Mathematics against infectious diseases

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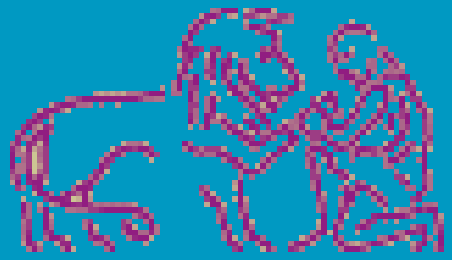
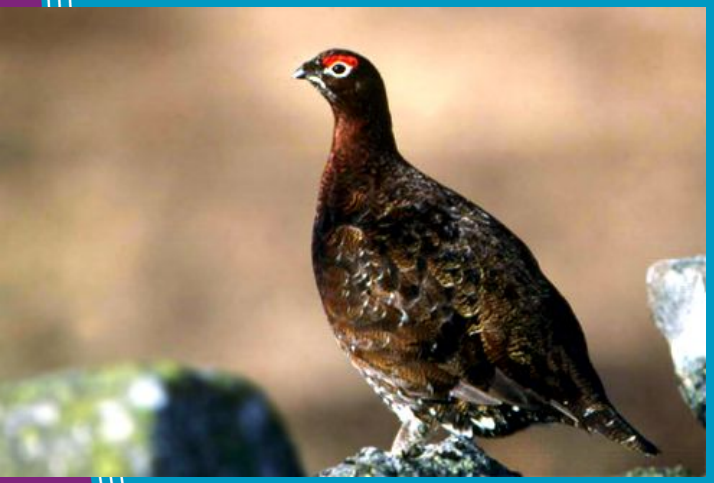


Research interest

- Epidemiology studies disease in populations, in space and time, with the aim to trace and understand factors that are responsible for, or contribute to, patterns in occurrence

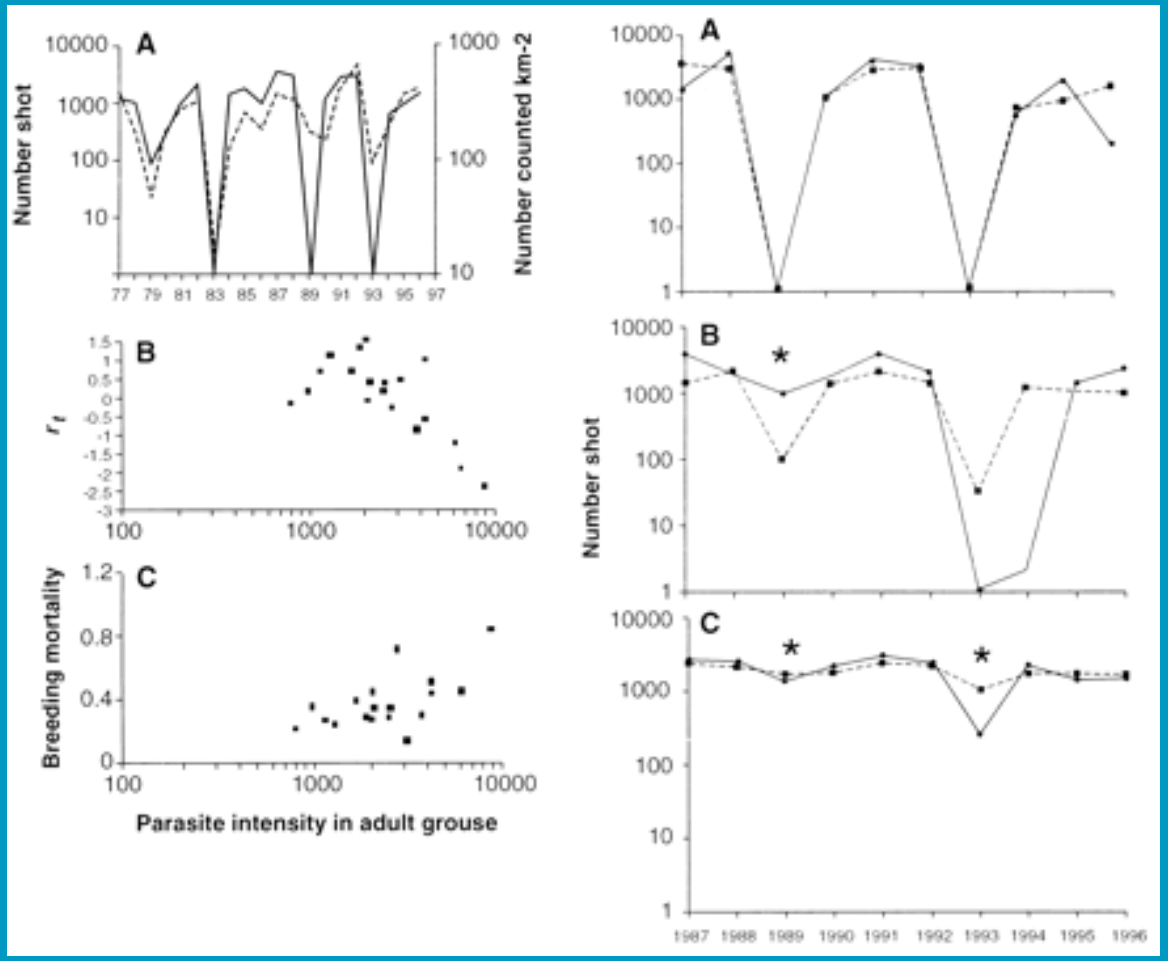
- Typical: non-linear feedback on various levels + threshold phenomena

Regulation in red grouse



Parasite:
Trychostrongilus tenuis

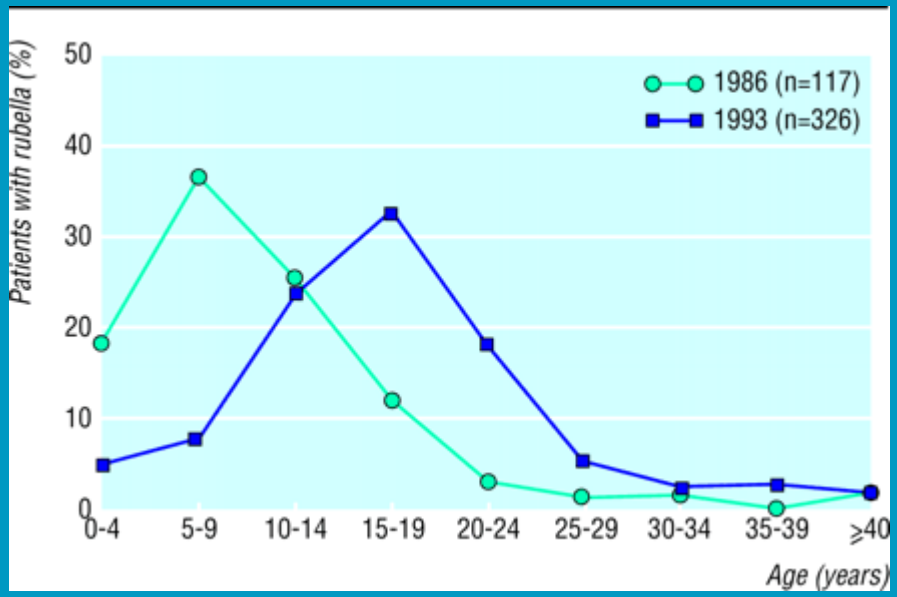
Mathematical model gave understanding of the mechanisms involved (simple ODE system)



Hudson, P.J., Dobson, A.P. & Newborn, D. 1998. Prevention of population cycles by parasite removal. *Science 282, 2256-2258.*

Vaccination against rubella

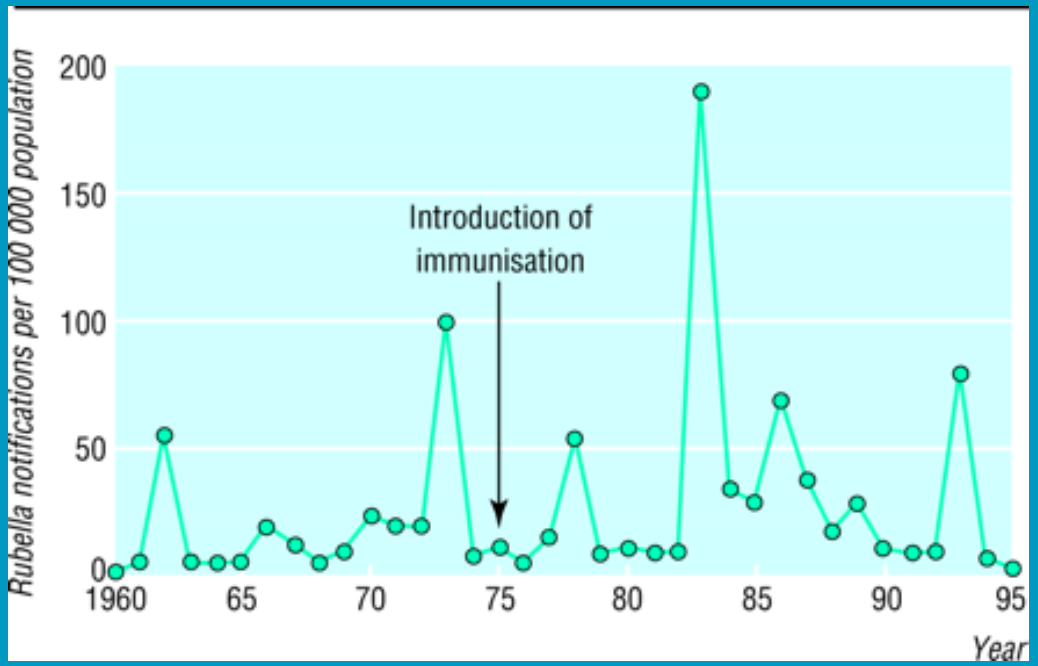
- Age at first exposure usually low (child-hood infection)
- Shift observed in age distribution of rubella patients in Greece
- Shift of peak into fertile age classes



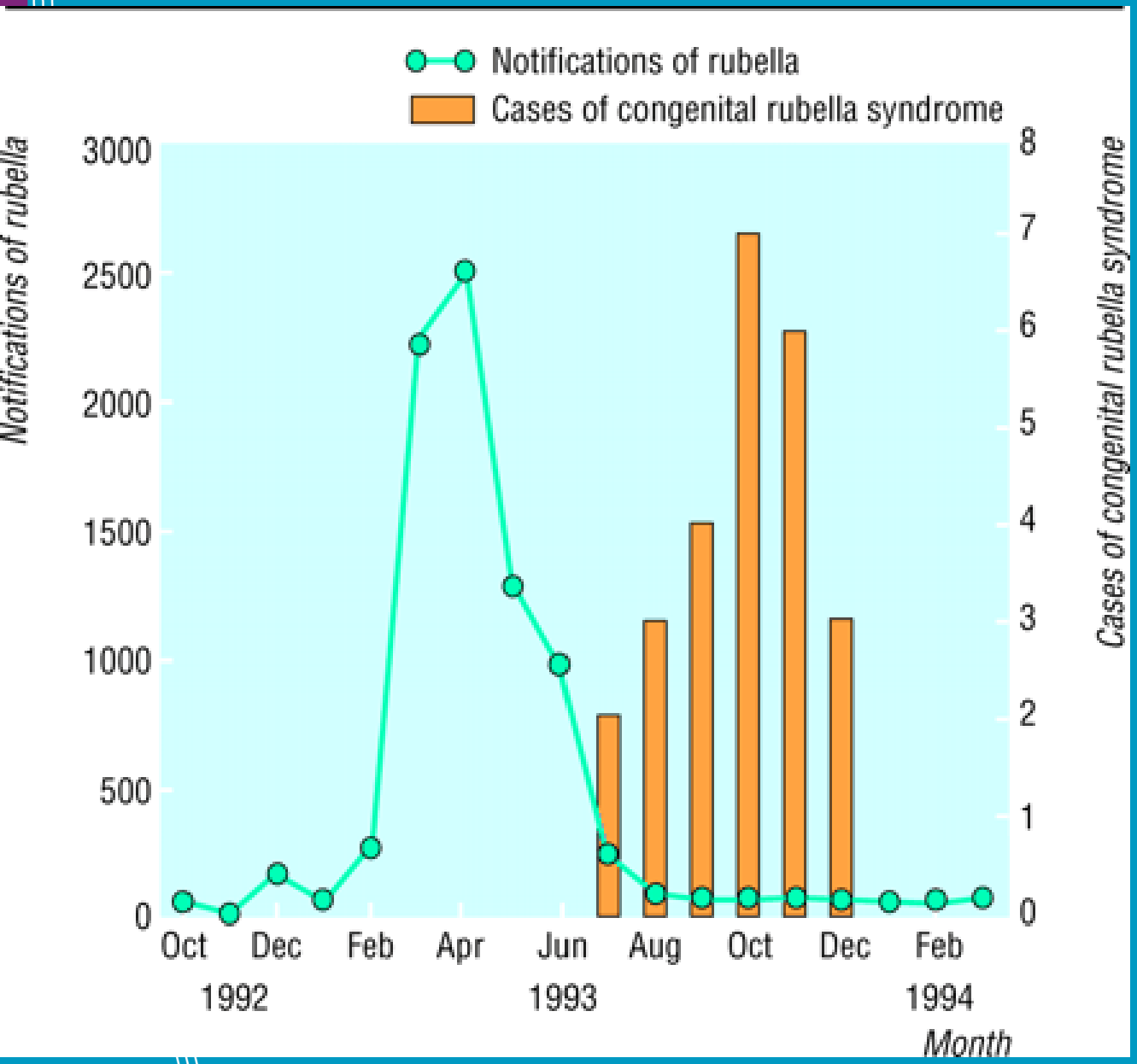
Age distibution of rubella patients in Greece
BMJ, 1999, 319, 1462-7

Rubella & CRS

- Rubella vaccination aimed at reducing CRS (congenital rubella syndrome) in newborns
- Greece: coverage 1970's-90's: 50%



Outbreaks of rubella in Greece
BMJ, 1999, 319, 1462-7



Epidemic of CRS
In Greece, 1992-1993
BMJ, 1999, 319, 1462-7

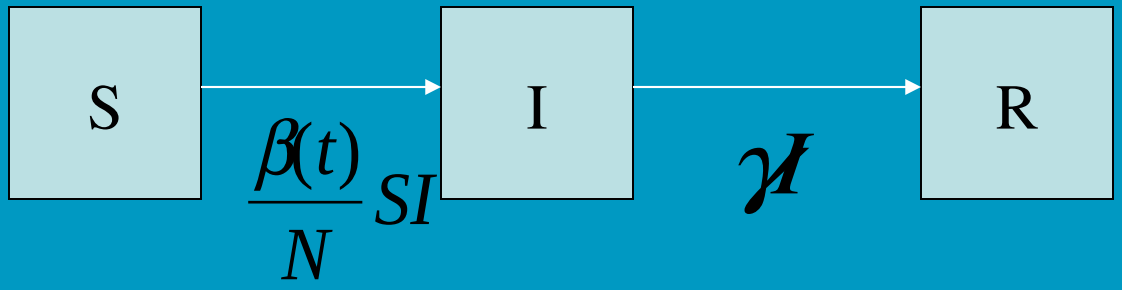
Vaccination can have the opposite effect and be harmful for the population as a whole even though it protects individuals who receive the vaccine

Phenomenon predicted by simple model with age structure (PDE system)

Influenza prepandemic planning

- Guidelines for contact reduction + stockpiling of medicine
- Aim: to combat epidemic in six-month period before effective vaccine becomes available
- Priority: Minimize # deaths? Minimize # infections (peak prevalence)? Minimize # people seeking medical help at the same time (peak incidence)? (minimize societal distruption)
- Problem:
  - Governments are not clear in their criteria (they want it all)
  - Can show with simple models that choice for one precludes success with others & some combinations of measures are counterproductive

A basic model for well-mixed populations



$$\frac{dS}{dt} = -\frac{\beta(t)}{N} SI$$

$$\frac{dI}{dt} = \frac{\beta(t)}{N} SI - \gamma I$$

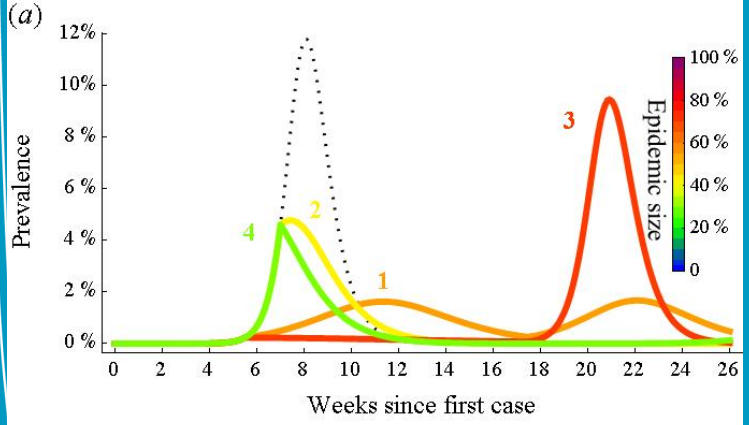
$$\frac{dR}{dt} = \gamma I$$

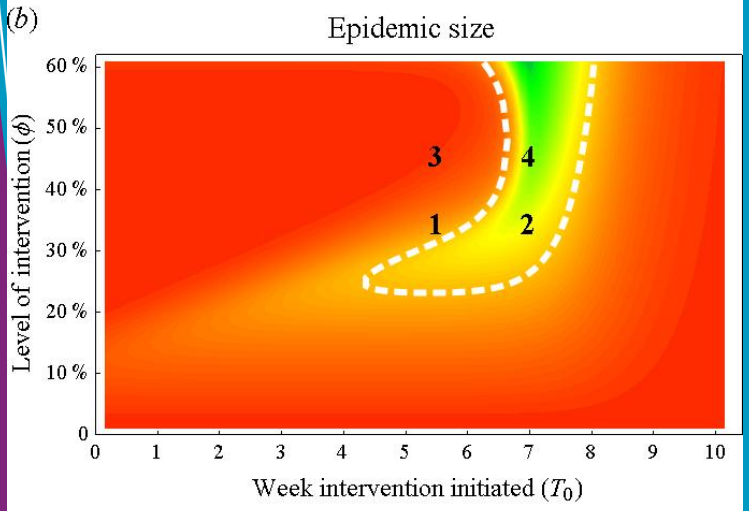
Transmission rate depends on intervention measures that are implemented at time *t*

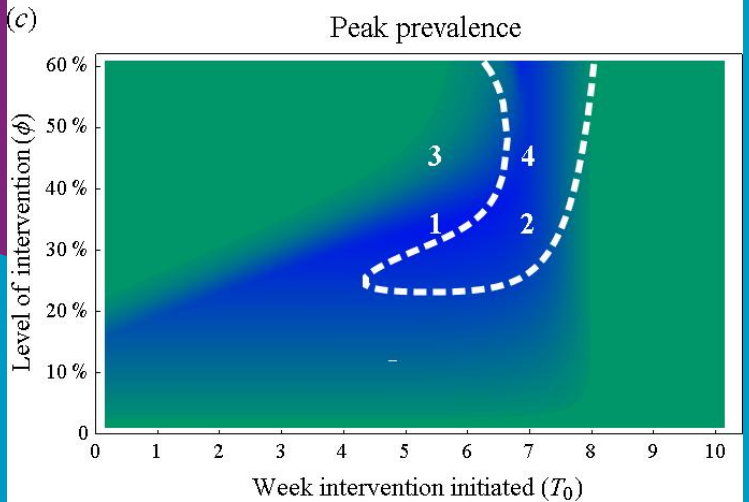
Example: contact reduction (social distancing) for fixed period after start of outbreak (USA: 12 weeks)

When to start; how strong?

Interventions for pandemic influenza







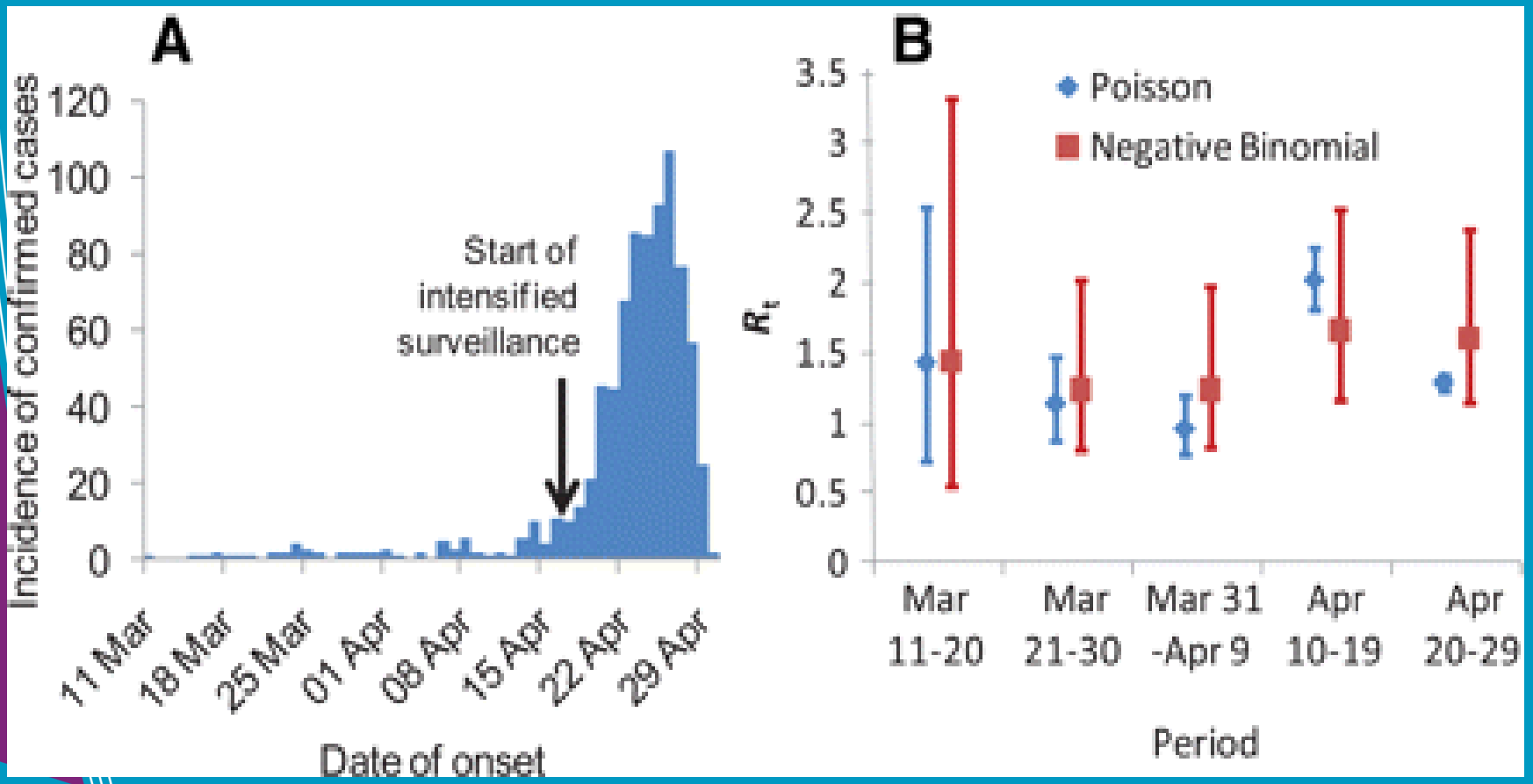
- Social distancing: 12 weeks
- Eradication not possible
- Early and strong intervention gives severe second peak
- Conflicting policy options: ‘size’, ‘incidence’, ‘prevalence’
- Usual level of antiviral stockpile (25%) only sufficient for small subset of strategies

Work with Hollingsworth, Klinkenberg & Anderson, 2010, unpublished

Basic reproduction number R_0

- R_0 is the average number of new cases caused by one case in a fully susceptible population
- $R_0 > 1$: each infected spreads the infection to more than one other person/animal:
  $\Rightarrow$ chain reaction = epidemic
- $R_0 < 1$: on average an infected does not replace itself in the infected population
  $\Rightarrow$ infection cannot grow

A/Mexico/2009 H1N1: $R_0 \approx 1.5$



Fraser et al, *Science*, August 2009

Use of R_0

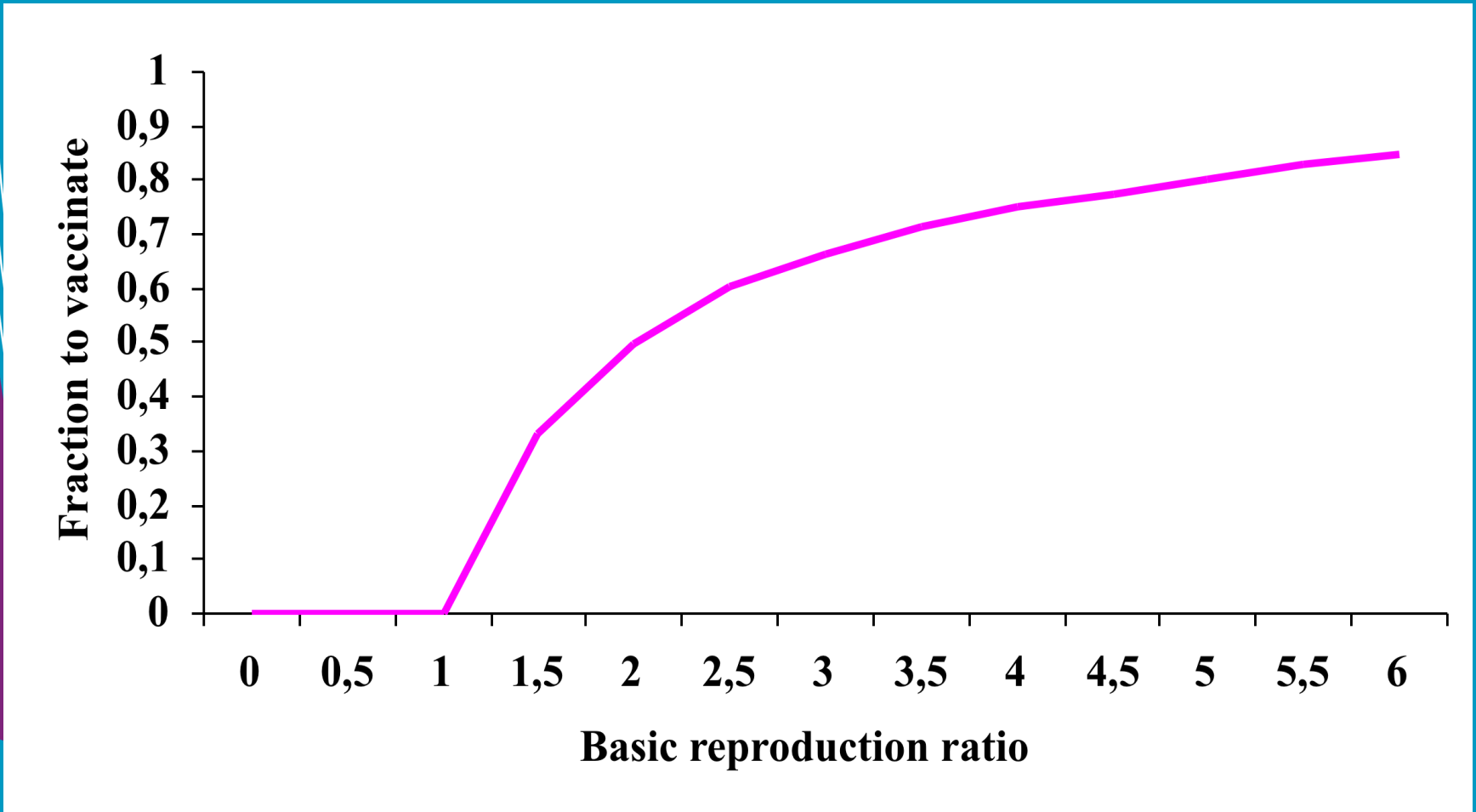
- Integrator of knowledge
- Population effects of control measures

  Vaccinate fraction v at birth in a well-mixed population with a perfect vaccine

  Control successful if $R_v = (1 - v)R_0 < 1$

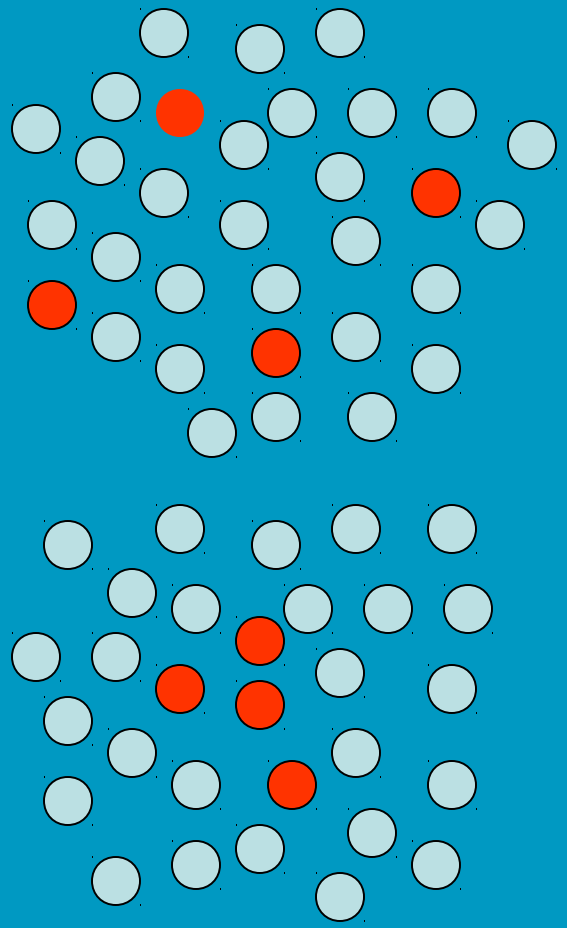
$$v > 1 - \frac{1}{R_0}$$

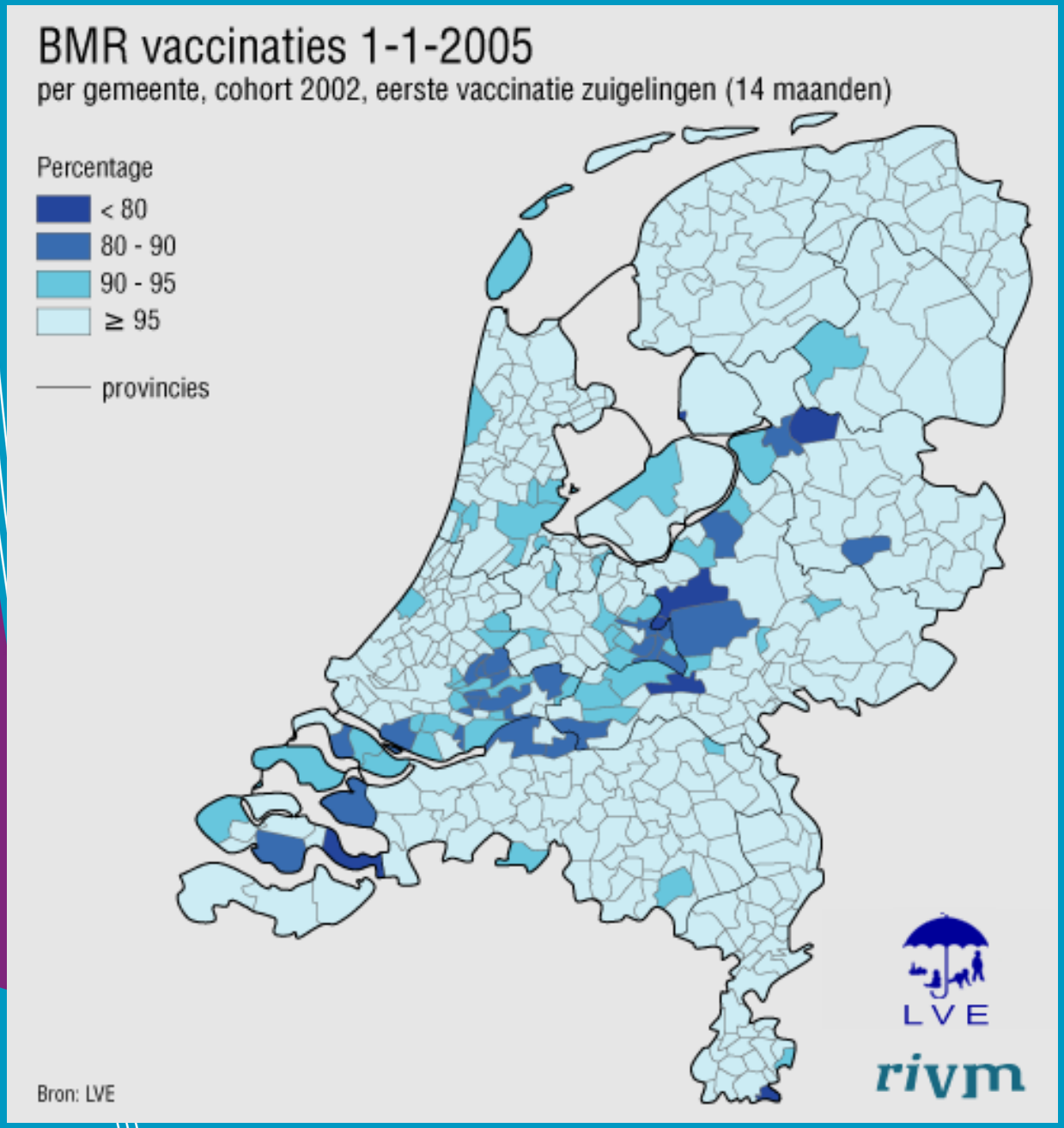
Fraction to vaccinate (well-mixed population)



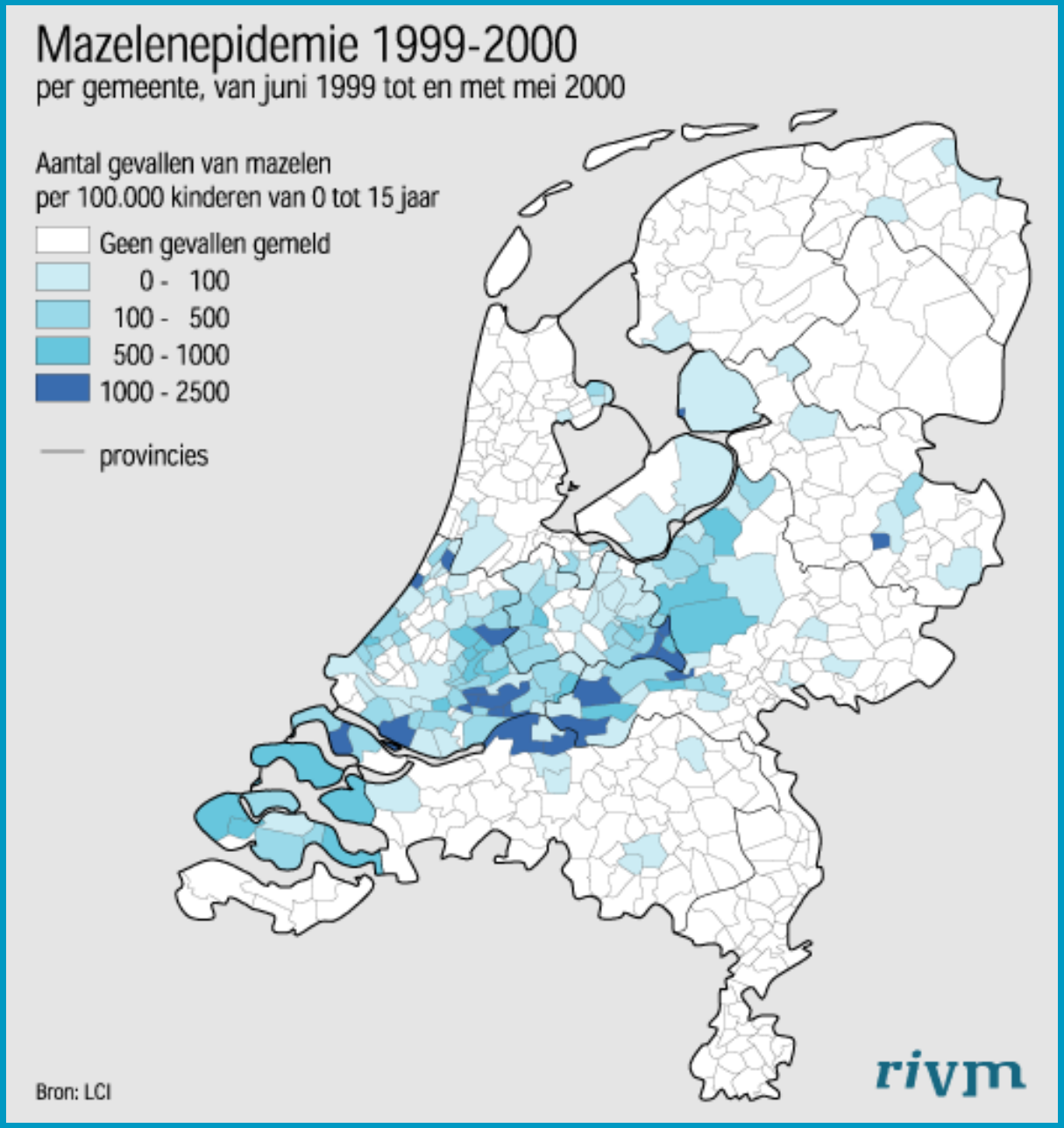
Herd immunity

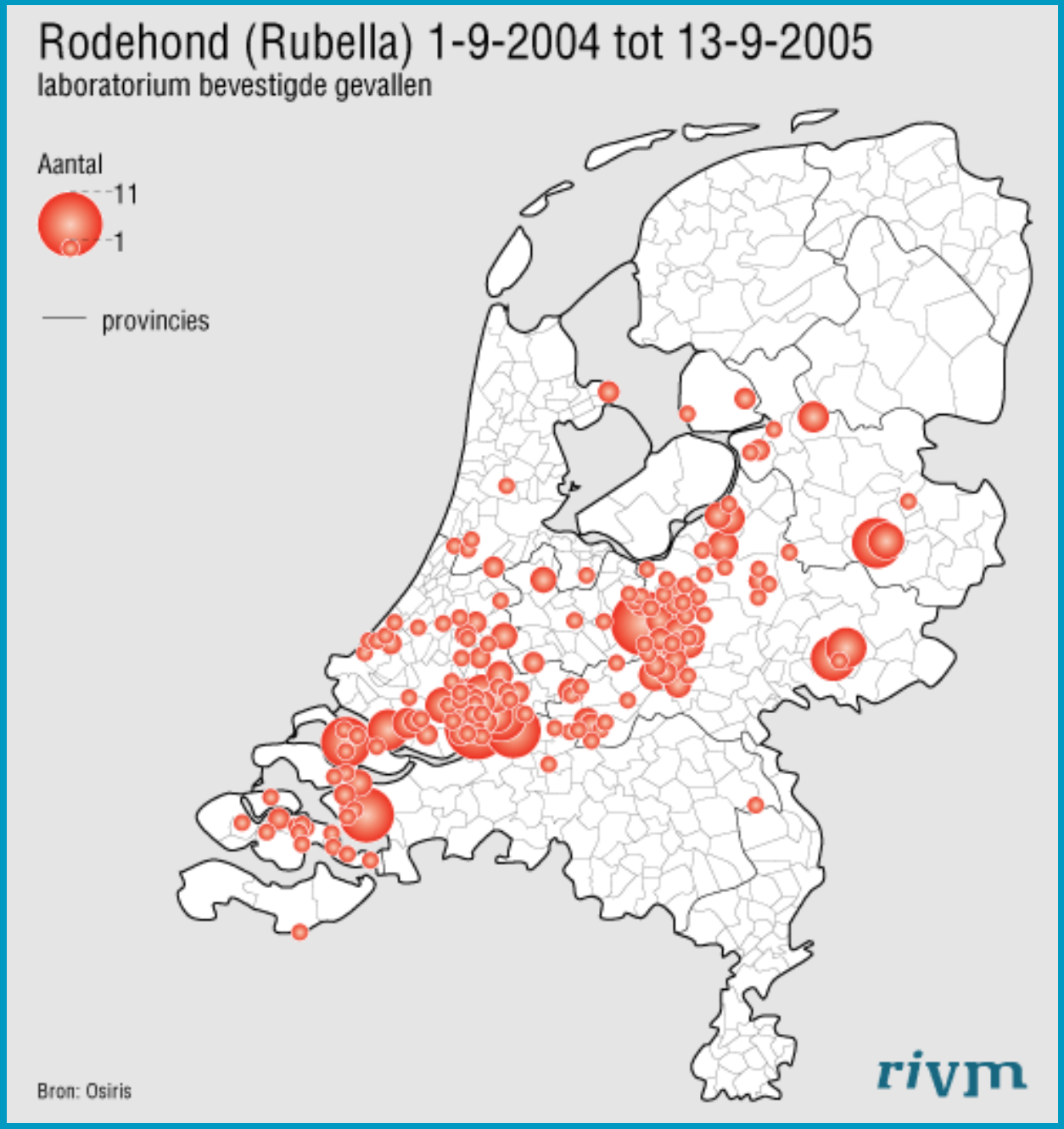
- Measles in NL: $R_0 \approx 20$
- $v > 95\%$
- vaccination coverage
  Netherlands ≈ 94%
- If susceptibles well-mixed: protected by herd immunity
- But: often susceptibles clustered

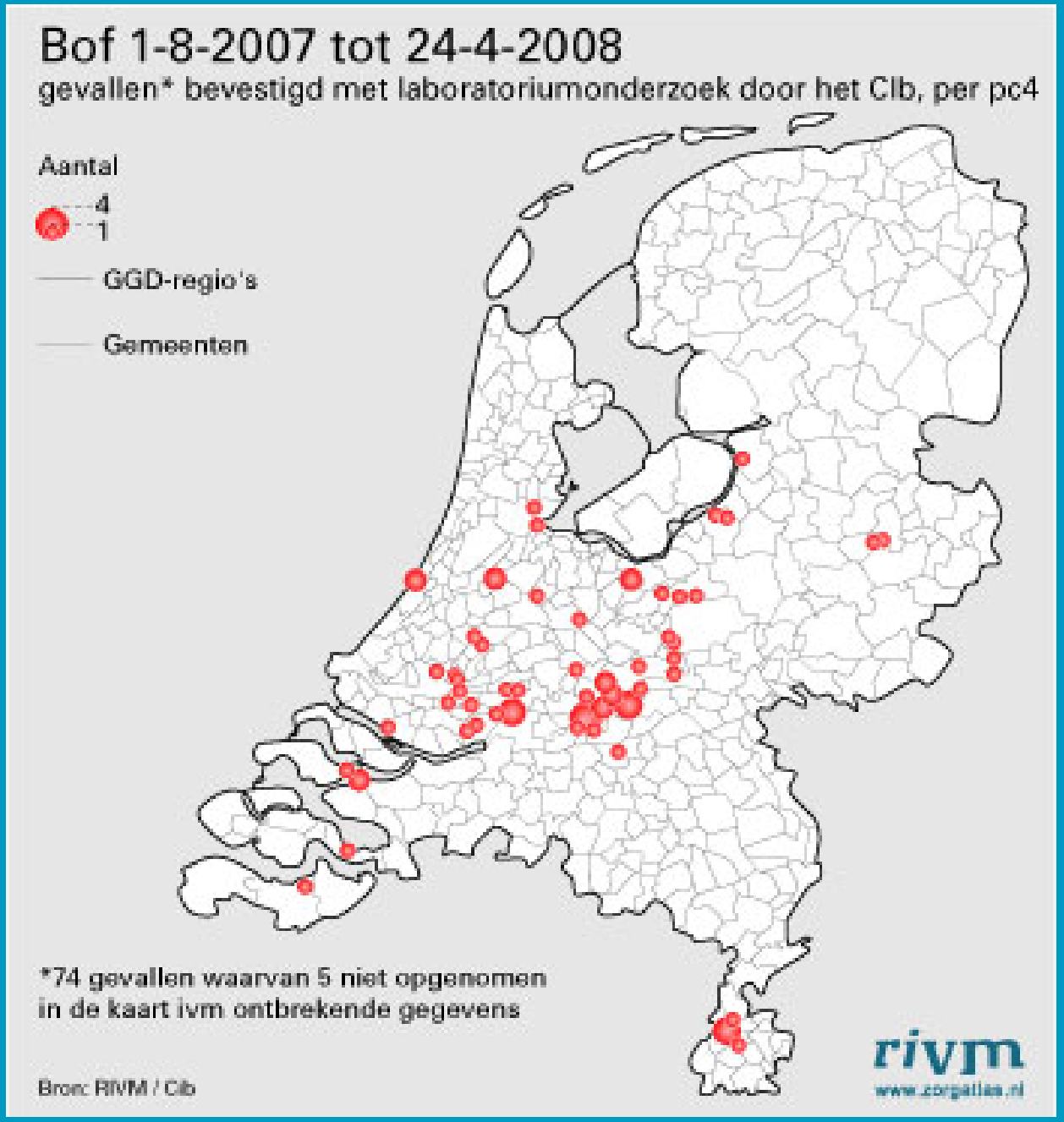




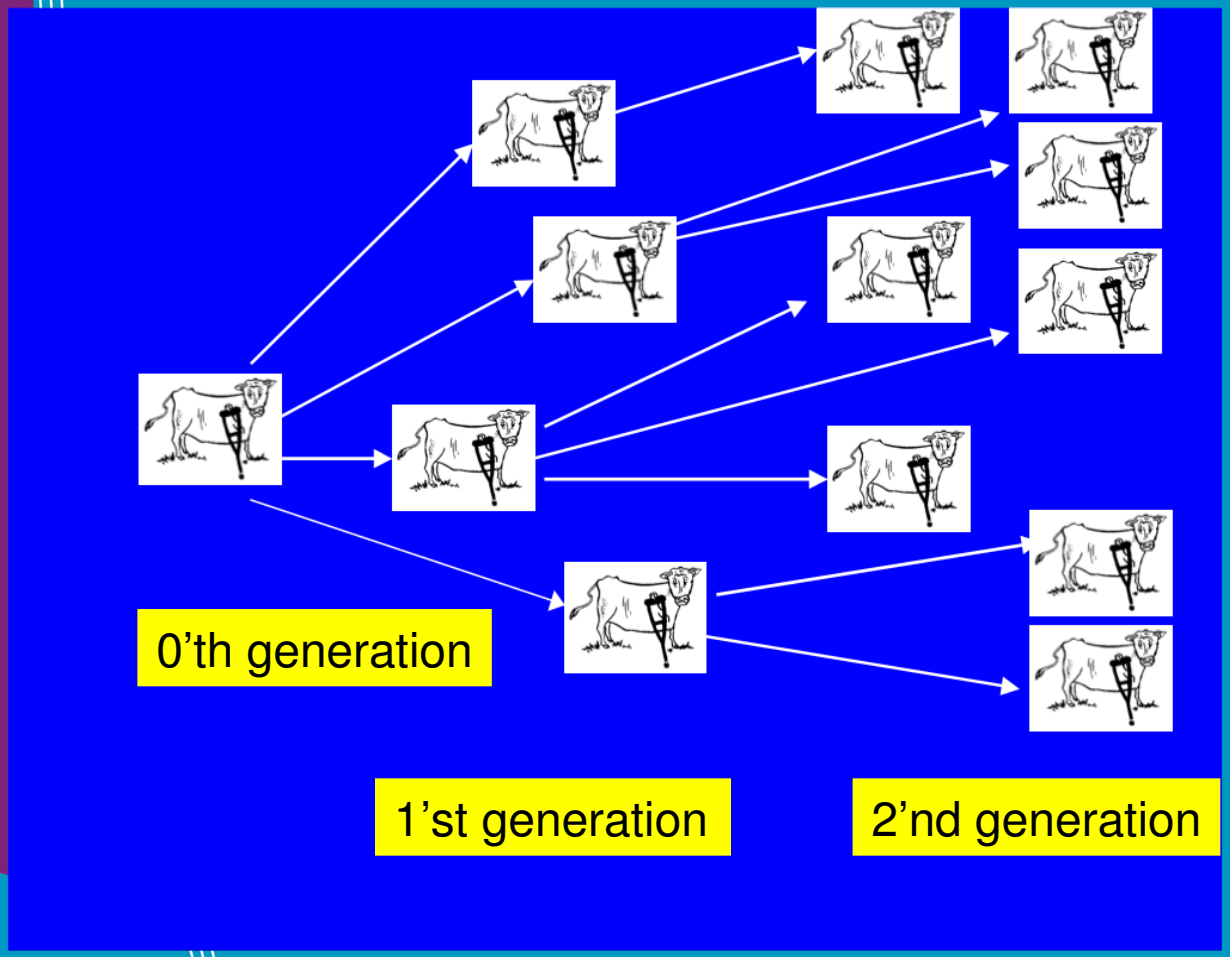
Measles, Rubella, Mumps vaccine coverage


Mazelenepidemie 1999-2000
per gemeente, van juni 1999 tot en met mei 2000
Aantal gevallen van mazelen
per 100.000 kinderen van 0 tot 15 jaar
Geen gevallen gemeld
0 - 100
100 - 500
500 - 1000
1000 - 2500
provincies
Bron: LCI
rivm


Rodehond (Rubella) 1-9-2004 tot 13-9-2005
laboratorium bevestigde gevallen
Aantal
11
1
provincies
Bron: Osiris
rivm


Bof 1-8-2007 tot 24-4-2008
gevallen* bevestigd met laboratoriumonderzoek door het Clb, per pc4
Aantal
4
1
GGD-regio's
Gemeenten
*74 gevallen waarvan 5 niet opgenomen
in de kaart ivm ontbrekende gegevens
Bron: RIVM / Clb
rivm
www.zorgatlas.nl

Generations



Drawing: Synthia Saint James

Next-generation matrix K

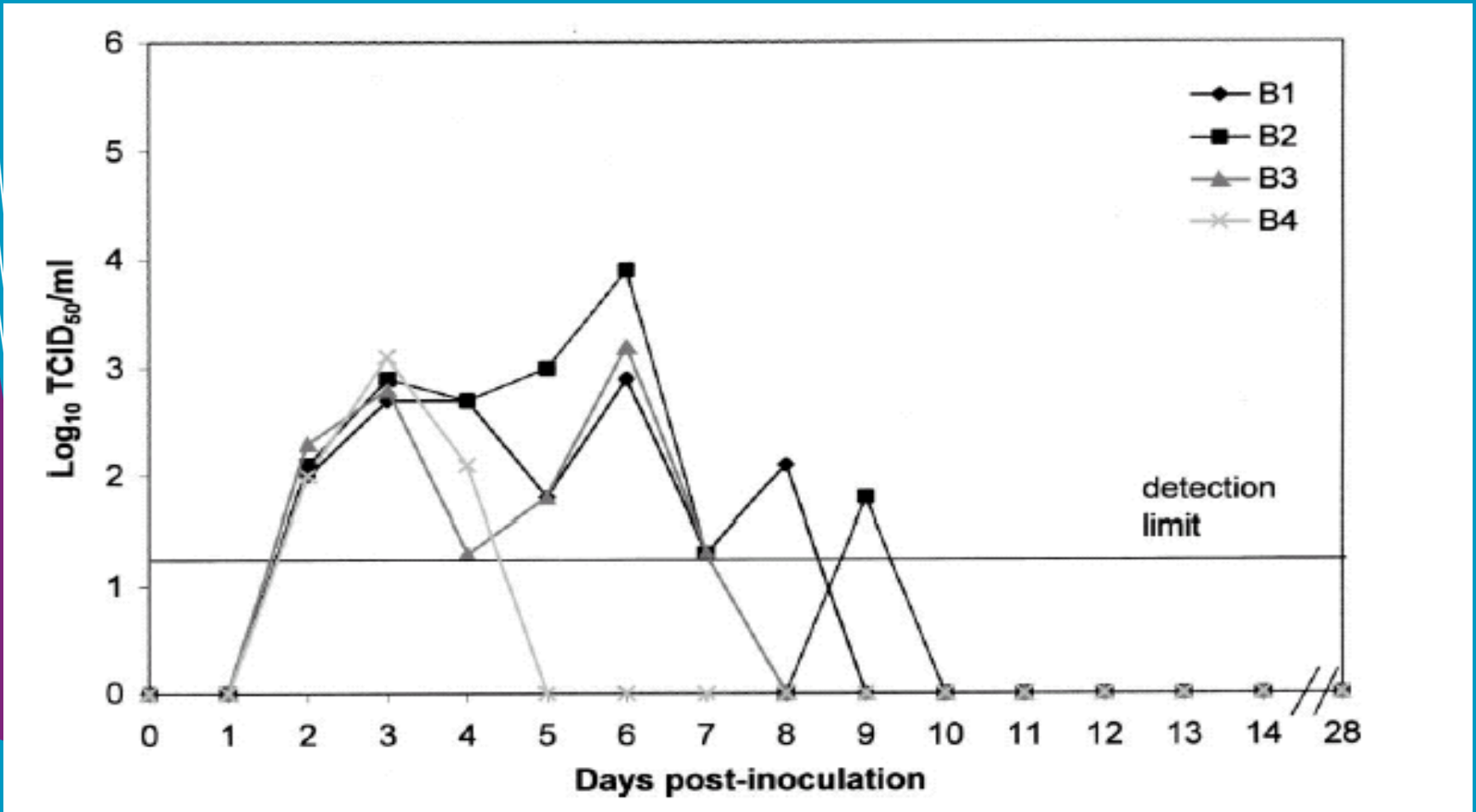
- n types: $i = 1,\ldots,n$
- n^2 'reproduction numbers' k_{ij}
- k_{ij} = expected total number of cases of type i caused by one infected individual of type j ; combine into nxn-matrix $K \geq 0$
- Let φ be the vector describing the current generation of infecteds
- The next generation is given by $K\varphi$

Definition of R_0

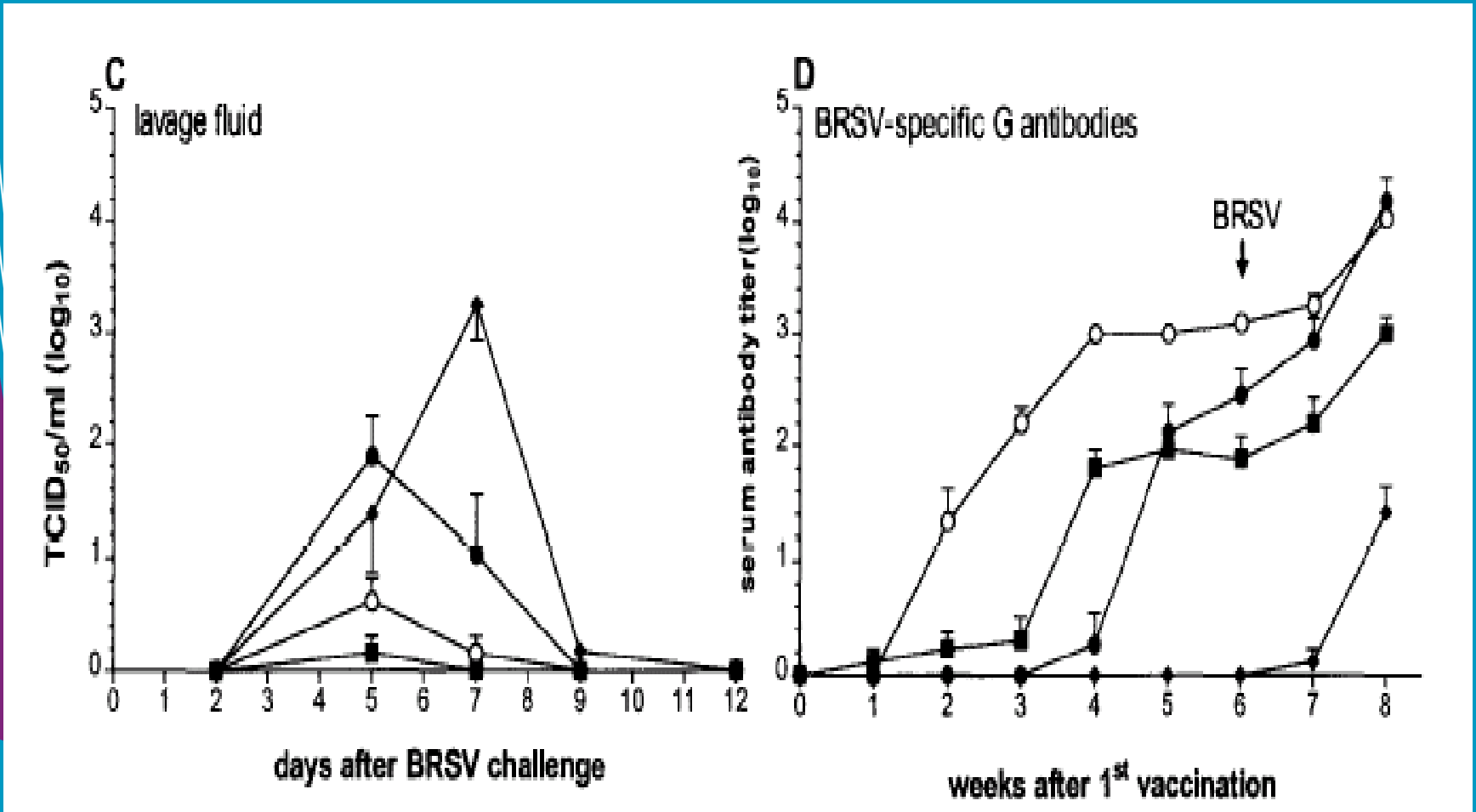
- Dominant (positive) *eigenvalue* λ of K
- After many generations:
  - Distribution of cases over types: fixed, $\boldsymbol{X}$
  - Growth or decline per generation fixed, λ
- n'th generation from 0'th generation X_0:

  $X_n \approx c(X_0)\ \lambda^n\ \boldsymbol{X}$

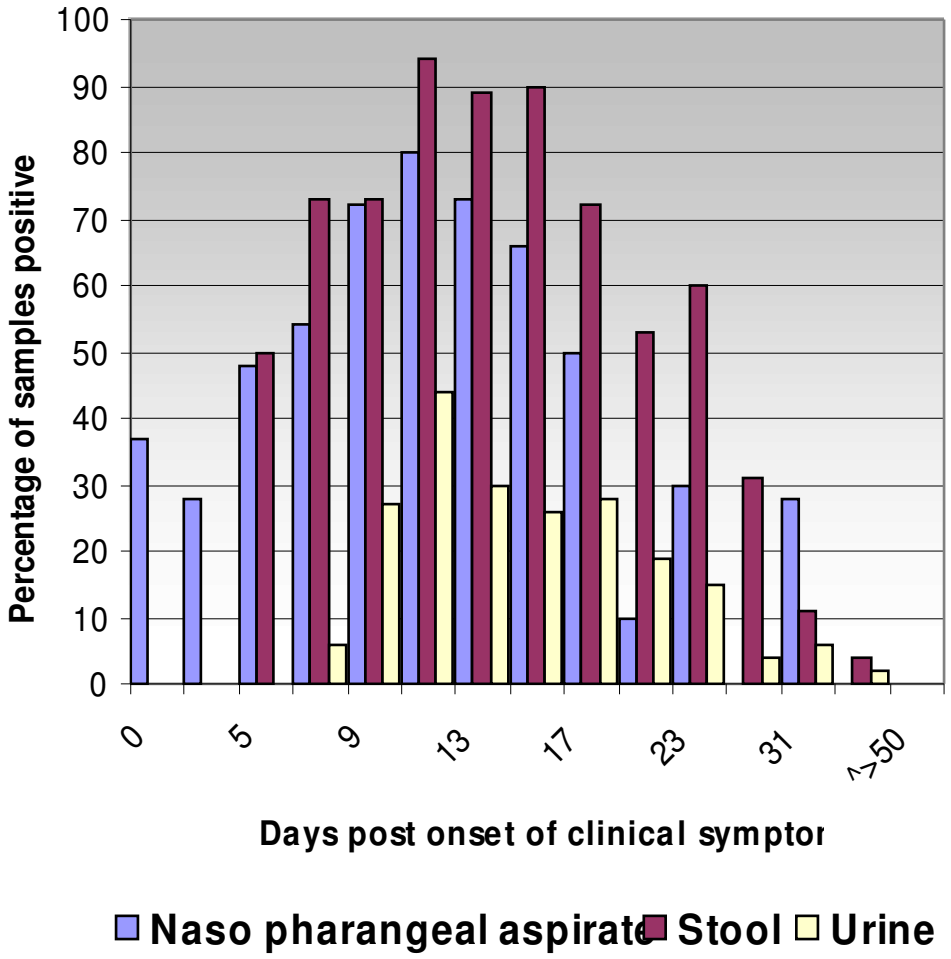
- **Conclusion:** R_0 = dominant eigenvalue of K



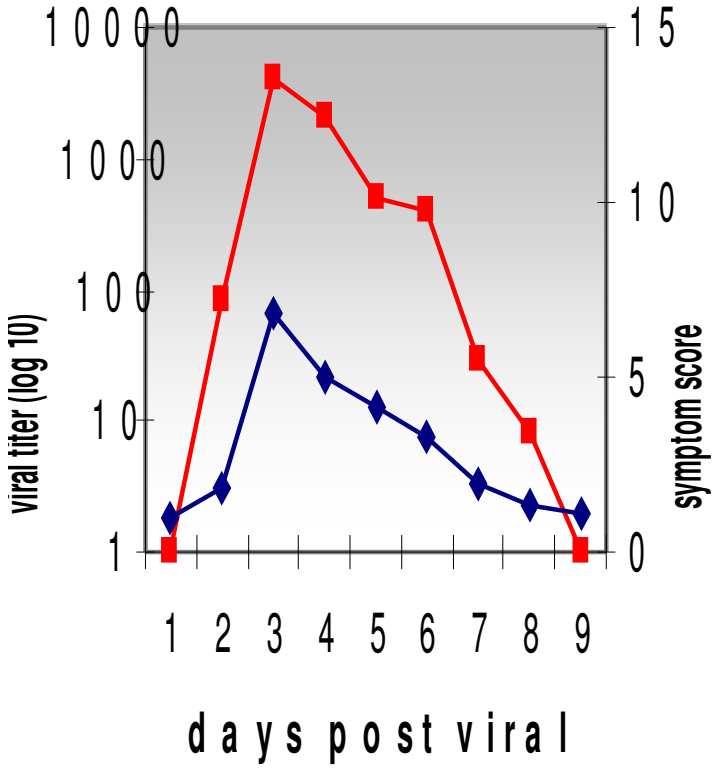
Wellenberg *et al.*, 2002, BHV1



Schrijver *et al.* 1997, BRSV

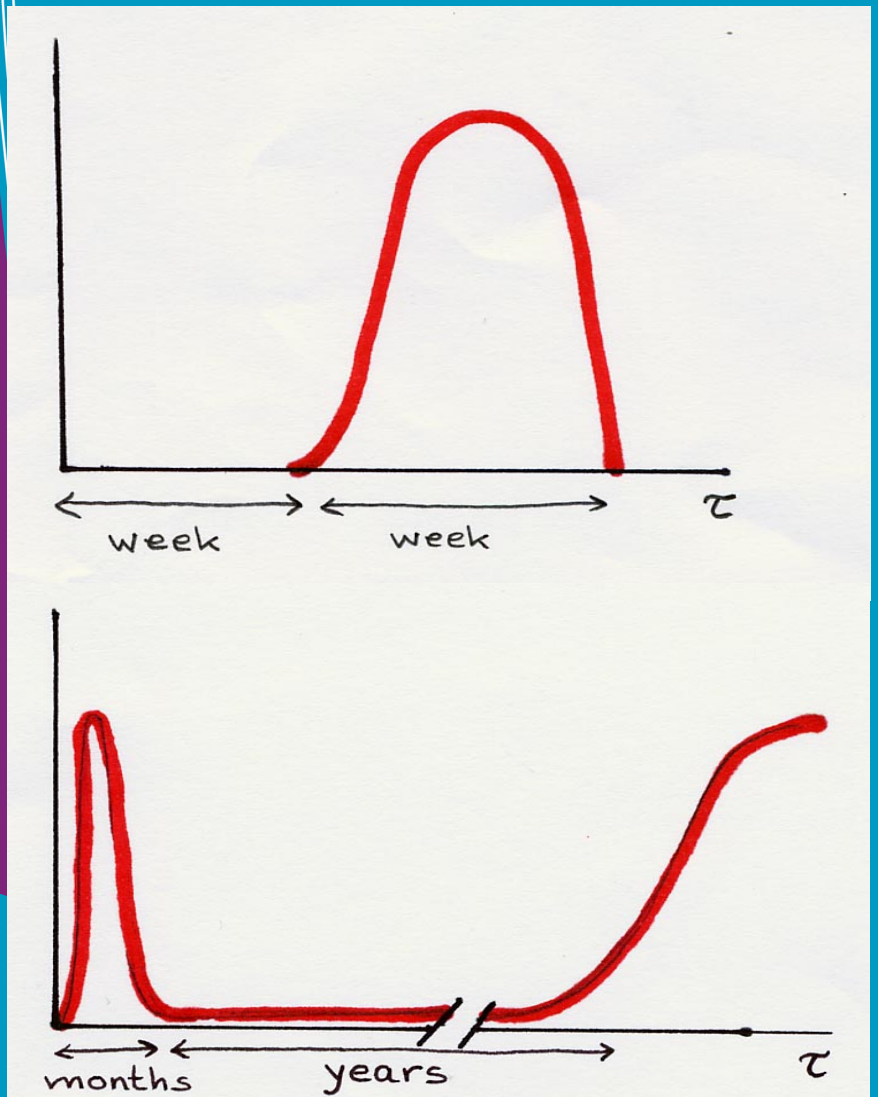


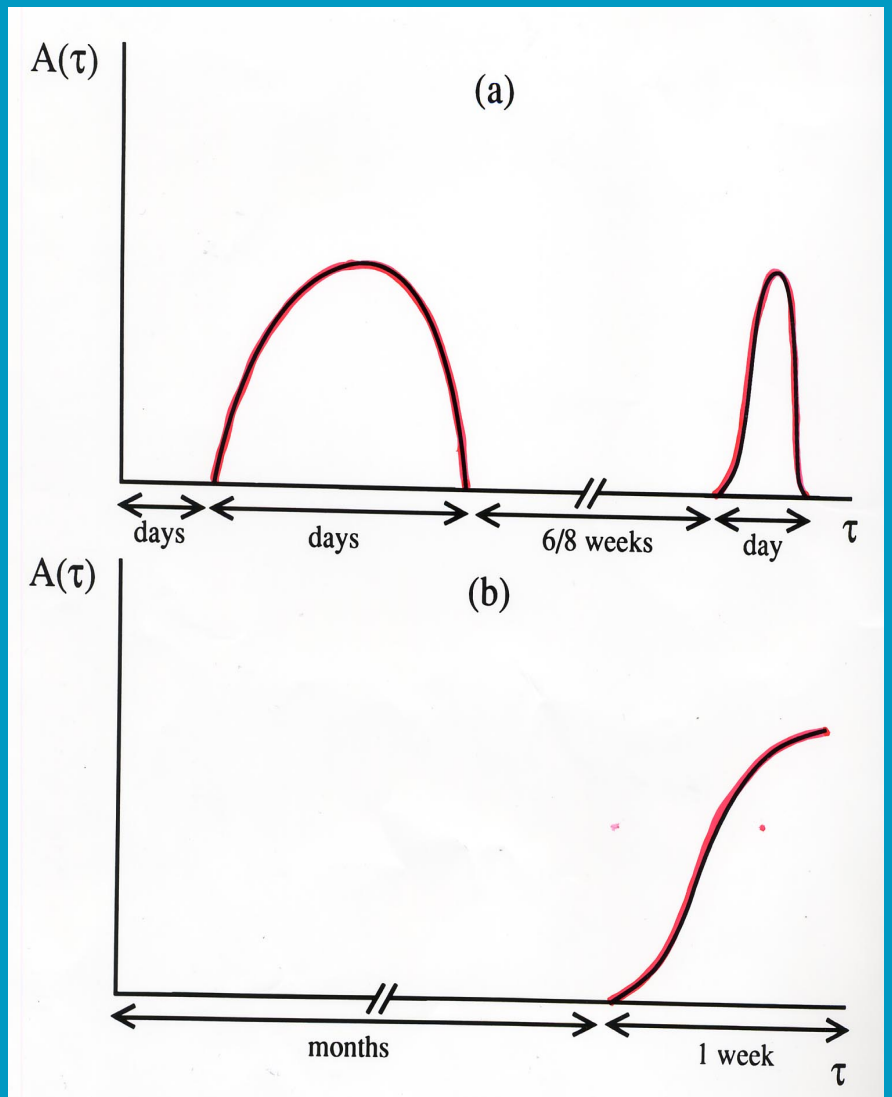
Peiris *et al.* 2003, SARS



Haydon *et al.* 1998, influenza A

Infectivity function $A(\tau)$





Model in terms of $A(\tau)$

$$i(t) = S(t)\int_0^\infty A(\tau)i(t-\tau)d\tau$$

Individuals that were infected τ time units ago

These currently have infectivity $A(\tau)$

Acting on the susceptibles available at time t

Resulting in new infected individuals at time t

Choosing $A(\tau) = \beta \exp(-\gamma\tau)$ leads to SIR-type ODE model

Adding heterogeneity: *n* types

$$i(t,j) = S(t,j)\sum_{l=1}^{n}\int_0^{\infty} A_{jl}(\tau)i(t-\tau,l)d\tau$$

Individuals that were infected τ time units ago with type l

These currently have infectivity $A(\tau,k,l)$

Acting on the susceptibles of type j available at time t

Resulting in new infected individuals at time t with type j

Define $k_{jl} = \overline{S}_j \int_0^{\infty} A_{jl}(\tau)d\tau$

Next-generation matrix K

Heterogeneous models

$$i(t,\xi) = S(t,\xi)\int_{\Omega}\int_{0}^{\infty} A(\tau,\xi,\eta)i(t-\tau,\eta)d\tau d\eta$$

Individuals that were infected τ time units ago of type η

These currently have infectivity $A(\tau,\xi,\eta)$ towards susceptibles of type ξ

Acting on the susceptibles of type ξ available at time *t*

Resulting in new infected individuals at time *t* with type ξ

Type space Ω

Defining R_0: general case

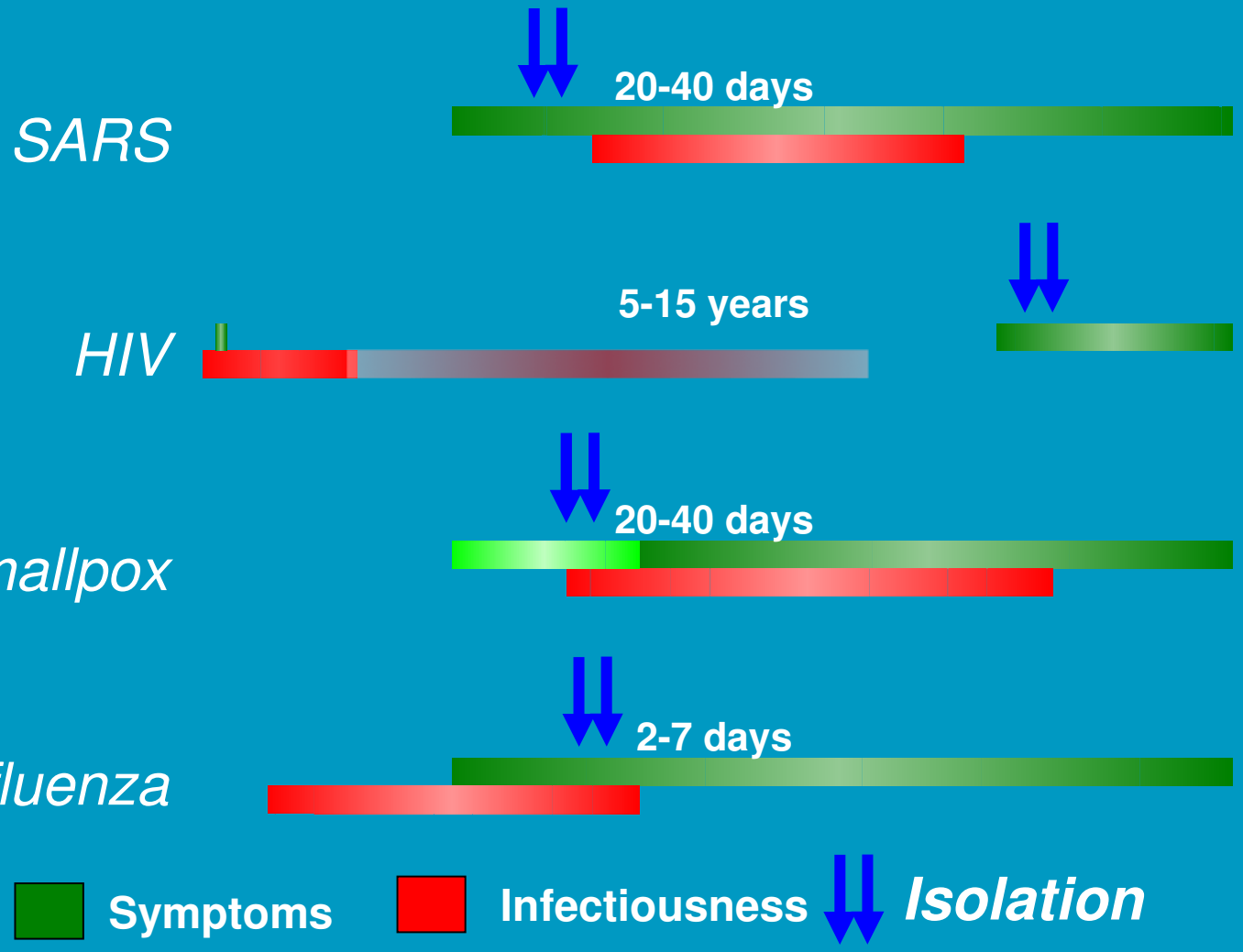
- Type space Ω
- Positive linear operator K on $L_1(\Omega)$
- K involves: infectivity function $A(\tau, . , .)$
  steady st. susceptibles distributed over Ω

$$K(\phi)(\xi) = \overline{S}(\xi) \int_{\Omega} \int_0^{\infty} A(\tau, \xi, \eta) \phi(\eta) d\tau d\eta$$

- R_0 = *spectral radius* of K

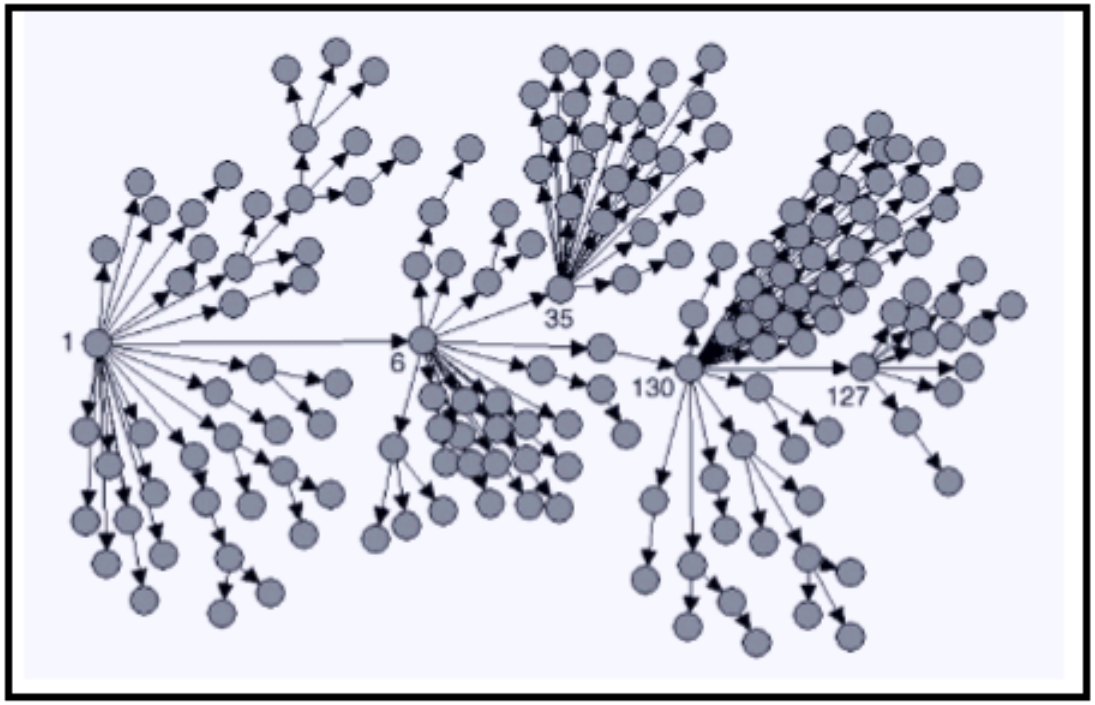
Infectivity before symptoms

slide courtesy
of Imperial College
London



Fraction of infectivity released before symptoms vs R_0

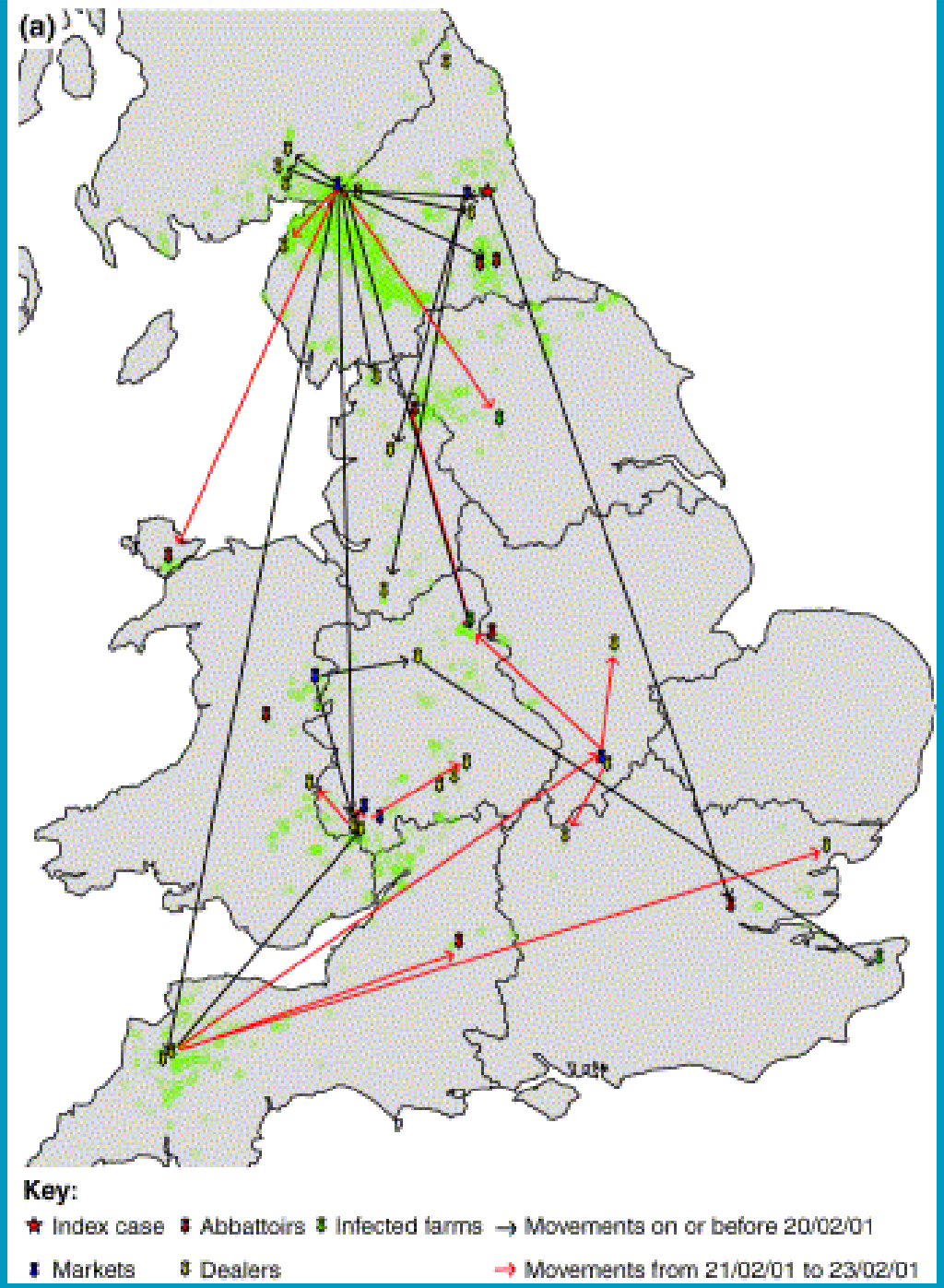
FIGURE 2. Probable cases of severe acute respiratory syndrome, by reported source of infection* — Singapore, February 25–April 30, 2003



* Patient 1 represents Case 1; Patient 6, Case 2; Patient 35, Case 3; Patient 130, Case 4; and Patient 127, Case 5. Excludes 22 cases with either no or poorly defined direct contacts or who were cases translocated to Singapore and the seven contacts of one of these cases.

Reference: Bogatti SP. Netdraw 1.0 Network Visualization Software. Harvard, Massachusetts: Analytic Technologies, 2002.

Foot-and-Mouth disease
Early spread from day zero (20/2/01) until time of transport ban (23/2/01)



Graph from Gibbens *et al.* *Veterinary Record,* 2001

The critical tracing fraction p^* in contact tracing

- Work of Don Klinkenberg, Christoph Fraser
- $R_0 = R_0^{asy} + R_0^{sy}$
- Perfect isolation of symptomatics: $R_0^{sy} = 0$
- Various forms for $A(\tau)$
- Gamma distribution for incubation period
- When random mixing individuals: critical tracing fraction

$$p^* = 1 - \frac{1}{R_0^{asy}}$$

How does this change if we take Infection tree into account?

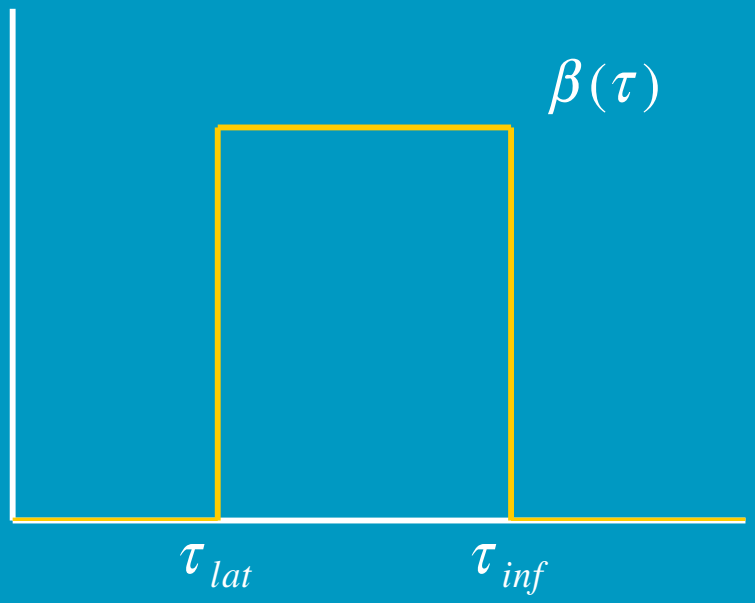
The effectiveness of contact tracing

- Each contact of a symptomatic is traced with probability *p* and quarantined (perfect)
- Determine critical tracing probability *p*.* So for

  $p > p^*$ we have: infection dies out
- Influenced by: latent period, infectious period, incubation period, delay in tracing, tracing method

Infectivity

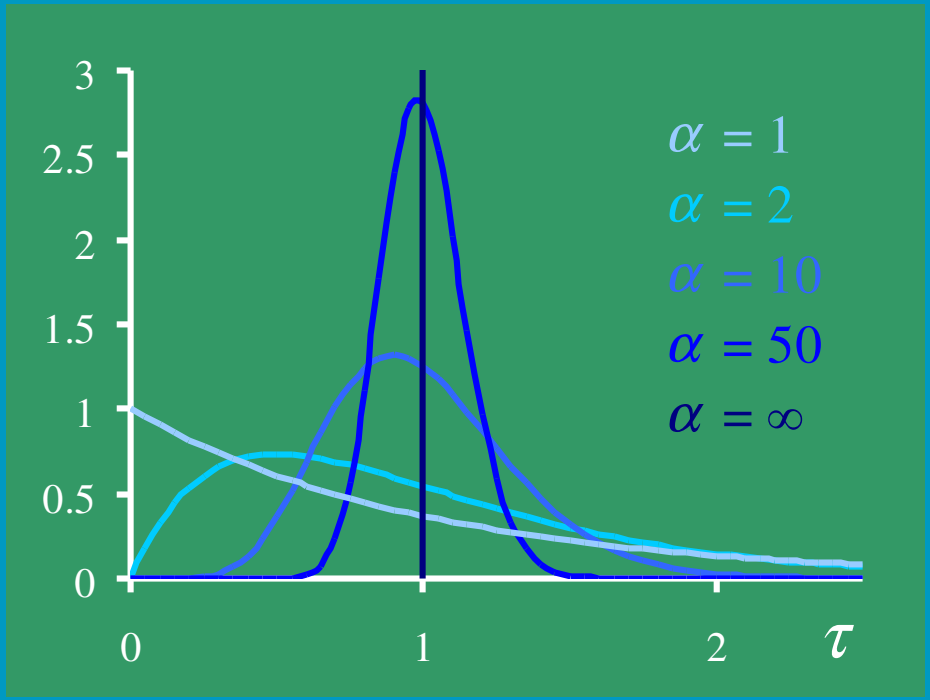
Infectivity: rate at which new infecteds are produced



Incubation

Incubation period distribution:

- Everyone same
- Maximum variability

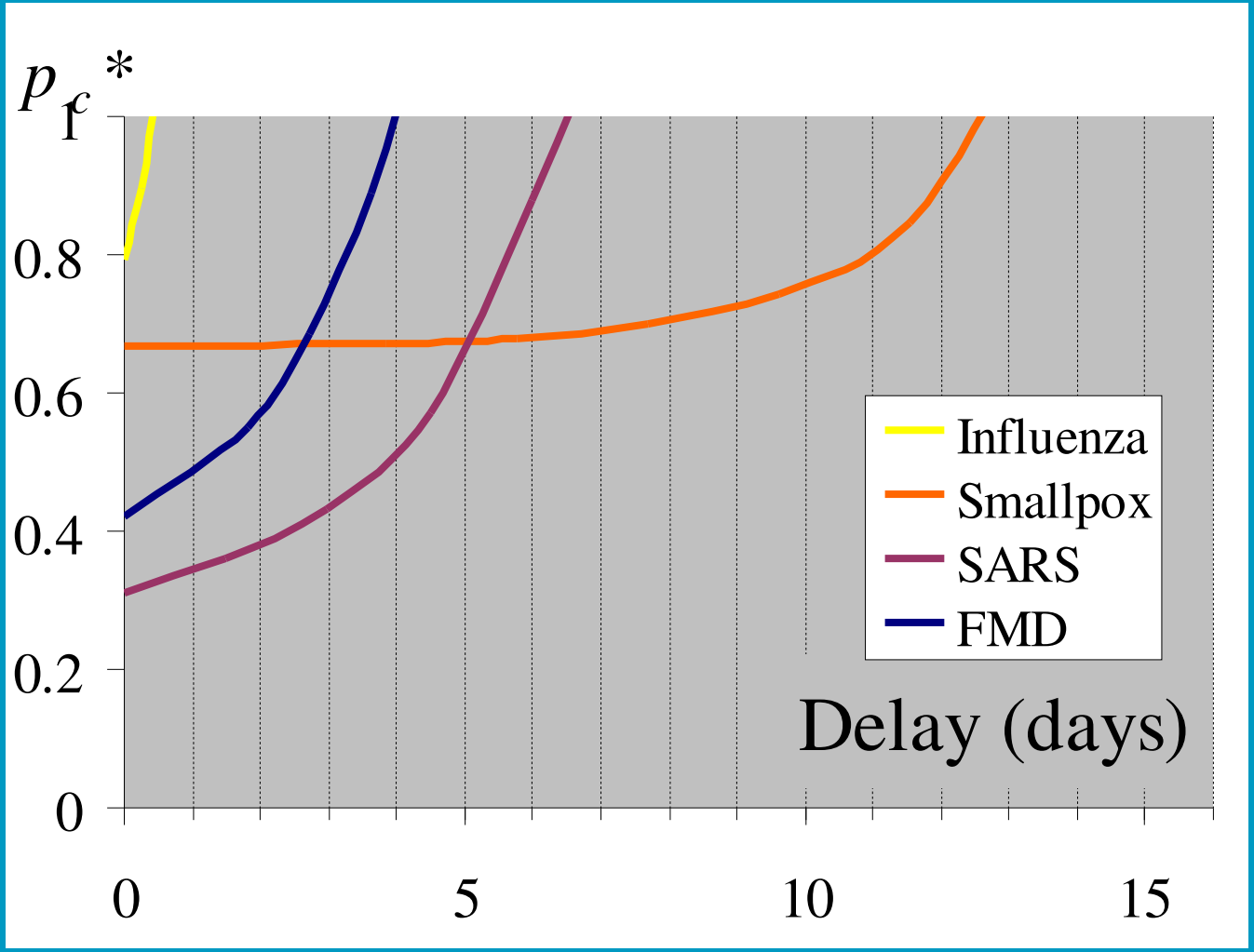


Example: real infections

Table 2. Parameter values for the real infections

Infection	R_0^{asyx}	Incubation period			Infectious period	
		mean	variance	α	τ_{lat}	τ_{inf}
Influenza	1.5	1.48	0.221	9.92	0.5	5
SARS	1.5	3.81	8.34	1.74	5	27
Smallpox	3	15.5	4.08	58.8	15	26
FMD (82%)[1]	1.6	7.8[1]	2.03[1]	30[1]	3	∞
FMD (18%)[1]		14.9[1]	6.12[1]	4[1]		

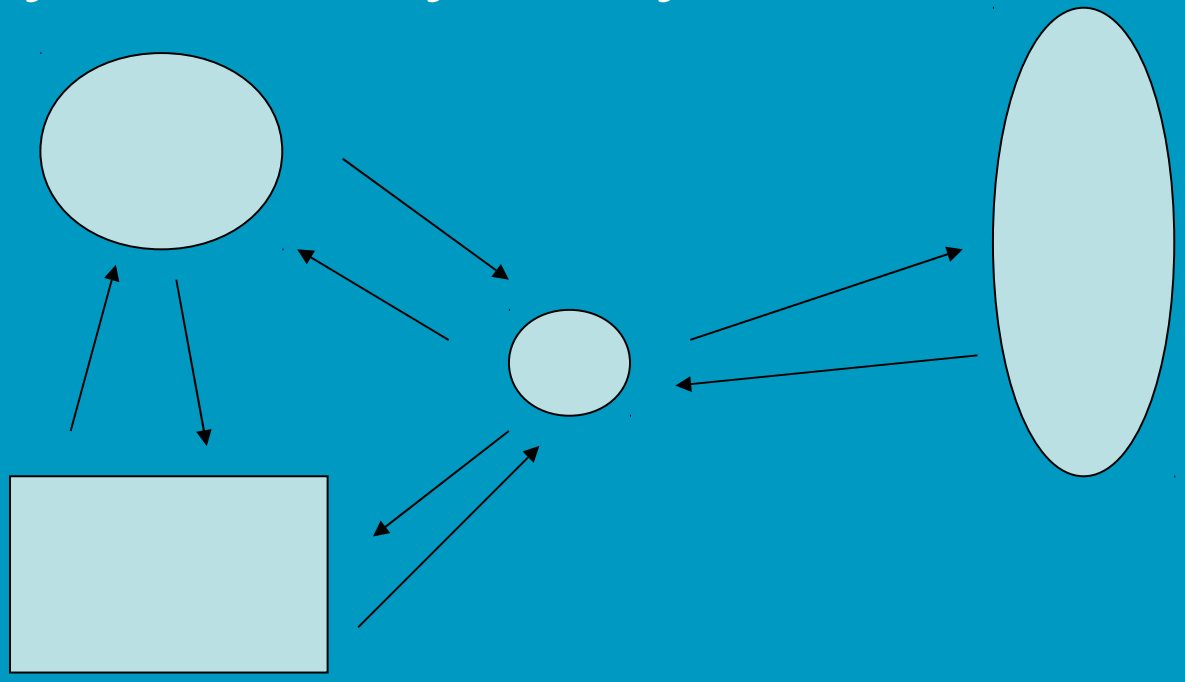
Contact tracing results



Klinkenberg, Fraser & Heesterbeek, *PLoS ONE*, Dec 2006

Spatial metapopulation

- Several habitat patches with local populations connected by migration: few, many, incredibly many



Very many: Plague in Kazachstan

- Zoonotic bacterial infection; flea transmission;
- Predicting outbreaks in a metapopulation of wildlife hosts (Great gerbils)
- First example of percolation in a biological natural system

- Percolation theory: transport through a porous medium, with thresholds for success

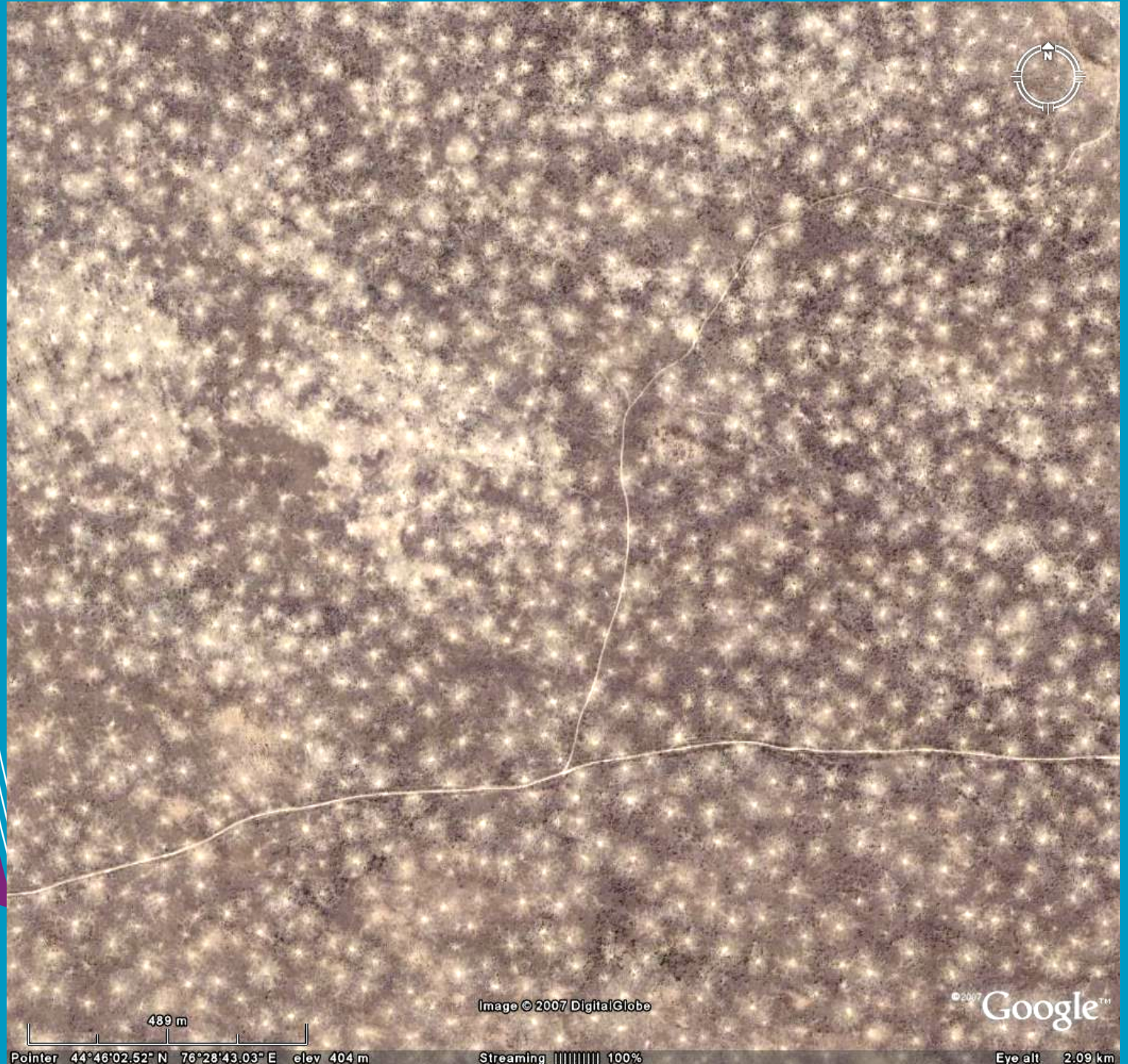

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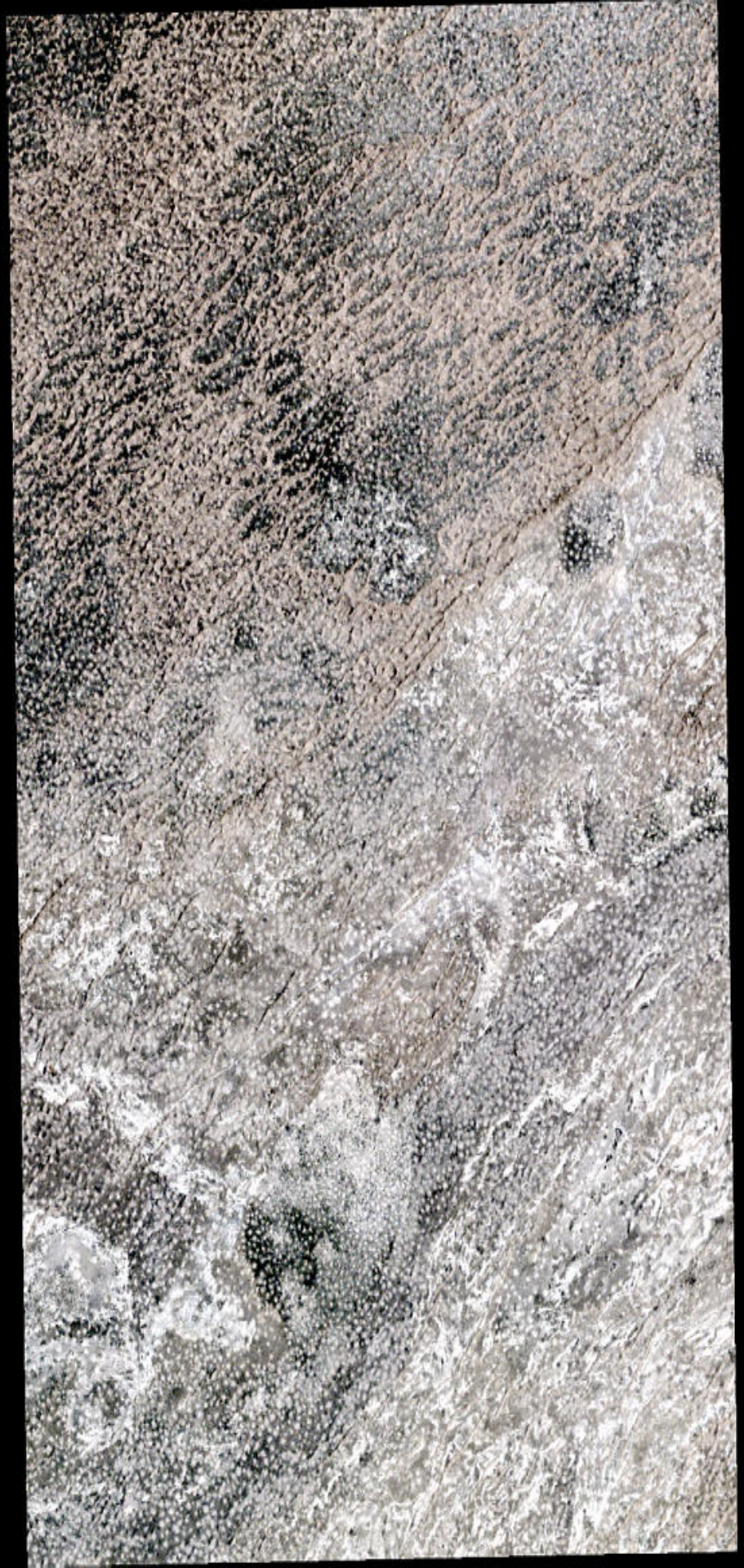
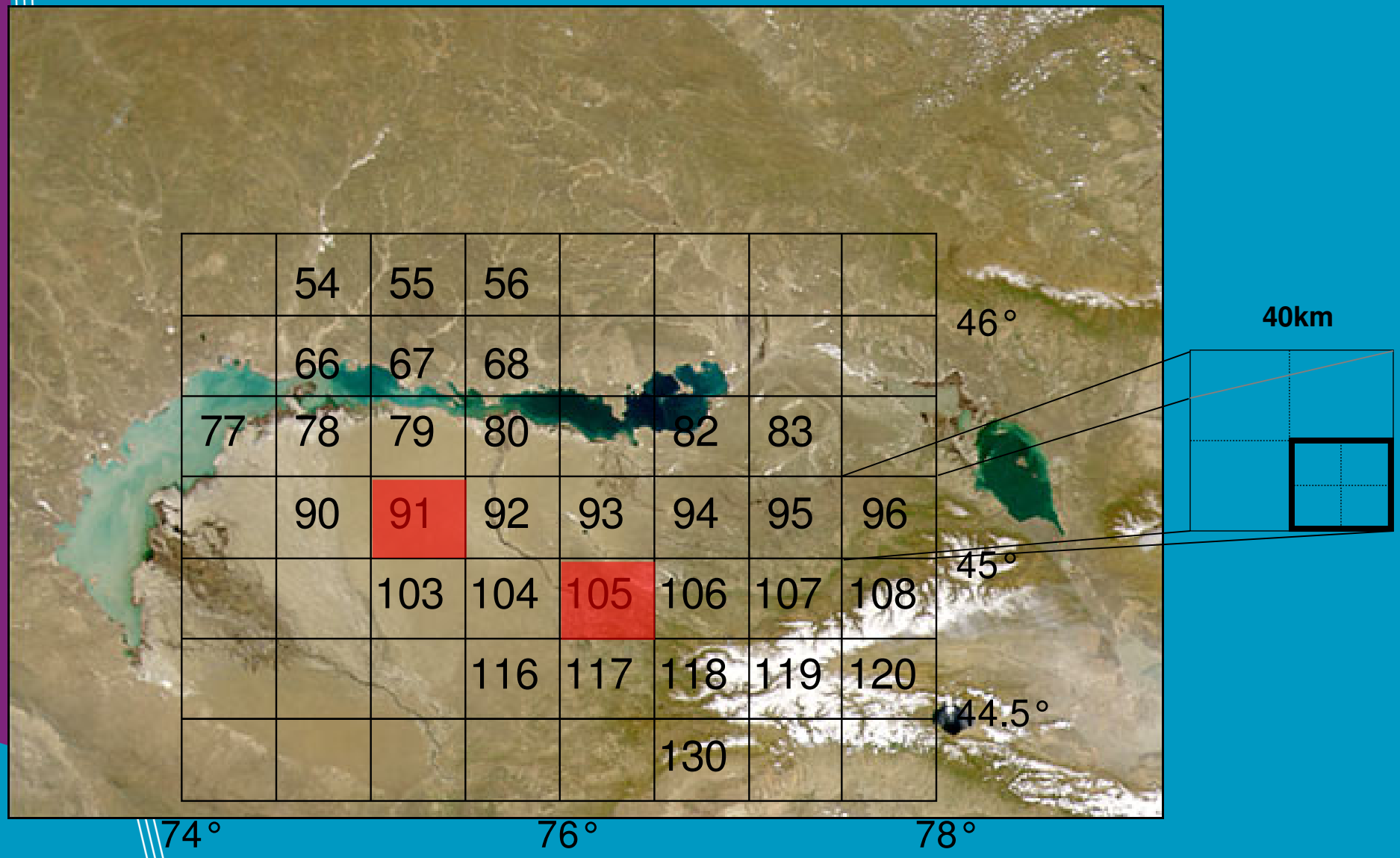
Image © 2007 DigitalGlobe
©2007 Google™
489 m
Pointer 44°46'02.52" N 76°28'43.03" E elev 404 m
Streaming 100%
Eye alt 2.09 km



The Caucasus and Central Asia

RUSSIA
BELARUS
UKRAINE
KAZAKHSTAN
KYRGYZSTAN
UZBEKISTAN
CHINA
TURKMENISTAN
TAJIKISTAN
PAKISTAN
AFGHANISTAN
INDIA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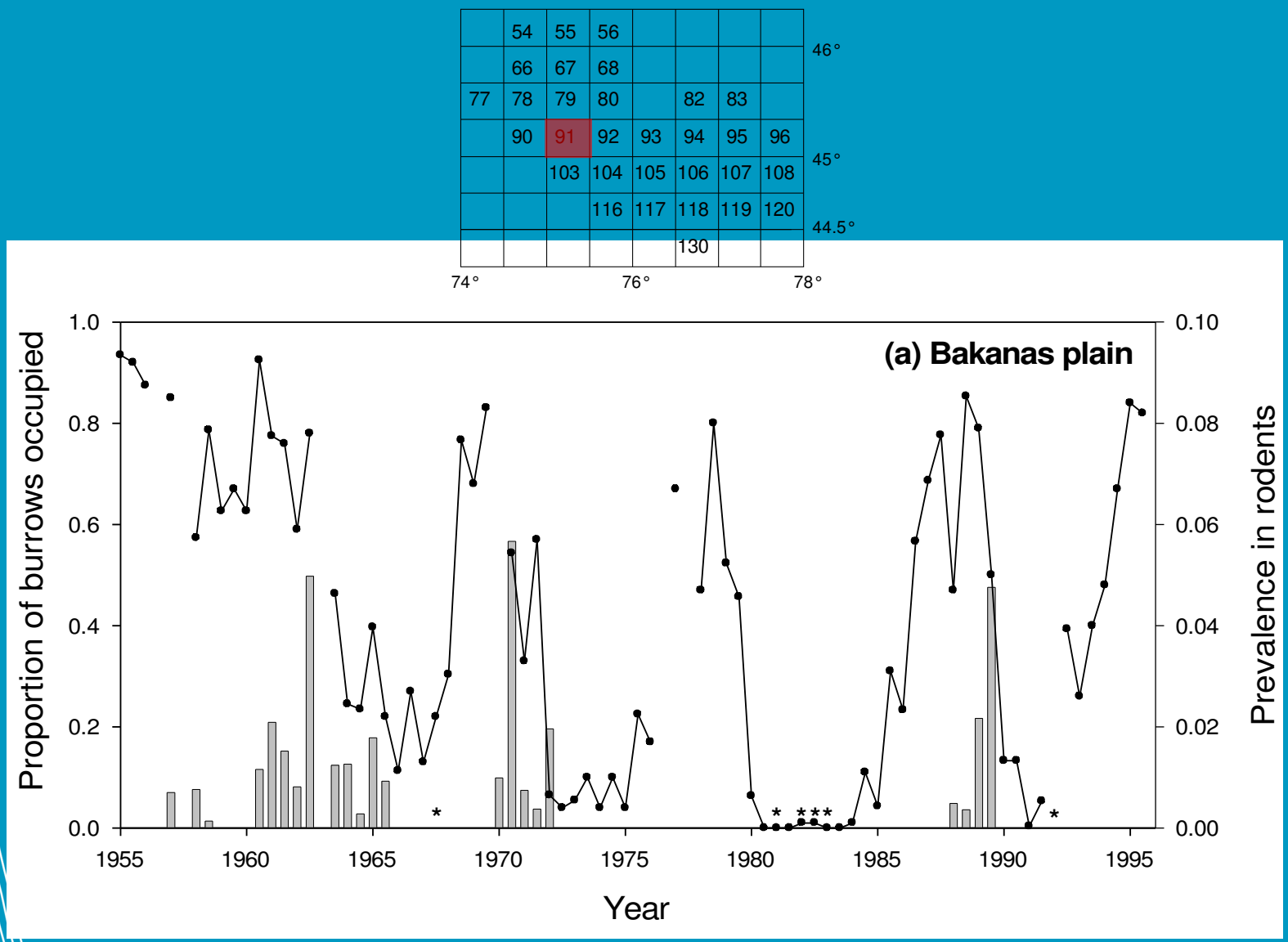
45°
44.5°
74°
76°
78°
40km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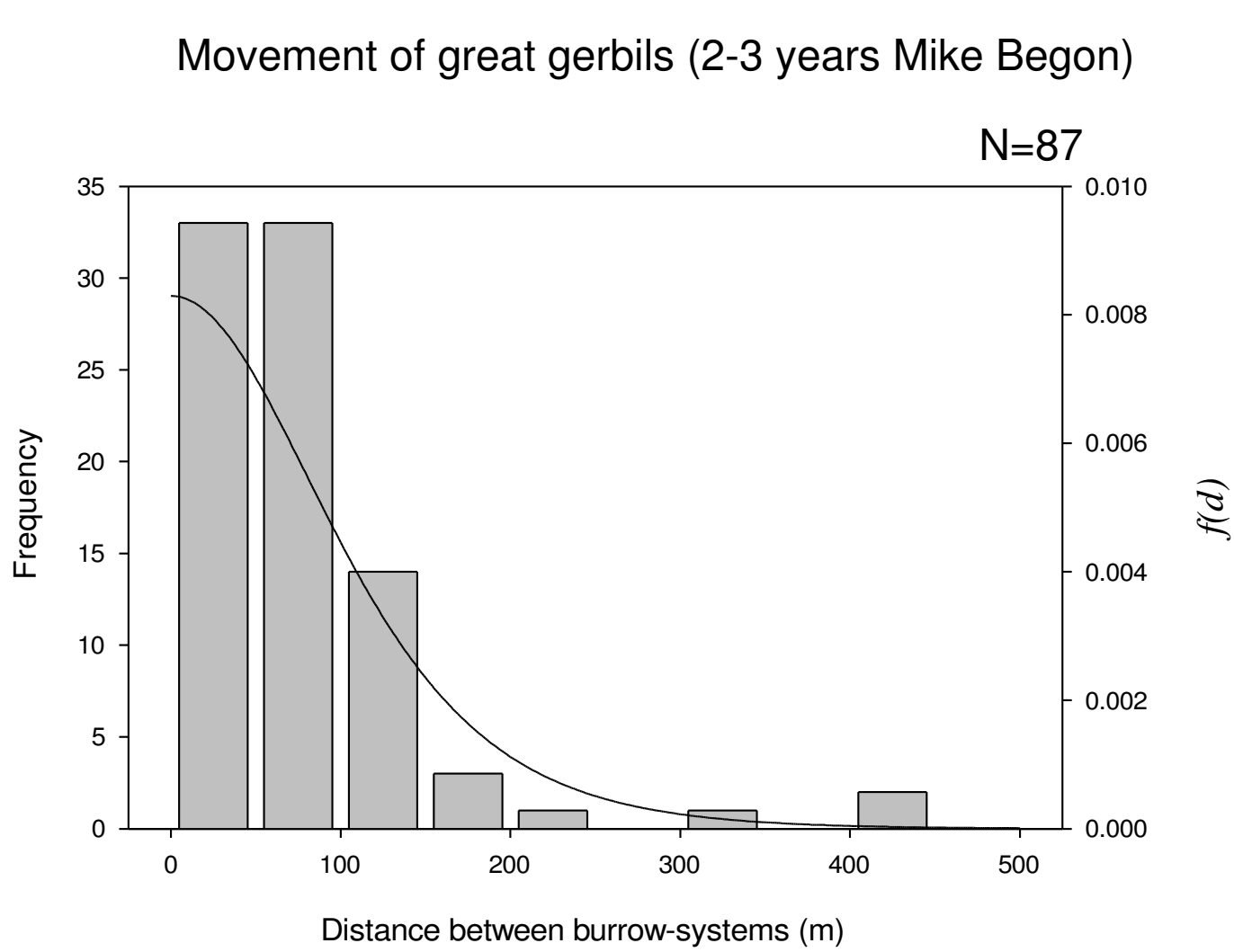
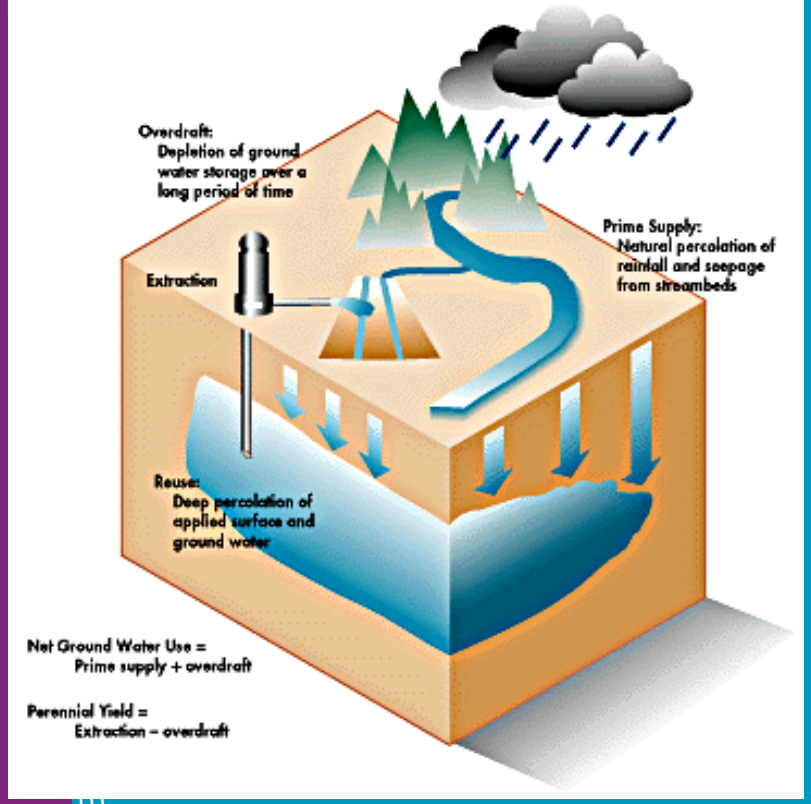
77 78 79 80 82 83
90 91 92 93 94 95 96
103 104 105 106 107 108
116 117 118 119 120
130
46°
45°
44.5°
74°
76°
78°
(a) Bakanas plain
Proportion of burrows occupied
Prevalence in rodents
Year
1.0
0.8
0.6
0.4
0.2
0.0
0.10
0.08
0.06
0.04
0.02
0.00
1955
1960
1965
1970
1975
1980
1985
1990
1995

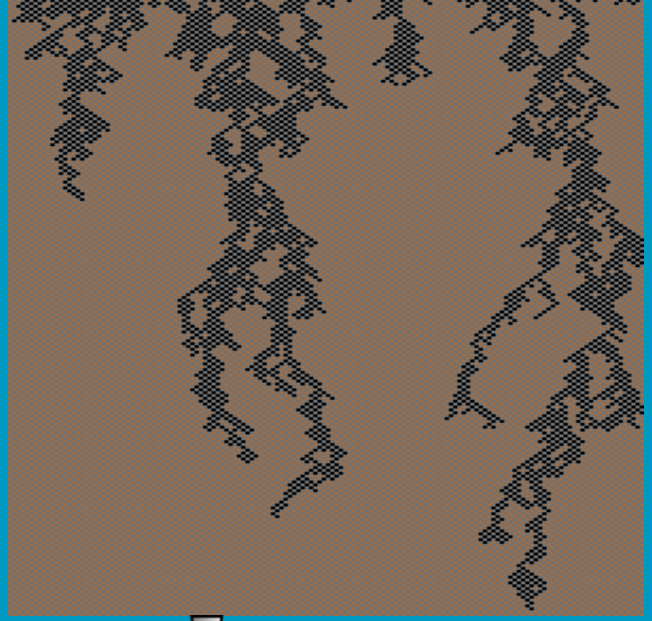
Mark-recapture data of gerbils and fleas

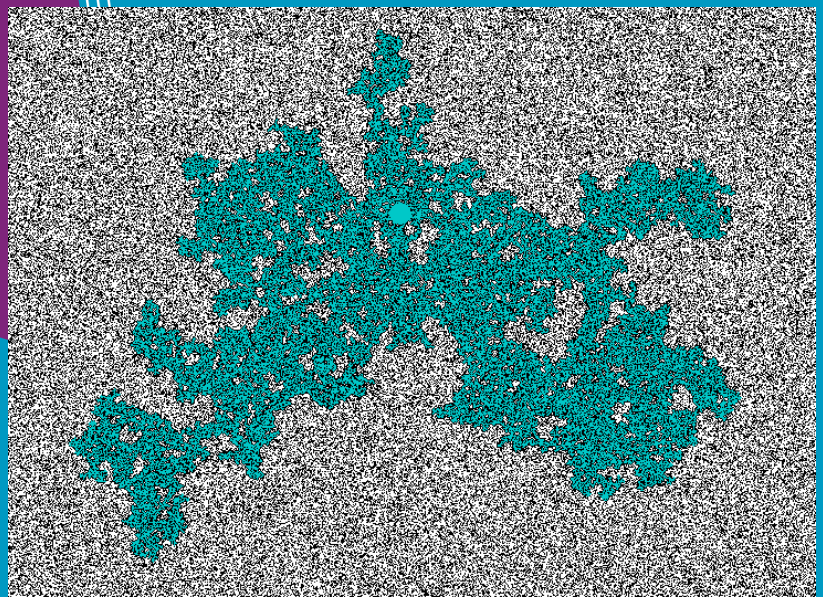


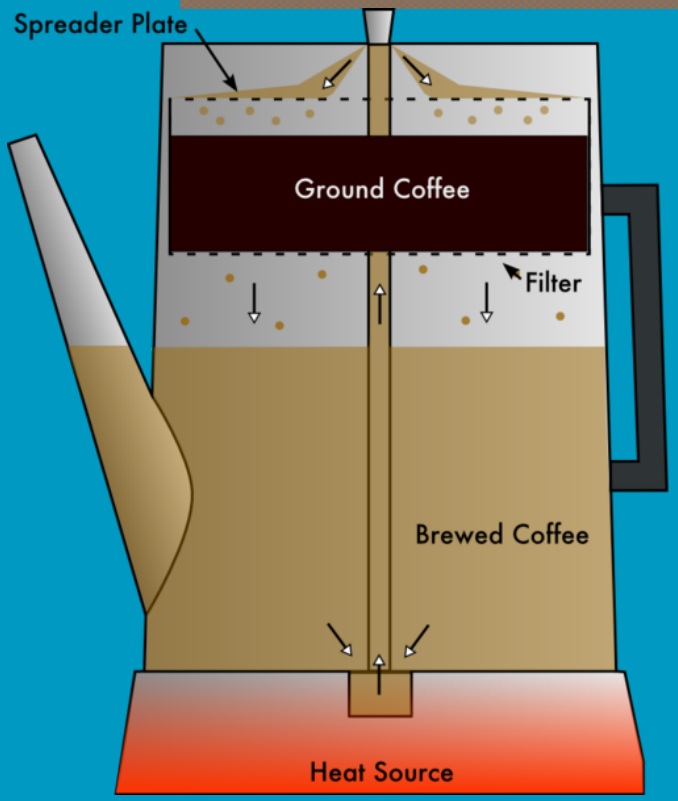
Russian studies of flea Movement:

Fleas marked with radio-nucleotides: 95% of movements <200m… and indications of a thick tail for the distribution. (Rundenchik ‘67; Korneyev 1968)

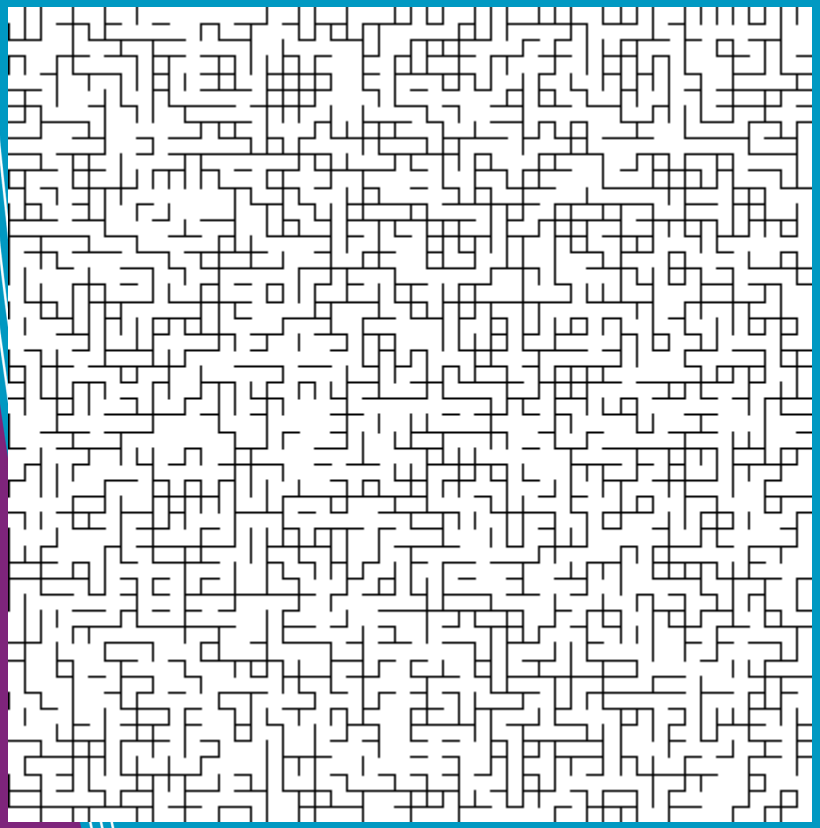

Overdraft:
Depletion of ground water storage over a long period of time
Extraction
Prime Supply:
Natural percolation of rainfall and seepage from streambeds
Reuse:
Deep percolation of applied surface and ground water
Net Ground Water Use =
Prime supply + overdraft
Perennial Yield =
Extraction – overdraft






Spreader Plate
Ground Coffee
Filter
Brewed Coffee
Heat Source

Random bonds on a square lattice



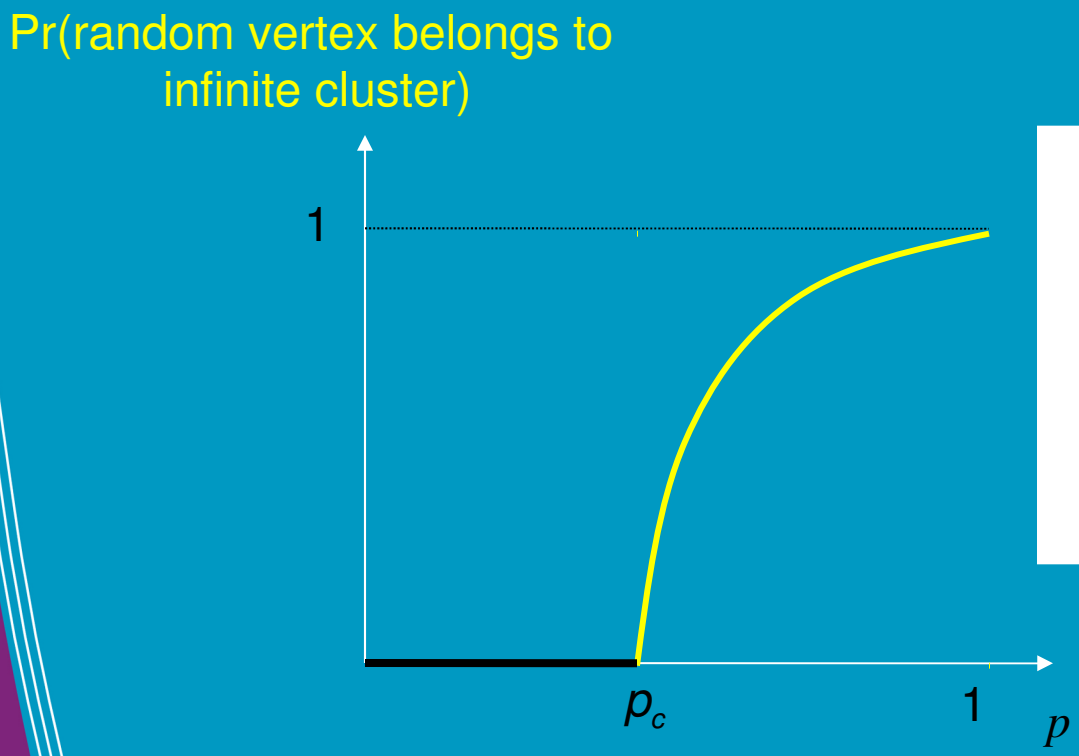
p=0.51

For an infinite lattice, is there an infinite cluster?

Is it unique?

Will a random vertex in the lattice belong to the infinite cluster?

The percolation threshold…



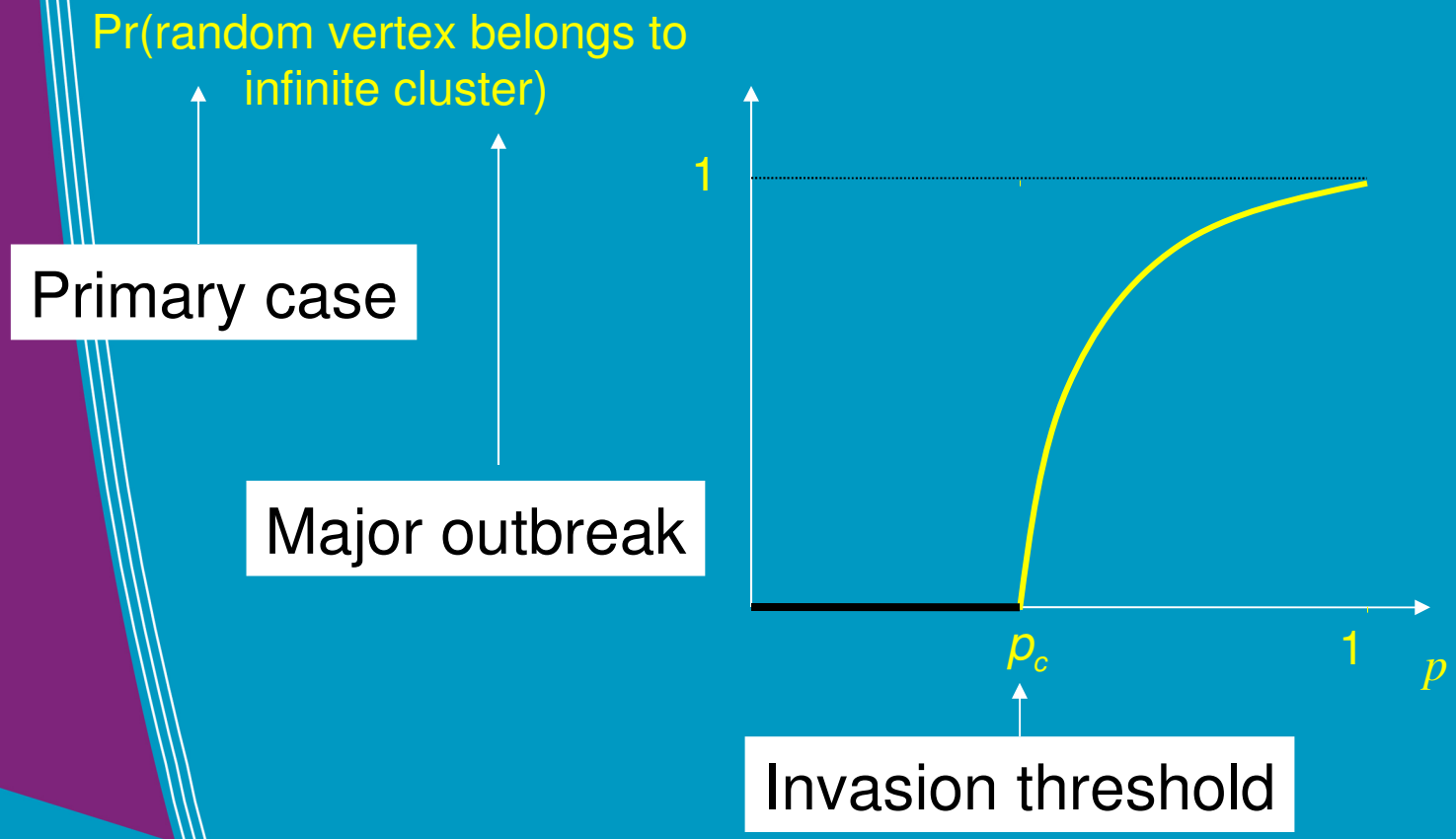
Two distinct regions…

$p < p_c$: no such infinite cluster

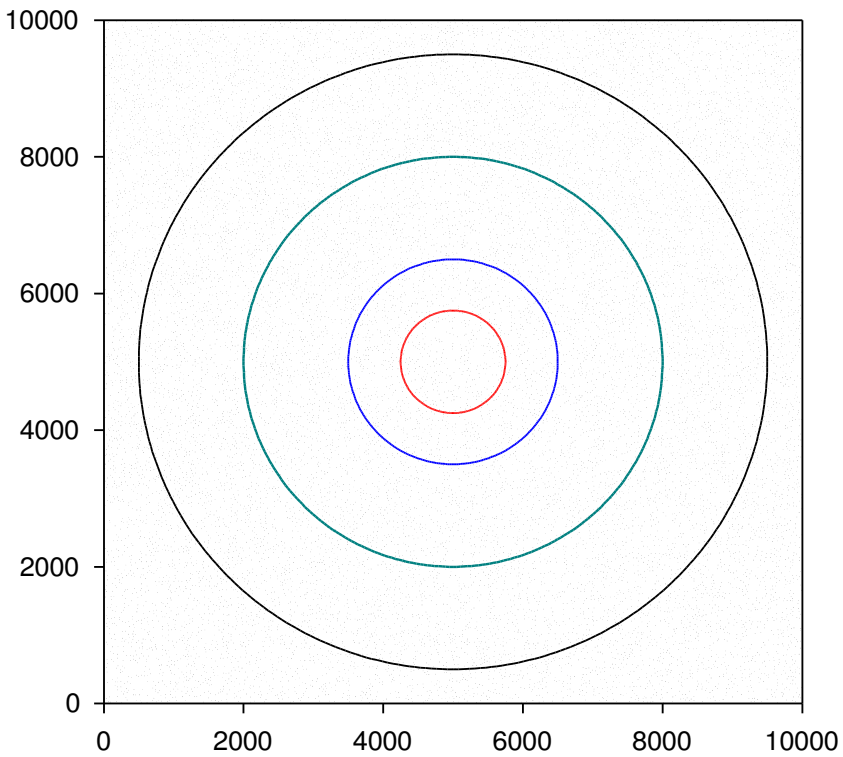
$p > p_c$: an infinite cluster exists with increasing probability that a given vertex belongs to it

Bond percolation on the square lattice… p_c=0.5.

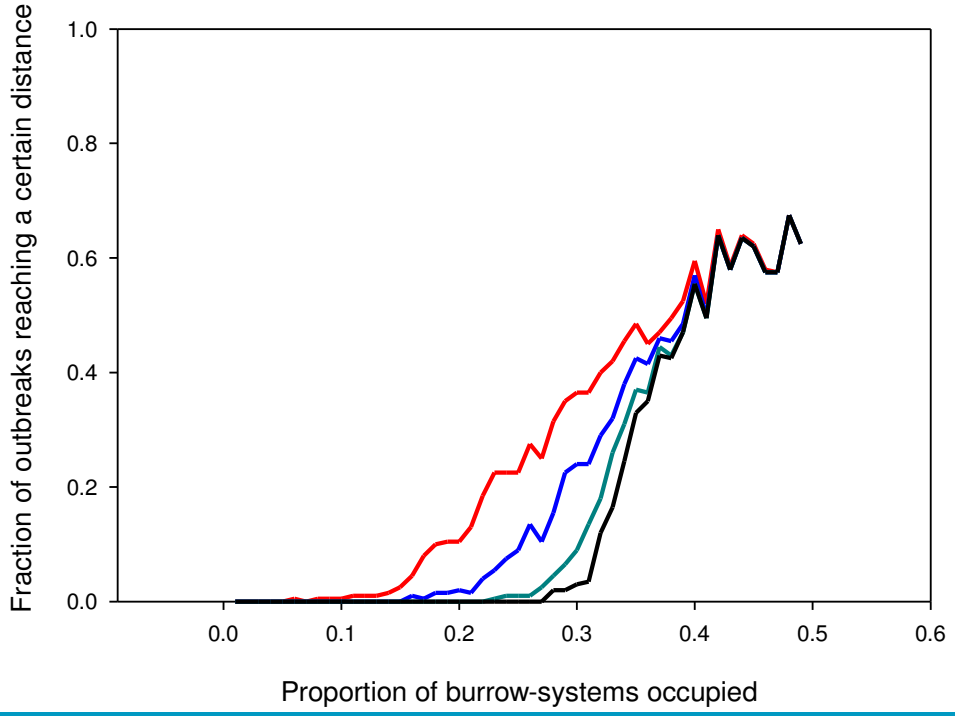
Epidemiological translation



Results of network model…

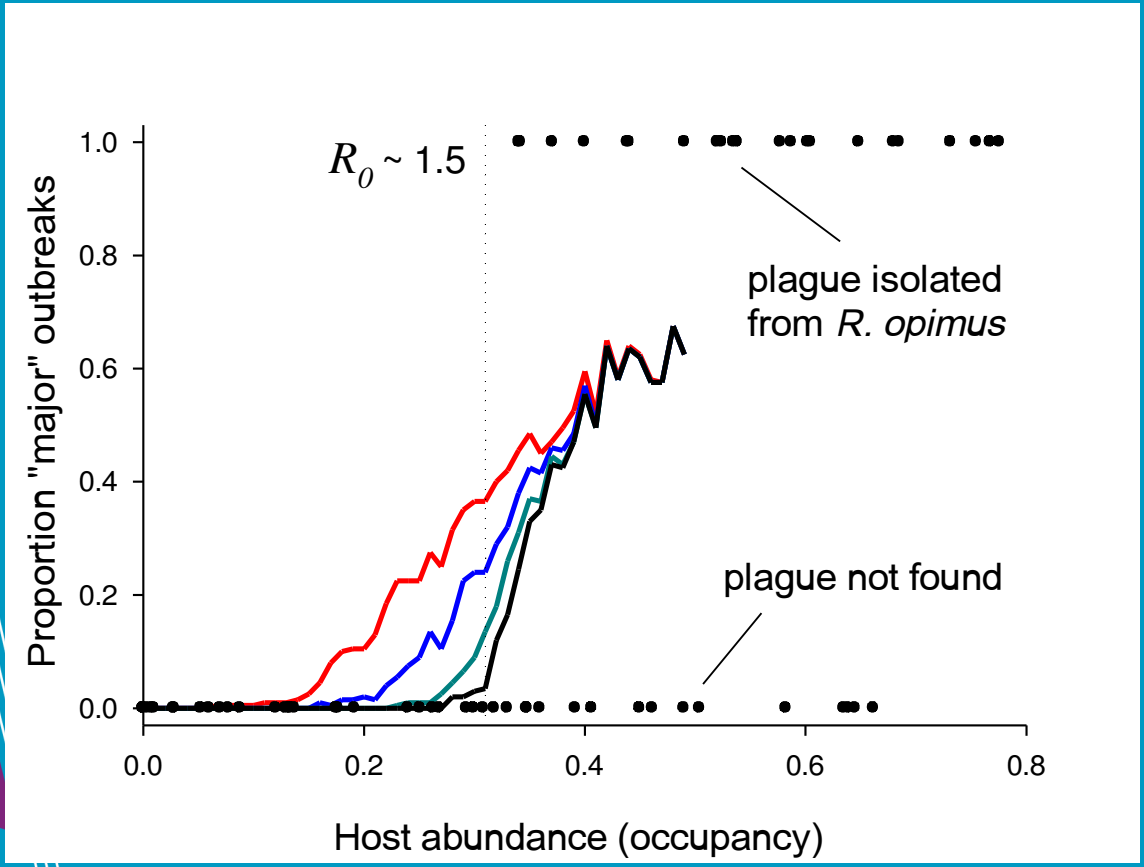


750m
1.5km
3km
4.5km



- Density of burrows from satellite images
- Start process in center
- Plot fraction of simulations where process escapes predefined ring as function of occupancy (major outbreaks)

Good agreement with plague epizootics



Remark: $R_0 > 1$ is necessary for spread, but not sufficient (depends on topology of the network; local depletion of suseptibles)

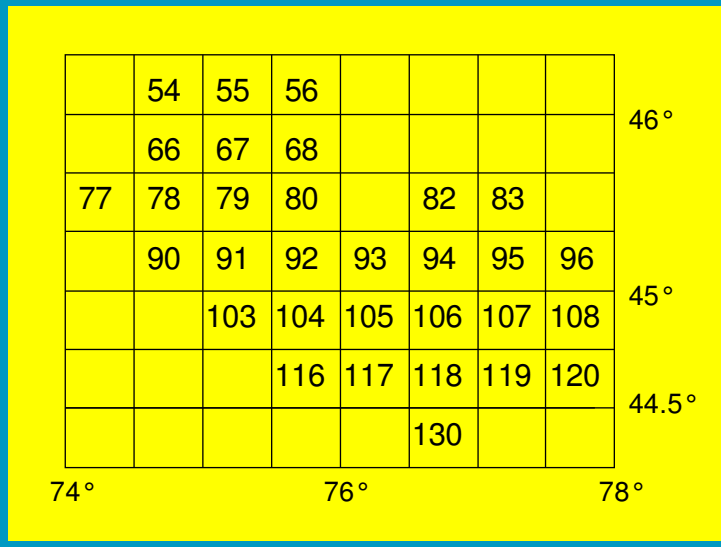
Mathematical challenge: Is there an R_0-like quantity for networks?

Necessary & sufficient + biological interpretation

Davis, Trapman, Leirs, Begon & Heesterbeek
Nature, 454, 634-637 (2008)

Combining many with very many

- Persistence in very large metapopulations
- Example: plague in Kazakhstan
  - Many large areas (patches) with different densities of (very many) burrows
  - ‘Understand’ when outbreaks happen in patch
  - ‘Understand’ persistence in metapopulation of patches
  - Investigate persistence at very large spatial scale




FOKKE & SUKKE
know what science is about
...very impressive, colleague...
but does it also work in theory?
F