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MRC Centre for Global Infectious Disease Analysis

Modelling Complex Interventions

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Responding

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- Can predict in theory what to do for known pathogens (e.g. flu, meningitis, polio etc.)
    i. Case/Contact Isolation
    ii. Vaccination
    iii. Treatment/Chemoprophylaxis
    iv. Behaviour Change
    v. Vector Control
- Response depends on:
    i. Speed of spread
    ii. Severity of threat – burden and case fatality; economic impact
    iii. Availability of interventions

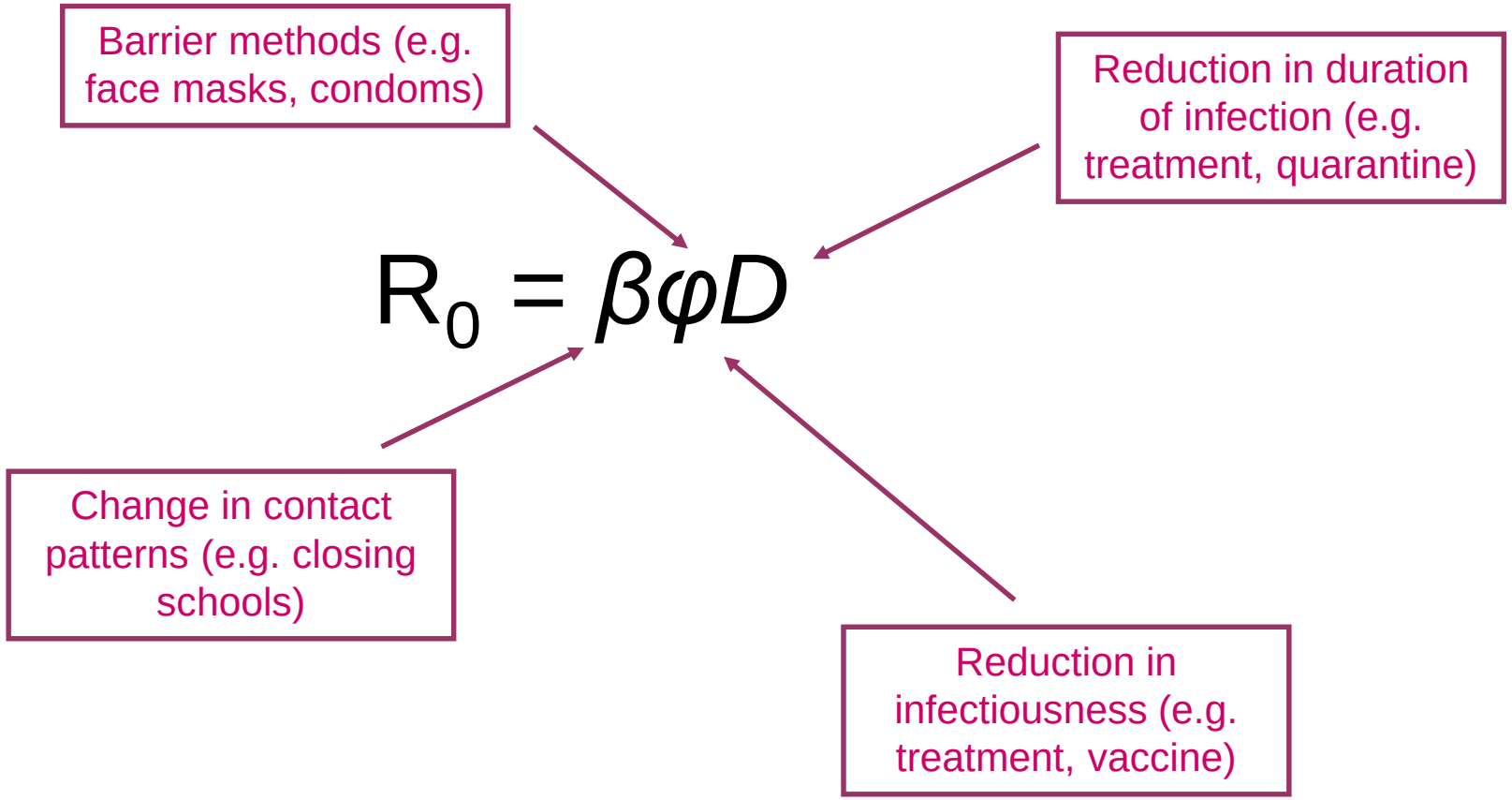
Impact of interventions

- Expression for R_0 often used to gain insight into expected impact

β = rate at which potential contacts occur

φ = probability that the contact results in infection

D = Duration of infection



Reproduction number under control

R_C = Reproduction number under control

- R_C is the average number of secondary cases due to each case in the presence of control measures

- To eliminate a disease: $R_C<1$

Outbreak of Ebola virus disease in the Democratic Republic of the Congo, April–May, 2018: an epidemiological study

*The Ebola Outbreak Epidemiology Team**

Lancet 2018; 392: 213–21

Published Online
June 29, 2018
http://dx.doi.org/10.1016/S0140-6736(18)31387-4

Interventions include:

- early identification
- isolation and care of cases
- contact tracing
- safe and dignified burials
- culturally appropriate community mobilisation
- + recombinant vesicular stomatitis virus–Zaire Ebola virus (rVSV-ZEBOV) vaccine

R_c = 1.03 (95% CrI: 0.83–1.37)

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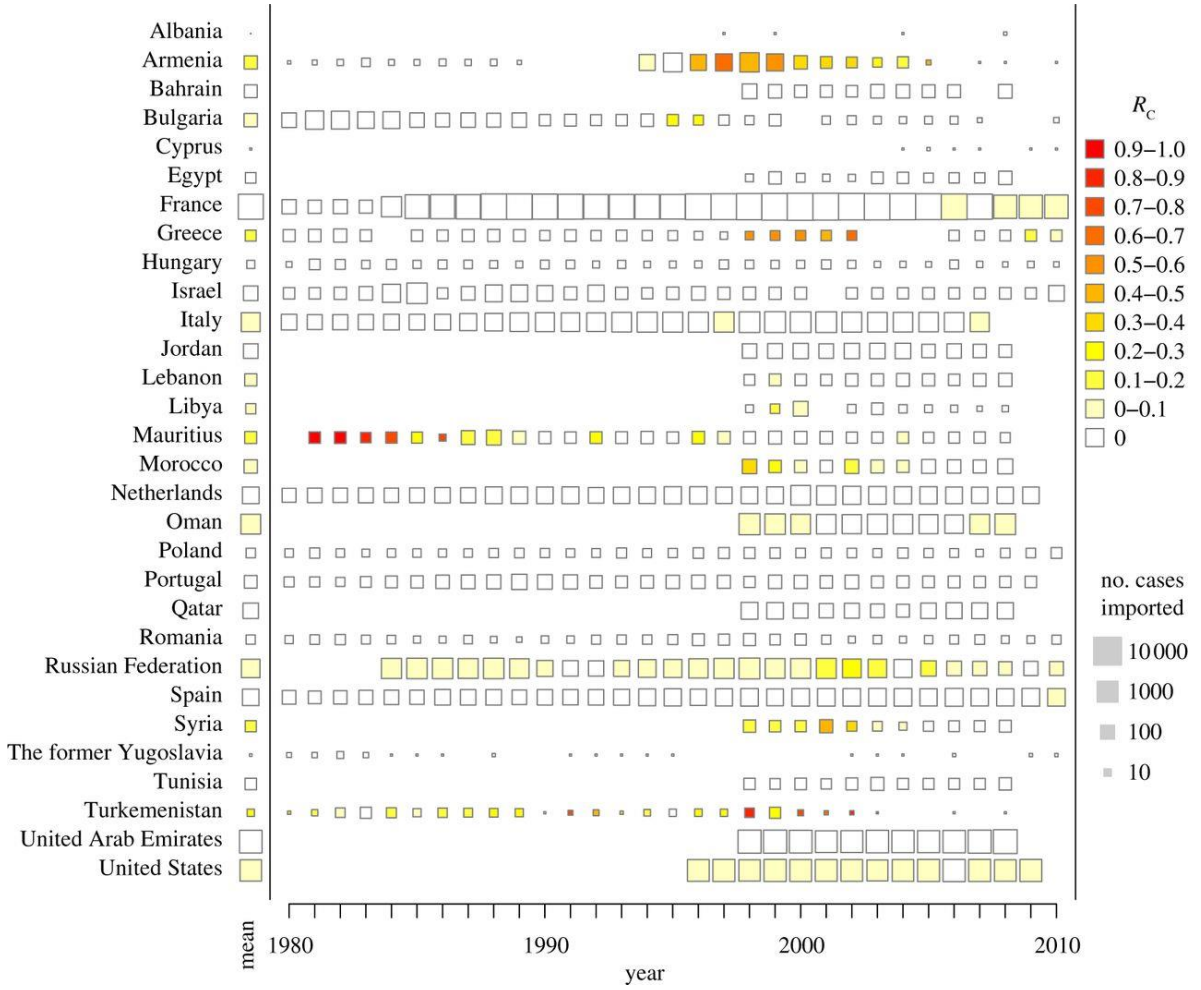


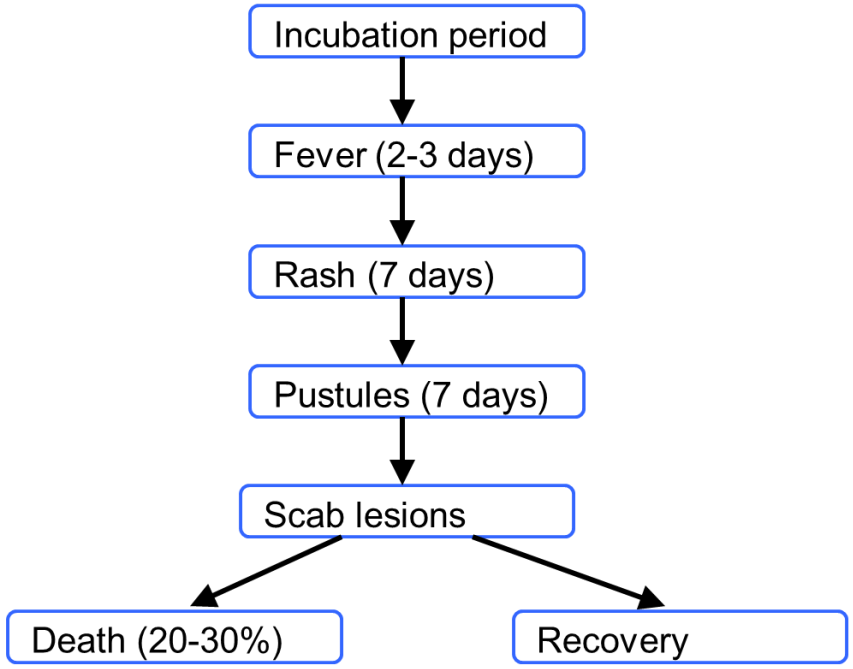
Smith, D. L. *et al.* A sticky situation: the unexpected stability of malaria elimination. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **368,** 20120145 (2013).

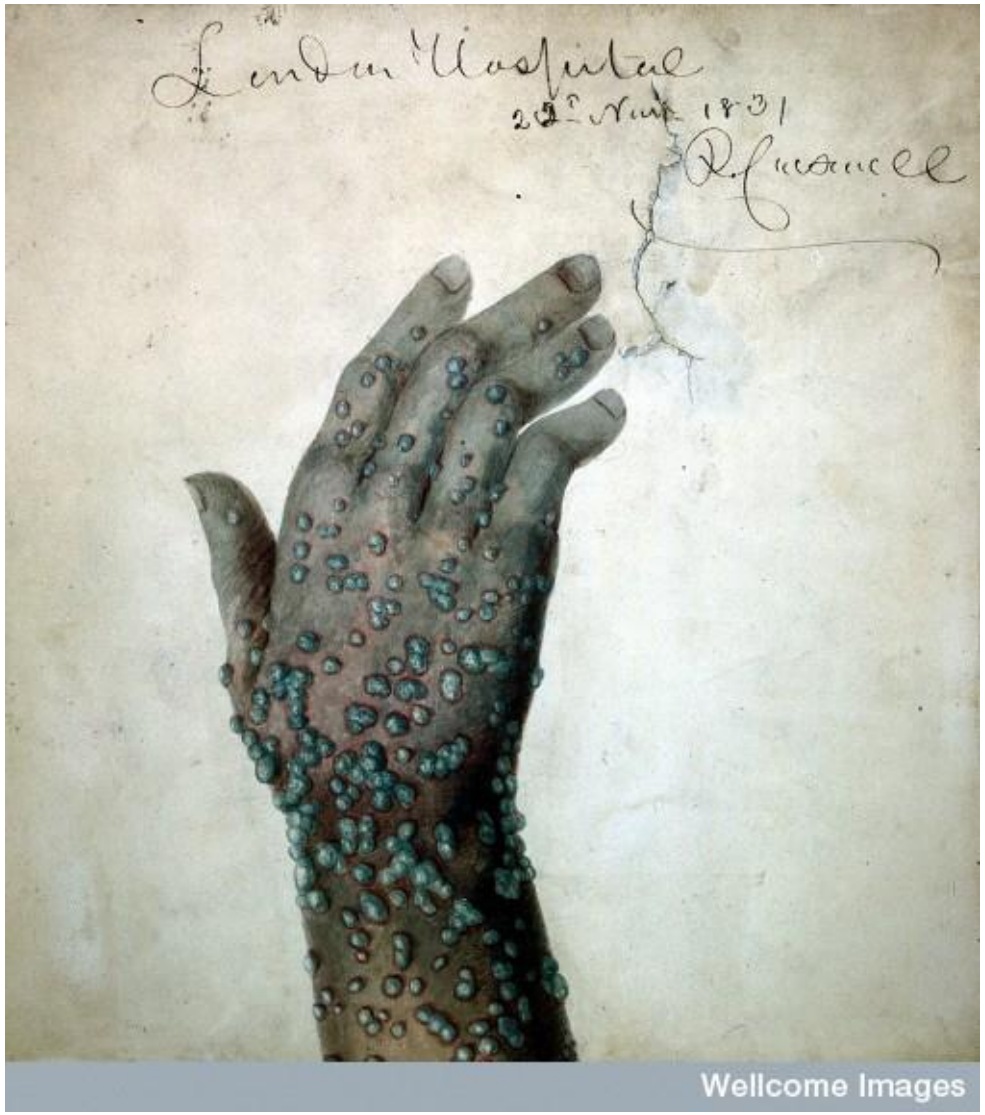
Dependent Interventions

- Often multiple interventions act at the same point in the process, or modify the same parameter
- Effect sizes are no longer independent – need to model the *process* to understand likely combined impact
- Intervention layering and ordering can then become counter-intuitive – but it is also possible to identify synergies

Example: Smallpox

- Historical disease – first documented over 3,000 years ago in India & Egypt
- Repeated epidemics from 16th century onwards
- High mortality rate for *Variola major*
- Eradicated using widespread vaccination in December 1979





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Policy Options for Control

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Table 1 **Policy options for controlling a smallpox attack**

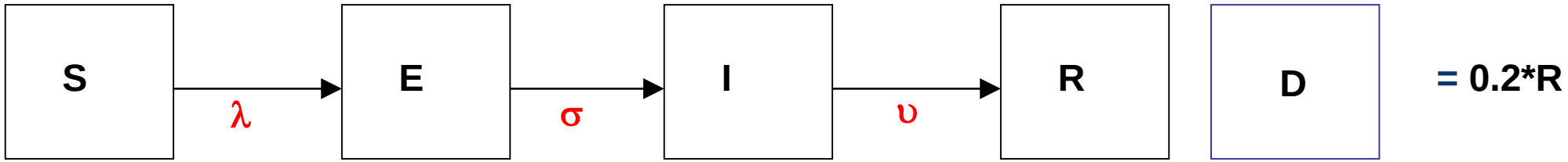
Policy	Benefits	Drawbacks
Quarantine/isolation		
Quarantine and isolation of suspect and confirmed cases.	If isolation facilities are adequate, it is highly effective at reducing transmission from known cases	Isolation facilities necessary, or compliance with voluntary policy. Compulsory policies necessarily coercive. Requires rapid detection of cases.
Movement restrictions		
For example, quarantine of neighbourhoods or closure of schools, airports or other transport systems.	Potentially useful in containing a small outbreak where community transmission is occurring. Used recently to control SARS spread in Hong Kong and Singapore.	Vaccination certificates issued in the past to prevent potential spread but difficult to assess effectiveness. Costly and difficult to police, compromised by any illegal movements. Coercive.
'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.	Contacts need to be found at an early stage of incubation for vaccine to be effective. Tracing needs to be highly effective to severely limit transmission.
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.	Effective when background levels of herd immunity high, but few systematic data on effectiveness in other contexts. Less sparing of vaccine use than ring vaccination. Risk of disease spreading beyond targeted area.
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.	Large numbers need to be vaccinated quickly. Might generate unnecessary vaccine-related morbidity and mortality. If policy implemented rapidly, screening for risk factors for adverse reactions might be suboptimal.
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.	If used to protect an entire population on an ongoing basis, policy has high, long-term cost, and a large number of probably unnecessary vaccine-associated adverse events would be expected for as long as policy is followed.

These policy options are unlikely to be applied in isolation of each other and will necessarily depend on availability of resources and levels of preparedness.

Ferguson *et al.* Nature 2003

Simple SEIR Smallpox Model

- SEIR structure appropriate
- May be useful to add an additional class to denote deaths



λ = the force of infection (rate at which susceptible individuals contract an infection)

$1/\sigma$ = Average duration of the latent period

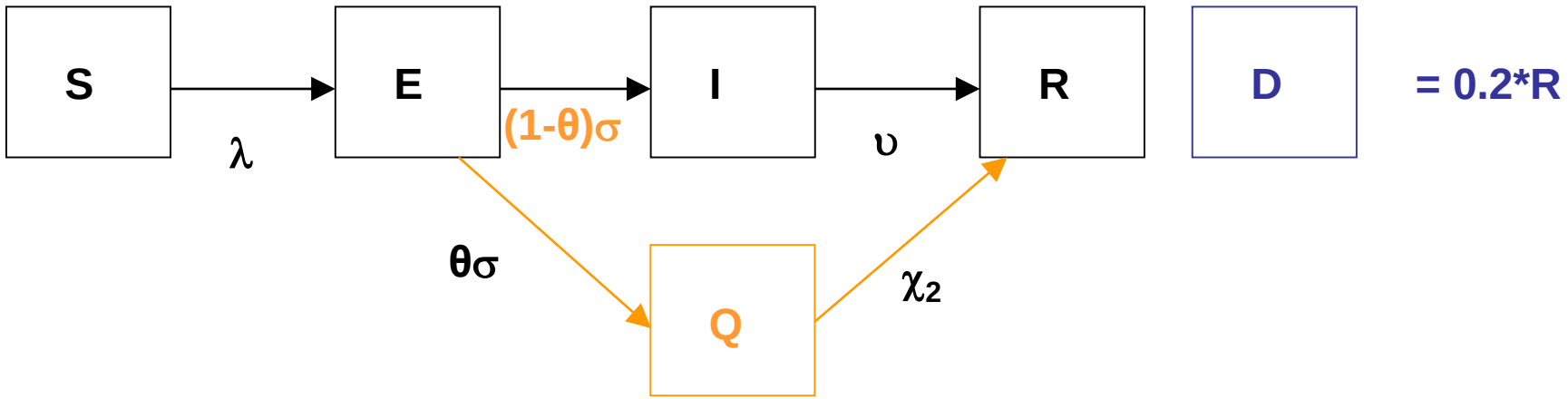
$1/\upsilon$ = Average duration of the infectious period

Extending the SEIR model to explore interventions

- For smallpox there are three main methods for control:
  1. **Quarantine** of cases (those with symptoms)
  2. **Contact tracing** (and potential quarantine of contacts)
  3. **Vaccination**
     i. Of infected individuals to reduce severity of disease
     ii. Of contacts to reduce chances of developing disease
     iii. Mass vaccination – within local vicinity or population-wide
- Note: the concepts here are applicable to many directly-transmitted pathogens e.g. influenza, SARS, ebola

Quarantine from the community

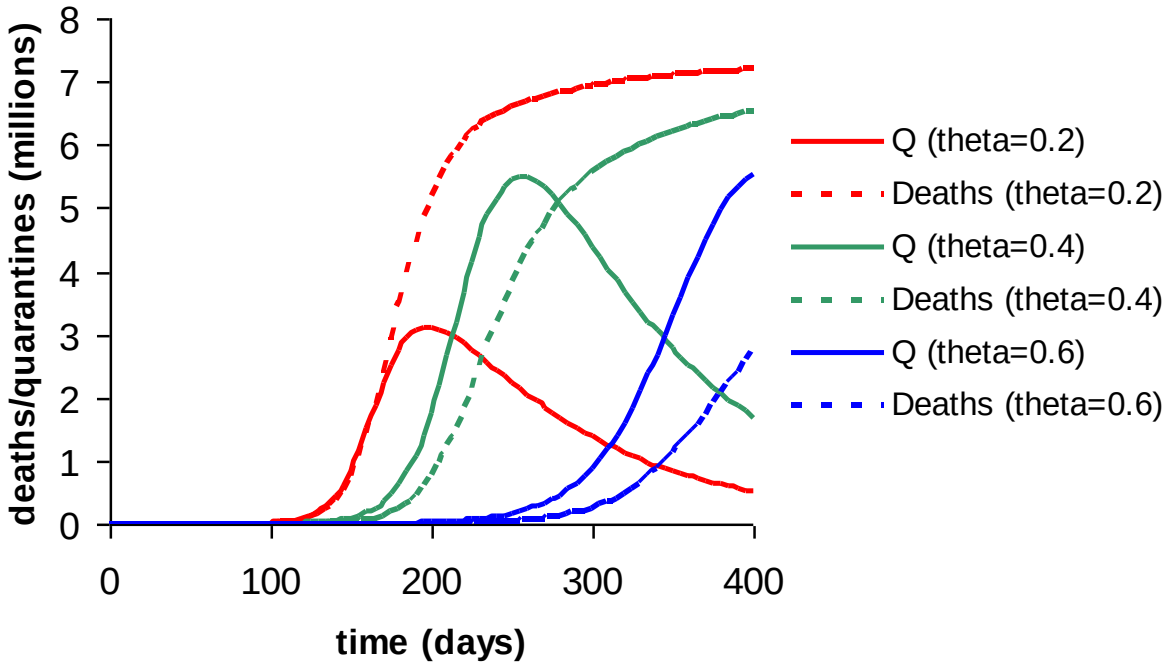
- Quarantine removes those that are infected into a state Q



- We will assume that a proportion, θ, of infected individuals are quarantined
- Quarantined individuals recover at rate which depends both on recovery from disease and duration of stay in quarantine
- Here we assume quarantine lasts, on average, 25 days so χ_2=0.04
- Assume that they go into quarantine as they become infectious

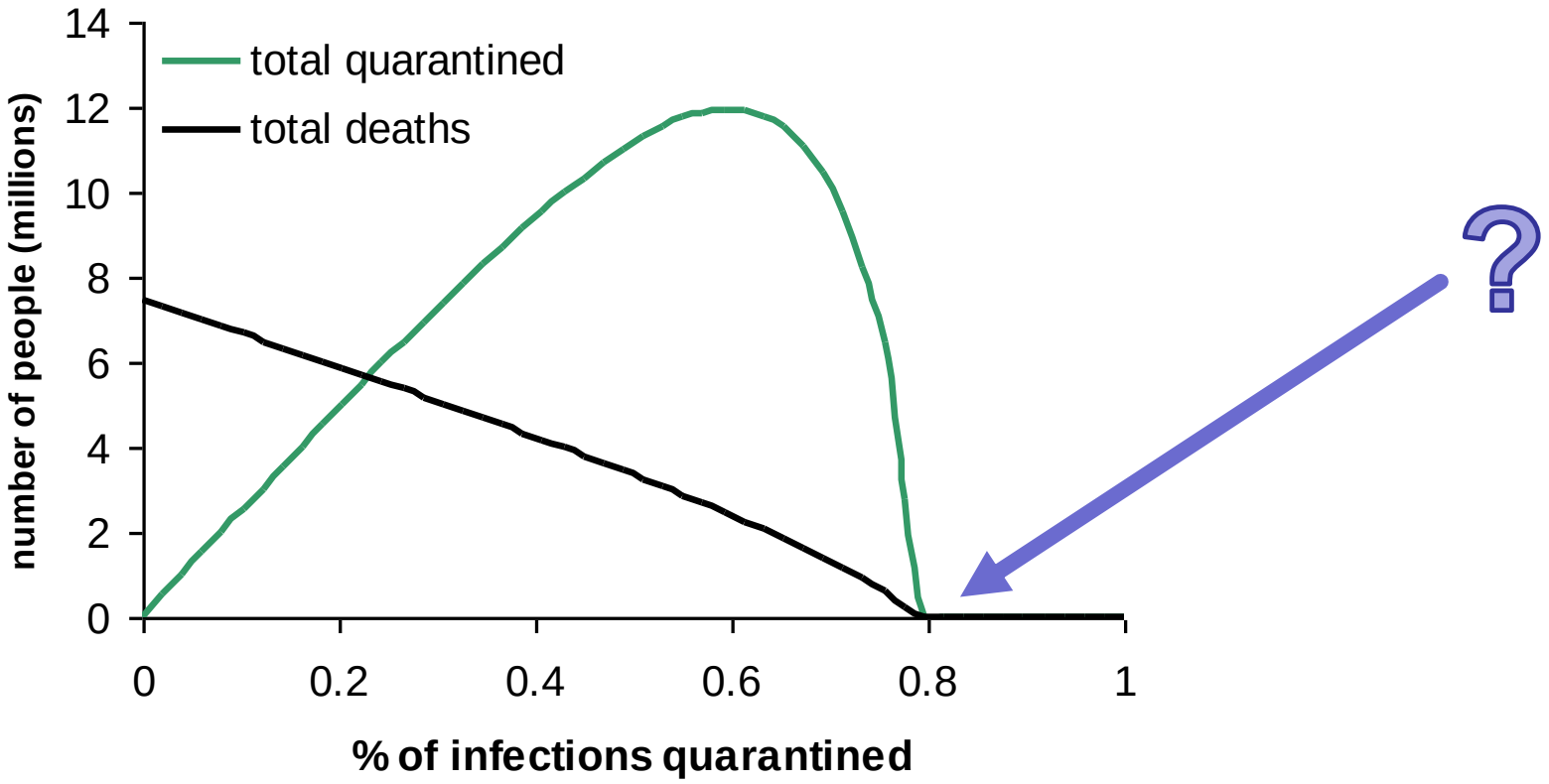
Effectiveness of quarantine

- We can see how increasing quarantine rates reduces the number of deaths

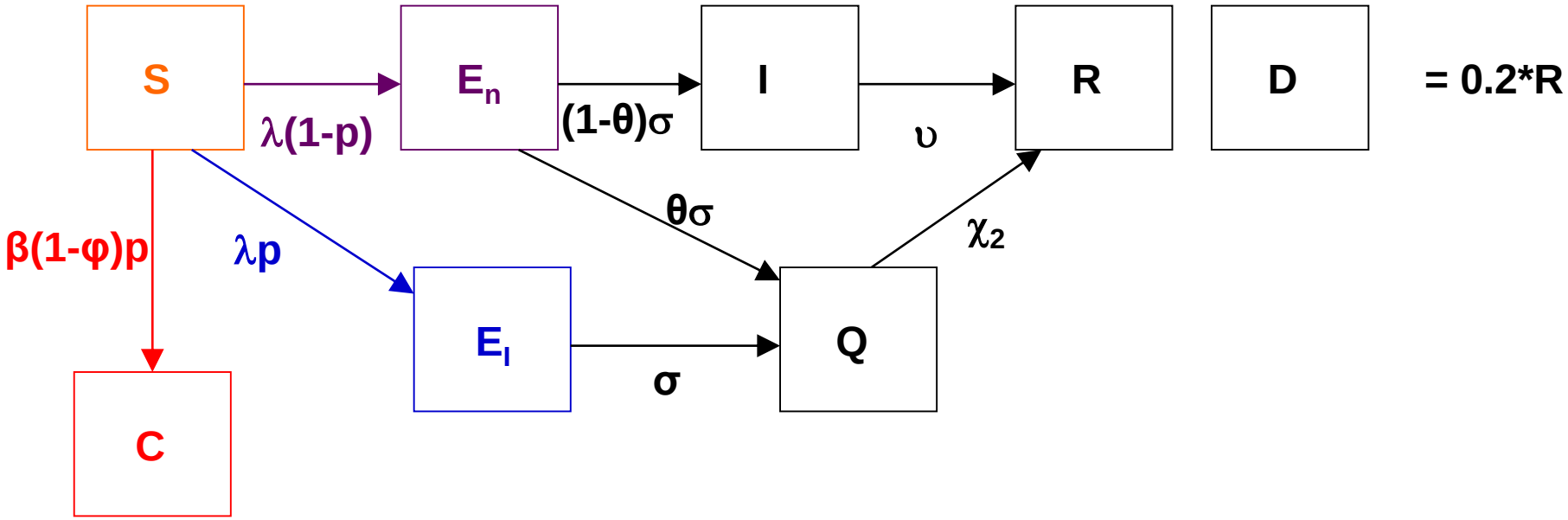


- Model could be used to look at resource constraints, cost-effectiveness (number quarantined per case averted) etc.

Effectiveness of quarantine continued…



Contact tracing



S = Untraced uninfected

E_n= Untraced latent

E_I= Traced latent

C = Traced uninfected

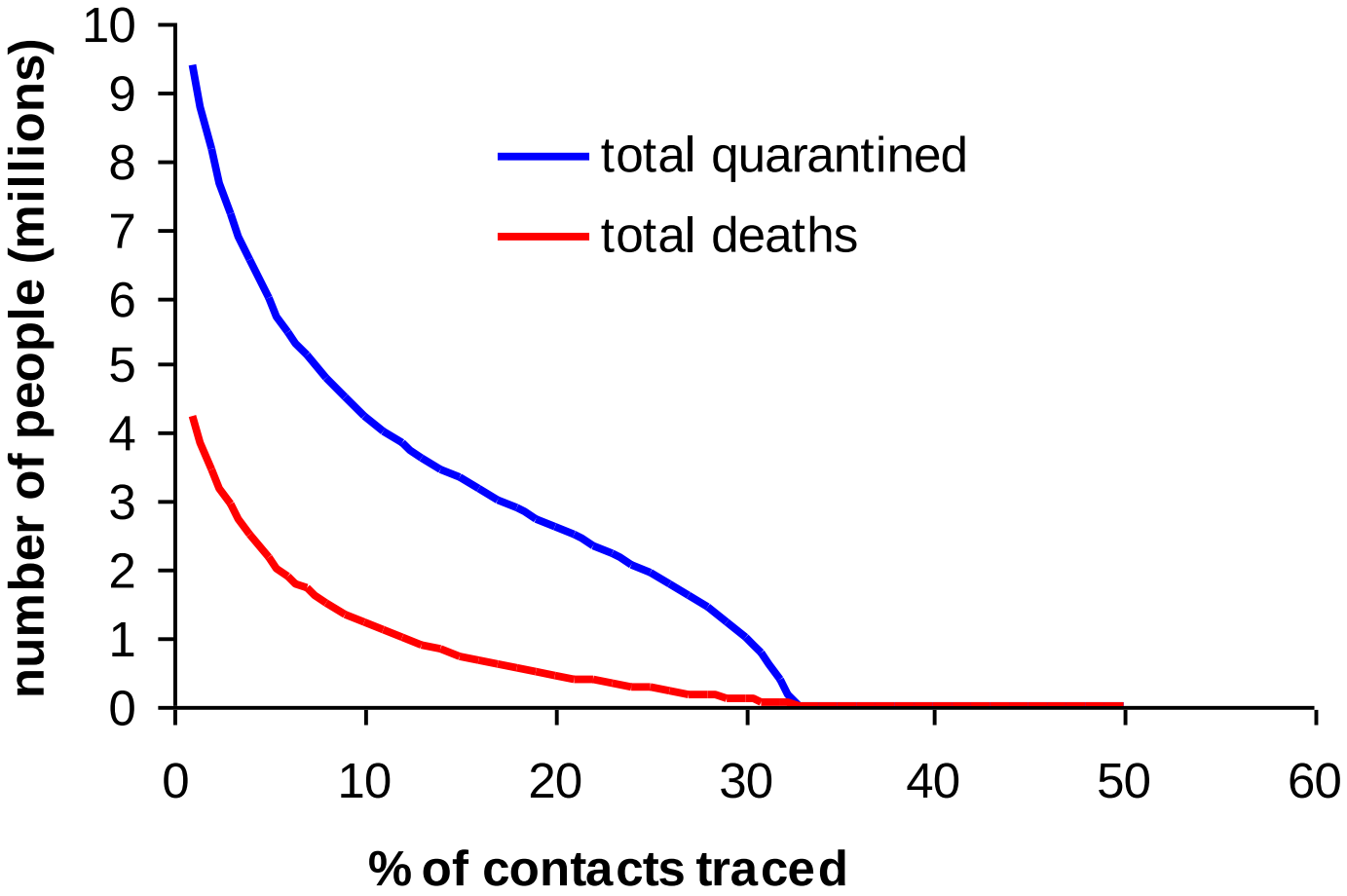
p = proportion of contacts traced

β = contact rate

φ = proportion of contacts infected

($\lambda = \beta\varphi$)

Effectiveness of contact tracing & quarantine

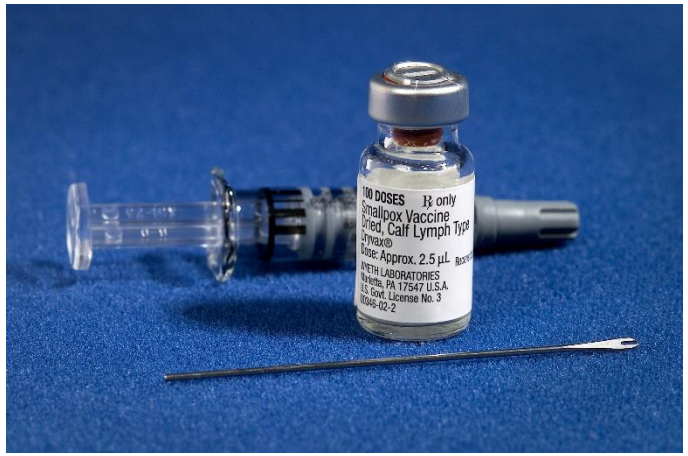


Vaccination

- Assume we have a perfect vaccine that confers life-long protection:

$$R_c = (1 - p_c)R_0 \qquad (1 - p_c)R_0 < 1 \qquad p_c = 1 - 1/R_0$$

- p_c = vaccine coverage



Infection	Location	Date	*R0*	*pc*	Reference
Measles	Senegal	1964	18	94%	Boue [13]
Smallpox	West Africa	1960s	2.3	57%	Foege *et al* [14]
Mumps	UK	1987	8	87%	Farrington [15]
Rubella	USA	1967	6	83%	Hayden *et al* [16]

Scherer & McLean Br. Med. Bull. (2002)

Interventions so far

Considered a number of interventions that can be layered:

- Quarantine:

  removing infectious individuals from the infector pool

- Contact tracing and quarantine

  Speeding up removal of infectious individuals from the infector pool

- Vaccination

What about additional model complexities?

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Additional complexities

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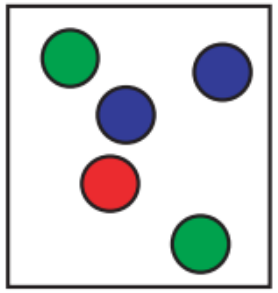
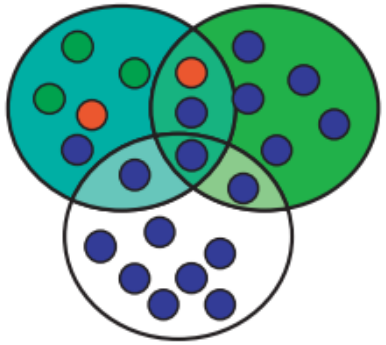
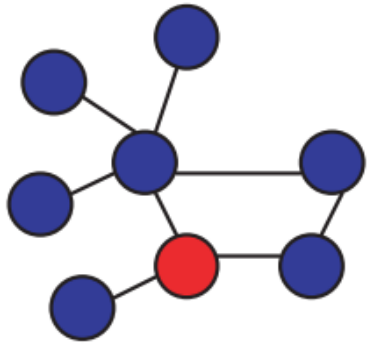


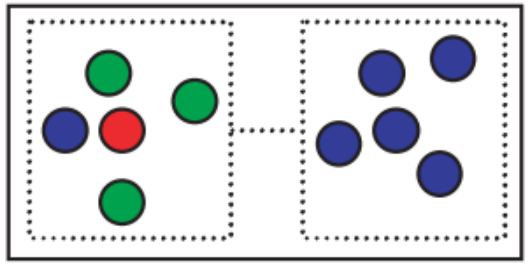
Homogenous mixing



Age/social structure



Network structure



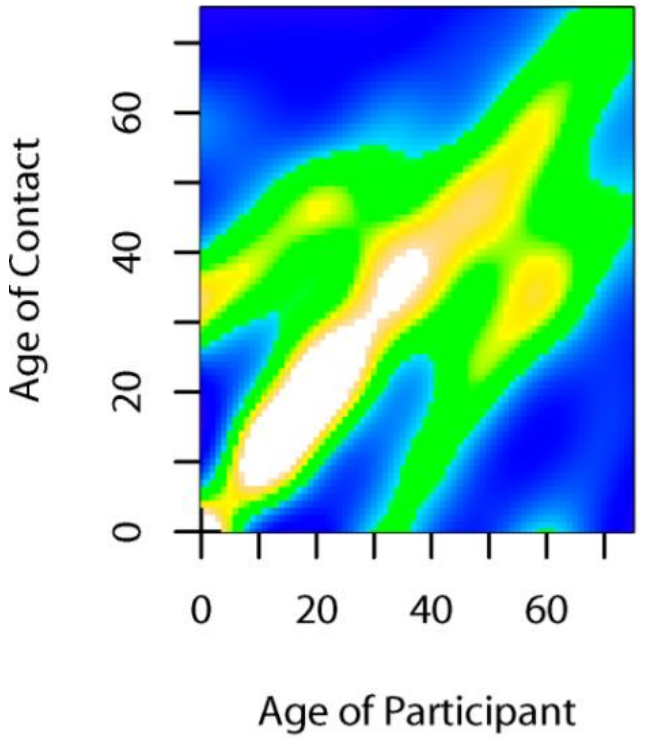
Patch structure

Individually based models

Ferguson *et al.* Nature 2003

Behavioural Change & Heterogeneity

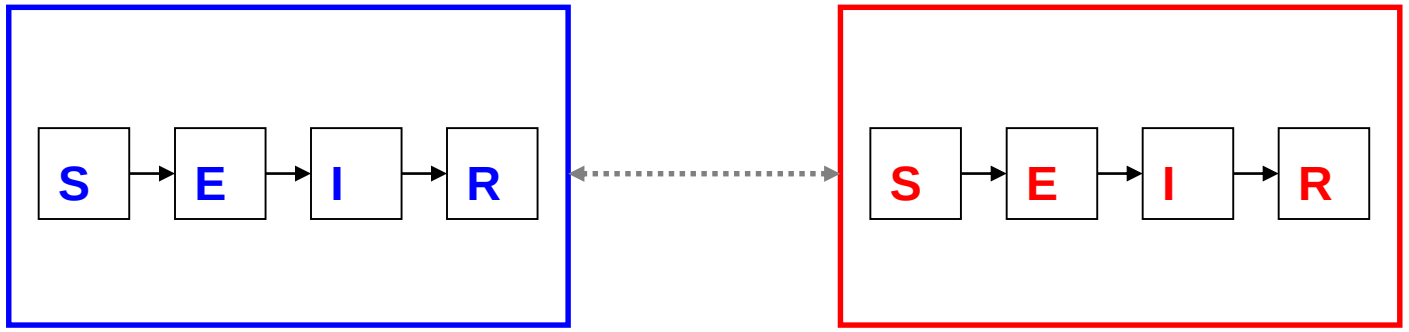
- In its simplest form, we can assume a reduction in the contact rate (β in our smallpox example)
- Also consider more complex patterns – but need contact structure
  - Age-heterogeneity and mixing patterns
  - Contact networks – more explicit representation of contact tracing
  - Spatial heterogeneity – reducing spatial distance of contacts, or targeting interventions spatially



Mossong J *et al*. (2008) PLOS Medicine

Meta-Population Models

- One of the simplest ways to model spatial spread is using a “meta-population” model
- Split the population into areas (e.g. squares) based on geography and consider them as two or more different neighbourhoods
- Exactly the same model as:
  - Two (or more) age-groups
  - Two (or more) risk-groups



$$foi(i) = \beta \frac{I_i}{N_i} + \sum_{j \neq i} m\beta \frac{I_j}{N_j}$$

Force of infection from infected individuals within sub-population

Force of infection from infected individuals within other sub-populations

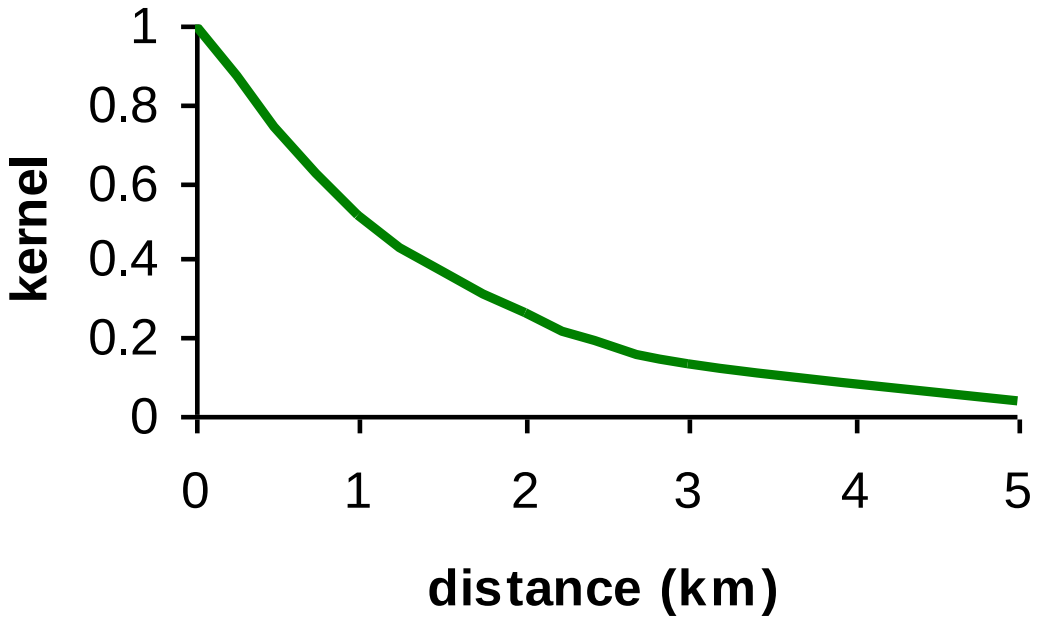
m = the relative strength of mixing between sub-populations

Spatial Kernel

- Sometimes we may not want to restrict to contiguous “neighbourhoods” but allow the probability of transmission to decay naturally as the distance between 2 or more regions increases
- This is termed a “spatial kernel”

- Suppose *d* is the distance between two neighbourhoods and *f(d)* is the spatial kernel
- The new infections in neighbourhood B from A which is distance x away is:

$$f(x)*beta*S_B*I_A/N_A$$



Human movement

- Human movement may vary as a function of distance *and* the size of the location
  - Trips may be short in a local area
  - Trips may be long to large towns and cities further away

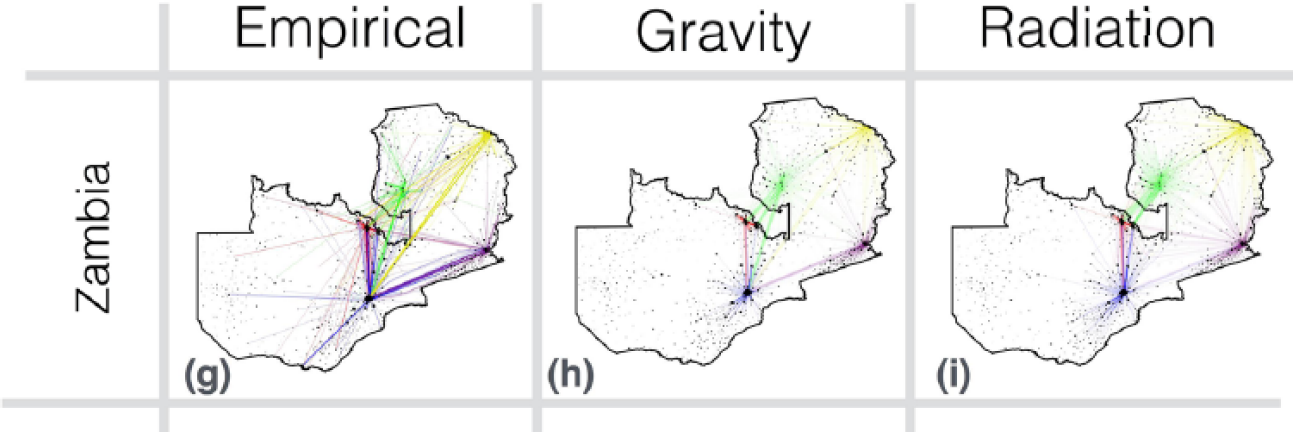
- Specific models can capture these effects:
  - Gravity model
  - Radiation model

$$P(j|i) \propto N_j^T k(d_{i,j})$$

Probability of moving to *j* given location *i*

Size of *j*

Distance kernel



Marshall *et al* (2018) Nature scientific reports

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Spatial modelling example: malaria

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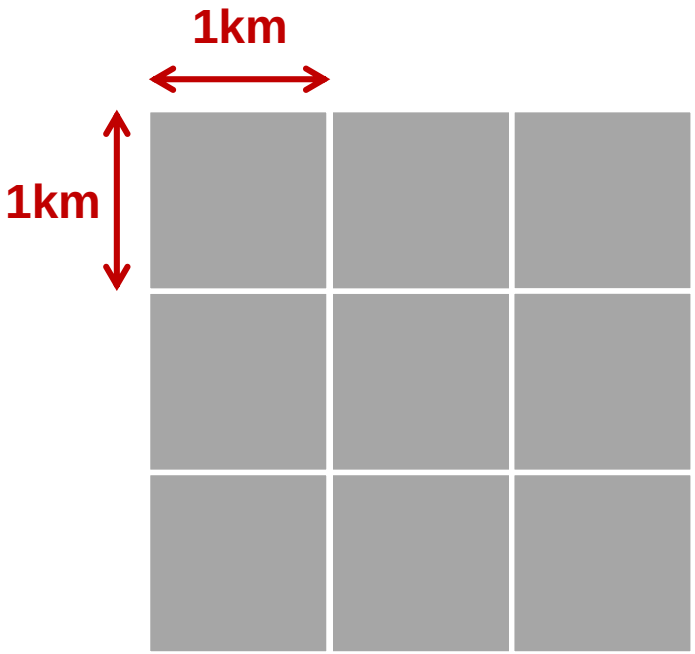
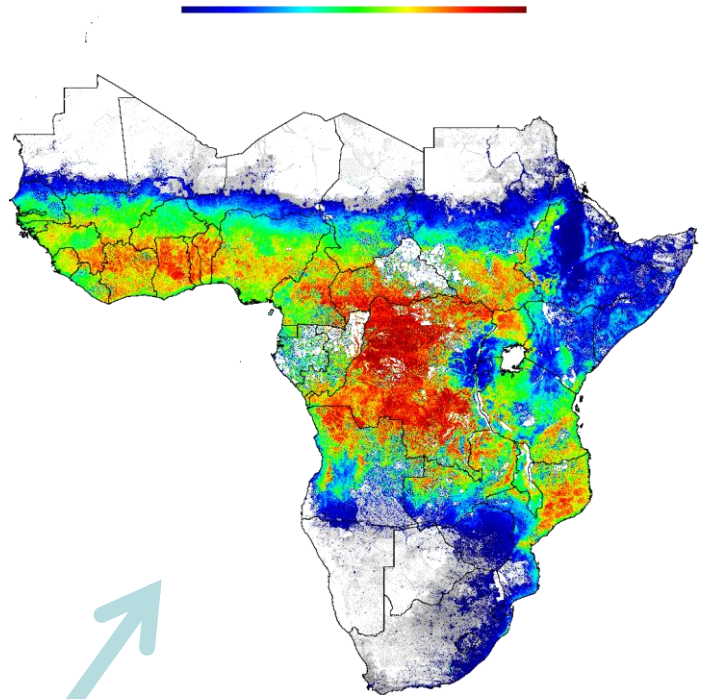
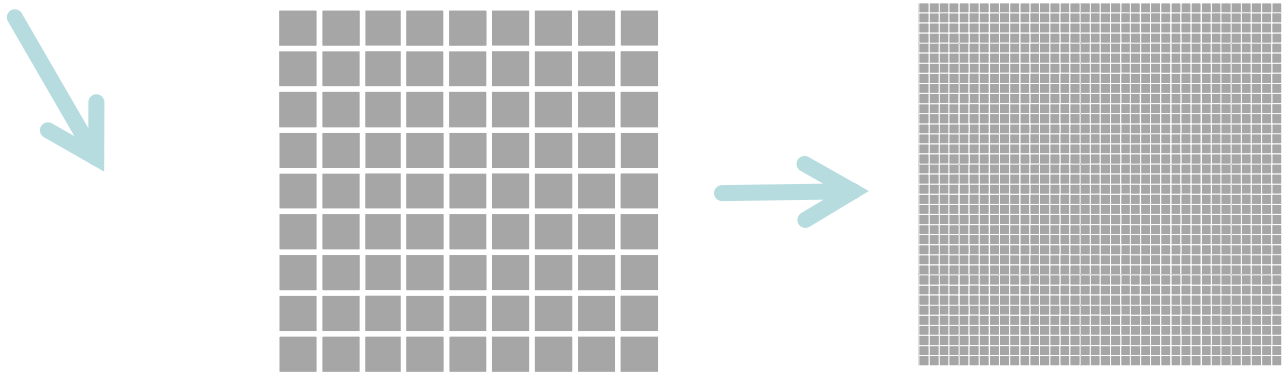


Dynamic human-vector transmission model simulated on 1km cells for the whole of Africa





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Spatial modelling example: malaria

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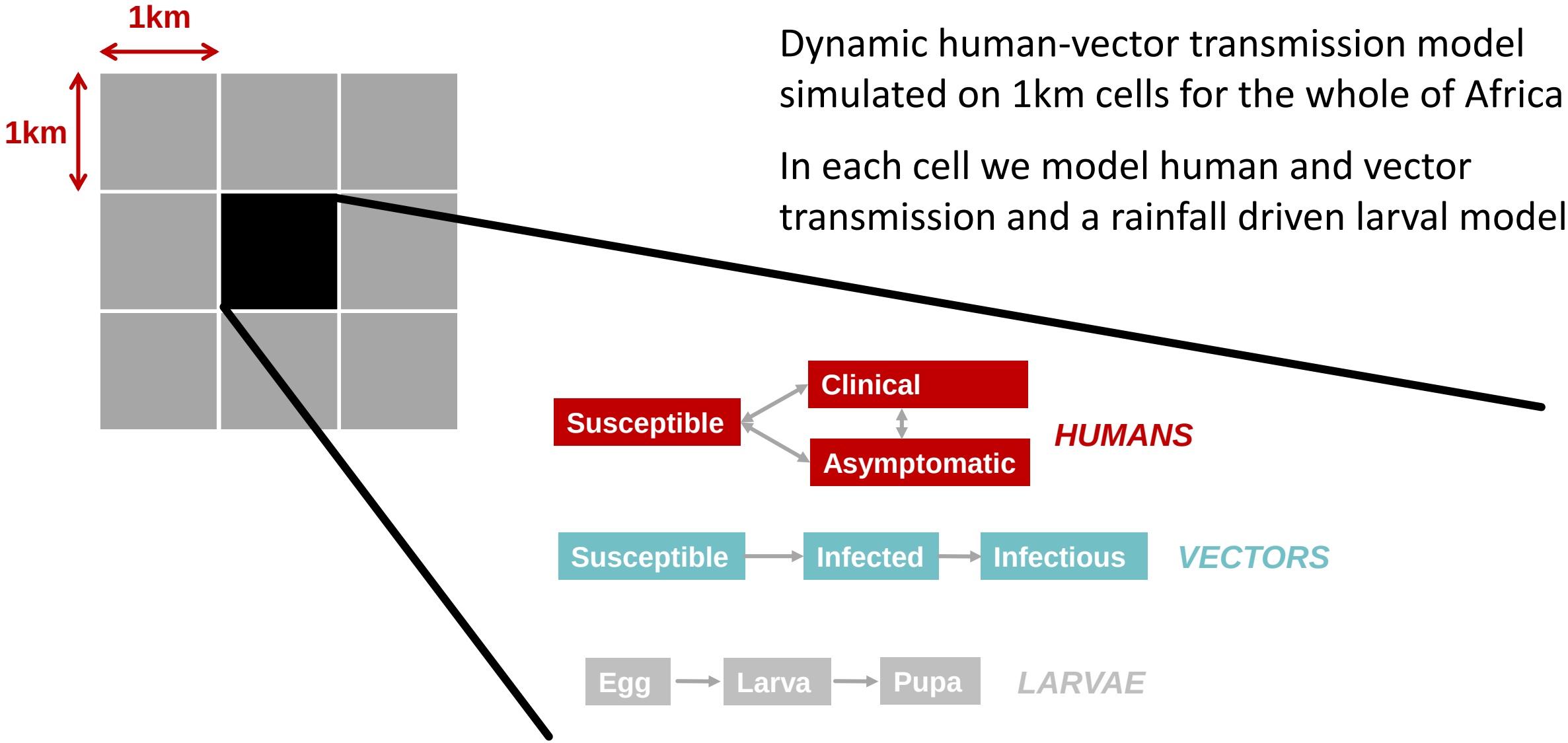


Dynamic human-vector transmission model simulated on 1km cells for the whole of Africa

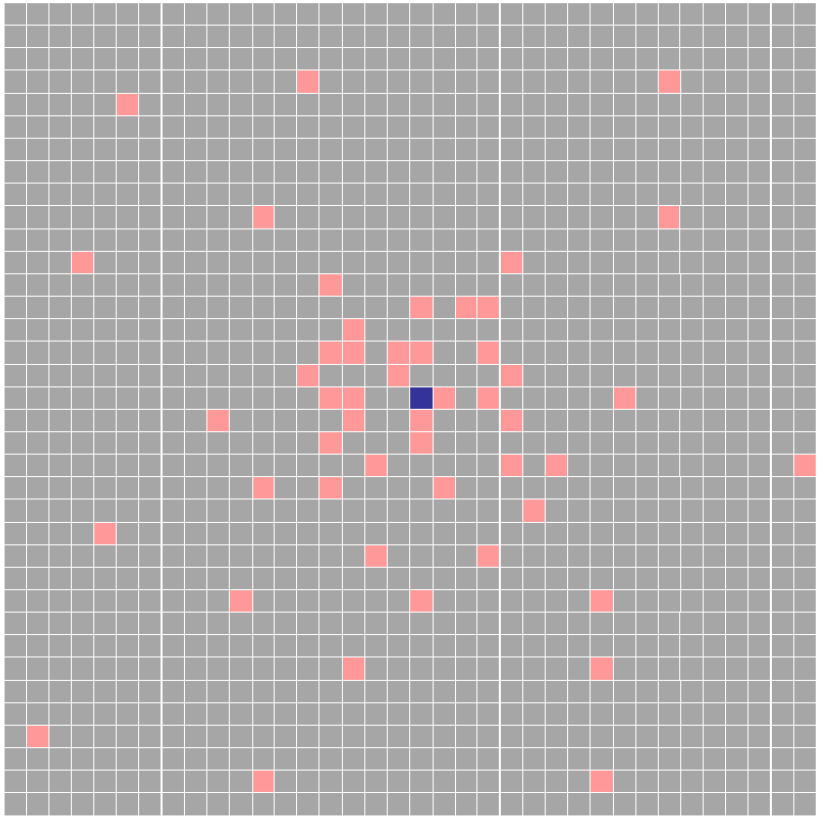
In each cell we model human and vector transmission and a rainfall driven larval model

Spatial modelling example: malaria

Model movement of ***mosquitoes*** and ***humans*** by assuming FOI experience in a given cell depends partly on the FOI in:

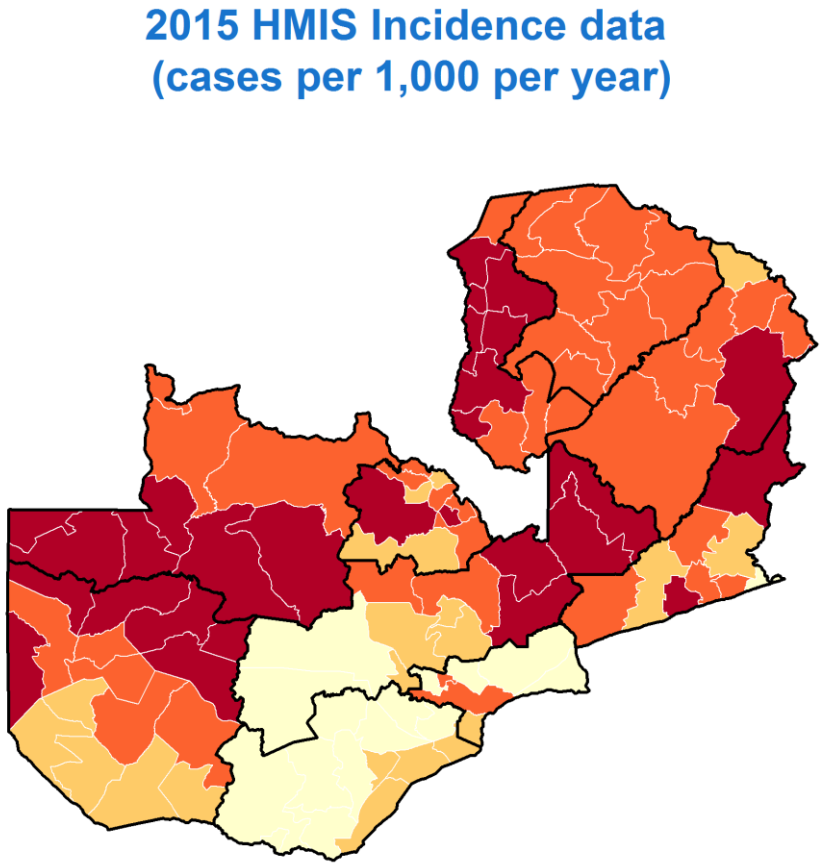
Mosquito model – neighbouring cells

Human model - nearby cells based on a distance kernel



Humans

Spatially targeted interventions



Taking the example of malaria in Zambia:

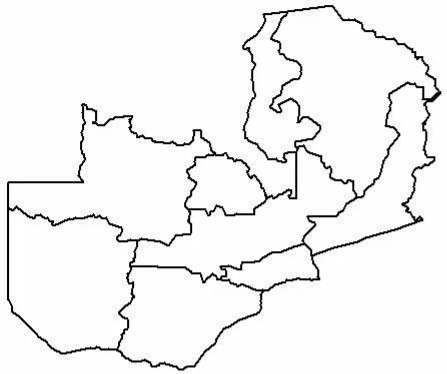
Some interventions may be required everywhere: **Vector control & treatment**

Some interventions may be more impactful in higher transmission areas: **Indoor residual spraying**

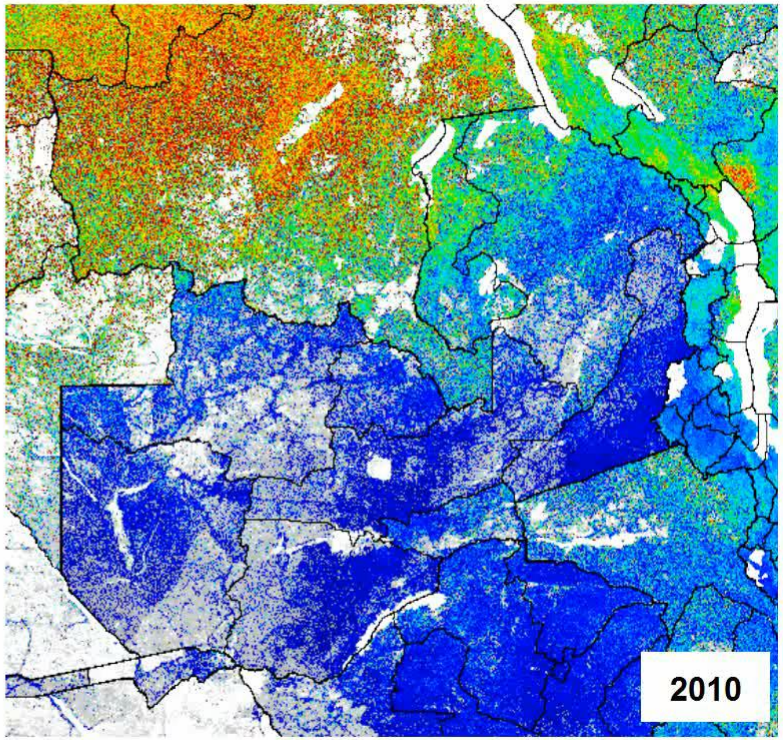
Some interventions may be targeted and impactful but not-sustainable: **Mass drug administration** (MDA)

Spatially targeted interventions

Reactive policy



Slide prevalence



POST-2015 interventions

- Incidence > 200: vector control scale up – Bed nets= 75%, IRS = 100%
- 200 > Incidence > 90: 3 annual rounds of MDA at 90% coverage
- 90 > Incidence > 20: 2 annual rounds of MDA at 90% coverage
- CI < 20: Reactive strategy – small scale MDA in response to cases