of vaccinate remains controversial.

Further studies are weighing prophylactic and reactive vaccination strategies, and the impact of landscape heterogeneities

Keeling et al (2003, Nature 421: 136-142) studied vaccination policies using a spatial stochastic model that tracks the infection status of every livestock farm in UK.

Critical level of vaccination needed to stop epidemic



Basic reproductive number, R_0

Vaccination and the tragedy of the commons:

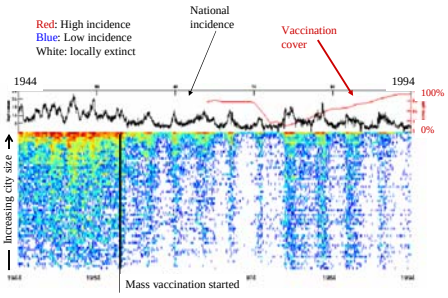
The individual gets all the benefits from refusing vaccine;
the costs of lower coverage are shared among the group

Game theoretical approach to vaccination uptake
Bauch et al (2003) PNAS 100: 10564-67
Bauch et al (2004) PNAS 101: 13391-94

There have been periodic vaccine scares, where the perceived risk has increased and vaccination coverage has dropped.

These can cause serious public health problems, but also provide excellent "natural experiments" to assess the dynamical effect of vaccination.

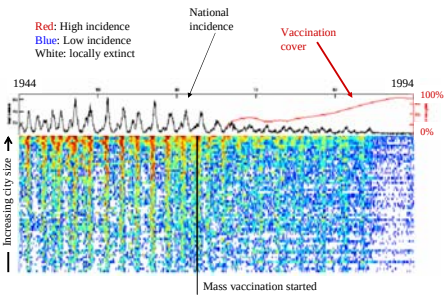
E.g. Whooping cough incidence in UK by city size and vaccination



Target vaccination cover: ca 95-97% Coverage in 1994: 90+%

Slump in immunisation after a vaccine 'scare' in the late 1970s. This led to 2-3 further epidemics, each epidemic affecting ½ million children. Immunisation rates then went up again, and most children are now immunised.

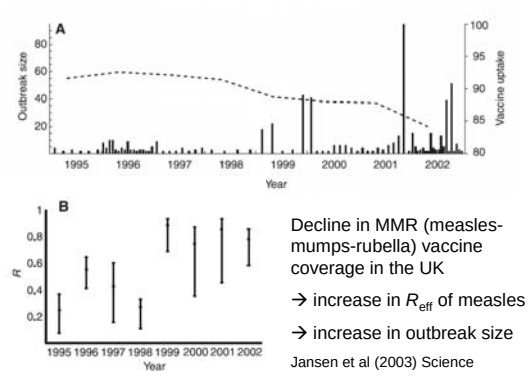
E.g. Measles incidence in UK by city size and vaccination



Target vaccination cover: ca 95-97%

Cover 1994: ca 93%

Challenges: Vaccine scares



Decline in MMR (measles-mumps-rubella) vaccine coverage in the UK

→ increase in R_{eff} of measles

→ increase in outbreak size

Jansen et al (2003) Science

Challenges: Drug resistance

Rapid evolutionary rates of pathogens

+ strong selection pressure imposed by drug treatments

→ evolution of drug resistant strains is a universal problem

Imperfect compliance to drug regimens (not taking pills) contributes to this problem by exposing pathogens to drug selection in insufficient doses to kill them all.

Penicillin: mass production began in 1943; drug-resistant strains appeared by 1947.

HIV: anti-retroviral resistance is a major threat to the effort to treat all people living with HIV/AIDS. "Primary drug resistance" means that resistant strains are being transmitted, not just evolving within hosts.

Malaria: chloroquine resistance eliminated cheap, effective treatment for malaria

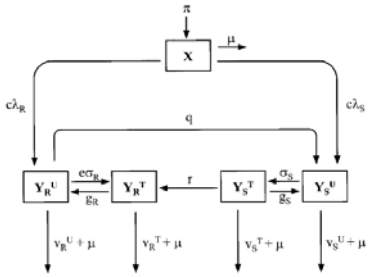
TB: from MDR to XDR…

Staphylococcus aureus: Multidrug resistant *Staph aureus.* (MRSA) now circulating in communities as well as hospitals.

Challenges: Drug resistance

Major questions in modelling of drug resistance:

- what is relative transmissibility of resistant strains?
- how fast do resistant mutants evolve?



Blower et al. (2000) Science 287: 650-654.

Challenges: Polio eradication

1. Vaccine scare in Nigeria

→ Major setback for global eradication effort

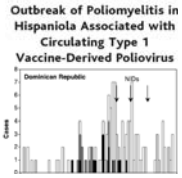
→ (Stochastic?) dispersal to neighboring countries

2. Oral polio vaccine is live attenuated virus,

- advantage because vaccine is transmissible

Problem: It can revert to virulent form (rarely).

→ Outbreaks of "circulating vaccine-derived polio-virus"



Kew et al (Science, 2002)