Modeling Infectious Diseases from a Real World Perspective

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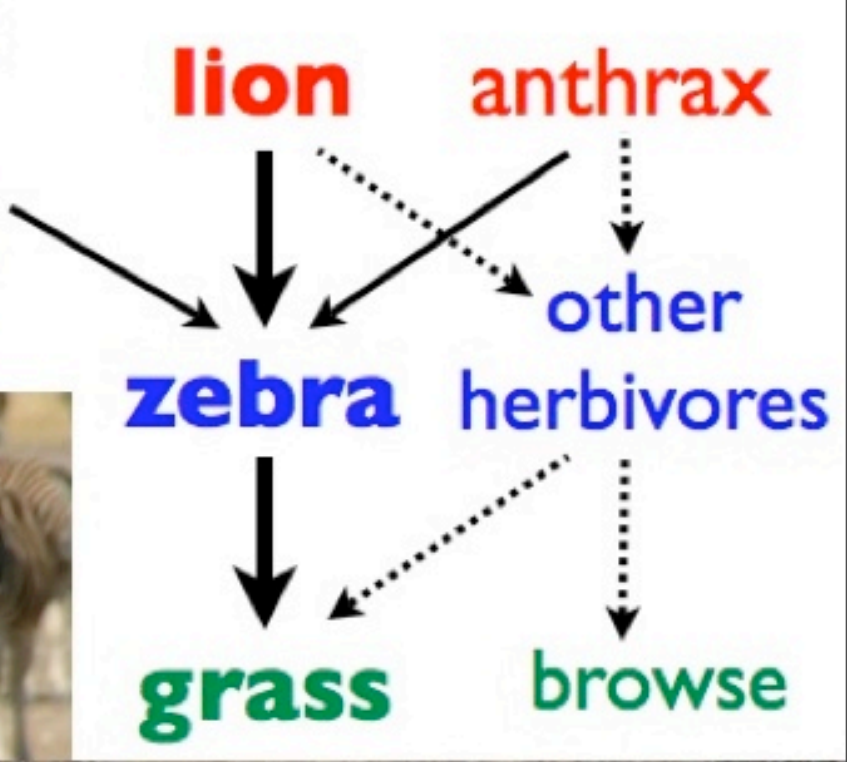
What is disease?

- **Disease** is an abnormal condition that impairs bodily functions
- **Infectious Disease** is transmitted from one individual to another (airborne, waterborne, sexually transmitted, contact transmission)
- **Vectored Disease** requires an agent to be involved in the transfer
- **Zoonotic Disease** has a non human source
- **Pathogens cause Disease**
  microparasites: virus, bacteria, protozoans, fungi
  macroparasites: cestodes, nematodes, ticks, fleas

Disease is an ecological process

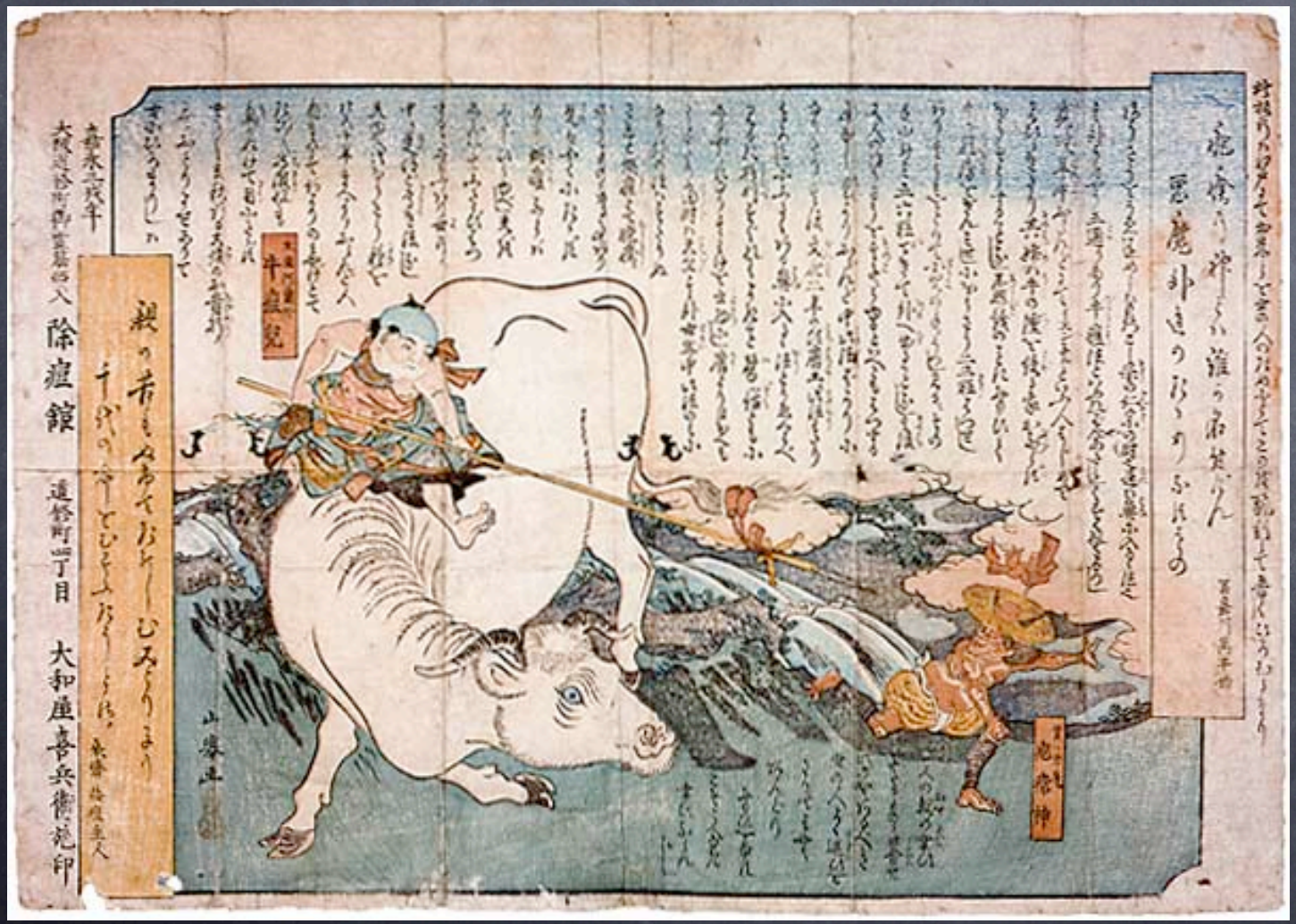
Disease mediation in grass-zebra-lion tri-trophic chain



Basic Elements

- **define species:** single pop, vectored system, ecological system
- **disease categories:** infected vs infectious, latent vs active, normal vs superspreader
- **demographic categories:** gender, age, other
- **interventions:** vaccination, quarantine, drug regimens, circumcision,
- **time:** fast diseases (e.g. pneumonia, influenza) vs. slow diseases (e.g. TB, HIV, leprosy).

Emerging Infectious Diseases:
What?, Where? How? and Why?



Cover: Vol 6(6), 2000
Emerging Infectious Disease (CDC Journal)

Japanese color woodcut print advertising the effectiveness of cowpox vaccine (circa 1850 A.D.)

WHAT? (Definition from MedicineNet.com)

Emerging infectious disease: An infectious disease that has newly appeared in a population or that has been known for some time but is rapidly increasing in incidence or geographic range.

Examples of emerging infectious diseases include:

* Ebola virus (first outbreaks in 1976)
* HIV/AIDS (virus first isolated in 1983)
* Hepatitis C (first identified in 1989)
* Influenza A(H5N1) (bird 'flu first isolated from humans in 1997)
* Legionella pneumophila (first outbreak in 1976)
* E. coli O157:H7 (first detected in 1982)
* Borrelia burgdorferi (first detected case of Lyme disease in 1982)
* Mad Cow disease (variant Creutzfeldt-Jakob: first described 1996)

More WHAT!

CDC National Center for Infectious Disease information list for emerging and re-emerging infectious diseases

drug-resistant infections, bovine spongiform encephalopathy (Mad cow disease) and variant Creutzfeldt-Jakob disease (vCJD), campylobacteriosis, Chagas disease, cholera, cryptococcosis, cryptosporidiosis (Crypto), cyclosporiasis, cysticercosis, dengue fever, diphtheria, Ebola hemorrhagic fever, Escherichia coli infection, group B streptococcal infection, hantavirus pulmonary syndrome, hepatitis C, hendra virus infection, histoplasmosis, HIV/AIDS, influenza, Lassa fever, legionnaires' disease (legionellosis) and Pontiac fever, leptospirosis, listeriosis, Lyme disease, malaria, Marburg hemorrhagic fever, measles, meningitis, monkeypox, MRSA (Methicillin Resistant Staphylococcus aureus), Nipah virus infection, norovirus (formerly Norwalk virus) infection, pertussis, plague, polio (poliomyelitis), rabies, Rift Valley fever, rotavirus infection, salmonellosis, SARS (Severe acute respiratory syndrome), shigellosis, smallpox, sleeping Sickness (Trypanosomiasis), tuberculosis, tularemia, valley fever (coccidioidomycosis), VISA/VRSA - Vancomycin-Intermediate/Resistant Staphylococcus aureus, West Nile virus infection, yellow fever

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=: first recognized ’93, rodent excretions, rare but deadly

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=: identified ’72, stomach flu on cruise ships, schools, hotels

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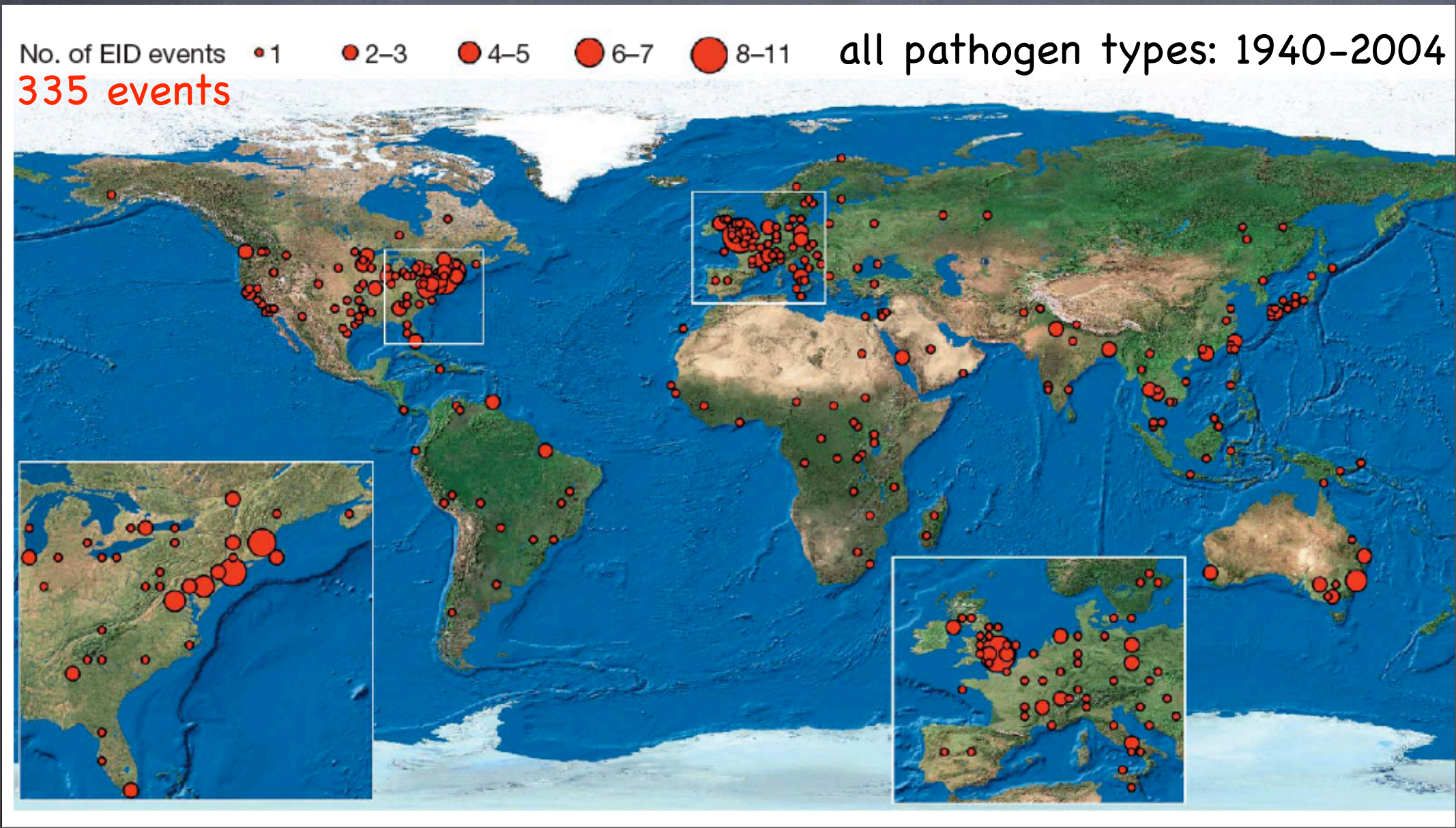
=: mosquito vector, 1st case N.Am. ’99 now ≈ 15000 cases 500 deaths

WHERE?

Global trends in emerging infectious diseases

Jones et al. Nature 451, 990-993(21 February 2008)



WHAT? by decade

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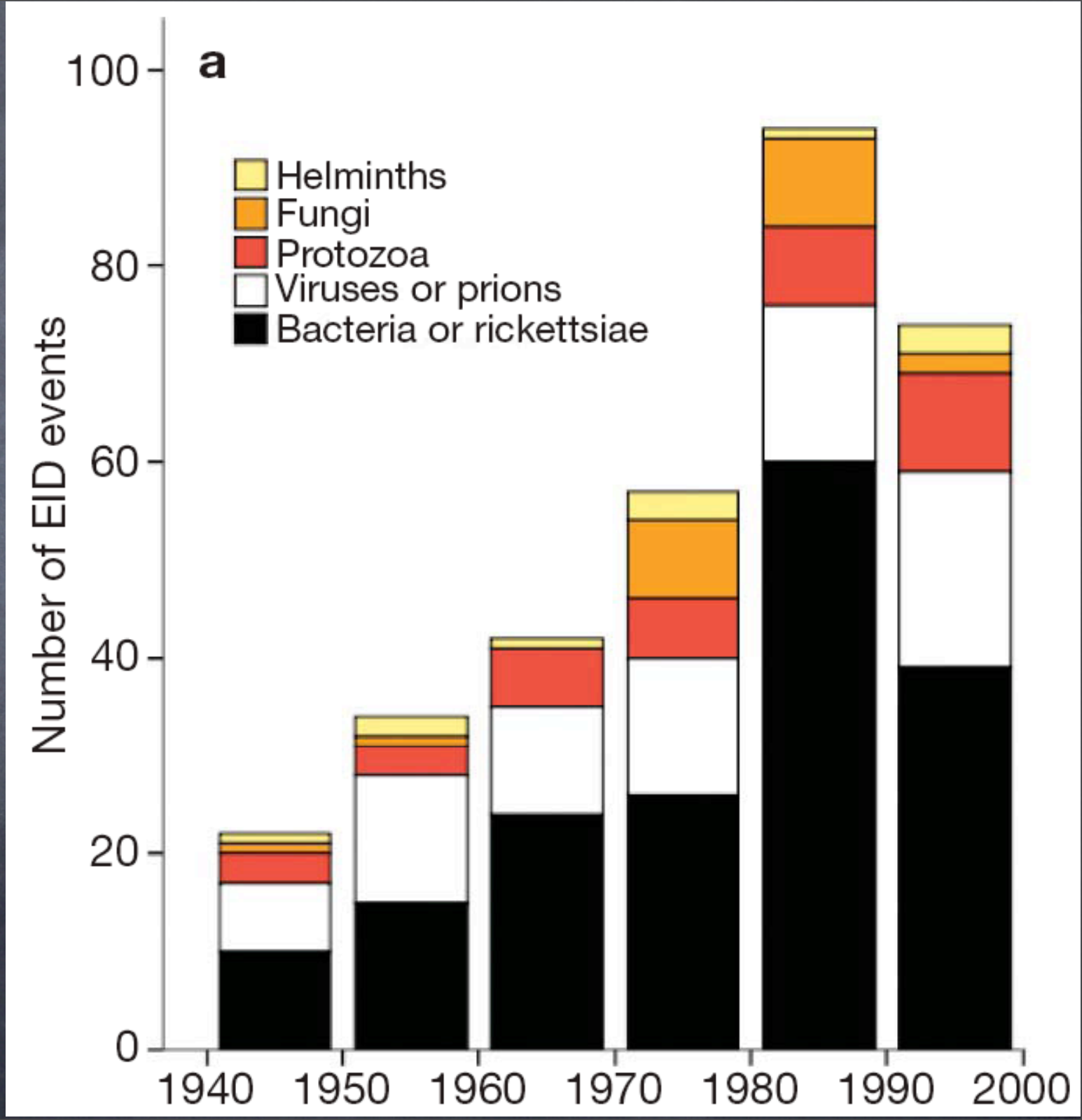

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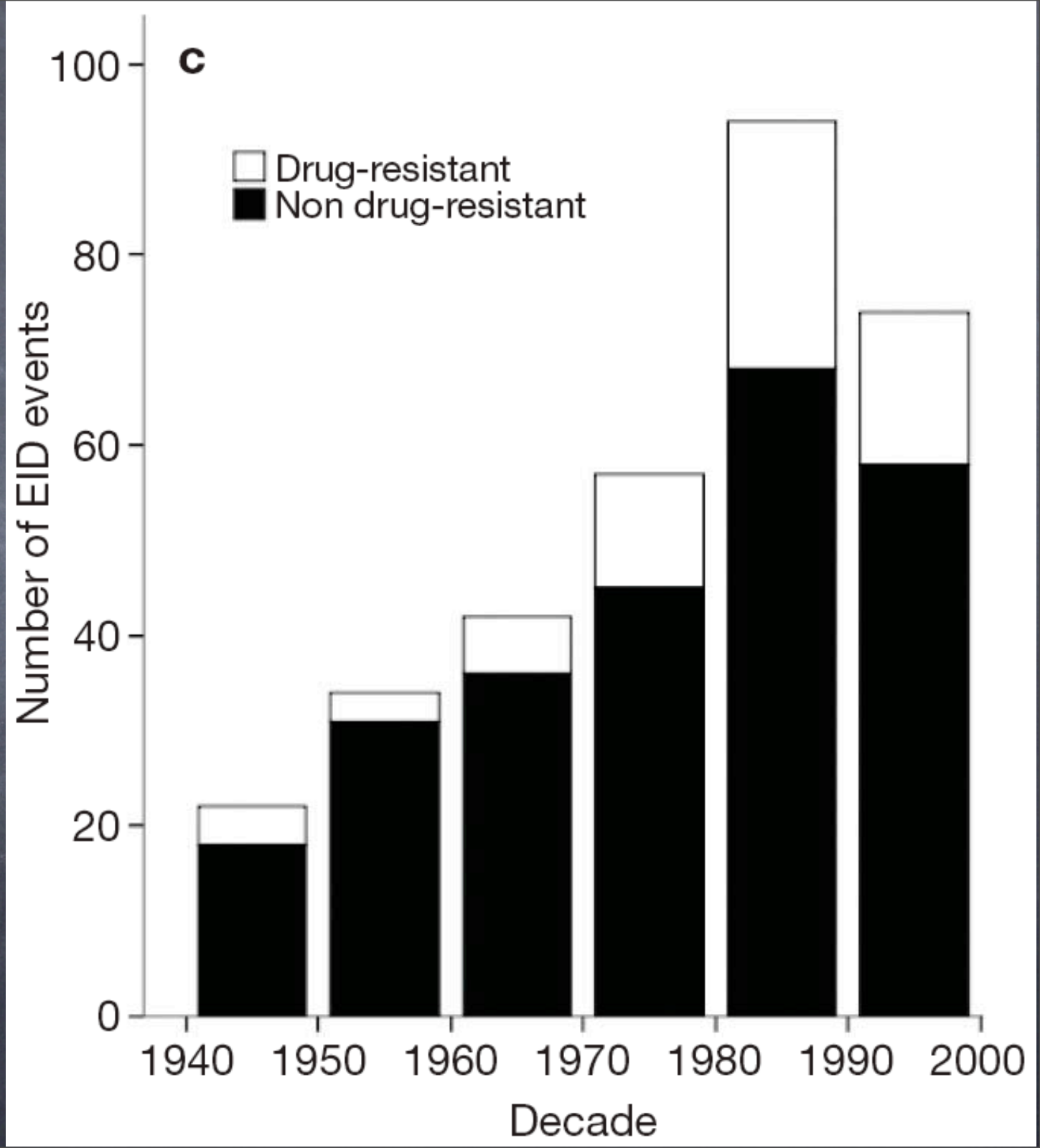

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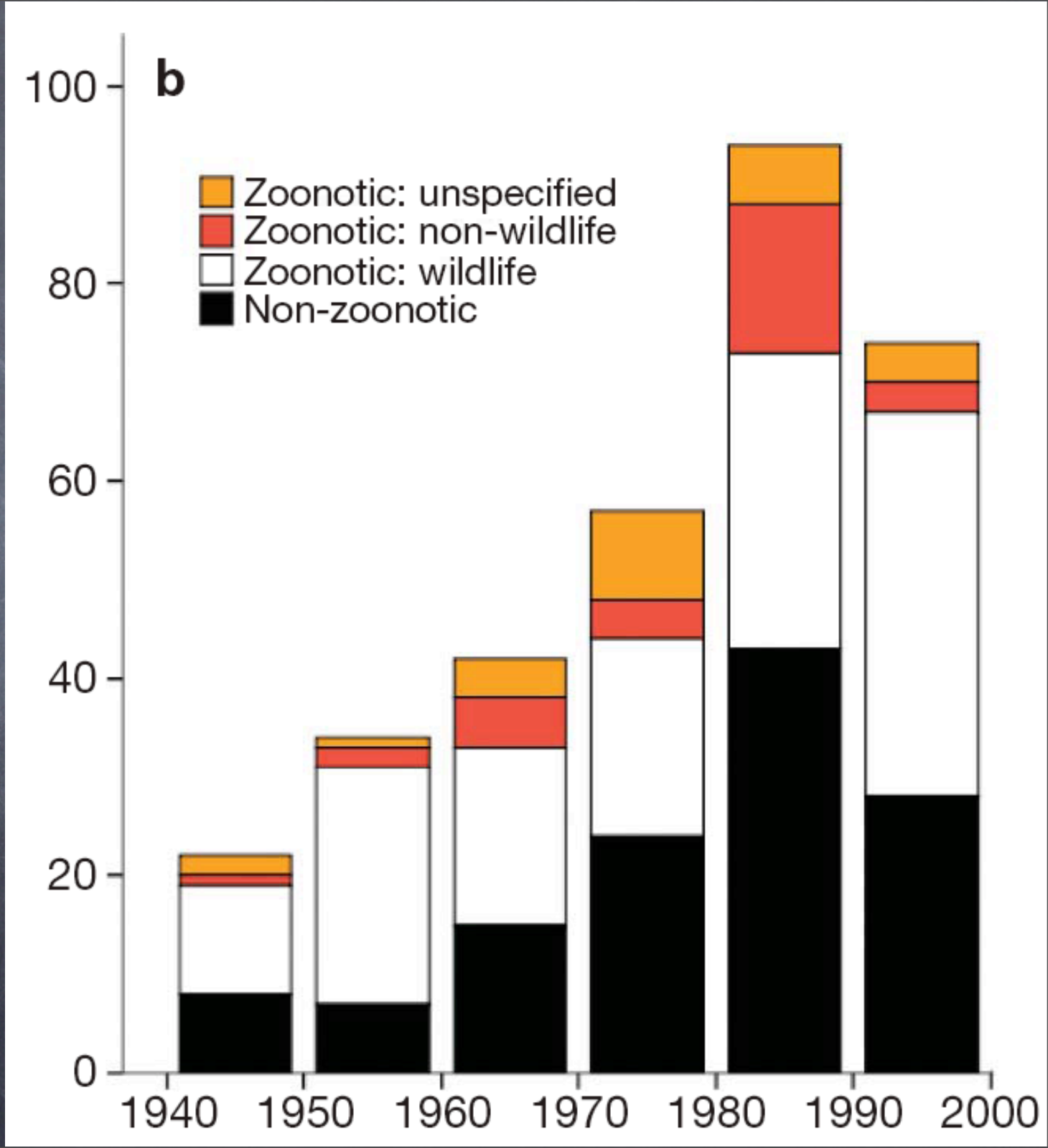


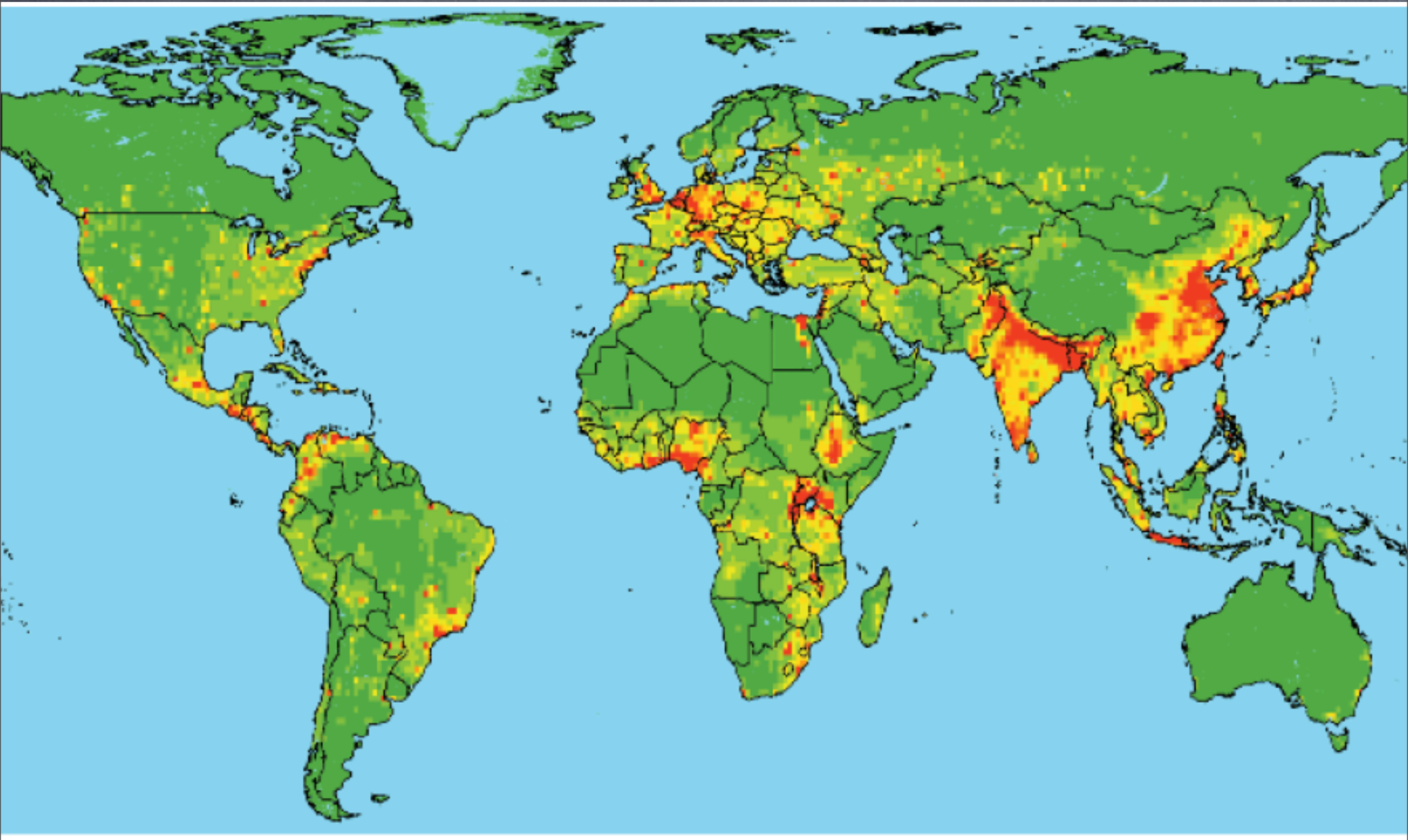
HOW?

- Contacts with wildlife
- Vulnerability to infection (elderly, HIV+)
- Strains evolving to resist treatments
- Contact networks particularly global travel
- new diagnostic tools

SARS Outbreak

Current risk of an EID zoonotic pathogen from wildlife

Jones et al. Nature 451, 990-993(21 February 2008)



Disease Categories and Transmission in Kermack-Mckendrick Models

W. O. Kermack and A. G. McKendrick: A Contribution to the Mathematical Theory of Epidemics, I, II (endemicity), and III (endemicity cont.)
I. *Proc. R. Soc. Lond. A,* 1927, **115**, 700-721 (doi: 10.1098/rspa.1927.0118)
II. *Proc. R. Soc. Lond. A,* 1932, **138**, 55-83 (doi: 10.1098/rspa.1932.0171)
III. *Proc. R. Soc. Lond. A,* 1933, **141**, 94-122 (doi: 10.1098/rspa.1933.0106)

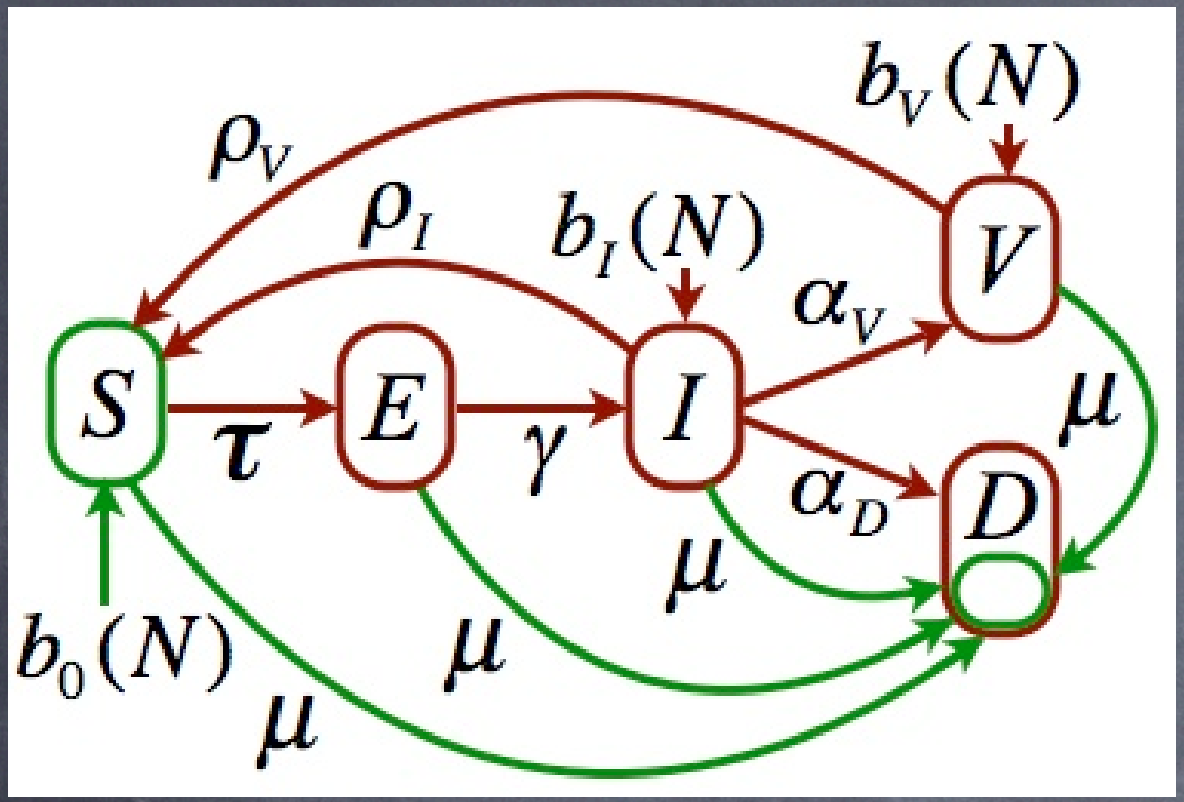
Hethcote, H. W. 2000. The mathematics of infectious disease.
SIAM Rev. 42, 599–653. (doi:10.1137/S0036144500371907)

Disease Categories and Transmission
SIR Models

S: susceptible, I: infected & infectious
R: "recovered & immune" (V) or "removed" (D)
N: Does N=S+I+V change with time?
Units: numbers vs. densities. vs proportions.
Transmission: mass action (densities of SxI)
frequency dependent (proportion of SxI)

Be Warned!: transmission = bSI holds for both frequency or mass action if N is constant or for variable N(t) if units are density (mass action) or proportions (frequency)

Epidemics with "lumped" demography



S: susceptible
E: exposed (infected)
I: infectious
V: recovered immune
D: dead
N: S+E+I+V
b_0 b_V: birth rate

τ	transmission rate
γ	refraction rate (latent period)
ρ_I ρ_V	reversion rate
μ	natural mortility
α_D α_V	disease induce mortality

Outline of remaining material

Preliminaries:

- Discrete versus continuous models in biology
- Discrete versus continuous models in epidemiology
- Discrete multi-compartment formulations based on probabilities

Case studies:

- Bovine TB and Vaccination
- Group structure and containment of SARS
- TB and drug therapies, TB-HIV dynamics
- General theory of heterogeneous transmission

Goals:

- Provide a flavor of how to incorporate complexity
- Illustrate how output used to understand complexities
- Lead you into some literature for you to explore further!

Continuous versus discrete models in biology

Simplest model: constant pop $N = S + I$; $S \to I$, transmission $\beta \frac{S}{N} I$:

$$\frac{dI}{dt} = \beta I \left(\frac{S}{N} \right) = \beta I \left(1 - \frac{I}{N} \right), \qquad I(0) = I_0.$$

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Logistic model with solution:

$$I(t) = \frac{I_0 N}{I_0 + (N - I_0) e^{-\beta t}}$$

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Discretized system ODE:

$$I(t + \Delta t) \approx I(t) + \Delta t \beta I(t) \left(1 - \frac{I(t)}{N} \right).$$

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Discretized Solution:

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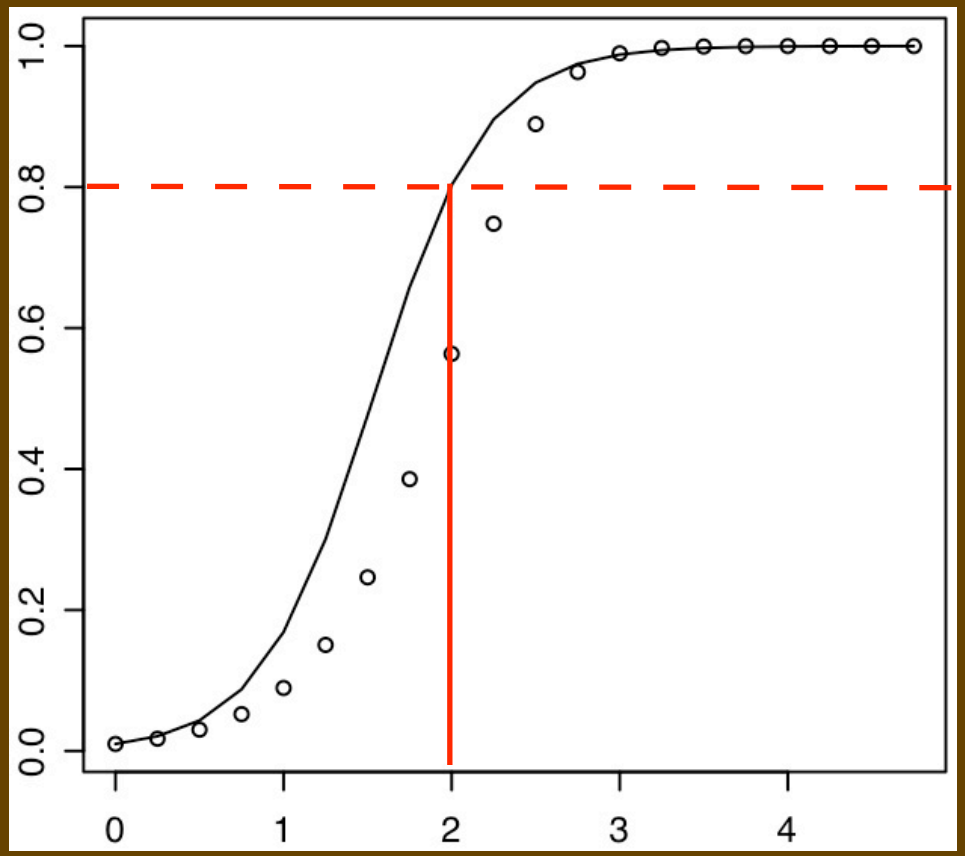
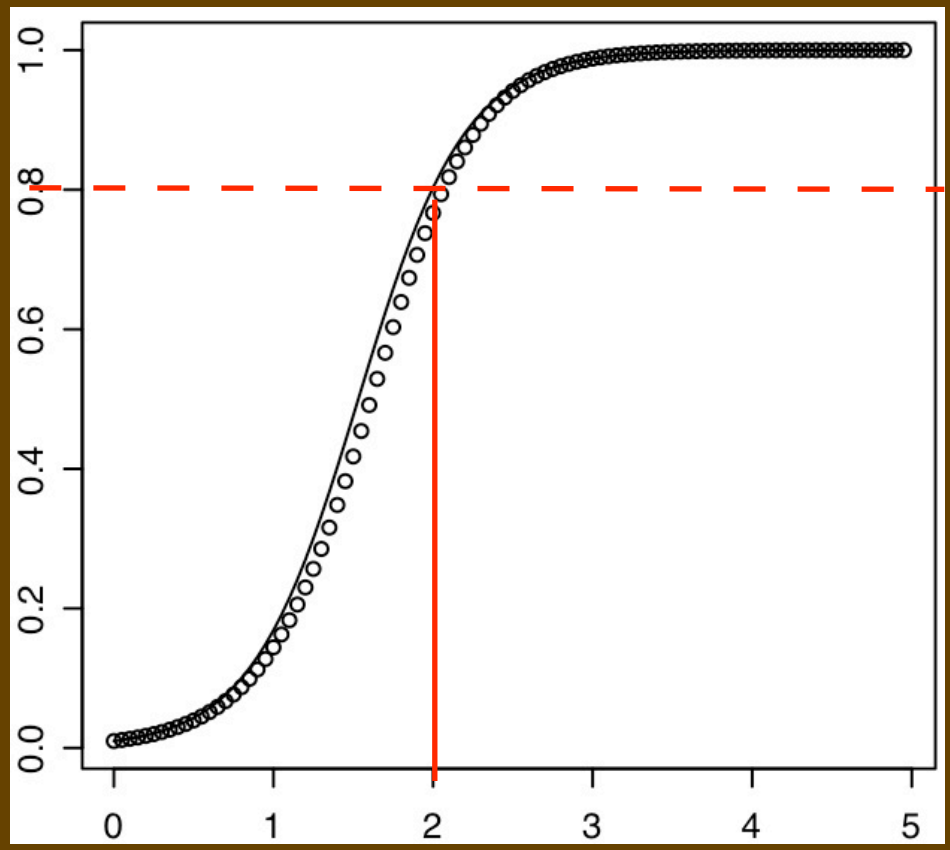
Which is the better discretization scheme?

Continuous versus discrete models in biology



Time (Δt=0.25)



Time (Δt=0.05)

Solid line: Iteration using solution
Circles: Iteration using discretized equations

Continuous Models with Demography

$$\frac{dS}{dt} = f^{\text{recruitment}}(S,I,R) - f^{\text{transmission}}(S,I,R)S - \mu S$$

$$\frac{dI}{dt} = f^{\text{transmission}}(S,I,R)S - (\alpha + \mu)I$$

$$\frac{dR}{dt} = \alpha I - \mu R$$

$f^{\text{recruitment}}$: recruits and/or births

μ: natural mortality rate

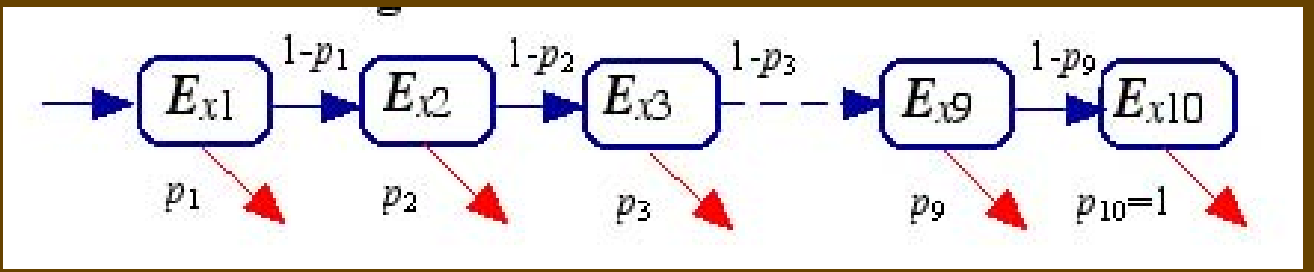
α: infectious → removed/recovered

Elaborations:

1. exposed class E
2. constant rate "exponential" transfers: → Weibull distribution

OR

→ "box car" staging: gamma distribution



Some basics on discrete epi models

Proportion that die or make transitions: e.g. mortality rate

$$p_\mu = \frac{N(k) - N(k+1)}{N(k)} = \frac{N(k)(1-e^{-\mu})}{N(k)} = 1 - e^{-\mu}$$

Continuous model SEI:

$$\begin{aligned}
\frac{dS}{dt} &= \lambda - \mu S - \tau(I,N)S \qquad S(0) = S_0 \\
\frac{dE}{dt} &= \tau(I,N)S - (\delta+\mu)E \quad E(0) = E_0 \\
\frac{dI}{dt} &= \delta E - (\alpha+\mu)I \qquad I(0) = I_0.
\end{aligned}$$

Equivalent discrete SEI: note transmission depends on *k*:

$$\begin{pmatrix} S(k+1) \\ E(k+1) \\ I(k+1) \end{pmatrix}' = \begin{pmatrix} (1-p_\mu)(1-p_{\tau_k}) & 0 & 0 \\ (1-p_\mu)p_{\tau_k} & (1-p_\mu)(1-p_\delta) & 0 \\ 0 & (1-p_\mu)p_\delta & (1-p_\mu)(1-p_\alpha) \end{pmatrix} \times \begin{pmatrix} S(k) \\ E(k) \\ I(k) \end{pmatrix} + \begin{pmatrix} (1-p_\mu)\lambda \\ 0 \\ 0 \end{pmatrix},$$

Ex: Use analytical/ numerical methods to

Characterize the distribution of $R(t)$ in the SE_nI_mR model with $S(0) = S_0,\ E_i(0) = 0,\ i = 1, ..., n,\ I_j(0) = 0,\ j = 1, ..., m,\ R(0) = 0$ in terms of β, δ, μ, m and n for the continuous and discrete formulations and compare (start with $\mu = \delta = 1$ and $m = 1$ and investigate in the discrete model $\delta < 1$)

Continuous

$$\begin{aligned}
\frac{dS}{dt} &= -\beta \left(\sum_{j=1}^{m} I_j \right) S \\
\frac{dE_1}{dt} &= \beta \left(\sum_{j=1}^{m} I_j \right) S - \delta E_1 \\
\frac{dE_i}{dt} &= \delta(E_{i-1} - E_i), \quad i = 2, \ldots, n \\
\frac{dI_1}{dt} &= \delta(E_n - I_1) \\
\frac{dI_j}{dt} &= \delta(I_{j-1} - I_j), \quad j = 2, \ldots, m \\
\frac{dR}{dt} &= \delta I_m - \mu R
\end{aligned}$$

Discrete

$$\begin{aligned}
S(t+1) &= S(t) - \beta \left(\sum_{j=1}^{m} I_j(t) \right) S(t) \\
E_1(t+1) &= \beta \left(\sum_{j=1}^{m} I_j \right) S + (1-\delta) E_1 \\
E_i(t+1) &= \delta E_{i-1}(t) + (1-\delta) E_i(t) \\
&\qquad i = 2, \ldots, n \\
I_1(t+1) &= \delta E_n(t) + (1-\delta) I_1(t) \\
I_j(t+1) &= \delta I_{j-1}(t) + (1-\delta) I_j(t) \\
&\qquad j = 2, \ldots, m \\
R(t+1) &= \delta I_m(t) - \mu R(t)
\end{aligned}$$

First Case Study: Bovine TB in African Buffalo

Cross & Getz (2006) *Ecological Modelling 196*: 494-504.

Important elements:

- Includes demography
- Herd structure: focus on one herd embedded in background prevalence assuming balanced movement into and out of herd
- SVEID structure (Susc, Vaccinated, Exposed, Infected, Dead)

BTB model with demography & ecology

Bovine TB model: X (susc), Y (infected), Z (infectious) & V (vac.), I (migr.)

$$X_{i+r,j}(t+1) = s_{i,j}(N(t))\left((1-\varepsilon_{i,j})\left(\left(1-\frac{\beta\sum_{i=1}^{18}\sum_{j=1}^{2}Z_{i,j}(t)}{N(t)^{\theta}}\right)(1-\psi_{i,j}(t))X_{i,j}(t)+\delta V_{i,j}(t)\right)+p_x I_{i,j}(t)\right)$$

$$Y_{i+r,j}(t+1) = s_{i,j}(N(t))\left((1-\varepsilon_{i,j})\left(\left(\frac{\beta\sum_{i=1}^{18}\sum_{j=1}^{2}Z_{i,j}(t)}{N(t)^{\theta}}\right)(1-\psi_{i,j}(t))X_{i,j}(t)+(1-\gamma)Y_{i,j}(t)\right)+p_y I_{i,j}(t)\right)$$

$$Z_{i+r,j}(t+1) = s^{z}_{i,j}(N(t))\left((1-\varepsilon_{i,j})(\gamma Y_{i,j}(t)+Z_{i,j}(t))+p_z I_{i,j}(t)\right)$$

$$V_{i+r,j}(t+1) = s_{i,j}(N(t))\left((1-\varepsilon_{i,j})(1-\delta)(V_{i,j}(t)+\psi_{i,j}(t)X_{i,j}(t))+p_v I_{i,j}(t)\right)$$

Density-dependent

$$s_{i,j}(N(t)) = \frac{s_0}{1+\left(\frac{N(t)}{k}\right)^{\phi}}, \quad i=1, \quad j=1,2$$

Model Parameters

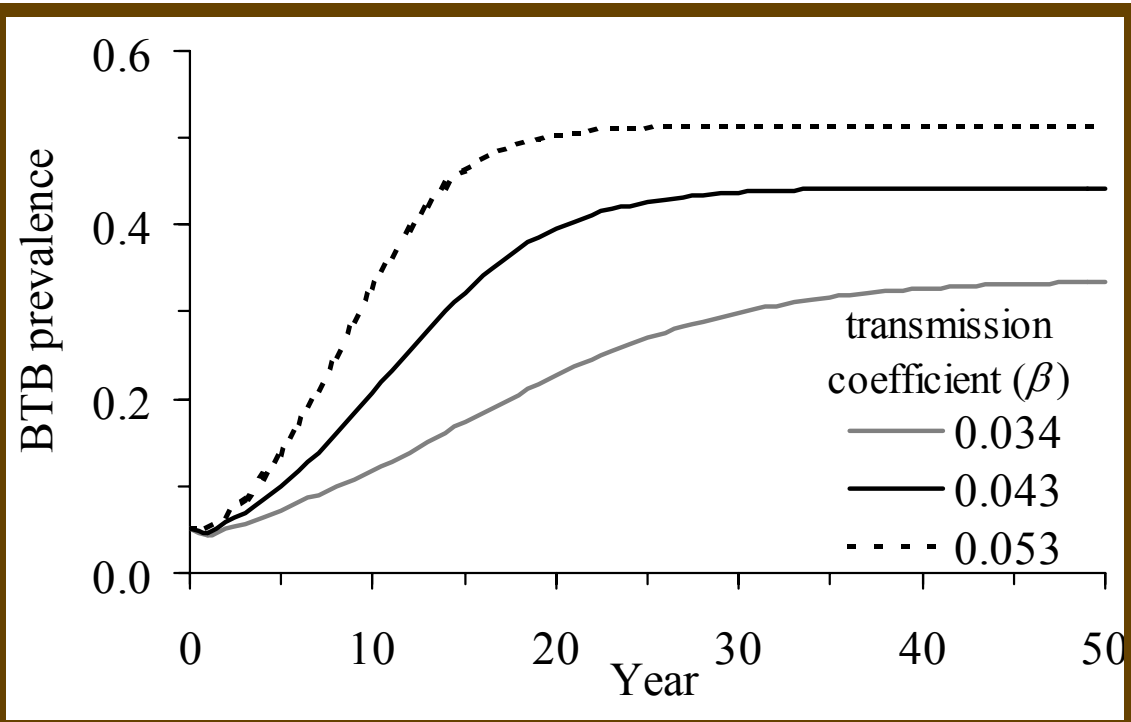
Table 1. Parameter estimates used in the buffalo vaccination model.

Parameter	Symbol	Minimum	Baseline	Maximum	Source
Annual buffalo survival					
Maximum calf survival	$s_{1,\ 1\text{-}2}$	0.95	1.00	1.00	1
Young males	$s_{2\text{-}8,1}$	0.74	0.84	0.90	1
Old males	$s_{9\text{-}18,1}$	0.20	0.59	0.86	1
Young females	$s_{2\text{-}8,2}$	0.83	0.95	0.99	1
Old females	$s_{9\text{-}18,2}$	0.35	0.86	0.98	1
Scaling parameter	κ	--	400	--	see text
Abruptness parameter	ϕ	2	4	6	2
Annual buffalo reproduction					
Cows 3-4	r_3	--	0.51	--	3
Cows 4-5	r_4	--	0.64	--	3
Cows 5+	r_{5+}	--	0.68	--	3
Monthly dispersal					
Immature males	$\varepsilon_{1\text{-}6,1}$	0.01	0.02	0.04	1
Mature males	$\varepsilon_{7\text{-}9,1}$	0.24	0.09	0.03	1
Old males	$\varepsilon_{10+,1}$	0.45	0.26	0.13	1
Females	$\varepsilon_{1+,2}$	0.04	0.02	0.01	1

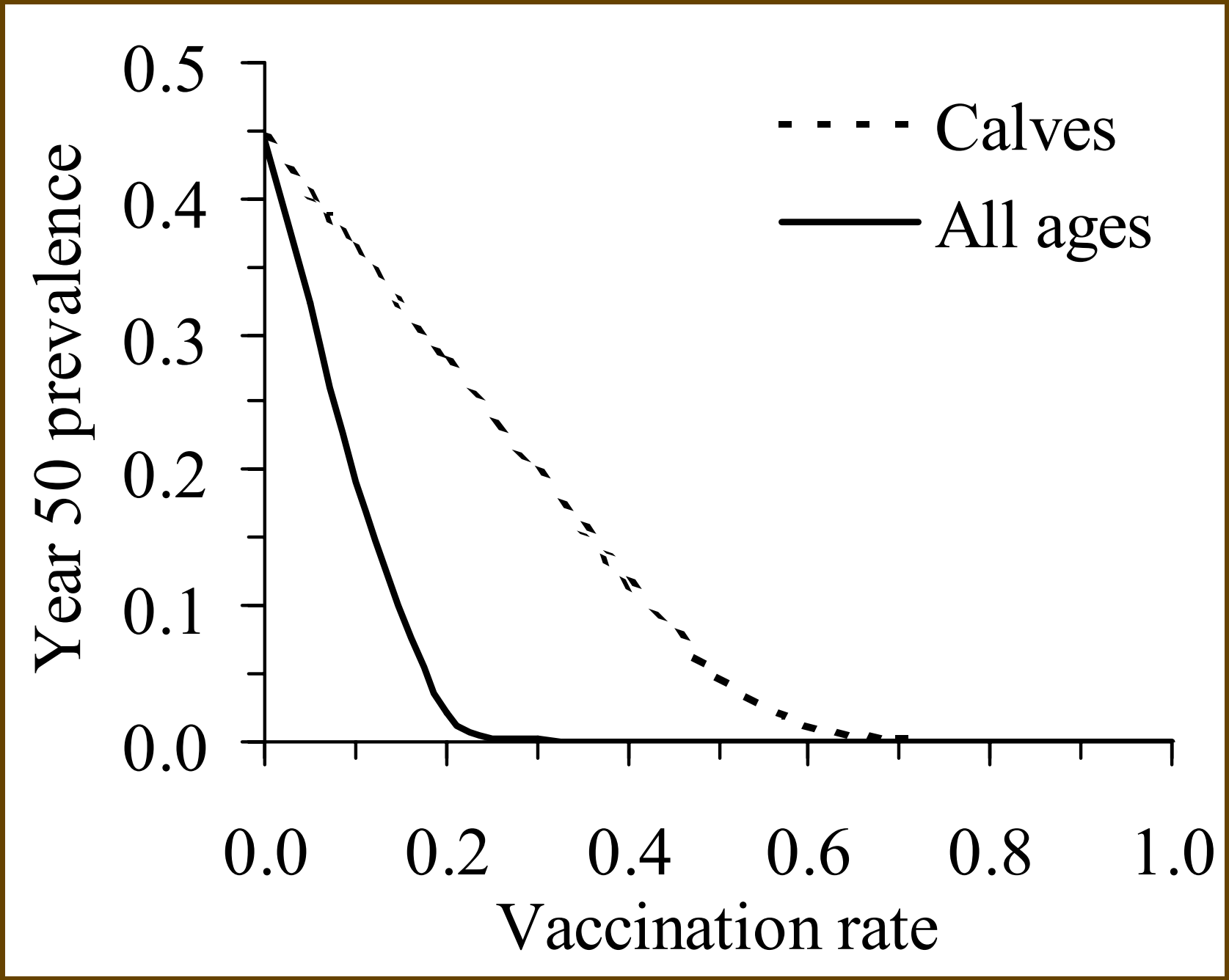
Model Parameters

Monthly disease parameters					
Transmission coefficient	β	0.034	0.043	0.053	1
Incubation rate	γ	0.056	0.21	1	4
Reduction in maximum juvenile surviva	α_0	0	0.0043	0.0084	5
Reduction in adult survival	α_1	0	0.0043	0.0084	5
Transmission exponent	θ	0	--	1	see text
Vaccination rate	ψ	0	--	1	see text
Vaccine failure rate	δ	0	--	0.056	6
Background prevalence	p_z	0	--	0.7	see text

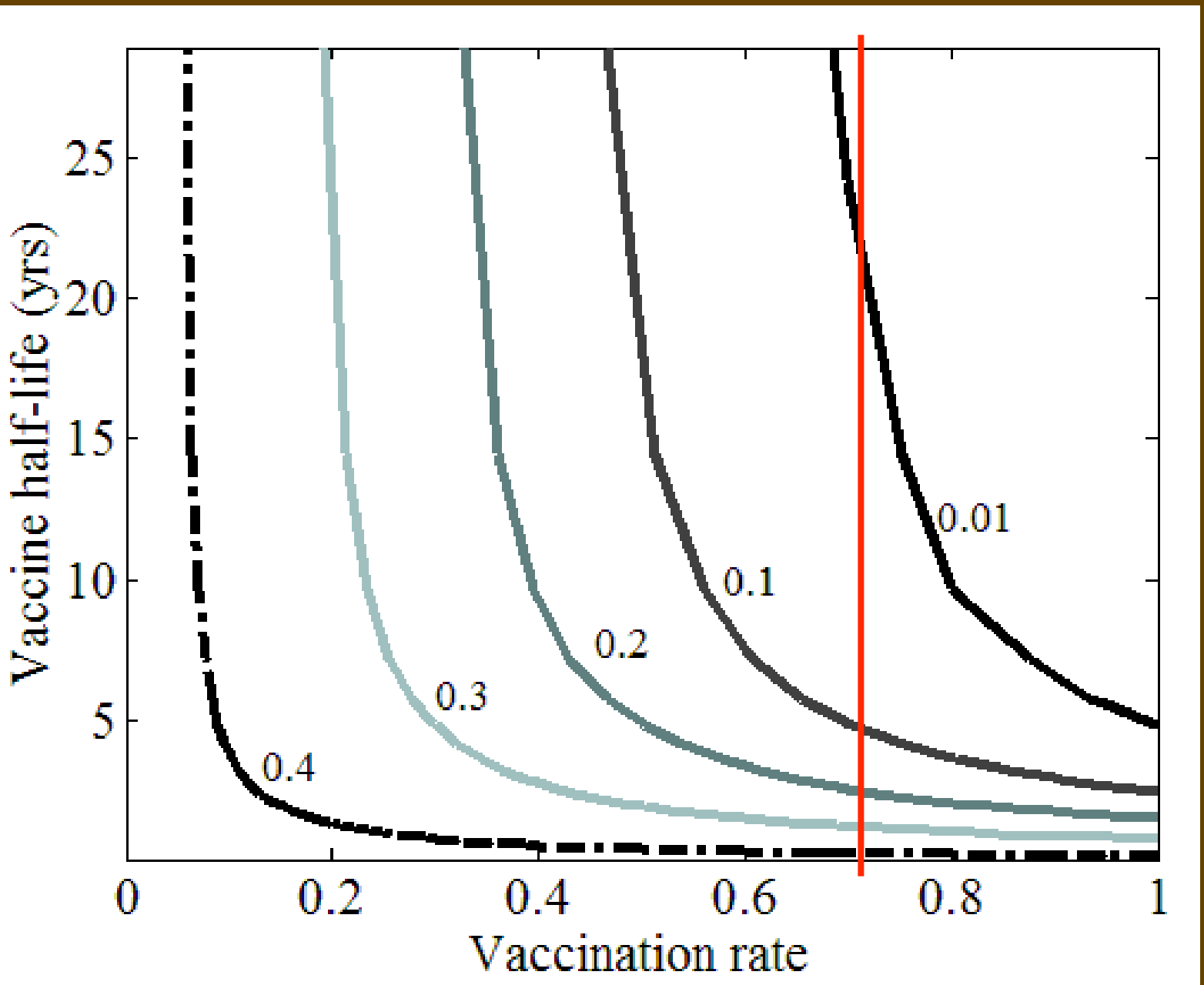
prevalence for low, baseline and high transmission coef. values



Efficacy of Vaccination



Prevalence isopleths after 50 years: calf only vaccination



0.75 vaccination rate of long-acting vaccine needed to reduce BTB below 1%

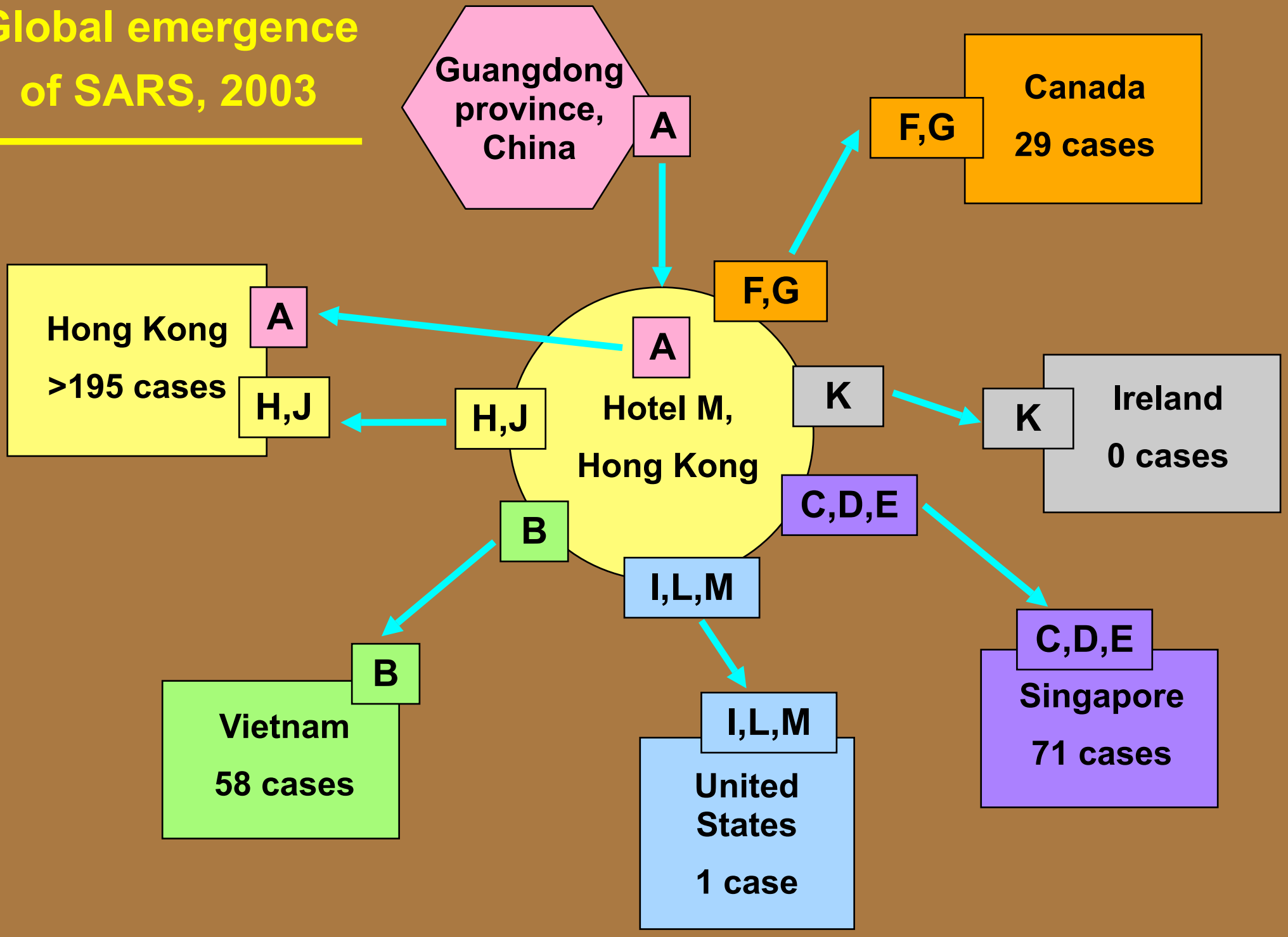
Second Case Study: SARS

Lloyd-Smith, Galvani, Getz (2003) *Proc. Royal Soc. B* **270**: 1979-1989.

Important elements:

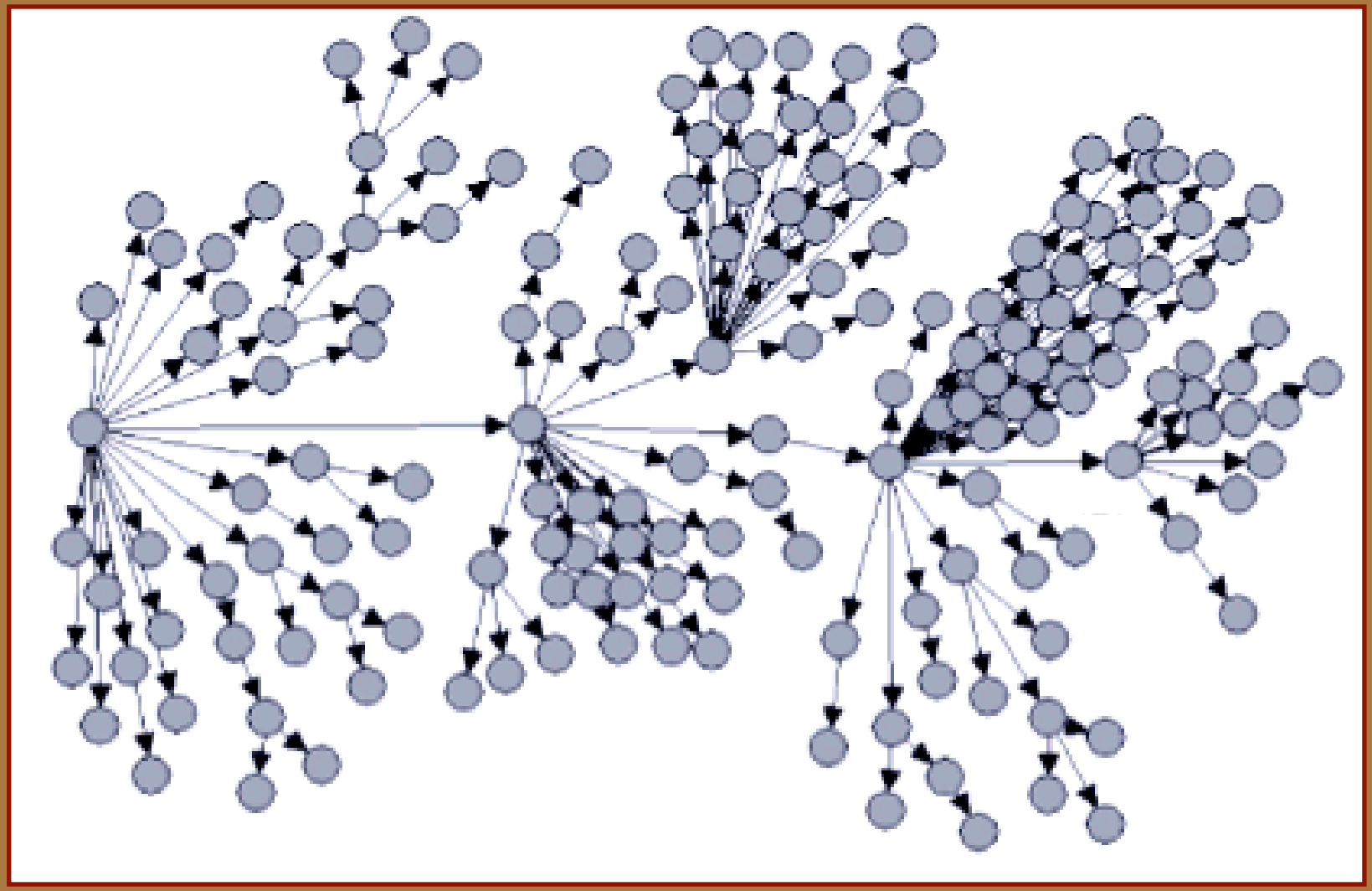
- No demography but group structure for disease classes
- Group structure relates to intervention and control strategies
- Time iteration is daily: relates to reporting and data structure

Global emergence of SARS, 2003



Adapted from Dr. J. Gerberding, Centers for Disease Control

SARS transmission chain, Singapore 2003

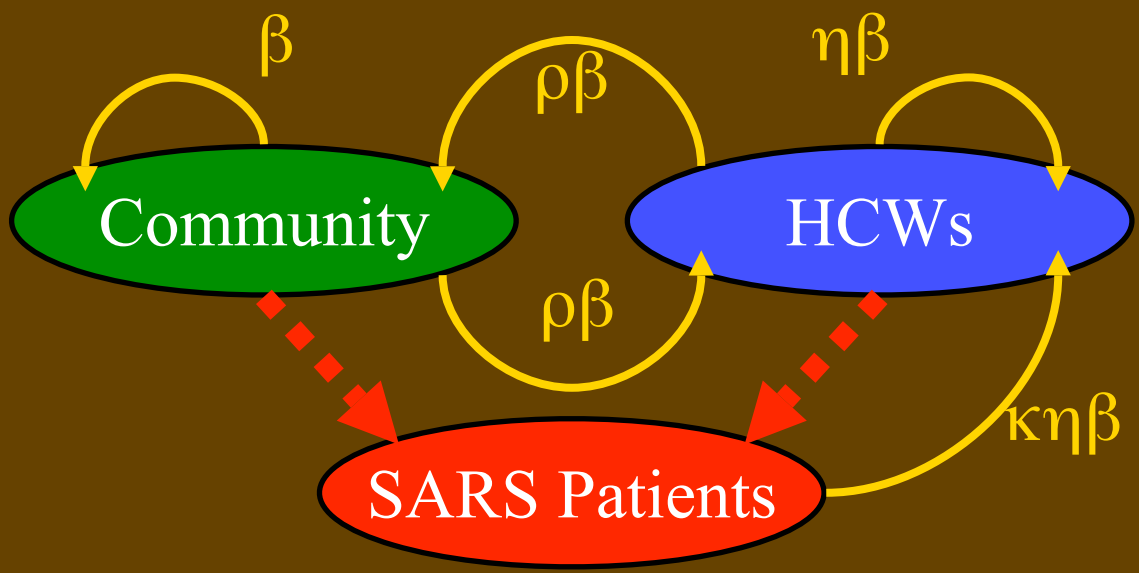


Morbidity & Mortality Weekly Report (2003)

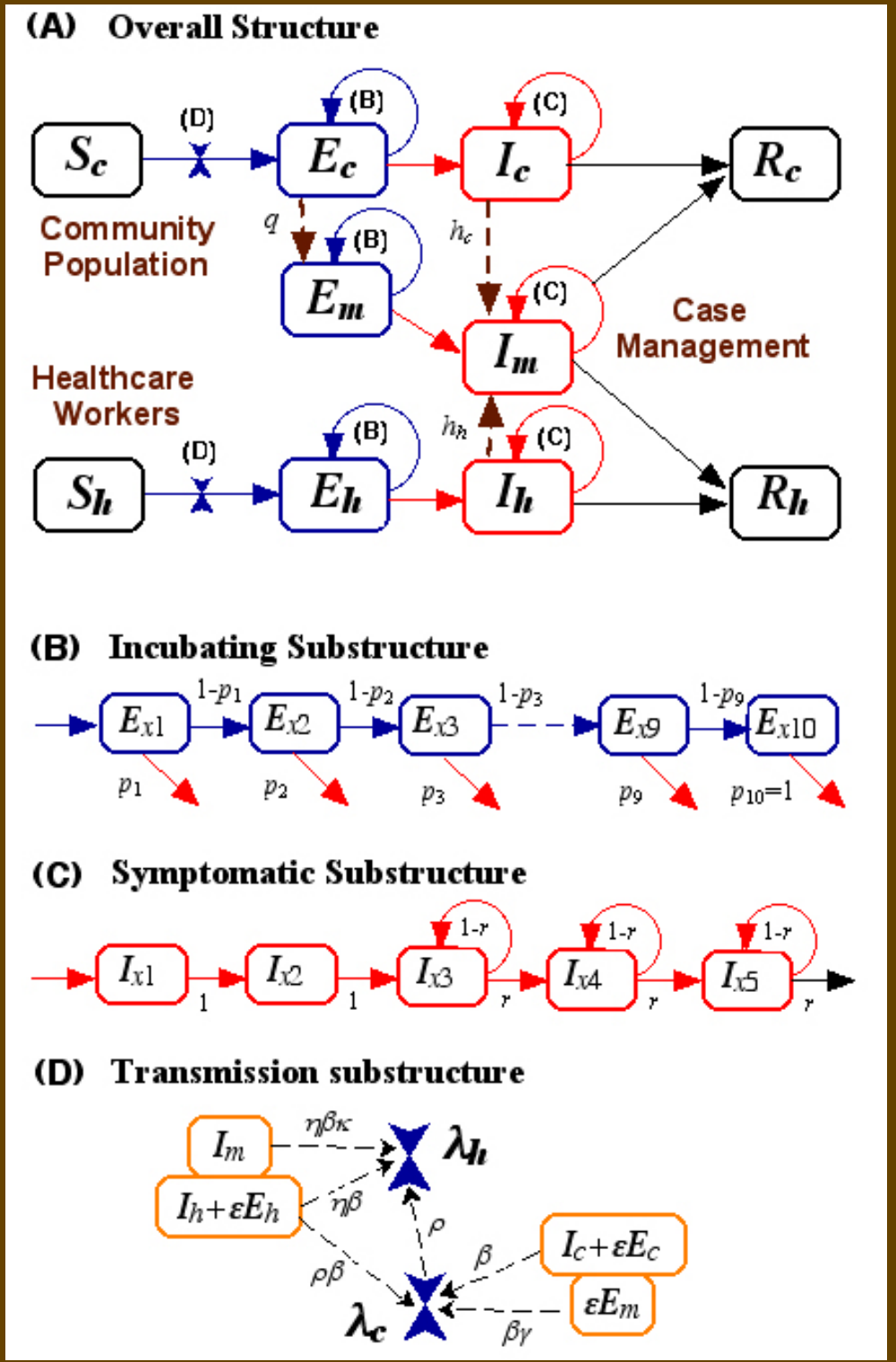
Group-level heterogeneity for SARS

Health care workers (HCWs) comprised 18-63% of cases in different locales

- Main control measures were hospitalization and quarantine.
- Strict infection control implemented in hospitals, and contacts with visitors were reduced.



Detailed structure of SARS: results from daily iterated stochastic simulations

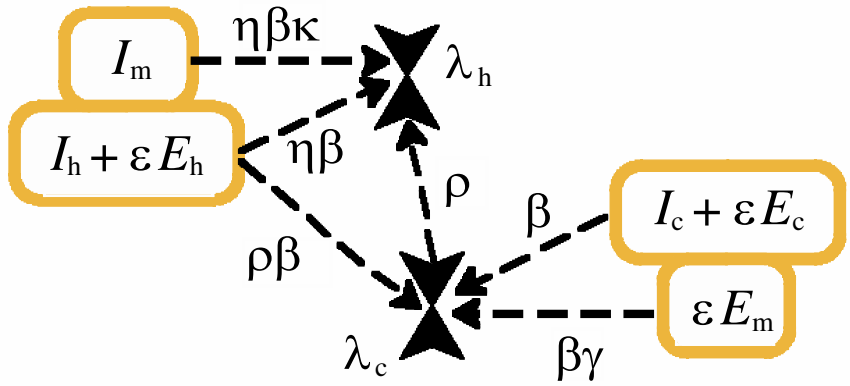


Equations: transmission hazard

h: health care workers; c: general community; *m*: managed patients

factors modifying transmission rate, owing to:

pre-symptomatic transmission	ε
hospital-wide contact precautions	η
reduced HCW–community mixing	ρ
case isolation	κ
quarantine	γ



$$\tau_c = \frac{\beta(I_c + \varepsilon E_c) + \rho\beta(I_h + \varepsilon E_h) + \gamma\beta\varepsilon E_m}{N_c}$$

and

$$\tau_h = \rho\tau_c + \frac{\eta\beta(I_h + \varepsilon E_h + \kappa I_m)}{N_h},$$

where E_i and I_i, $i = c, h$, represent sums over all sub-compartments in the incubating and symptomatic classes for pool j, and

$$N_h = S_h + E_h + I_h + V_h + I_m$$

and

$$N_c = S_c + E_c + I_c + V_c + \rho(S_h + E_h + I_h + V_h).$$

Epi Equations:

Community and HCW equations:

$$
\left.
\begin{aligned}
&S_i(t+1) = \exp\left(-\tau_i(t)\right) S_i(t) \\
&E_{i1}(t+1) = \left[1 - \exp\left(-\tau_i(t)\right)\right] S_i(t) \\
&E_{ij}(t+1) = (1-p_{j-1})(1-q_{ij-1}) E_{ij-1}(t) \quad j = 2, \ldots, 10 \\
&I_{i1}(t+1) = \textstyle\sum_{j=1}^{10} p_j (1-q_{ij}) E_{ij}(t) \\
&I_{i2}(t+1) = (1-h_{i1}) I_{i1}(t) \\
&I_{i3}(t+1) = (1-h_{i2}) I_{i2}(t) + (1-r)(1-h_{i3}) I_{i3}(t) \\
&I_{ij}(t+1) = r(1-h_{i\,j-1}) I_{i\,j-1}(t) + (1-r)(1-h_{ij}) I_{ij}(t) \quad j = 4, 5 \\
&V_i(t+1) = V_i(t) + r I_{i5}(t) + r I^i_{m5}(t)
\end{aligned}
\right\} i = c, h,
$$

$$
\left.
\begin{aligned}
&E^i_{m,j}(t+1) = (1-p_{c\,j-1}) \left(E^i_{m,j-1}(t) + q_{j-1} E_{c\,j-1}(t)\right) \quad j = 2, \ldots, 10 \\
&I^i_{m1}(t+1) = \textstyle\sum_{j=1}^{10} p_j \left(E^i_{mj}(t) + q_{ij} E_{ij}(t)\right) \\
&I^i_{m2}(t+1) = h_{i1} I_{i1}(t) + I^i_{m1}(t) \\
&I^i_{m3}(t+1) = h_{i2} I_{i2}(t) + I^i_{m2}(t) + (1-r)\left[h_{i3} I_{i3}(t) + I^i_{m1}(t)\right] \\
&I^i_{mj}(t+1) = r\left[h_{i\,j-1} I_{i\,j-1}(t) + I^i_{m\,j-1}(t)\right] \\
&\qquad\qquad + (1-r)\left[h_{ij} I_{ij}(t) + I^i_{mj}(t)\right] \quad j = 4, 5
\end{aligned}
\right\} i = c, h.
$$

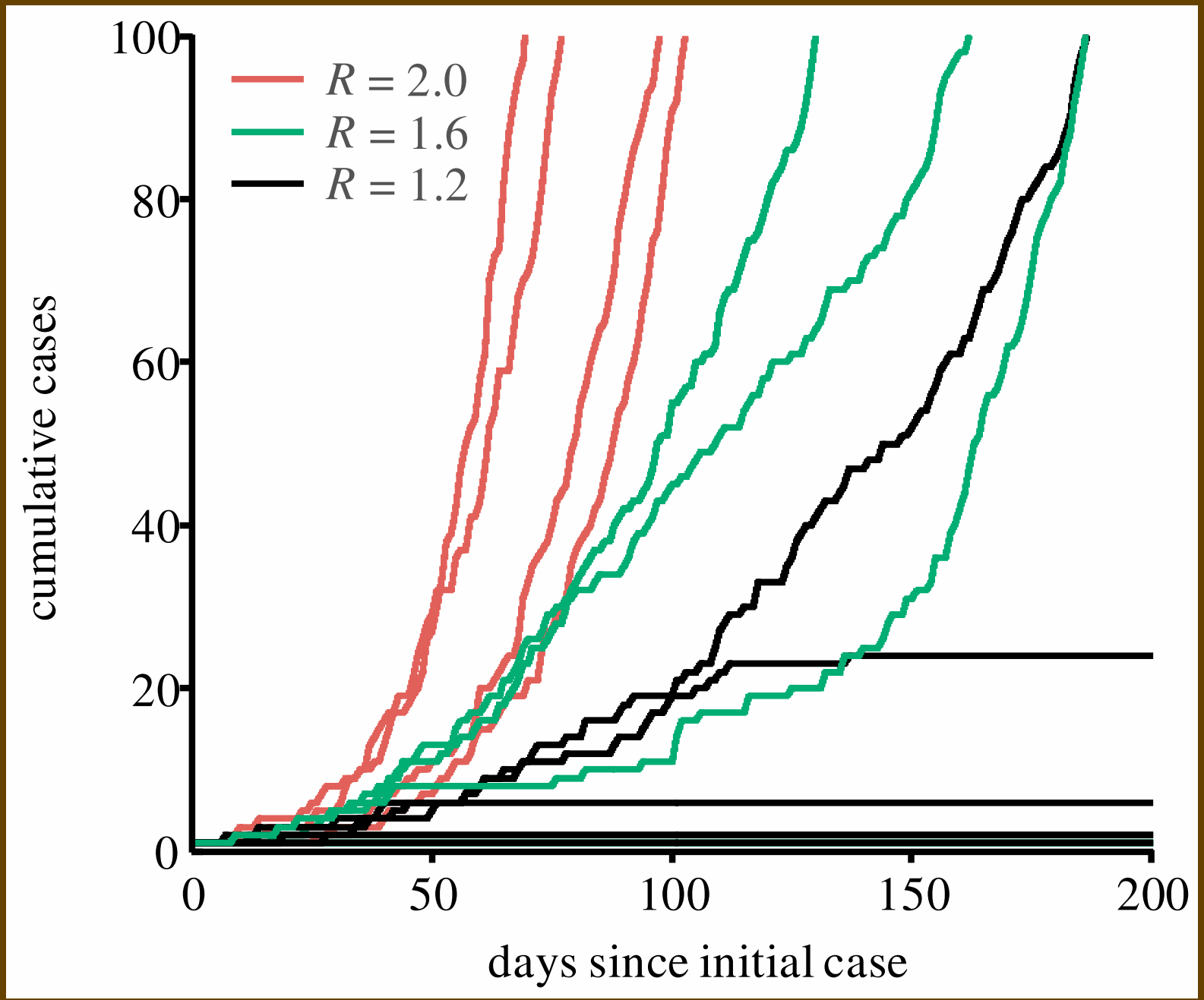
q: quarantine rates; *h*: hospitalization rates; *r*: recovery/death

Parameter values used in simulations

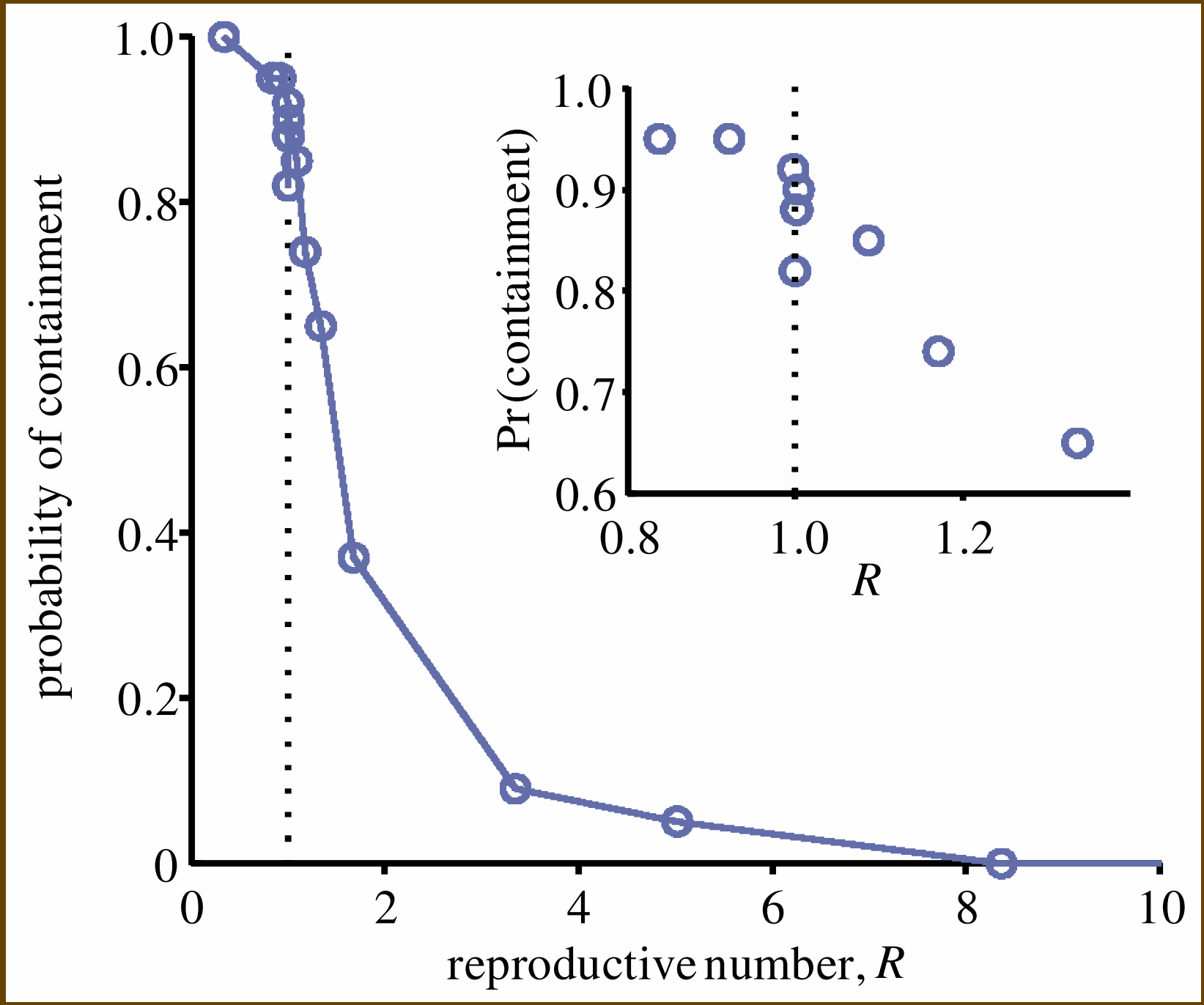
Table 1. Summary of transmission and case-management parameters, including the range of values used throughout the study and the three control strategies depicted in figure 3.

parameter	symbol	range examined	figure 3 (1)	figure 3 (2)	figure 3 (3)
baseline transmission rate (day^{-1})	β	0.08–0.26 (R_0 = 1.5–5)	0.15 (R_0 = 3)	0.15 (R_0 = 3)	0.15 (R_0 = 3)
factors modifying transmission rate, owing to:					
pre-symptomatic transmission	ε	0–0.1	0.1	0.1	0.1
hospital-wide contact precautions	η	0–1	0.5	0.9	0.5
reduced HCW–community mixing	ρ	0–1	0.5	1	0.5
case isolation	κ	0–1	1	0.5	0.5
quarantine	γ	0–1	0.5	0.5	0.5
daily probability of:					
quarantining of incubating individuals in the community (E_c)	q	0–1	0	0.5	0.5
isolation of symptomatic individuals in the community (I_c)	h_c	0–1	0.3	0.9	0.9
isolation of symptomatic HCWs (I_h)	h_h	0.9	0.9	0.9	0.9

Individual runs: Cumulative cases for different R (effective reproduction numbers--i.e. R_0 when some control is applied)



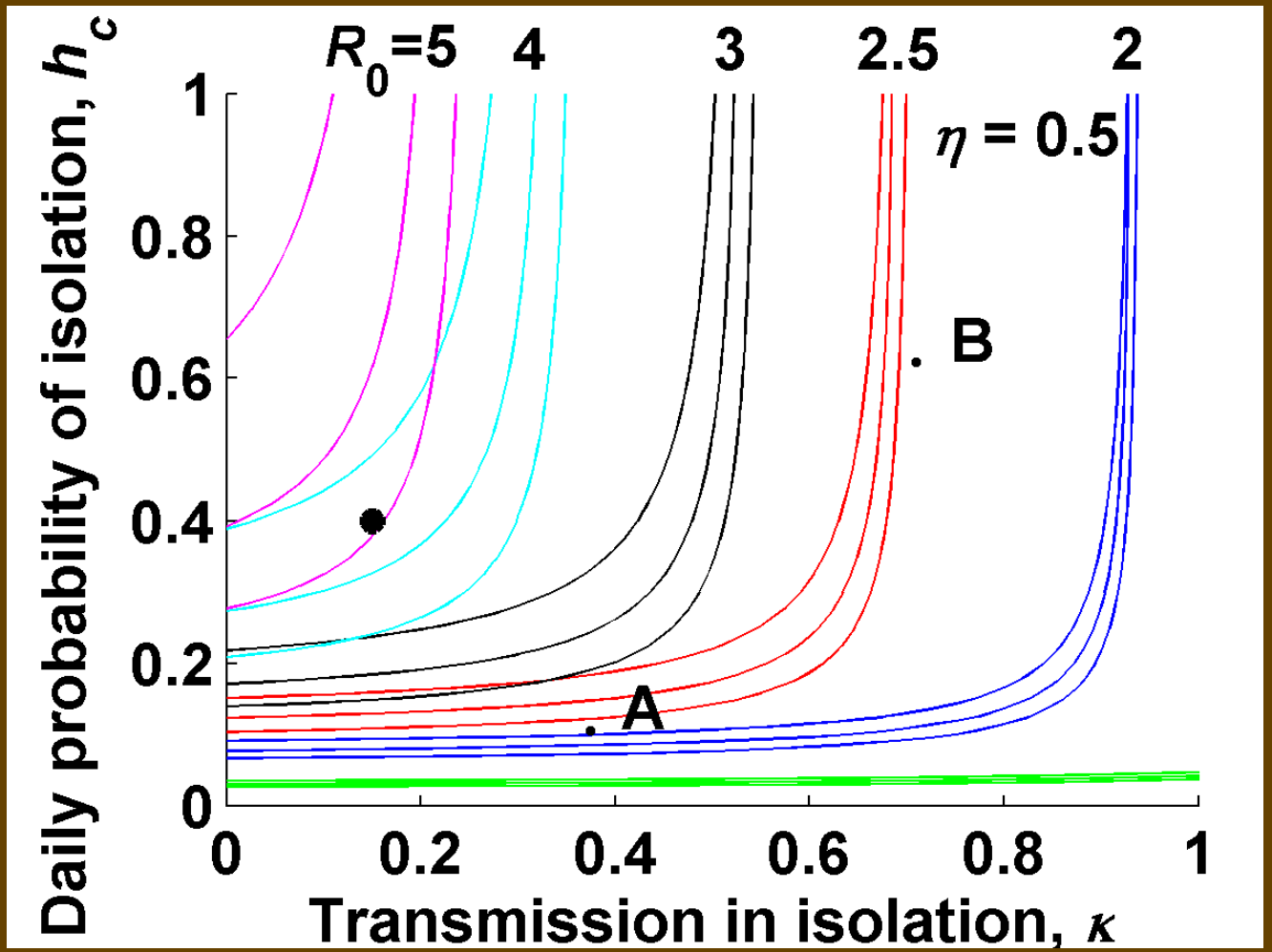
Probability of epidemic containment for different effective *R*'s



R=1 contours (right side of curves guarentees control of epidemic) for the effects of isolation leves h_c and transmission curtailment (1-κ) for epidemics with different R_0

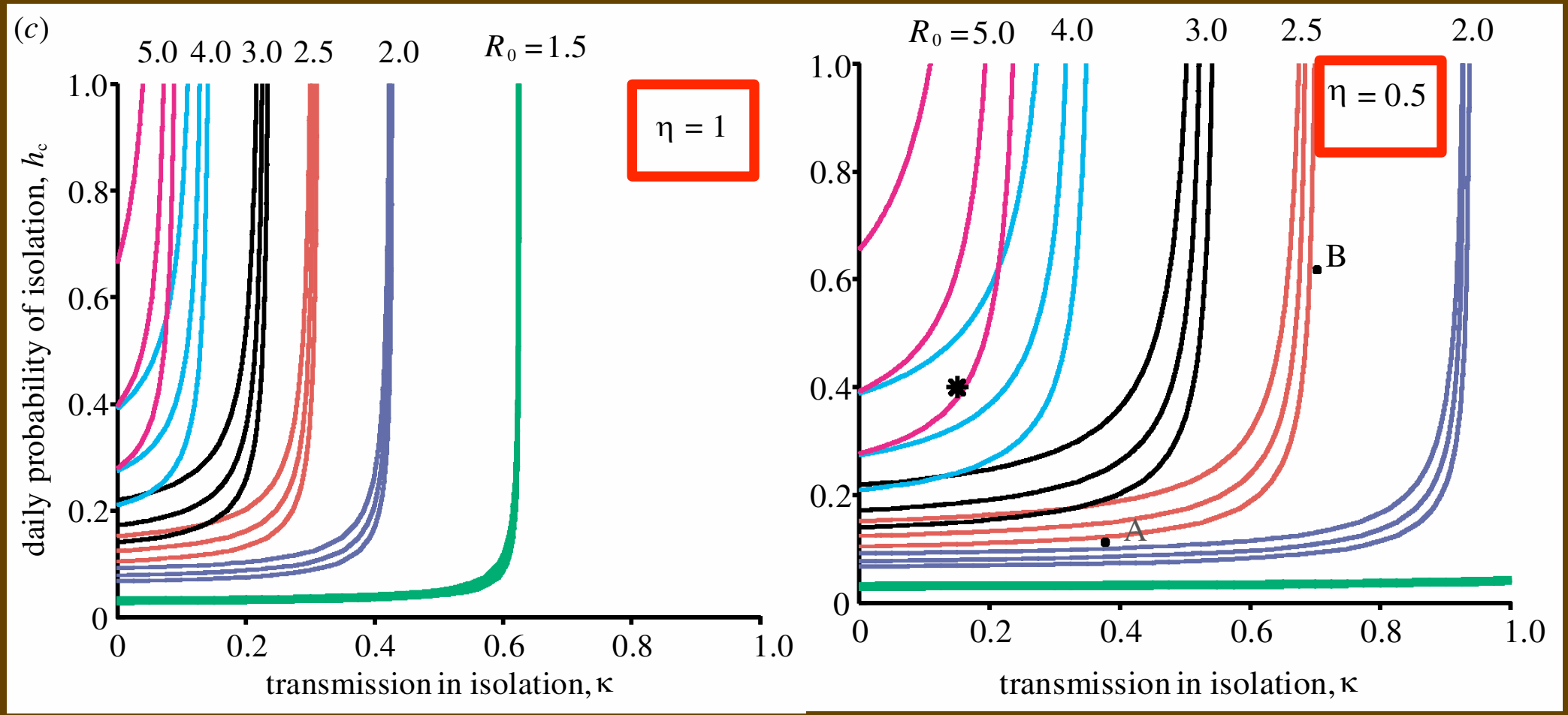
η: hospital precautions reduce transmission by 1/2

3 lines right to left: increasing delays in isolation of patients



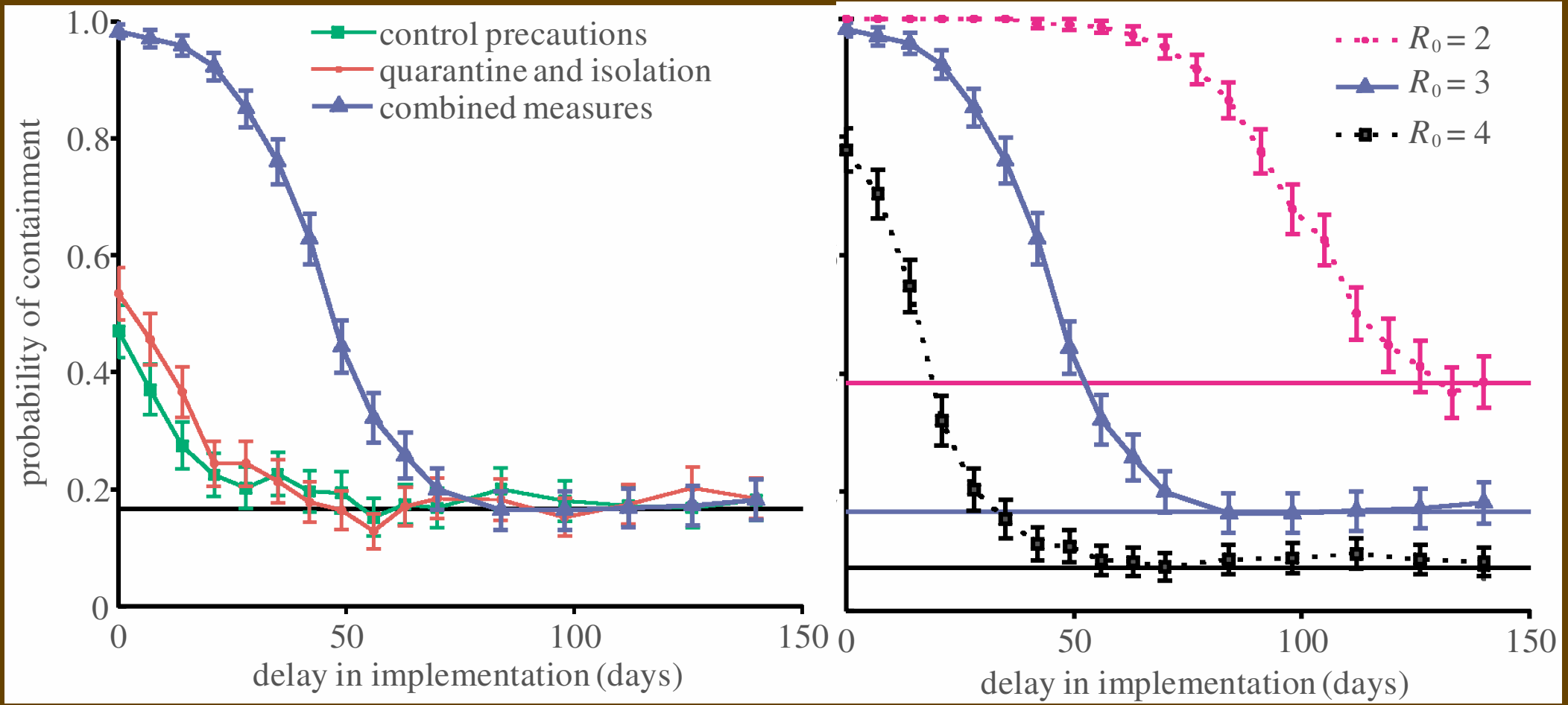
Combinations of policies that lead to containment: plots of R=1 contours

(three lines represent increasing delays in isolating patients)

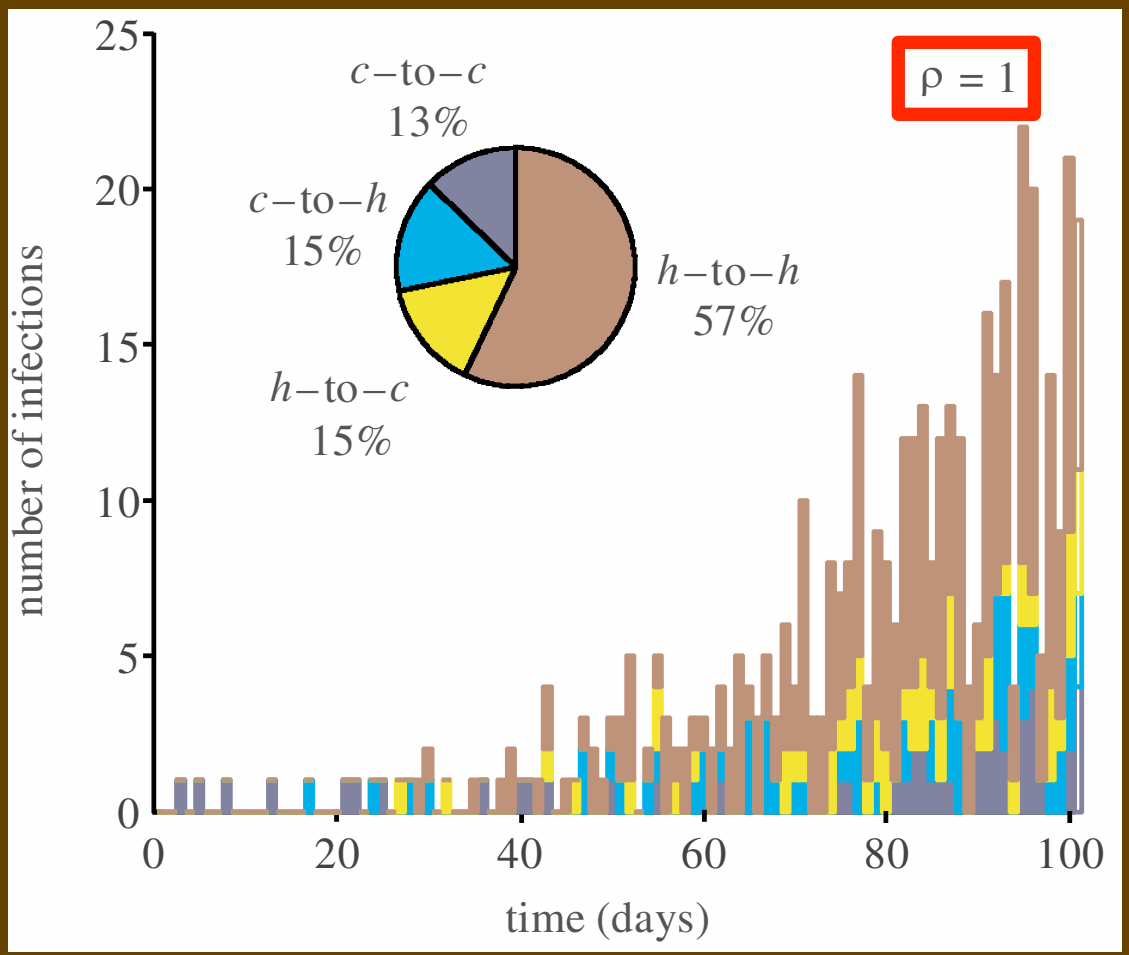


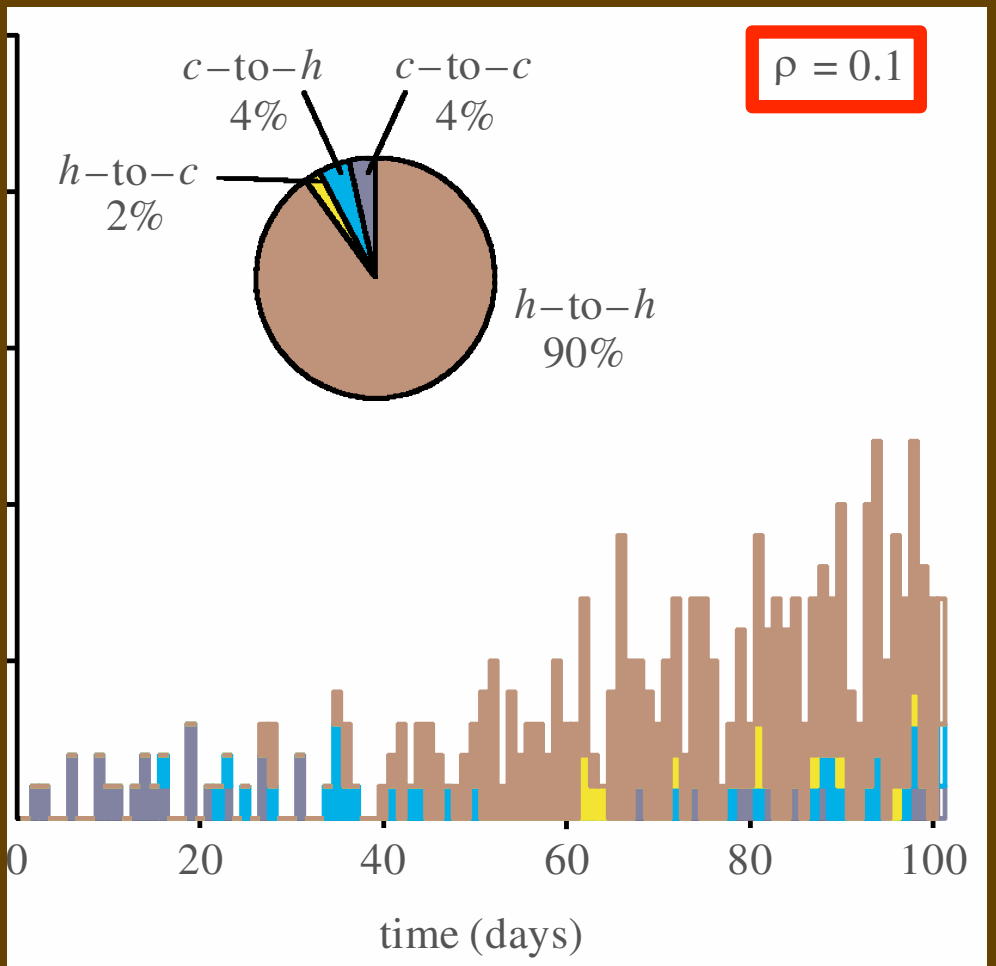
Probability of containment in terms of implementation of control after epi onset

Left: 3 strategies; Right: combined measure for 3 R_0



Importance of HCW mixing restrictions ρ in preventing epidemics (control after 14 days): histograms -- 1 run; pie charts -- 500 runs c=community pool, h=hospital pool





Third Case Study: TB in Humans

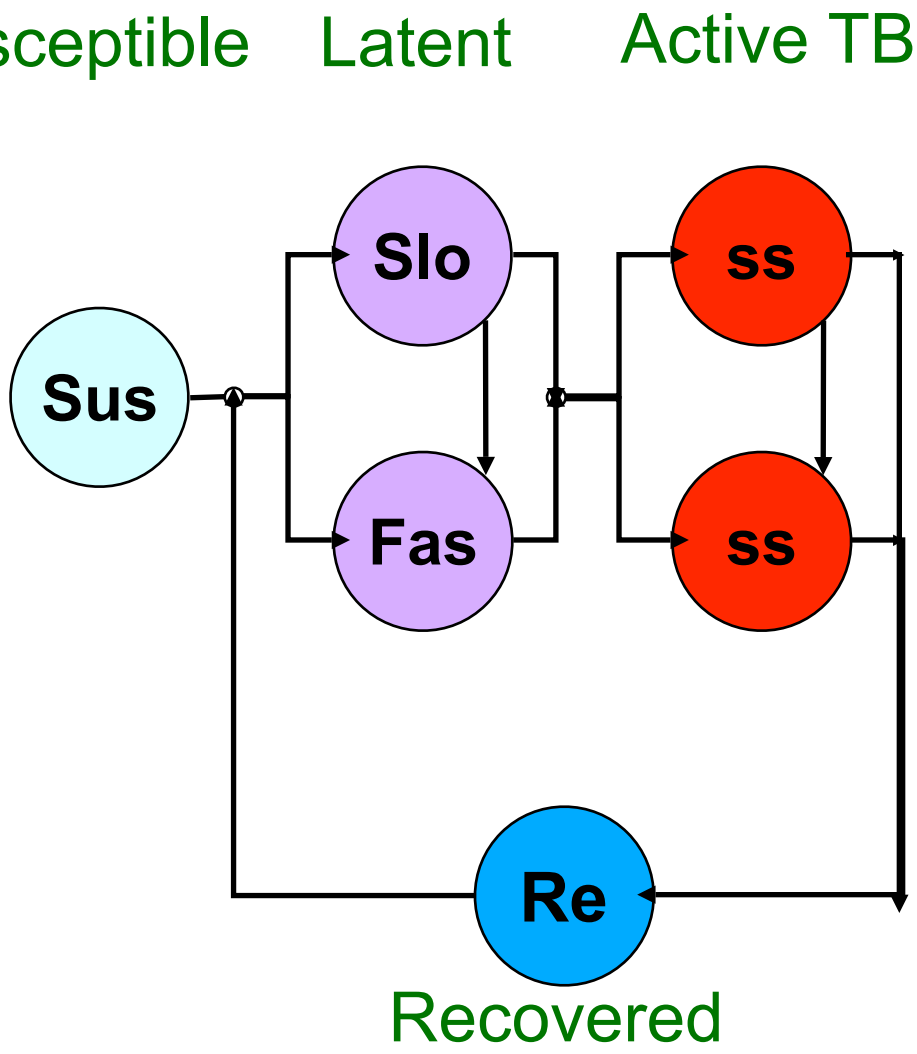
Salomon, Lloyd-Smith, Getz, Resch, Sanchez, Porco, & Borgdorff, 2006. PLoS Medicine. 3(8), e273.

Sánchez M. S., J. O. Lloyd-Smith, T. C. Porco,B. G. Williams, M. W. Borgdorff, J. Mansoer, J. A. Salomon, W. M. Getz, 2008. Impact of HIV on novel therapies for tuberculosis control. AIDS 22:963-972.

Important elements:

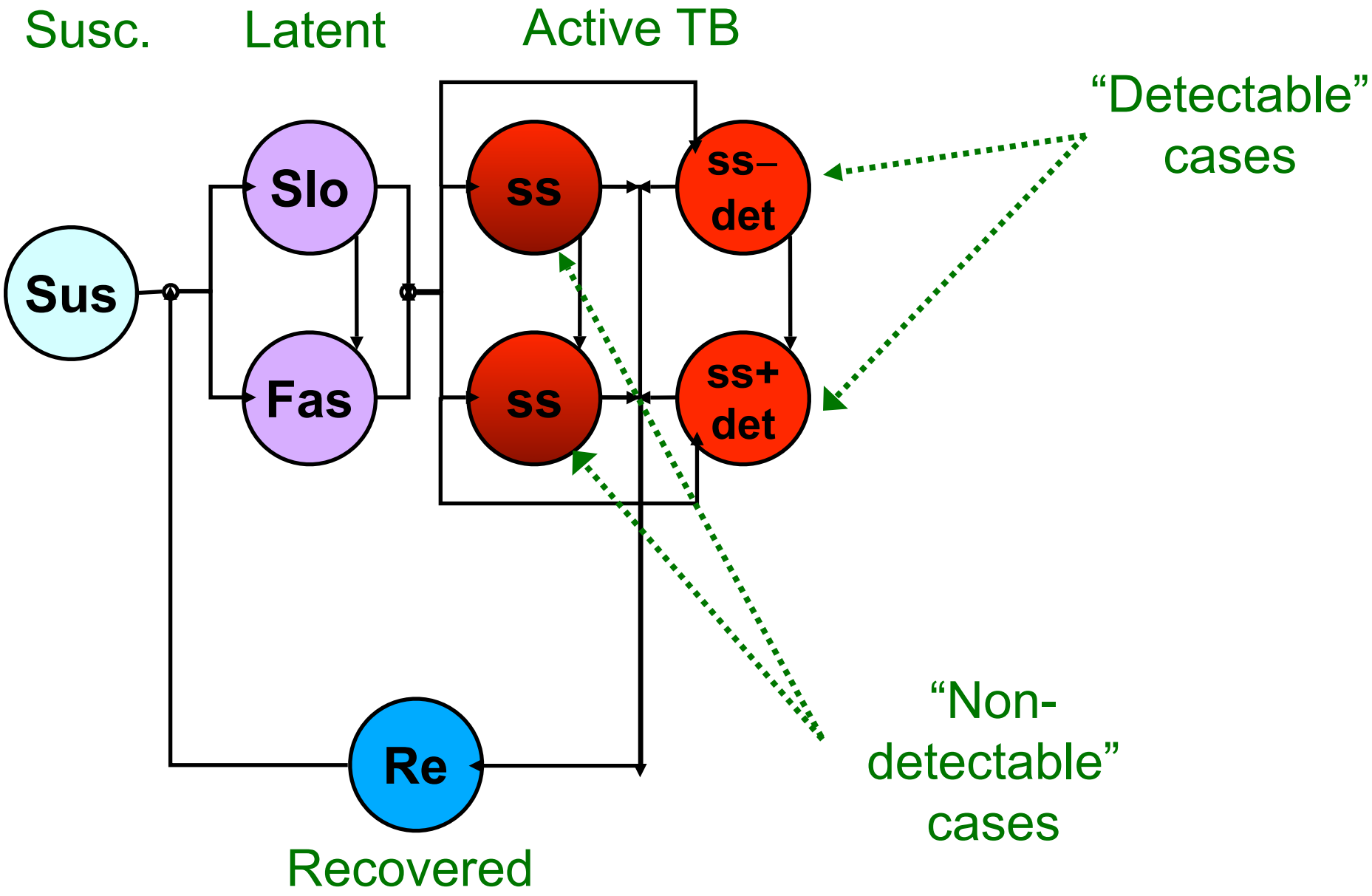
- Includes important disease classes relating to latent vs. active, sputum smear positive vs. negative TB, DOTS vs Non-DOTS treatment, detectable vs. non-detectable
- Follows a competing rates formulation
- Time iteration is monthly: relates well to treatment regimen
- **TB in and HIV background**

Core model of TB – elaborated SEIR framework

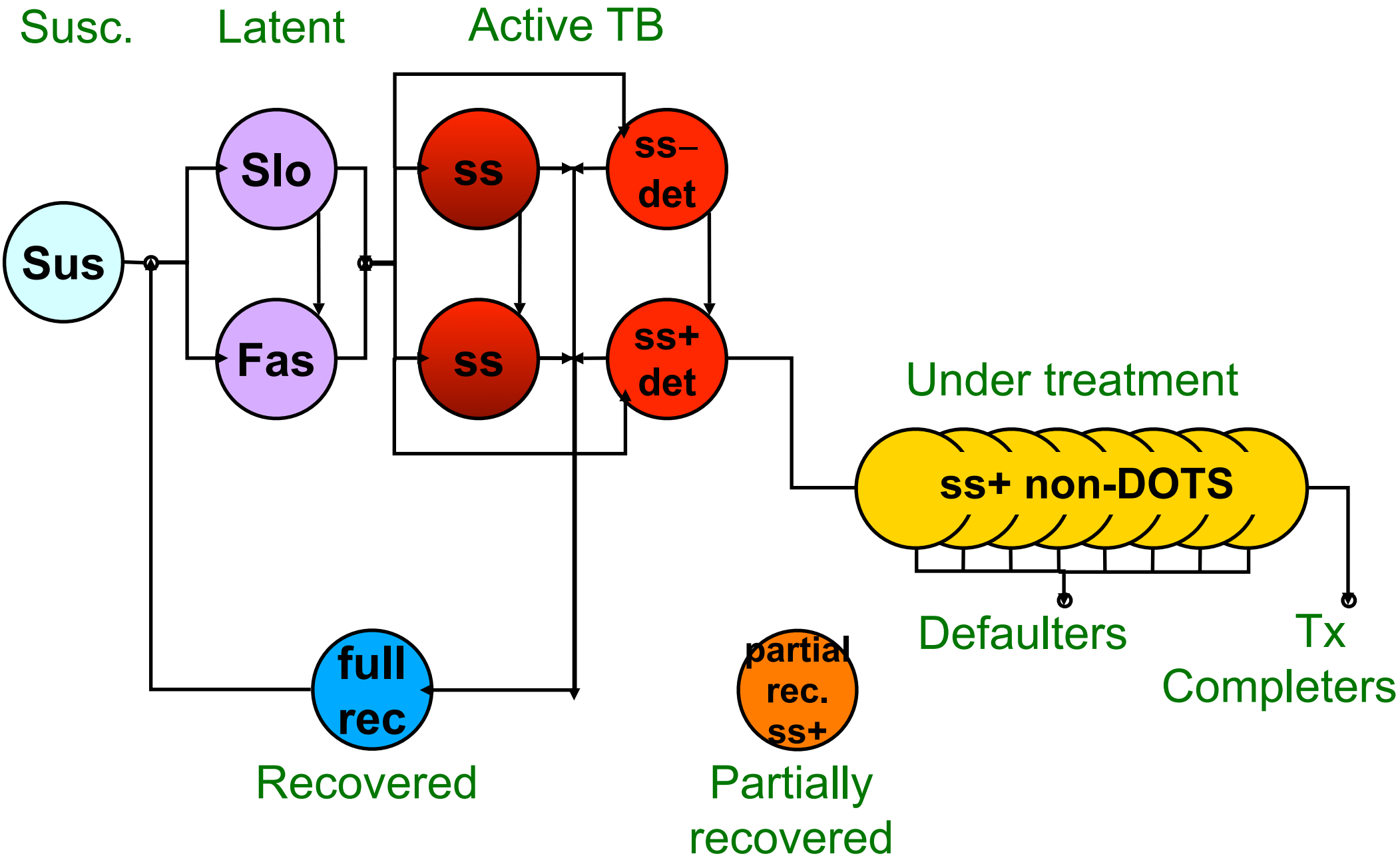


Not shown: all classes suffer natural mortality
active cases suffer additional mortality

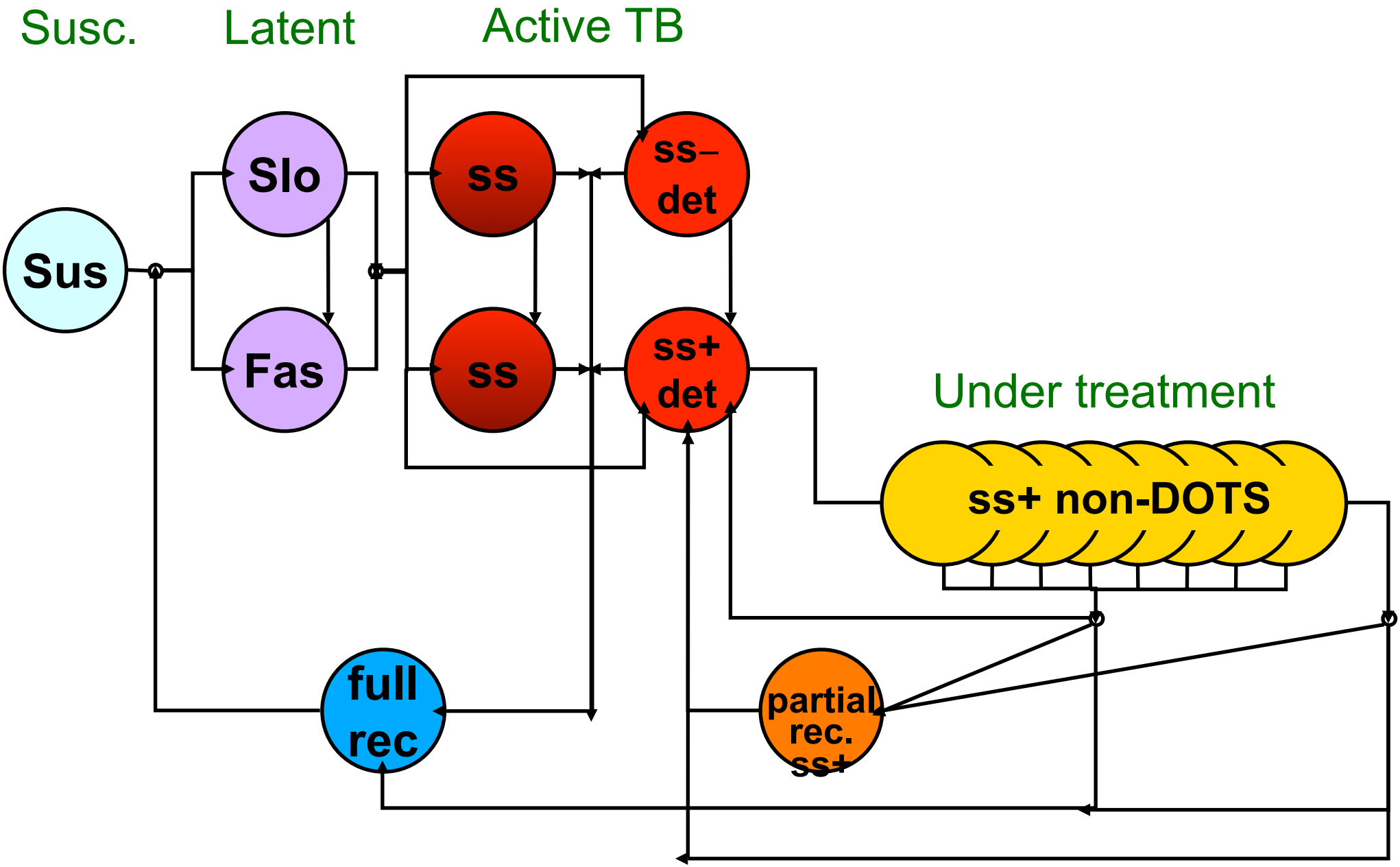
TB treatment model



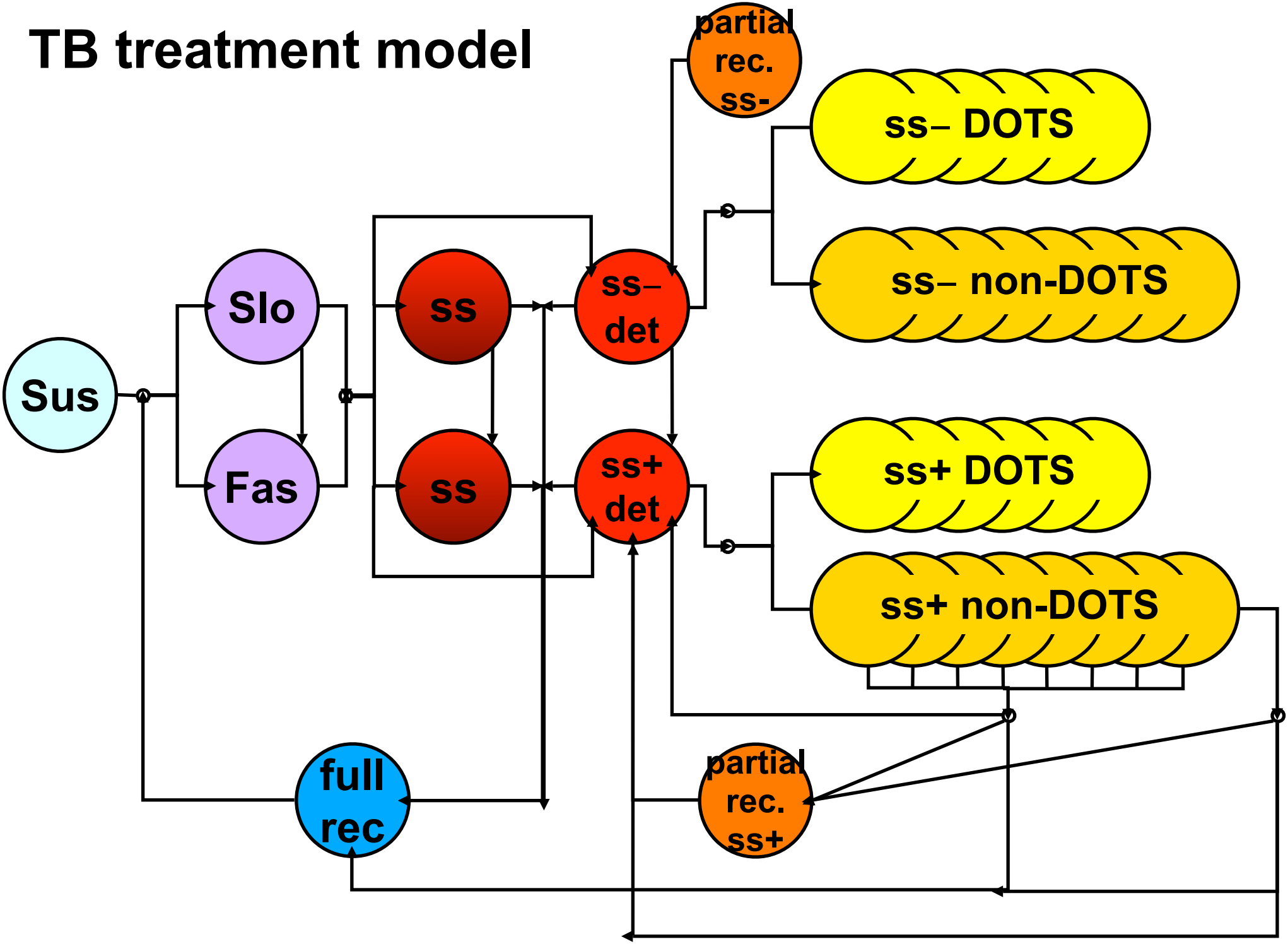
TB treatment model



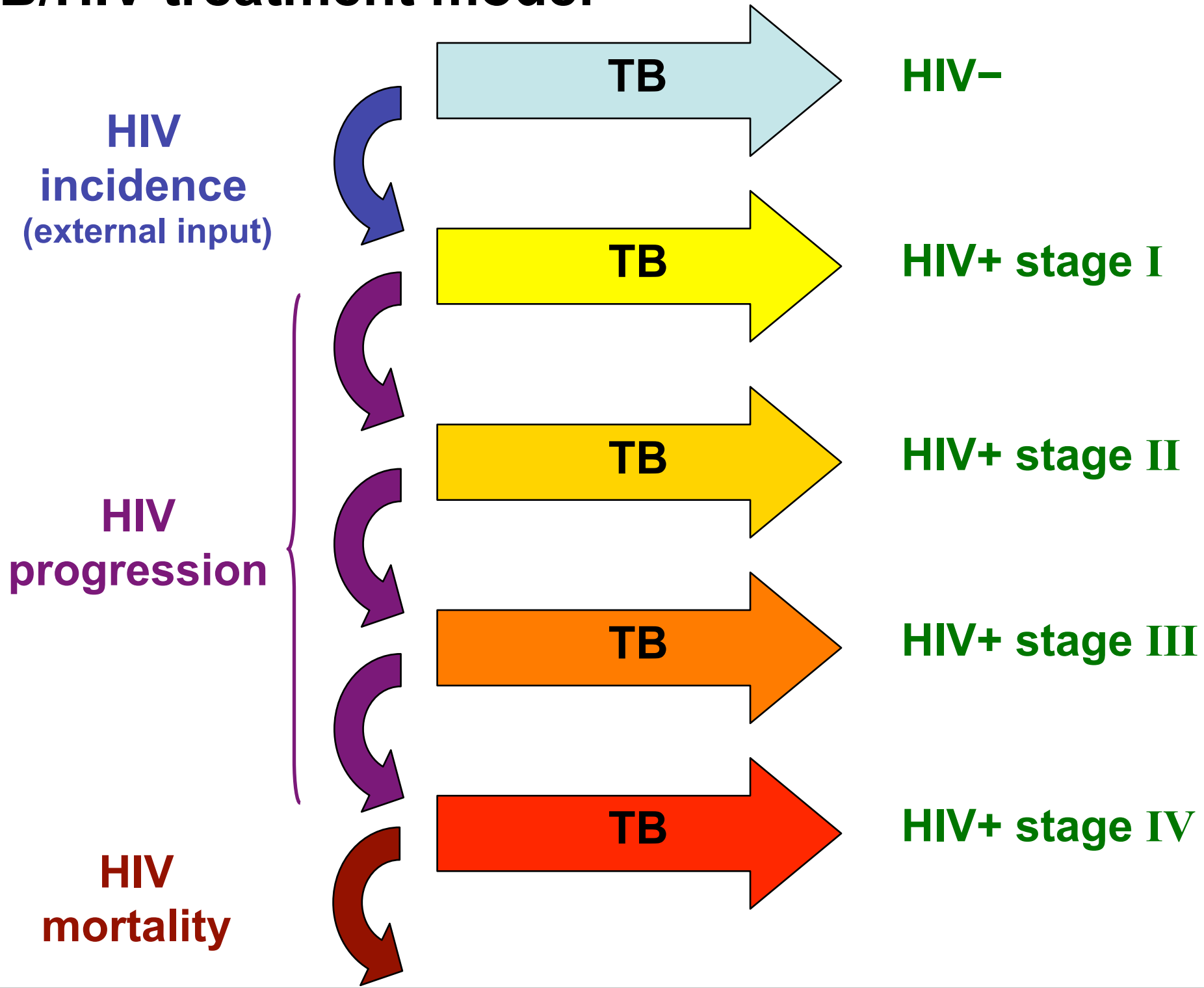
TB treatment model



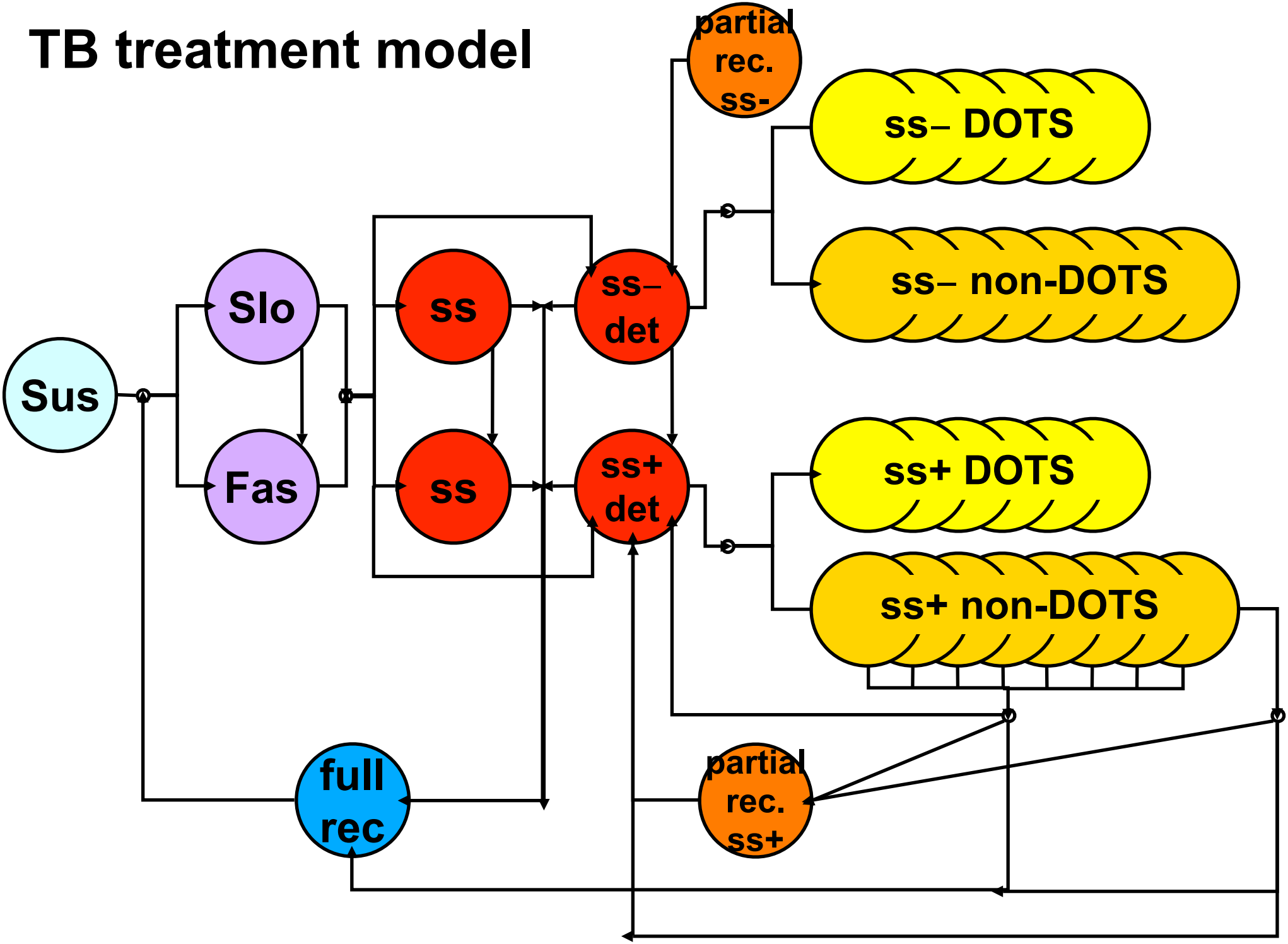
TB treatment model



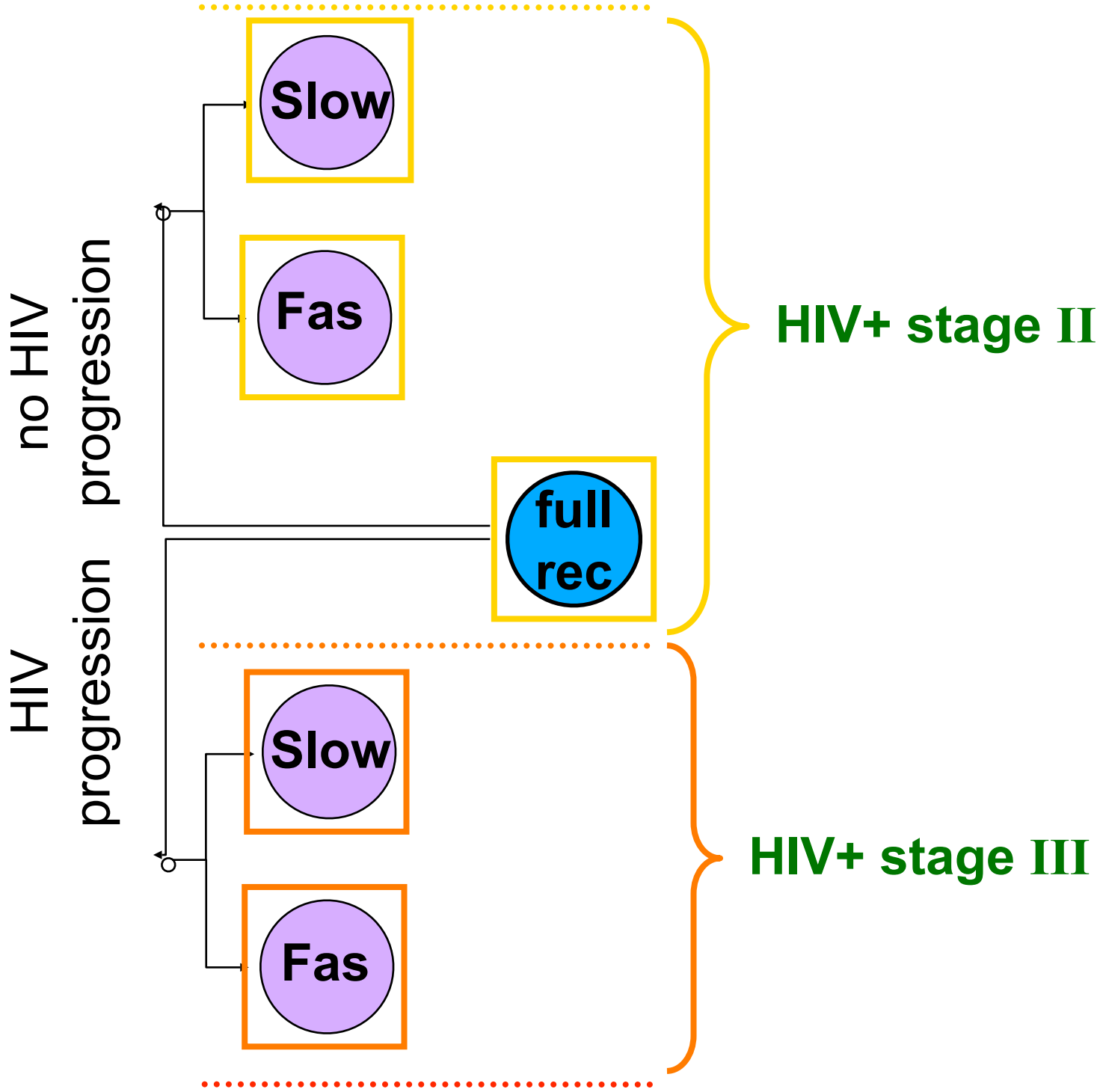
TB/HIV treatment model



TB treatment model



TB REINFECTION



TB-HIV CO-DYNAMICS IN KENYA: Monitoring Interacting Epidemics

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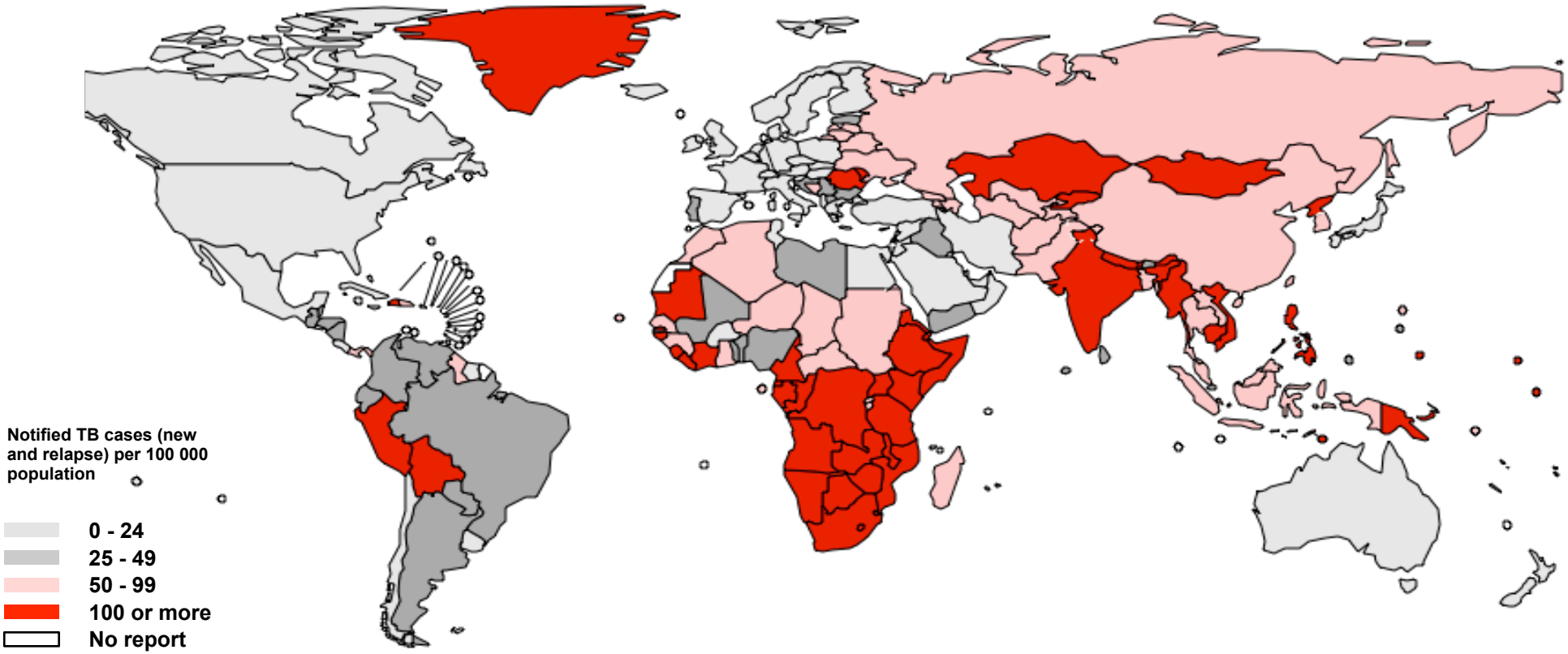
Sánchez M. S., J. O. Lloyd-Smith, B. G. Williams, T. C. Porco, S. J. Ryan, M. W. Borgdorff, J. Mansoer, C, Dye, W. M. Getz, 2009. Incongruent HIV and Tuberculosis Co-dynamics in Kenya: Interacting Epidemics Monitor Each Other. Epidemics 1:14-20.

Tuberculosis notification rate, 2004



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.
Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
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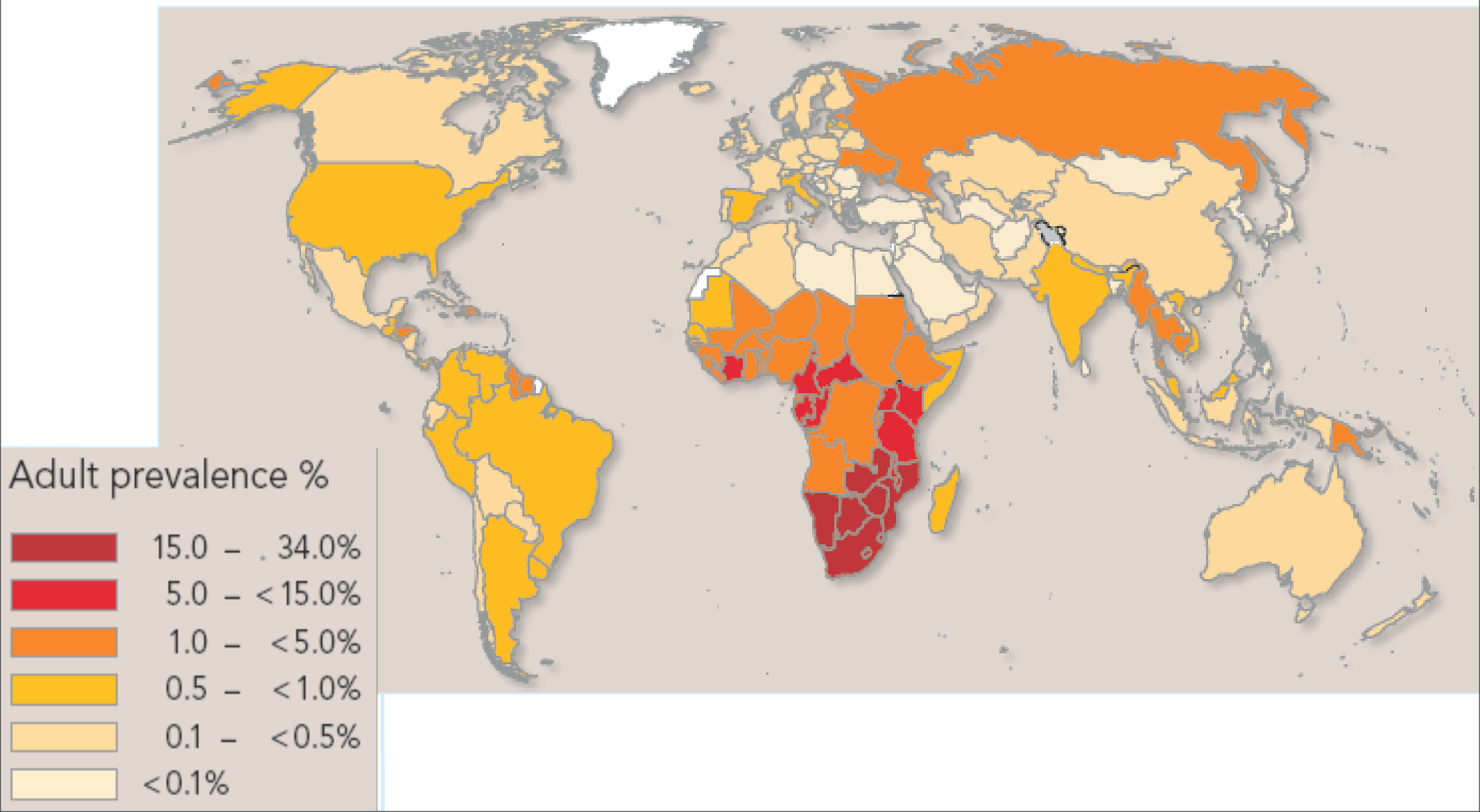
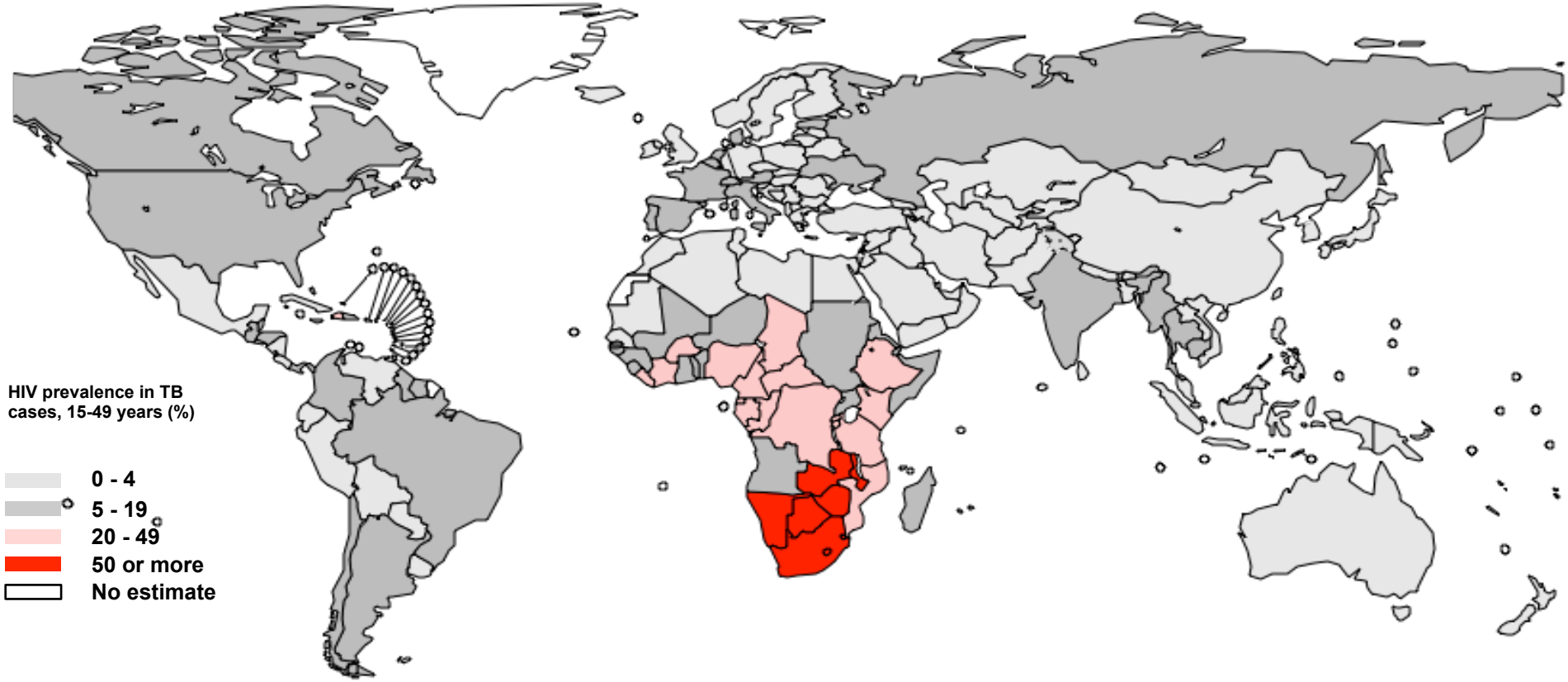
HIV prevalence in adults, 2005

38.6 million people [33.4-46.0 million] living with HIV, 2005



Estimated HIV prevalence in new adult TB cases, 2004



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Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
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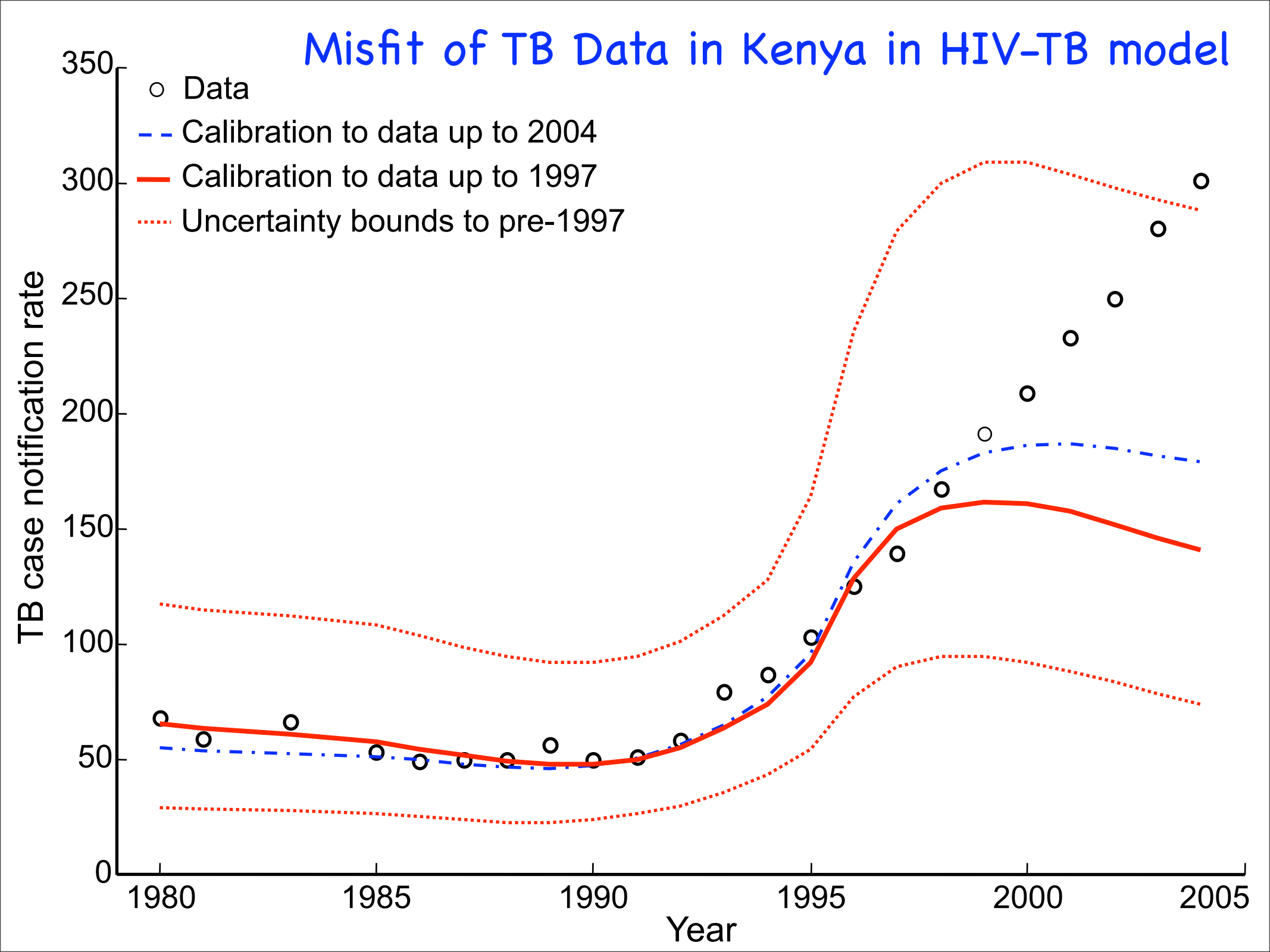

Misfit of TB Data in Kenya in HIV-TB model
Data
Calibration to data up to 2004
Calibration to data up to 1997
Uncertainty bounds to pre-1997
TB case notification rate
Year
0
50
100
150
200
250
300
350
1980
1985
1990
1995
2000
2005

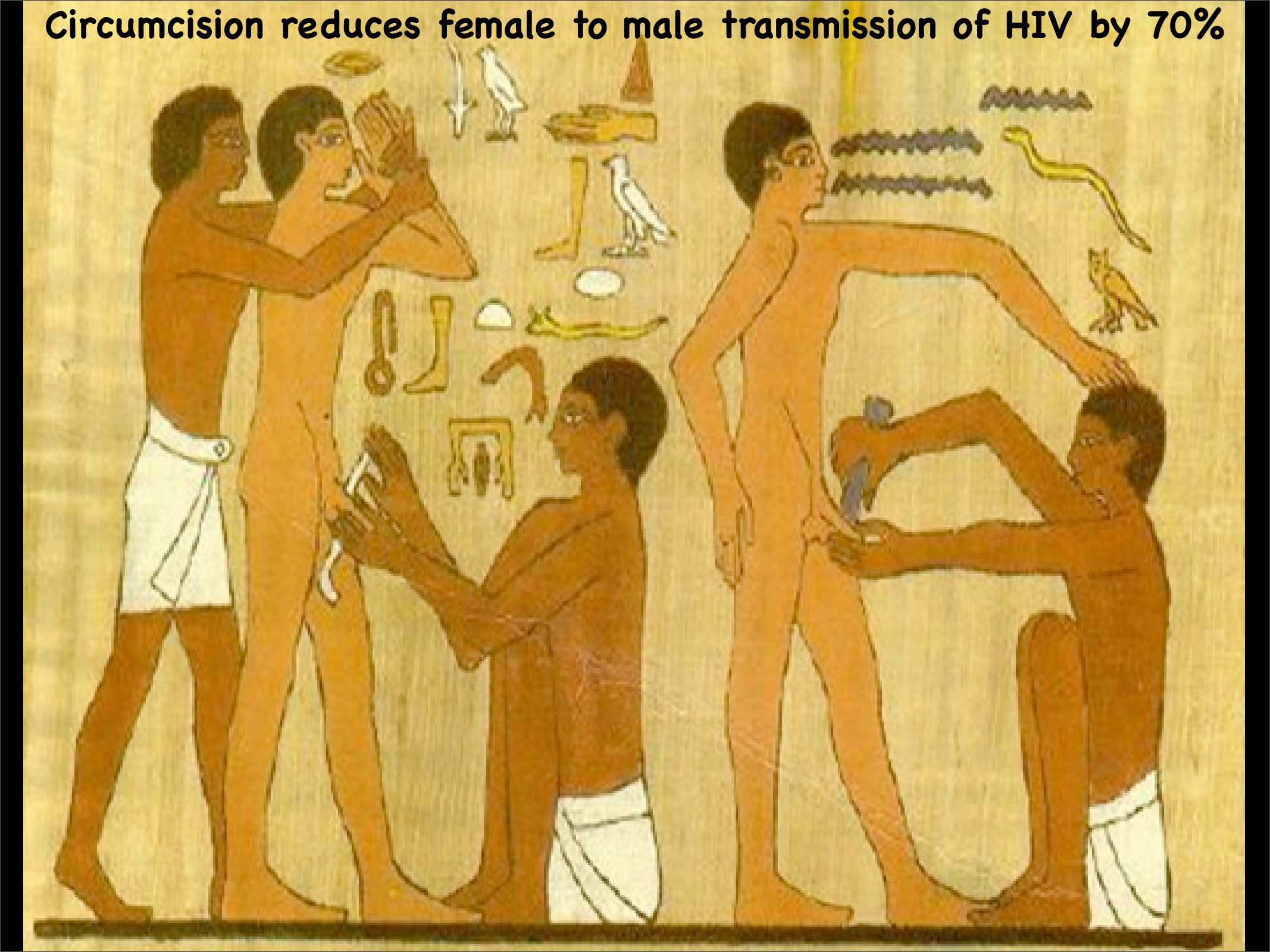
Case Study: Circumcision & HIV

Williams, B.G., Lloyd-Smith, J.O., Gouws, E., Hankins, C., Getz, W.M., Dye, C.,1, Hargrove, J., de Zoysa, I., Auvert, B, 2006. The potential impact of male circumcision on HIV incidence, HIV prevalence and AIDS deaths in Africa. PLoS Medicine 3(7):e262.

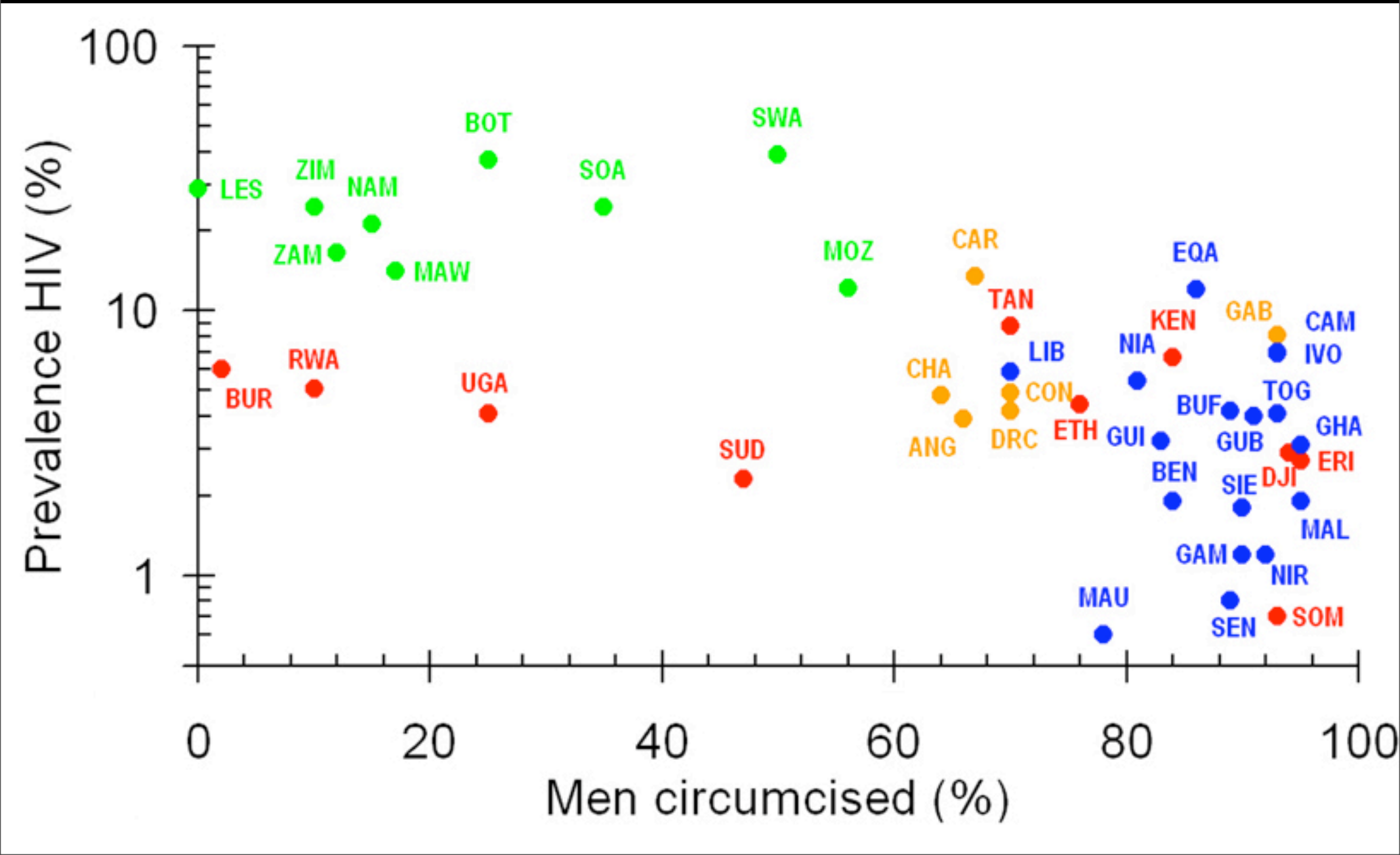
Important elements:

- two sex model
- circumcised versus uncircumcised male categories
- Weibull

Circumcision reduces female to male transmission of HIV by 70%

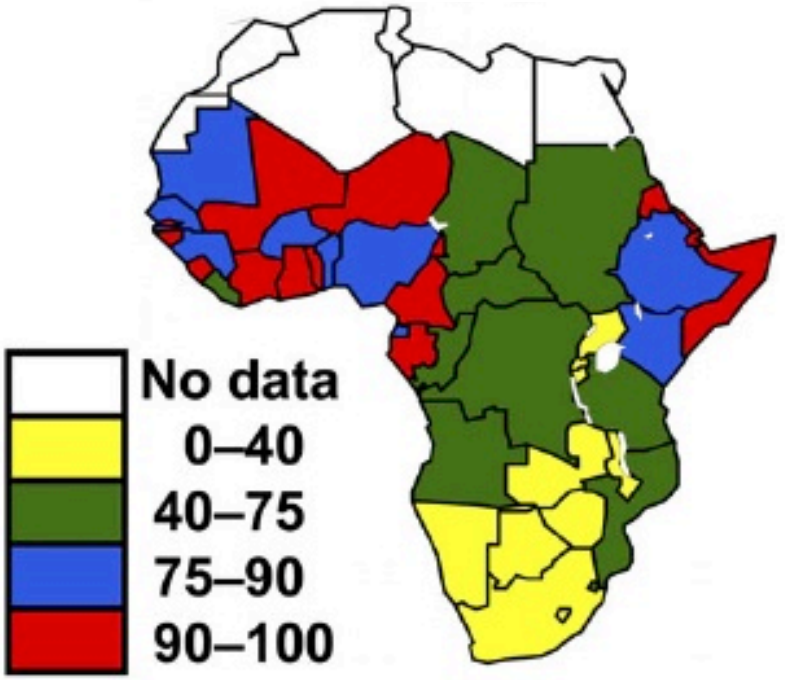


green: S. Af.; red. E. Af.; orange: cent. Af.; blue, W. Af.

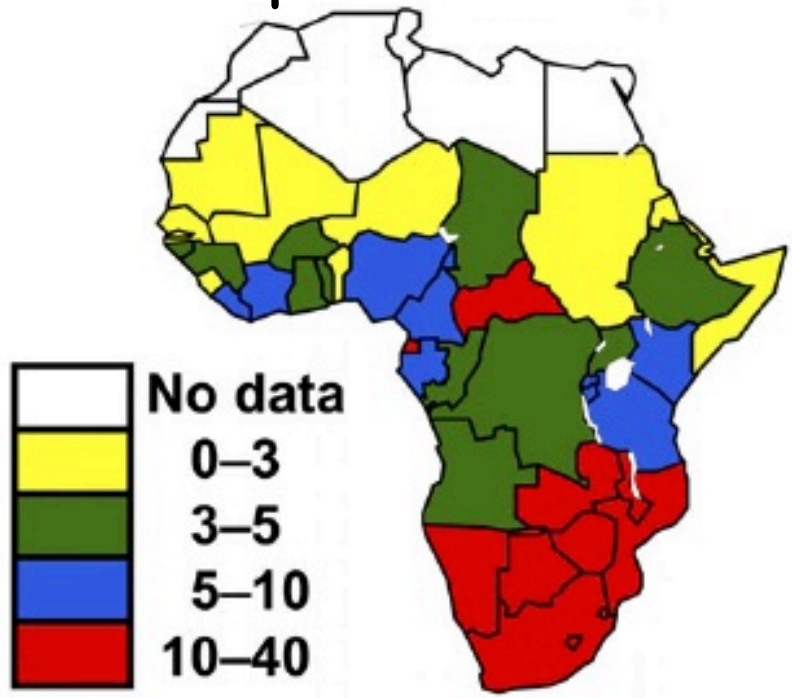


Currently

% circumcised



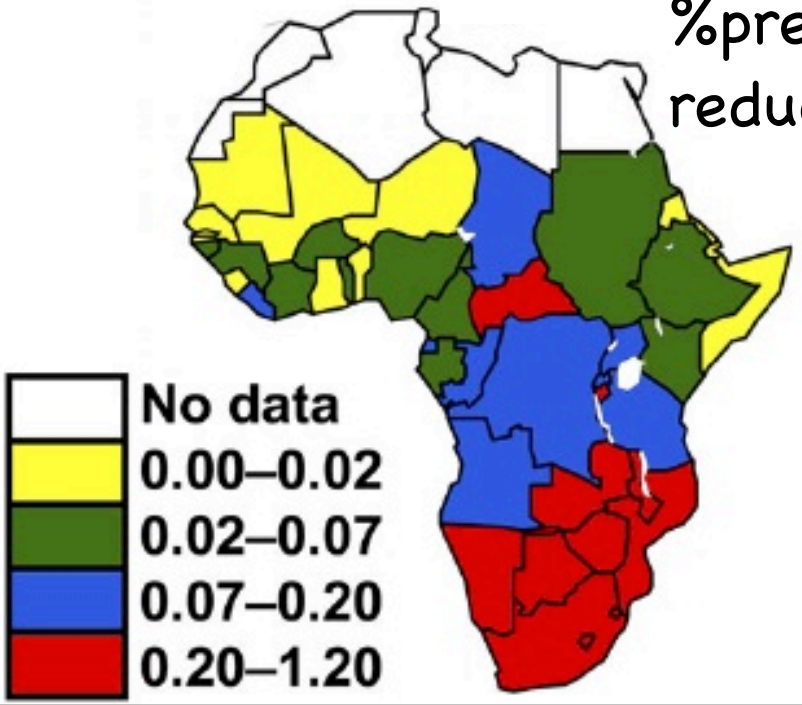
% prevalence



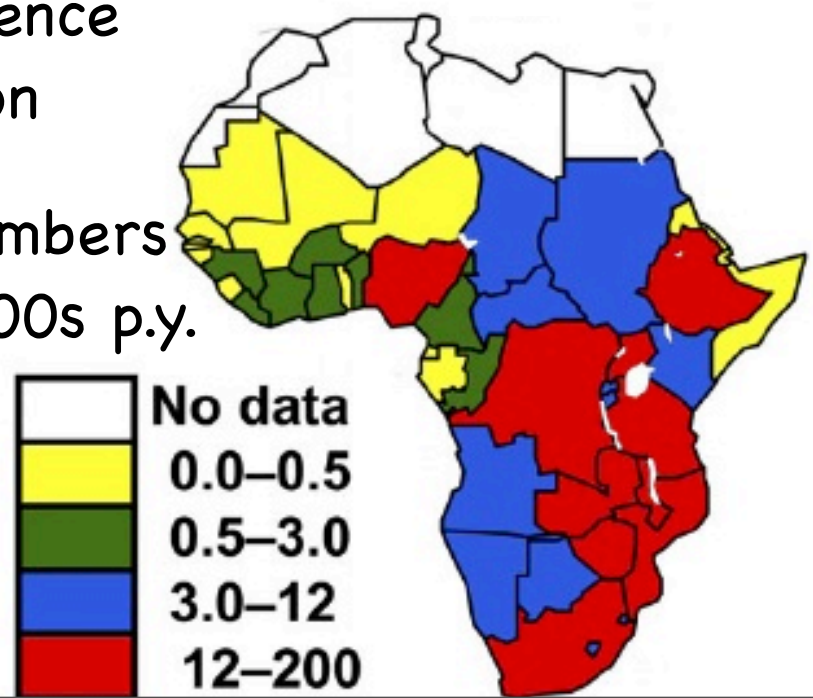
MC equivalent to a vaccine with 37% efficacy

impact

%prevalence reduction



numbers 1000s p.y.



Stochastic models in homogeneous populations

Discrete Markov Chain Binomial Models

Reed-Frost (class room lectures late 1920s at Johns Hopkins)

E.g. Daley and Gani's book: Epidemic Modelling, 1999

Graph theory interpretations of Reed-Frost models

unidirected graph on N nodes, probability p of connections

Giant component iff $R_0 = pN > 1 \Rightarrow z = 1 - \exp(R_0 z)$

where z is expected value for $(1-S_\infty)$

Stochastic models in homogeneous populations

Continuous time stochastic jump process models

SIR + demography

E.g Ingemar Nasell, Math. Biosci. 179:1-19, 2002.

Stochastic simulation of discrete time equivalents of SIR models with demography (including age structure)

(e.g. HIV models, TB models, SARS models, bovine TB models)

Problem with homogeneity!

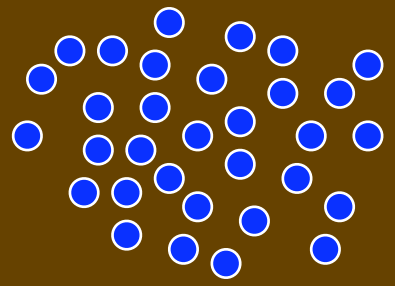
1. Variation in host behavior: contact rates
2. Variation in host susceptibility: probability of infection
3. Variation in intensity of host infectivity: probability of infection
4. Variation in period of infectiousness: number of contacts and probability if infection
5. Several host strains with varying transmissibility and virulence.
6. Lots of others!

Superspreaders: the effect of heterogeneity on disease emergence

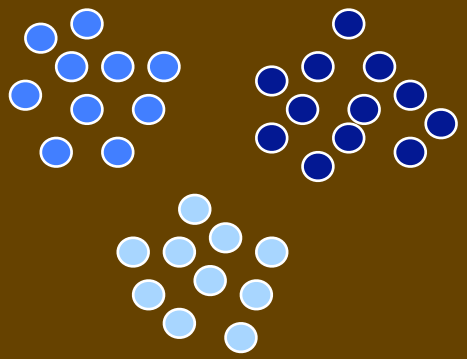
Lloyd-Smith, J. O., S, J. Schreiber, P. E. Kopp, and W. M. Getz, 2006. Superpreading and the impact of individual variation on disease emergence. Nature 438:335-359.

Heterogeneity and epidemiology

We have discussed disease models that assume homogeneous

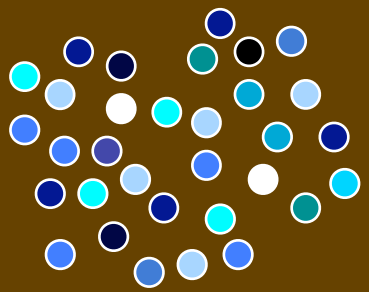


What about populations with heterogeneity?



Common approach: break population into many sub-groups, each of which is homogeneous.

What about continuous variability among individuals within well-mixed groups?



Homogeneous models of disease: **Individual Level**

Galton-Watson branching process theory:

A probability generating function approach

1. Probability that I infects k individuals is q_k: $\mathbf{q} = \{q_k\}_{k=0}^{\infty}$
2. Probability generating function $g_{\mathbf{q}}(z) = \sum_{k=1}^{\infty} q_k z^k, \ 0 \le z \le 1$
3. z_n is probability $I(t) = 0$ at generation n: $z_n = g_{\mathbf{q}}(z_{n-1}), \ z_1 = q_0$
4. $g_{\mathbf{q}}(0) = q_0, \quad g_{\mathbf{q}}(1) = 1, \quad g_{\mathbf{q}}'(1) = R_0$
5. Each individual expects to infect ν: Poisson process: $g_{\mathbf{q}}(z) = e^{\nu(z-1)}$

Invasion condition (infinite pop size assumption, fixed generation time):

Determistic: $R_0 > 1$

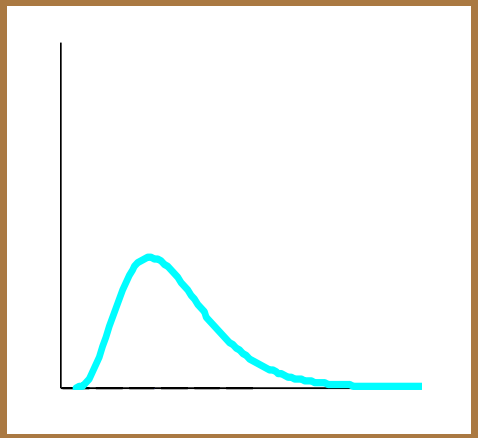
Stochastic (homogeneous): $R_0 > 1 \Rightarrow$ prob{invasion}=$1-1/R_0$

Heterogeneous models of disease:
Individual Level

5. Each individual expects to infect ν (homogenous $\Rightarrow$ Poisson process)
6. If ν is itself distributed (e.g. gamma) then process
   is not Poisson (e.g negative binomial)

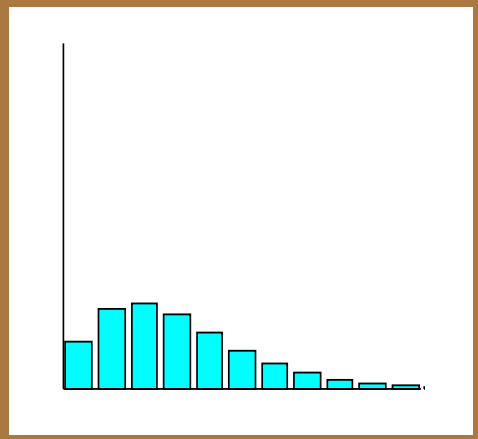
Parent distribution:

Individual reproductive number ν



Offspring distribution:

Distribution of cases caused by particular individuals



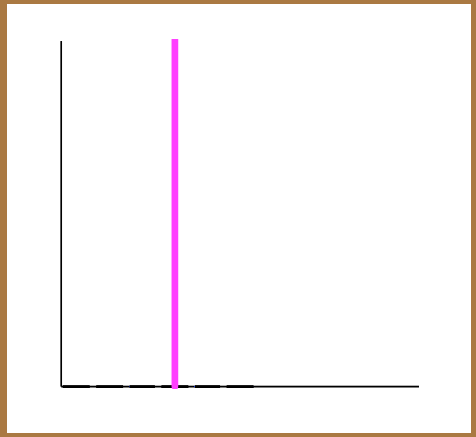
Standard Model I

Completely homogeneous population, all $\nu = R_0$

Constant

Parent distribution

ν

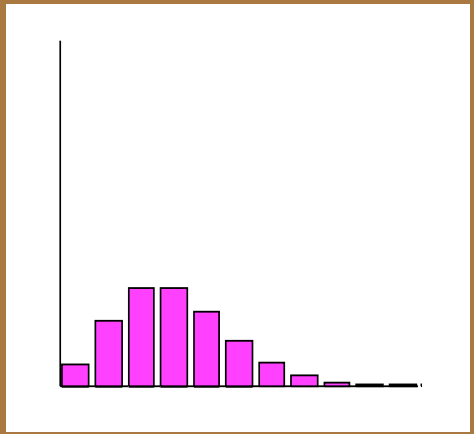


$$f_\nu(x) = \delta\left(x - R_0\right)$$

Poisson

Offspring distribution

Z



$$g(z) = \int_0^\infty e^{-x(1-z)} f_\nu(x)\,dx$$

$$= e^{-R_0(1-z)}$$

Standard Model II (SIR)

Homogeneous transmission, constant recovery

Exponential

Parent distribution

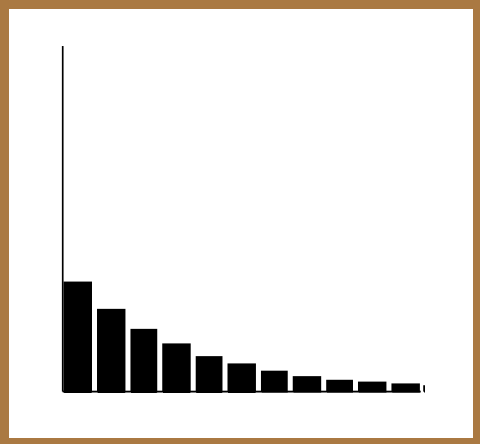
ν

$$f_\nu(x) = \frac{1}{R_0} e^{-x/R_0}$$

Geometric

Offspring distribution

Z



$$g(z) = \int_0^\infty e^{-x(1-z)} f_\nu(x)\,dx$$

$$= 1 + R_0(1-z)$$

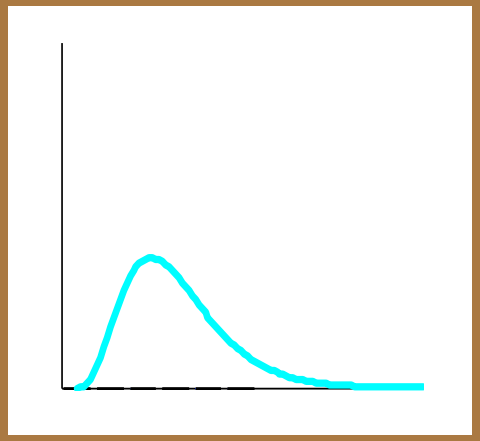
New Model

Heterogeneous force of infection
(superspreaders in right-hand tail)

Gamma

Parent distribution

ν

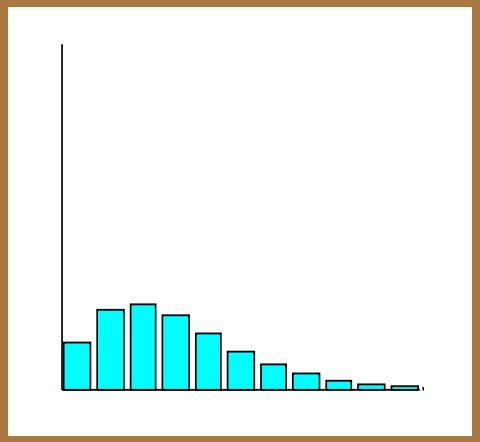


$$f_\nu(x) = \frac{1}{\Gamma(k)}\left(\frac{kx}{R_0}\right)^{k-1}\left(\frac{k}{R_0}\right)e^{-kx/R_0}$$

Negative Binomial

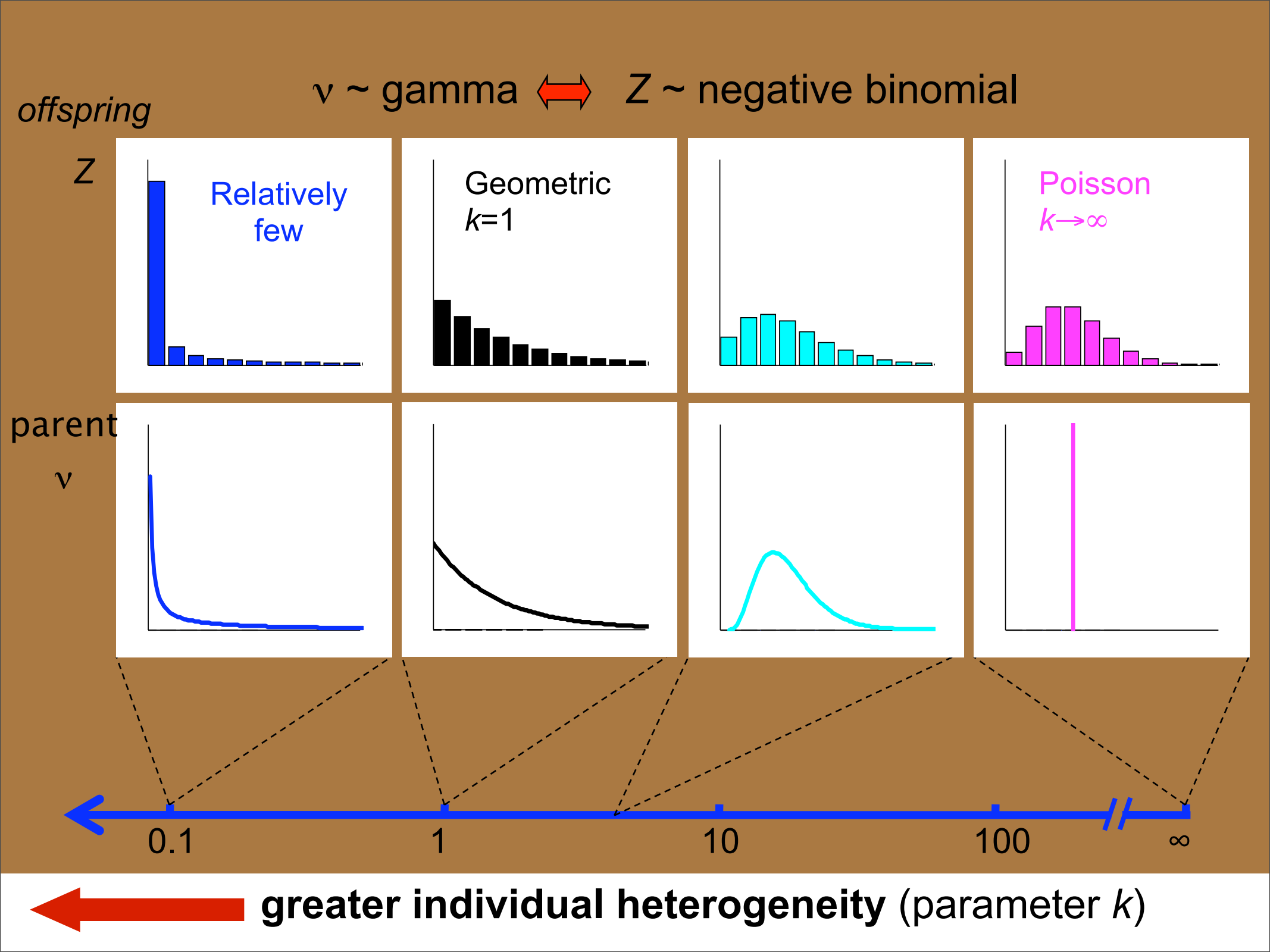
Offspring distribution

z



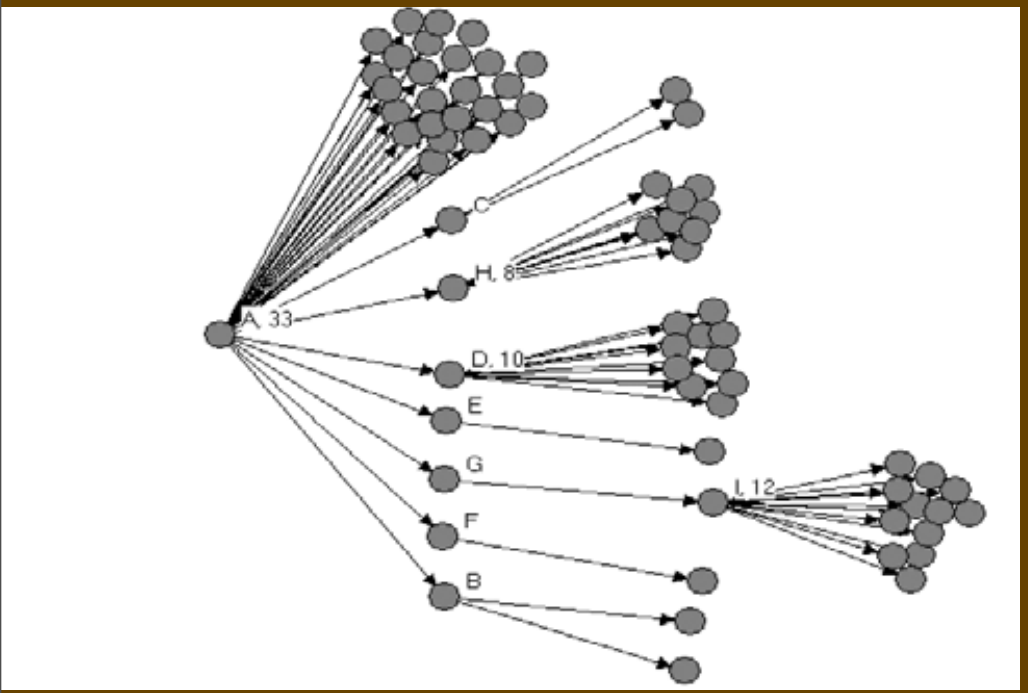
$$g(z) = \int_0^\infty e^{-x(1-z)} f_\nu(x)\,dx$$

$$= \left(1 + \frac{R_0}{k}(1-z)\right)^{-k}$$

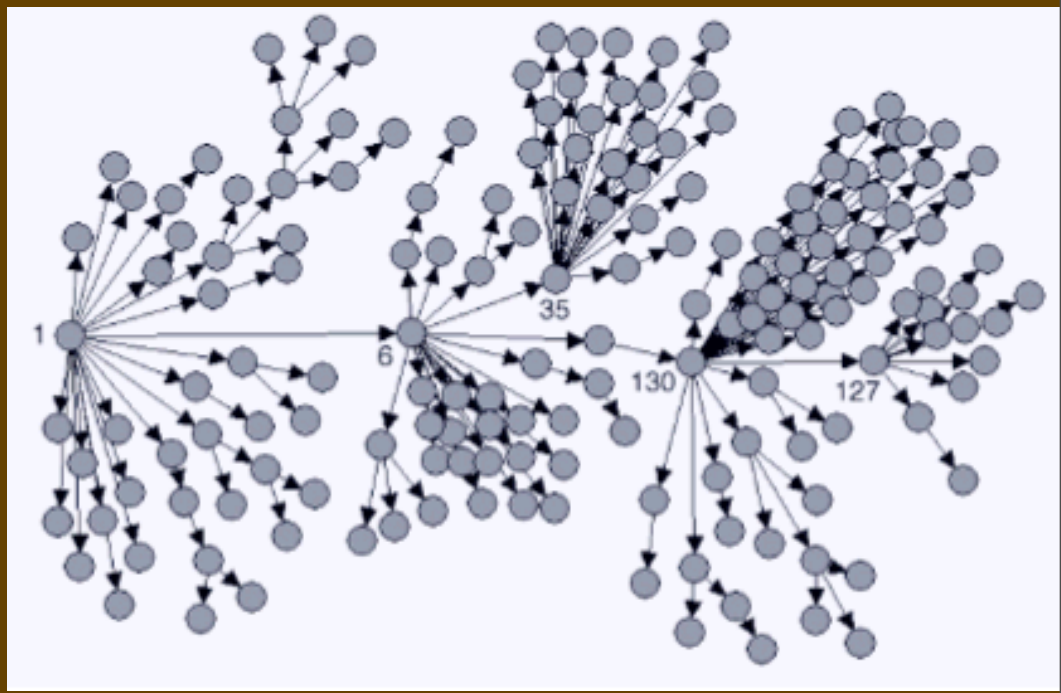

ν ~ gamma ⟺ Z ~ negative binomial
offspring
Z
parent
ν
Relatively few
Geometric
k=1
Poisson
k→∞
0.1
1
10
100
∞
greater individual heterogeneity (parameter k)

Empirical distributions

The unprecedented global effort to contain SARS generated extensive datasets through intensive contact tracing: unique opportunity to study individual variation in a disease of casual contact.



Beijing: Shen et al. EID (2004)



Singapore: Leo et al. MMWR (2003)

Superspreading events: Definition?
Useful concept?

Currently not useful!
Should measure variation

Beijing SARS hospital outbreak, 2003

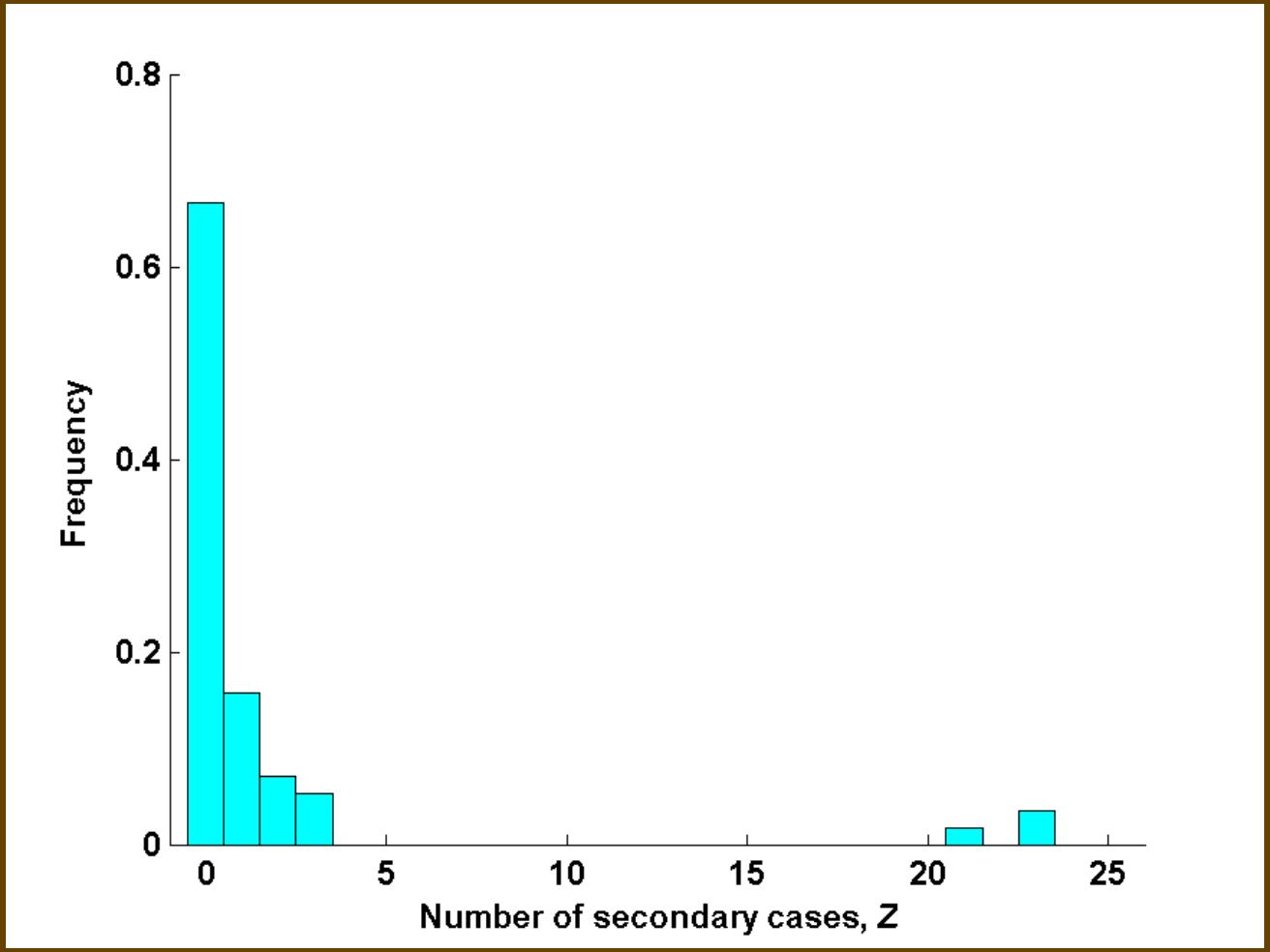
Number of secondary cases: note superspreader events in tail

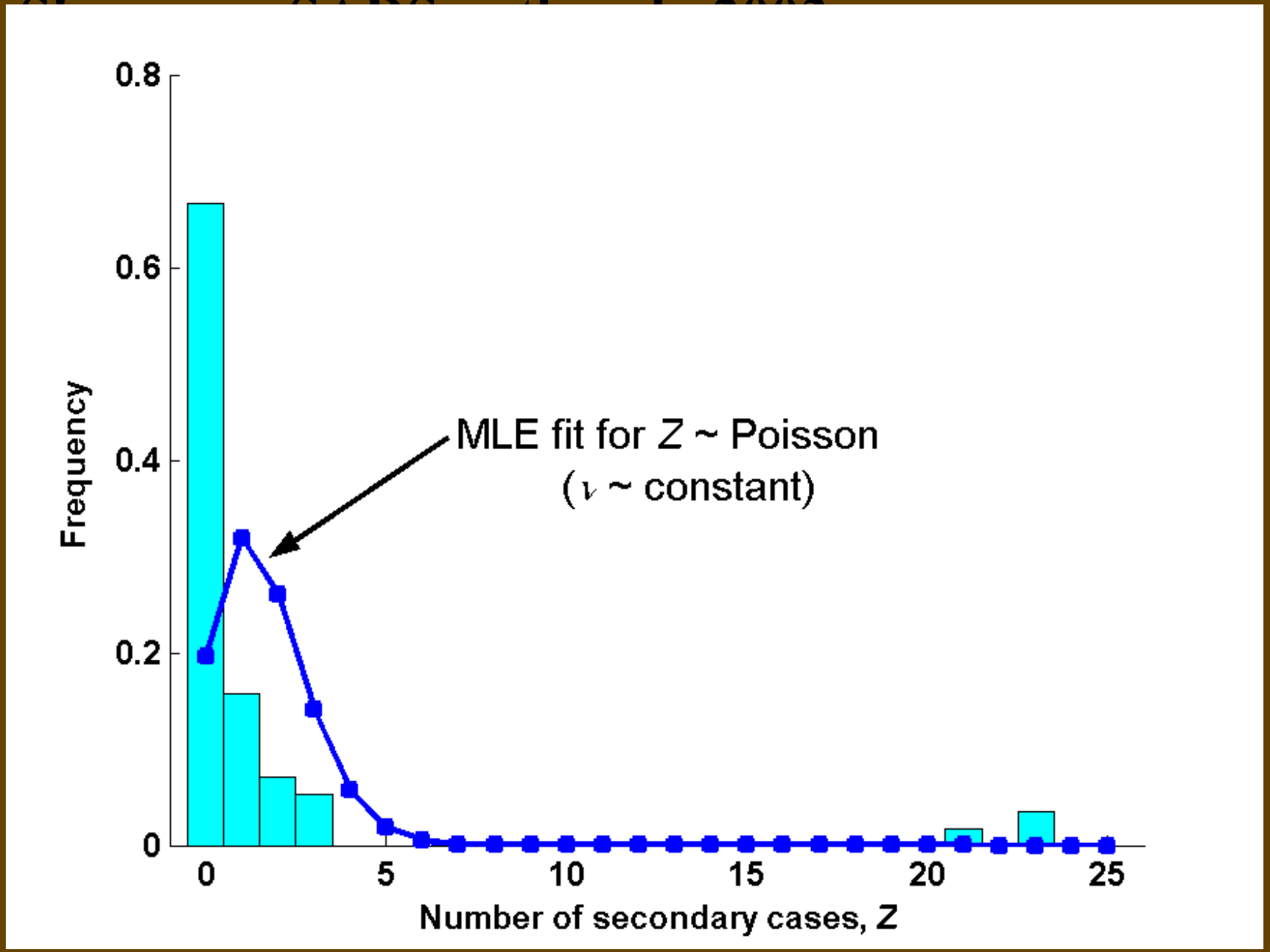
What fits best?

1. ν ~ constant
   $\Rightarrow$ Z ~ Poisson

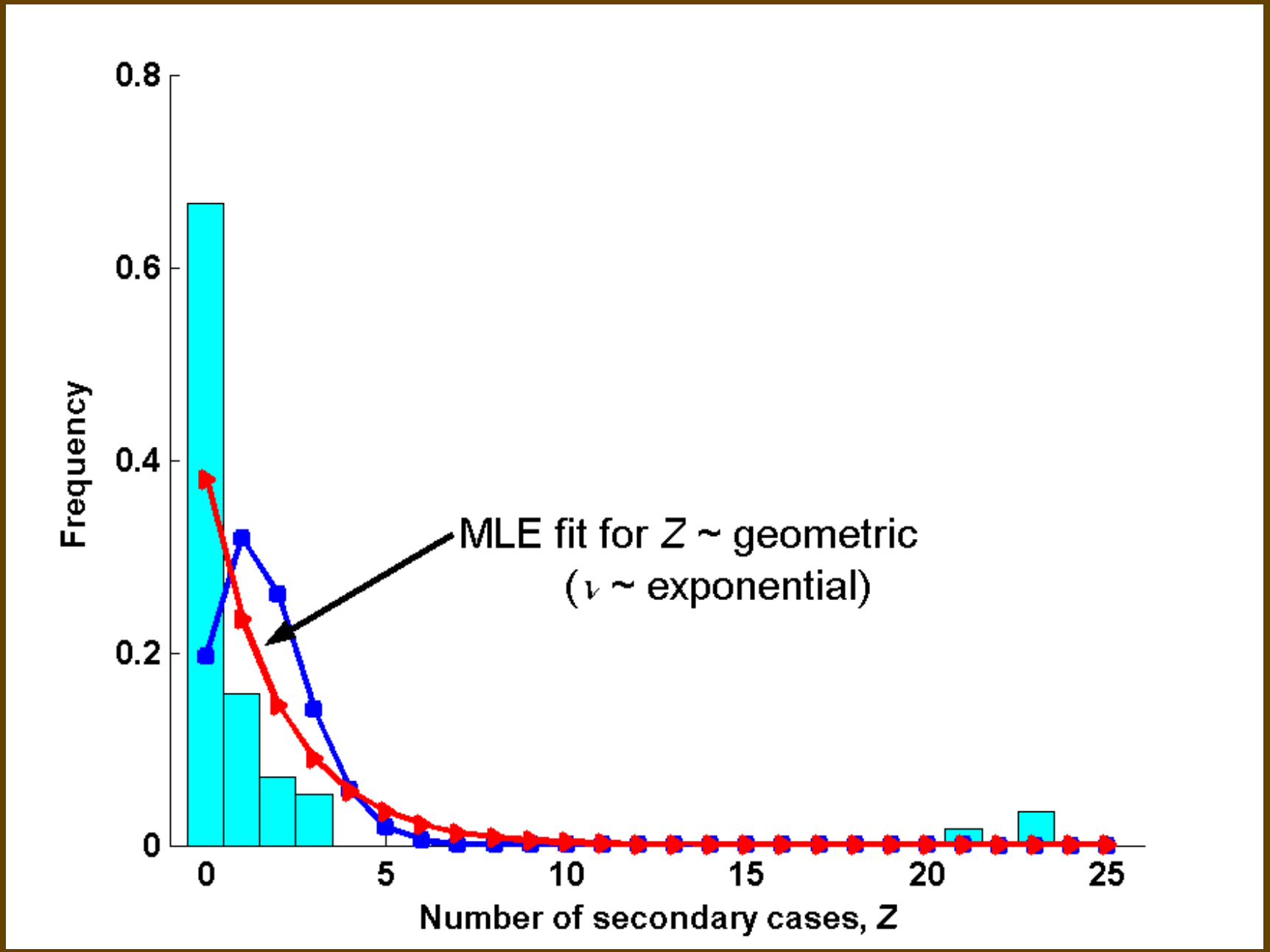
2. ν ~ exponential
   $\Rightarrow$ Z ~ geometric

3. ν ~ gamma
   $\Rightarrow$ Z ~ negative binomial

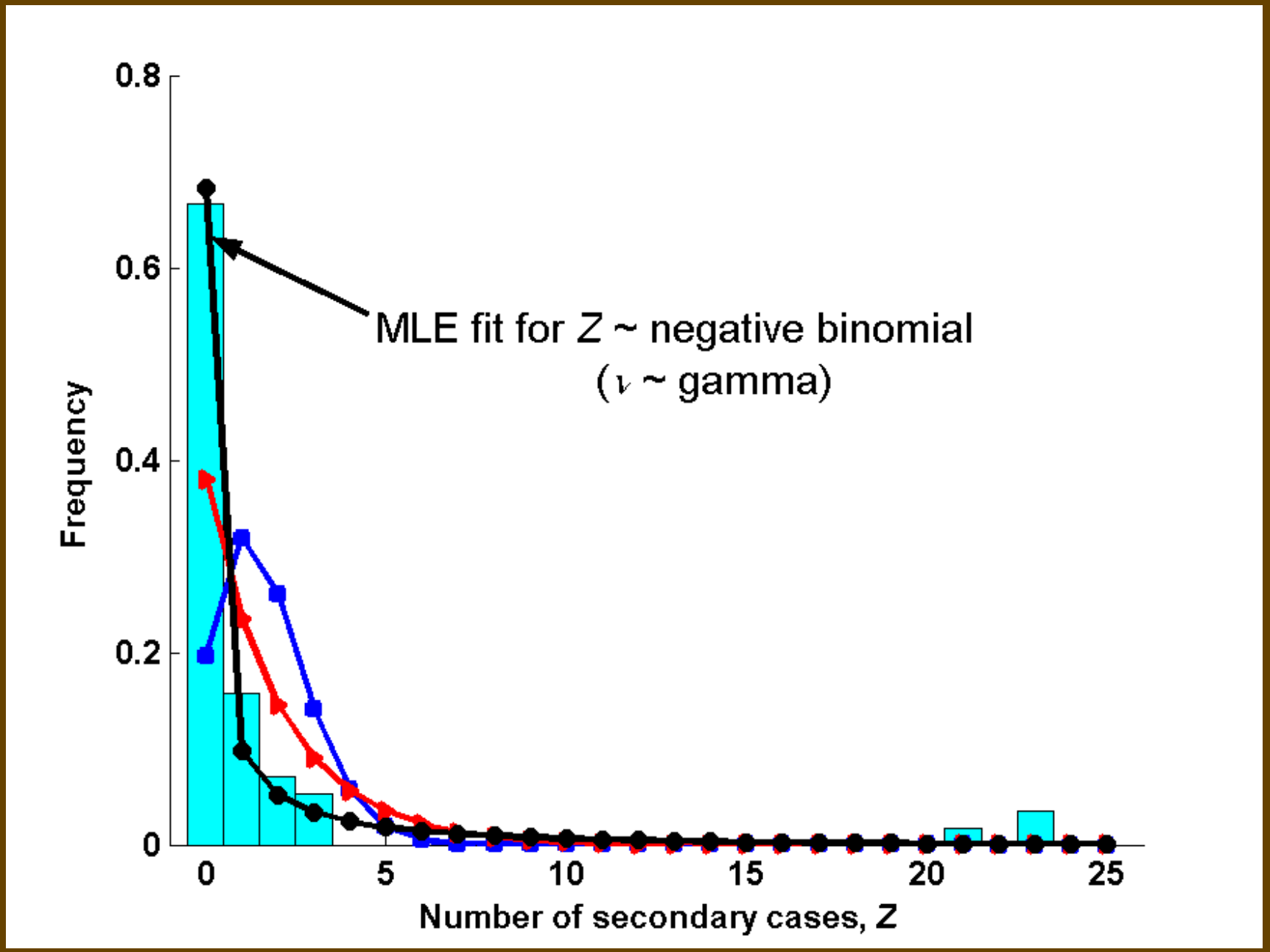



0.8
0.6
0.4
0.2
0
Frequency
MLE fit for Z ~ Poisson
(ν ~ constant)
0
5
10
15
20
25
Number of secondary cases, Z

Singapore SARS outbreak, 2003



Singapore SARS outbreak, 2003

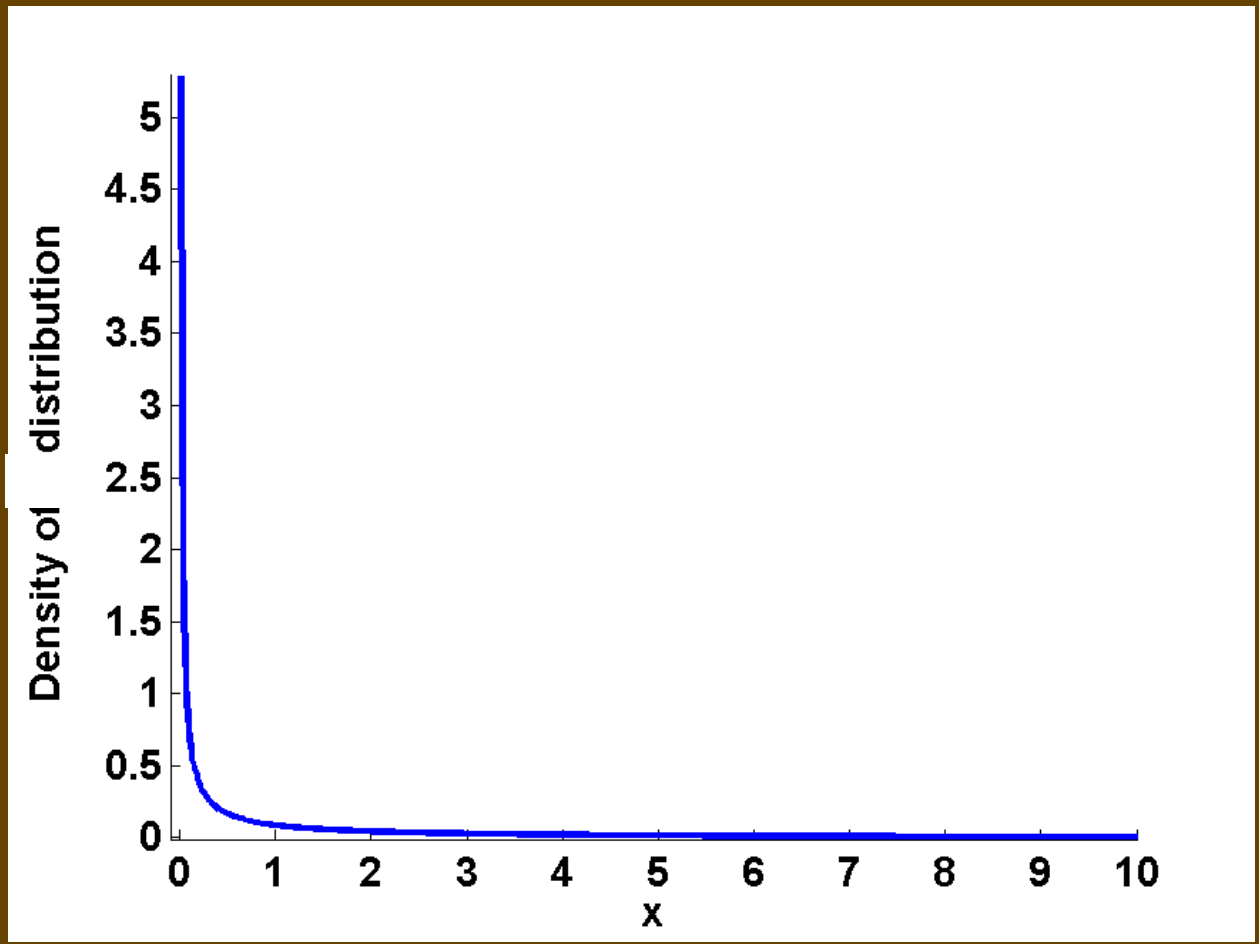


Singapore SARS outbreak, 2003

ν parent distribution	Z offspring distribution	ΔAIC_c	Akaike weight
$\nu \sim$ constant	Poisson	250.4	< 0.0001
$\nu \sim$ exponential	Geometric	41.2	< 0.0001
$\nu \sim$ gamma	Negative binomial	0	>0.9999

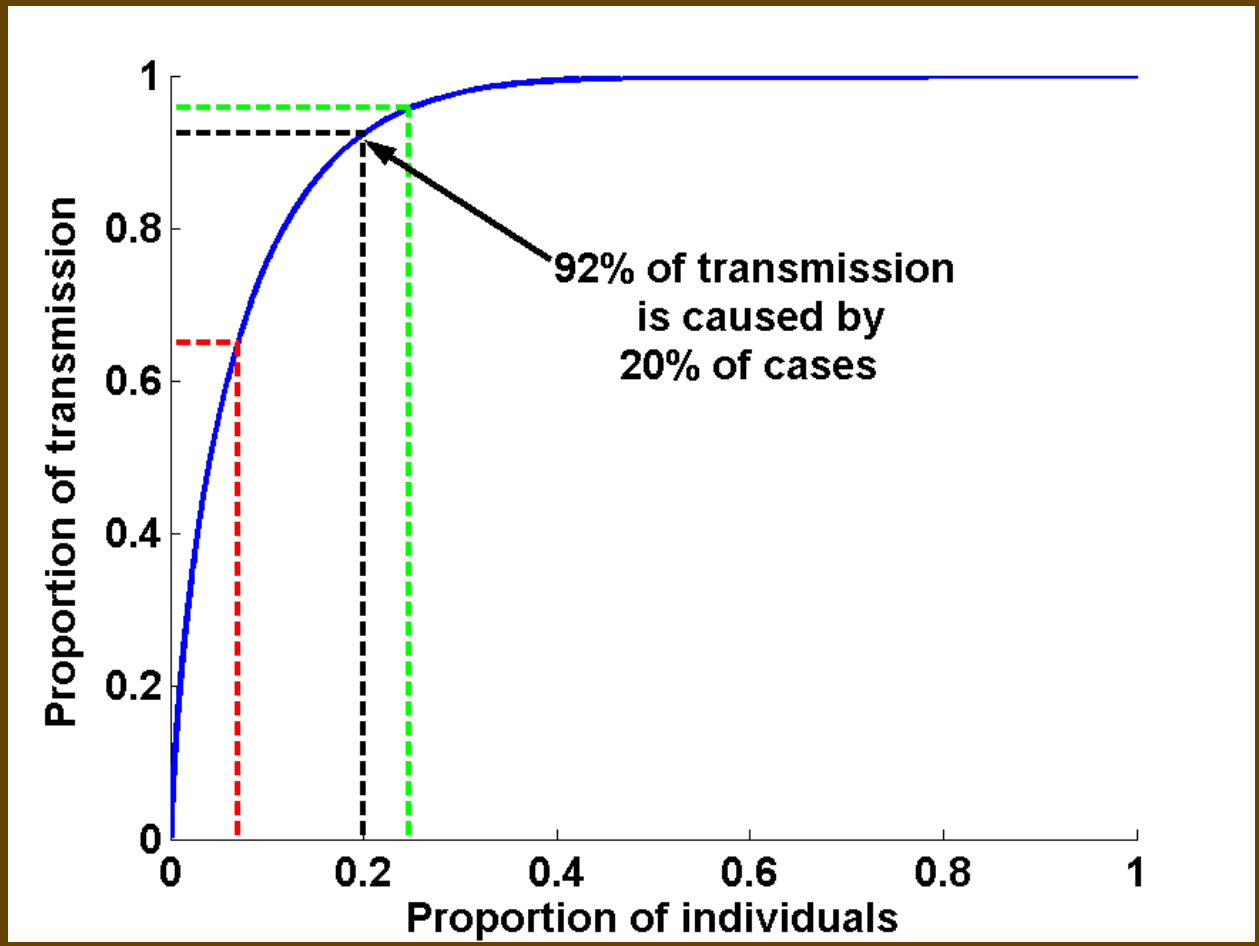
Model selection strongly favours NB distribution with MLE parameters R_0=1.63, k=0.16.

Singapore SARS outbreak, 2003



Parent distribution ν is highly overdispersed:
variance-to-mean ratio = 16.4

Singapore SARS outbreak, 2003



c.f. “20/80 rule”: 20% of cases cause 80% of transmission

Evidence heterogeneity in other diseases

SARS, smallpox, monkeypox, pneumonic plague, avian influenza, rubella

All show strong evidence for individual variation

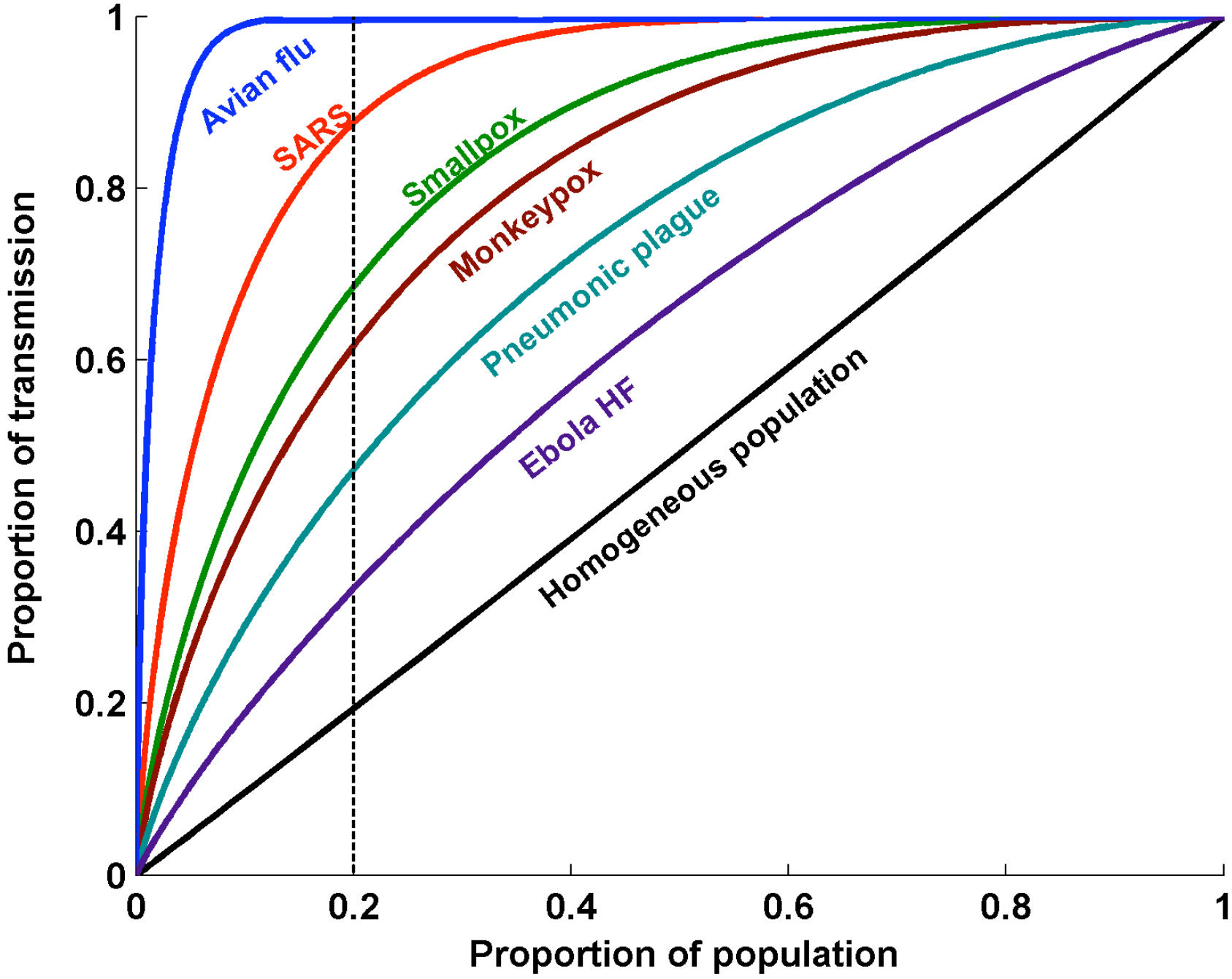
P = Poisson model for *Z*

generally rejected

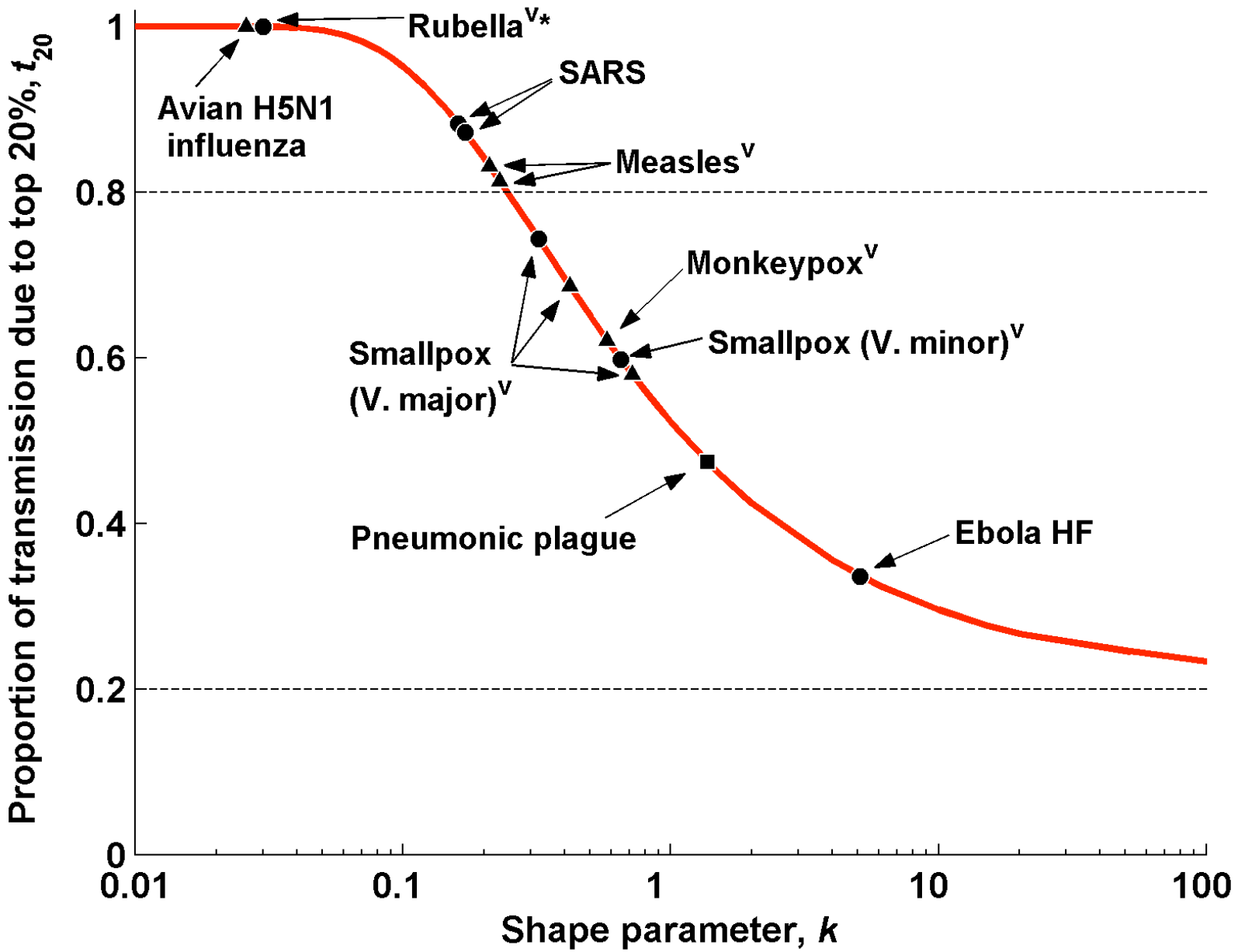
G = geometric model

NB = negative binomial model

Datasets	Model	ΔAIC_c	Akaike weight	$\hat{R}_{0,mle}$ (90% CI)	k_{mle} (90% CI)
SARS Singapore 2003 *N*=57	P G NB	250.4 41.2 0	0 0 1	1.63 (0.54,2.65)	0.16 (0.11,0.64)
SARS Beijing 2003 *N*=33	P G NB	49.2 10.6 0	0 0 1	0.94 (0.27,1.51)	0.17 (0.10,0.64)
Smallpox (V. major)[v80?] Europe 1958-1973 *N*=32[s]	P G NB	129.3 7.4 0	0 0.02 0.98	3.19 (1.66, 4.62)	0.37 (0.26, 0.69)
Smallpox (V. major)[v50] Benin 1967 *N*=25	P G NB	13.0 0.8 0	0 0.45 0.55	0.80 (0.32, 1.20)	0.32 (0.16,1.76)
Smallpox (V. minor)[v60?] England 1966 *N*=25	P G NB	16.4 0 1.7	0 0.71 0.29	1.60 (0.88,2.16)	0.65 (0.34,2.32)
Monkeypox[v70] Zaire 1980-84 *N*=147[s]	P G NB	10.6 0 1.0	0 0.62 0.37	0.32 (0.22,0.40)	0.58 (0.32,3.57)
Pneumonic plague 6 outbreaks *N*=74	P G NB	15.5 0 1.5	0 0.67 0.33	1.32 (1.01,1.61)	1.37 (0.88,3.53)
Avian influenza H5N1 Southeast Asia 2004 *N*=33[s]	P G NB	2.2 0.9 0	0.17 0.32 0.51	0.06 (0, 0.18)	0.026 $(0.026,\infty)$[u,b]
Rubella*[v50-70] Hawaii 1970 *N*=19	P G NB	83.5 25.4 0	0 0 1	1.00 (0.0,1.95)	0.032 $(0.013,\infty)$
Hantavirus (Andes)*† Argentina 1996 *N*=20	P G NB	1.0 0 2.3	0.31 0.52 0.17	0.70 (0.20,1.05)	1.66 $(0.24,\infty)$
Ebola HF† Uganda 2000 *N*=13	P G NB	0 1.4 2.4	0.56 0.28 0.17	1.50 (0.85,2.08)	5.10 $(1.46,\infty)$


Avian flu
SARS
Smallpox
Monkeypox
Pneumonic plague
Ebola HF
Homogeneous population
Proportion of transmission
Proportion of population
0
0.2
0.4
0.6
0.8
1

Revisiting the 20/80 rule



Superspreaders

washingtonpost.com

A 'Superspreader' of SARS

How One Woman Touched Off Beijing Outbreak

By Philip P. Pan
Washington Post Foreign Service
Thursday, May 29, 2003; Page A01

TAIYUAN, China -- She had been running a 1
week, and the city's best doctors were stumped
old businesswoman was suffering from a new
southern China, but knew nothing about how t

What makes a superspreader?

TIME
April 21, 2003

By Bryan Walsh/Hong Kong, With reporting by Genevieve Wilkinson/Singapore

IF you have to get sick, you might as well do it in Singapore. The Lion City state's public health-care system is one of the best in Asia, and its government-mandated obsession with hygiene borders on the compulsive. When the SARS epidemic first struck a month ago, Singapore earned praise for its decisive response of quarantining up to 1500 close contacts of SARS victims, even installing video cameras on their doorsteps to discourage excursions. Singapore's ring-fence approach seemed to work, as the number of new cases dropped to a daily handful--supporting early World Health Organization (WHO) statements that the spread of SARS, as dangerous as it was, could be stemmed with vigilant infection controls.

Is SARS spread by a modern-day Typhoid Mary?

Donald G. McNeil Jr. and Lawrence K. Altman Tuesday, April 15, 200
The New York Times

NEW YORK A child in China so infectious that he is nicknamed "the poison emperor." A Chinese doctor who infects 12 fellow guests in his Hong Kong hotel, who then fly to Singapore, Vietnam and Canada. An elderly Canadian woman who infects three generations of her family.

Watching as the mysterious illness called severe acute respiratory syndrome hopped around the world and exploded in new outbreaks, epidemiologists began to ask themselves an unsettling question: Is it carried by "superspreaders"?

The notion that some people are hyperinfective, spewing germs like boiling teakettles while others simmer quietly like stew pots, has been around for at least a century, ever since Typhoid Mary became notorious in 1907.

For some diseases, including tuberculosis, smallpox and staphylococcus infections,

Superspreaders May Hold SARS Clue

By Kristen Philipkoski | Also by this reporter

02:00 AM May. 21, 2003 PT

In the race to stop severe acute respiratory syndrome, a little-understood group known as "superspreaders" may hold important clues -- or they may be just a myth.

Superspreaders are individuals who seem to spread the virus to larger

Superspreading Events (SSEs)

How many cases make an SSE?

SARS, 2003:

- $Z \geq 8$, Shen *et al*. Emerg. Infect. Dis. (2003)
- $Z > 10$ Wallinga & Teunis, Am. J. Epidem. (2004)
- $Z \geq 10$ Leo *et al*. MMWR (2003)
- "many more than the average number", Riley *et al*. Science(2003)

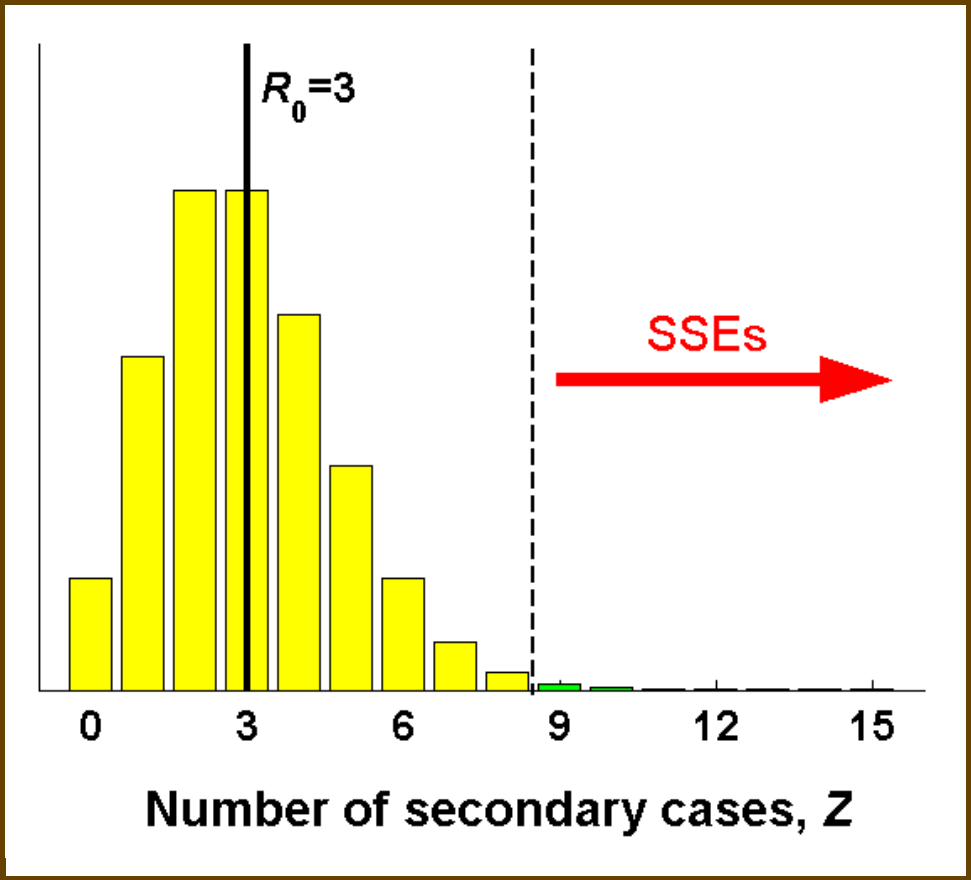
But what about measles (R_0~18) or monkeypox (R_0~0.8)?

How to account for the influence of stochasticity?

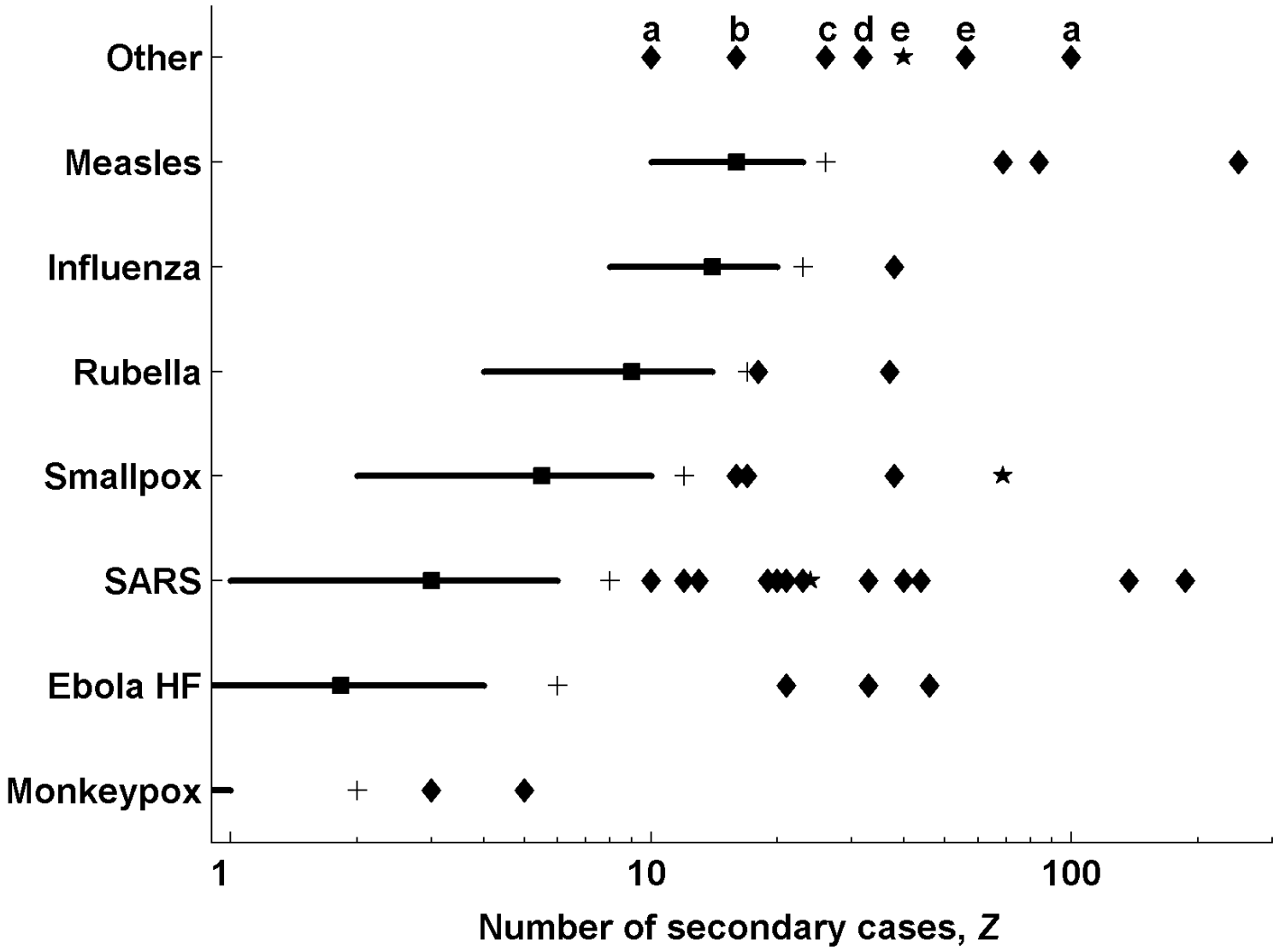
We need a general, scaleable definition of a SSE, based on probabilistic considerations.

Proposed definition for superspreading events

1. Set context for transmission by estimating effective R_0.
2. Generate Poisson (R_0) representing expected range in Z due to stochastic effects in absence of individual variation
3. Define an SSE as any case who infects more than $Z^{(99)}$ others, where $Z^{(99)}$ is the 99th percentile of Poisson (R_0).



Superspreading events (SSEs)



■ R_0

\+ 99th percentile of Poisson (R_0)

♦ reported SSEs

★ SSEs with >1 index case

Superspreading Load

Calculate R_0 from data and $Z^{\text{Pois-99}}$ using Poisson model

(number of infections demarcating 99 percentile)

Fit negative binomial $\text{NegB}(R_0,k)$ to data

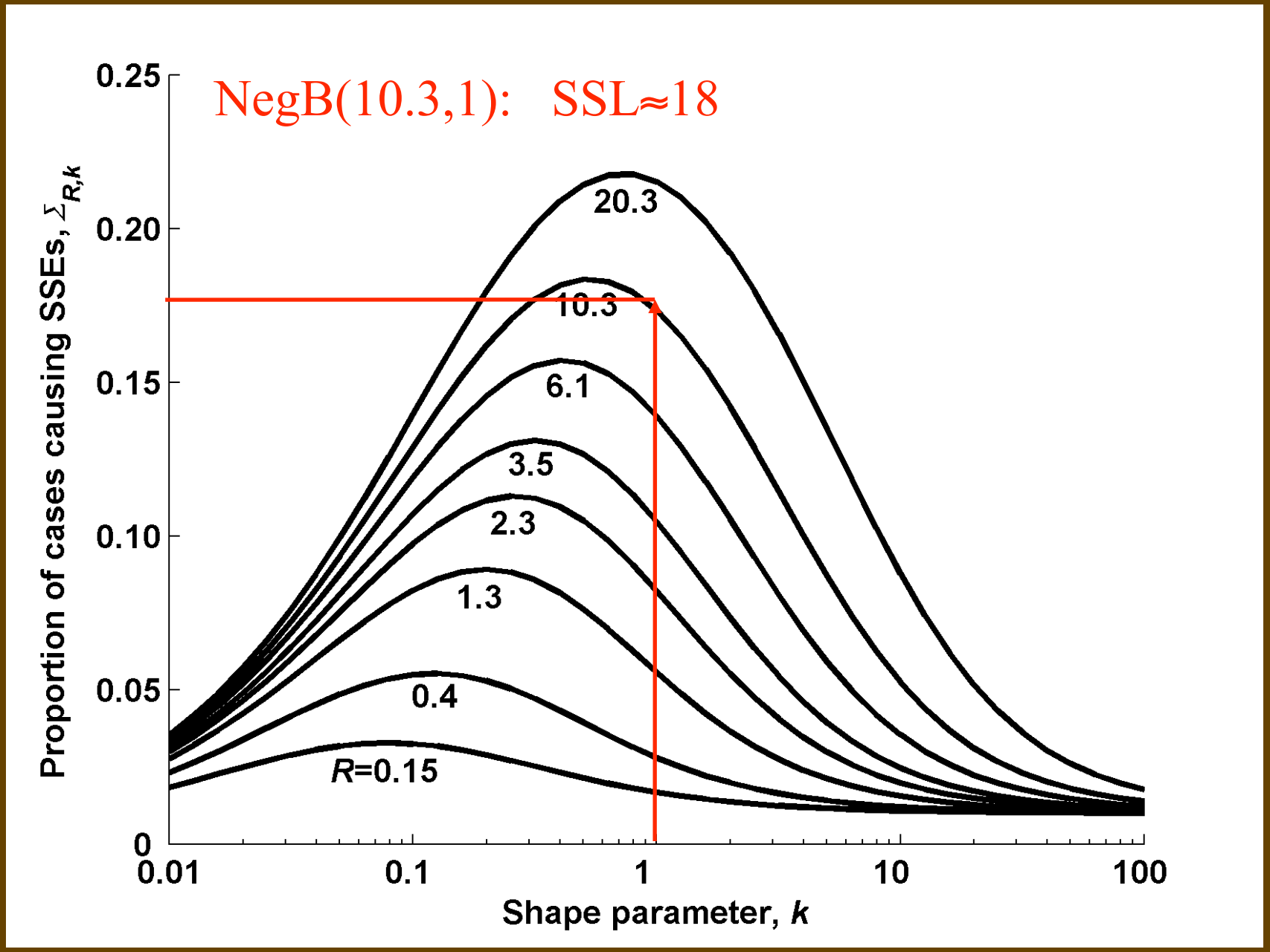
Construct cummulative distribution $\Phi_{\text{NB}}(Z^{\text{Pois-99}})$

Calculate proportion in tail beyond $Z^{\text{Pois-99}}$

$\Psi_{\text{NB}}(Z^{\text{Pois-99}}) = 1 - \Phi_{\text{NB}}(Z^{\text{Pois-99}})$

Superspreader load (SSL) is $1 - \Psi_{\text{NB}}(Z^{\text{Pois-99}}) / 0.01$

Predicting frequency of SSEs in Negative Binomial epidemics $\mathrm{NegB}(R_0,k)$



Implications for disease invasion

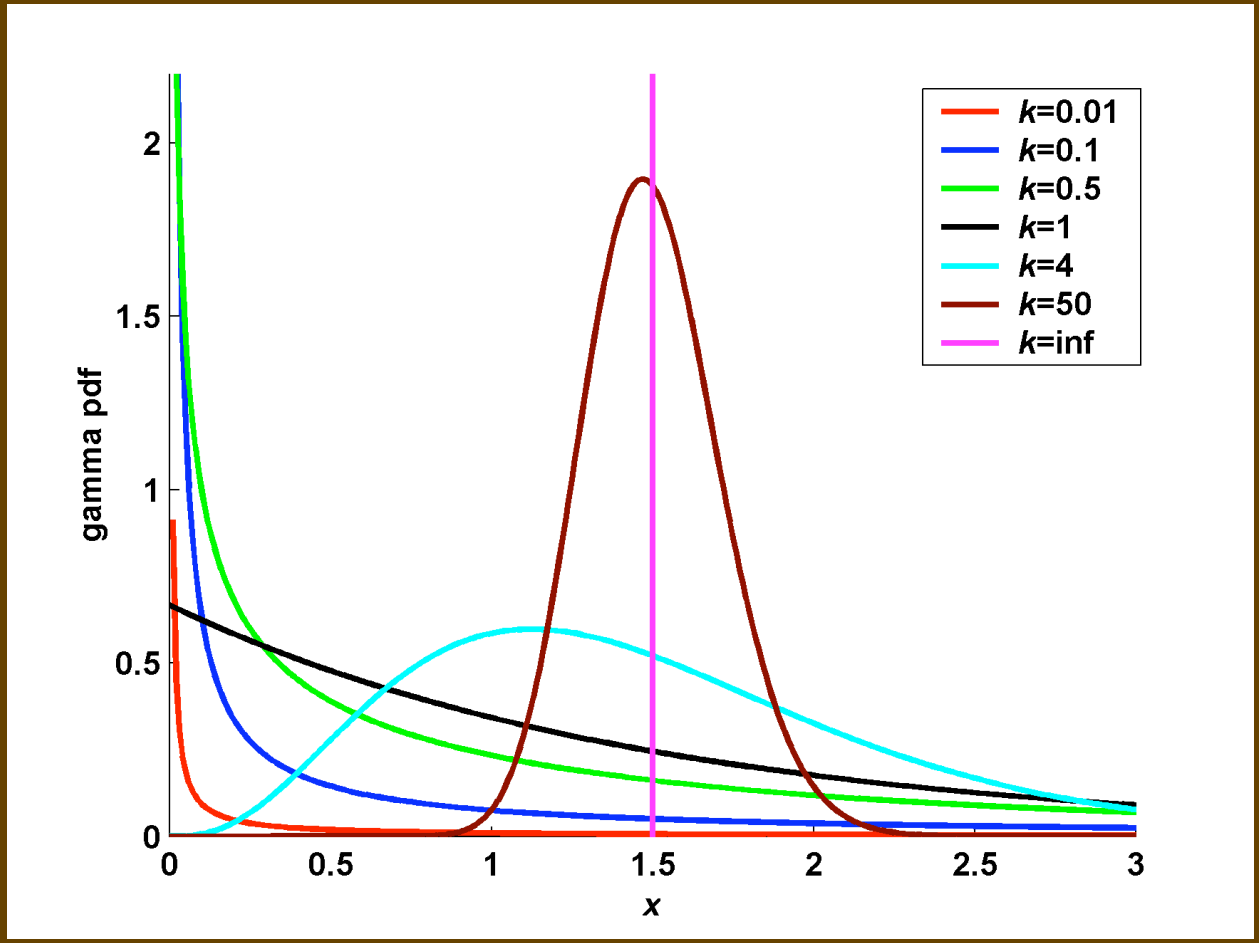
Data from 10 diseases of casual contact show that individual variability in ν is a universal phenomenon.

How does this variability affect:

- Probability of stochastic extinction? (infinite population)
- Timing of extinction?
- Size of minor outbreak? (i.e prior to extinction)
- Rate of growth if major outbreak occurs?

We explored these questions using branching process models for $\nu \sim$ gamma

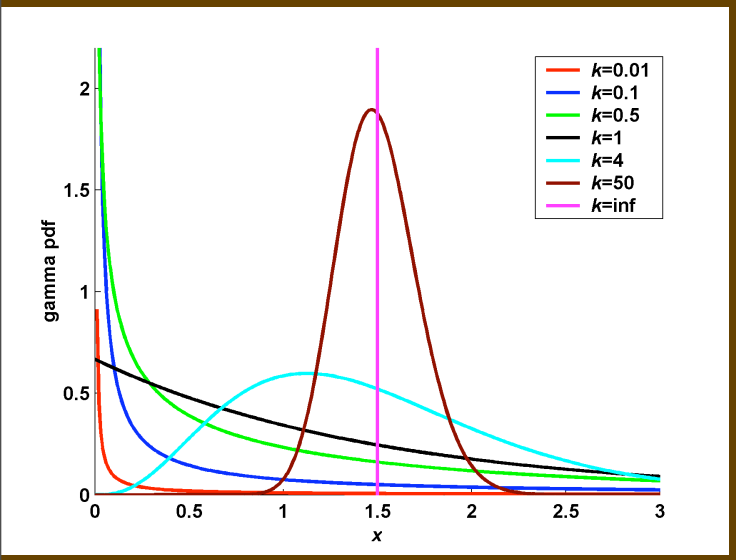
Various Gamma distributions with R_0=1.5



Special cases: $k = 1$ exponential ν: Geometric offspring dist.

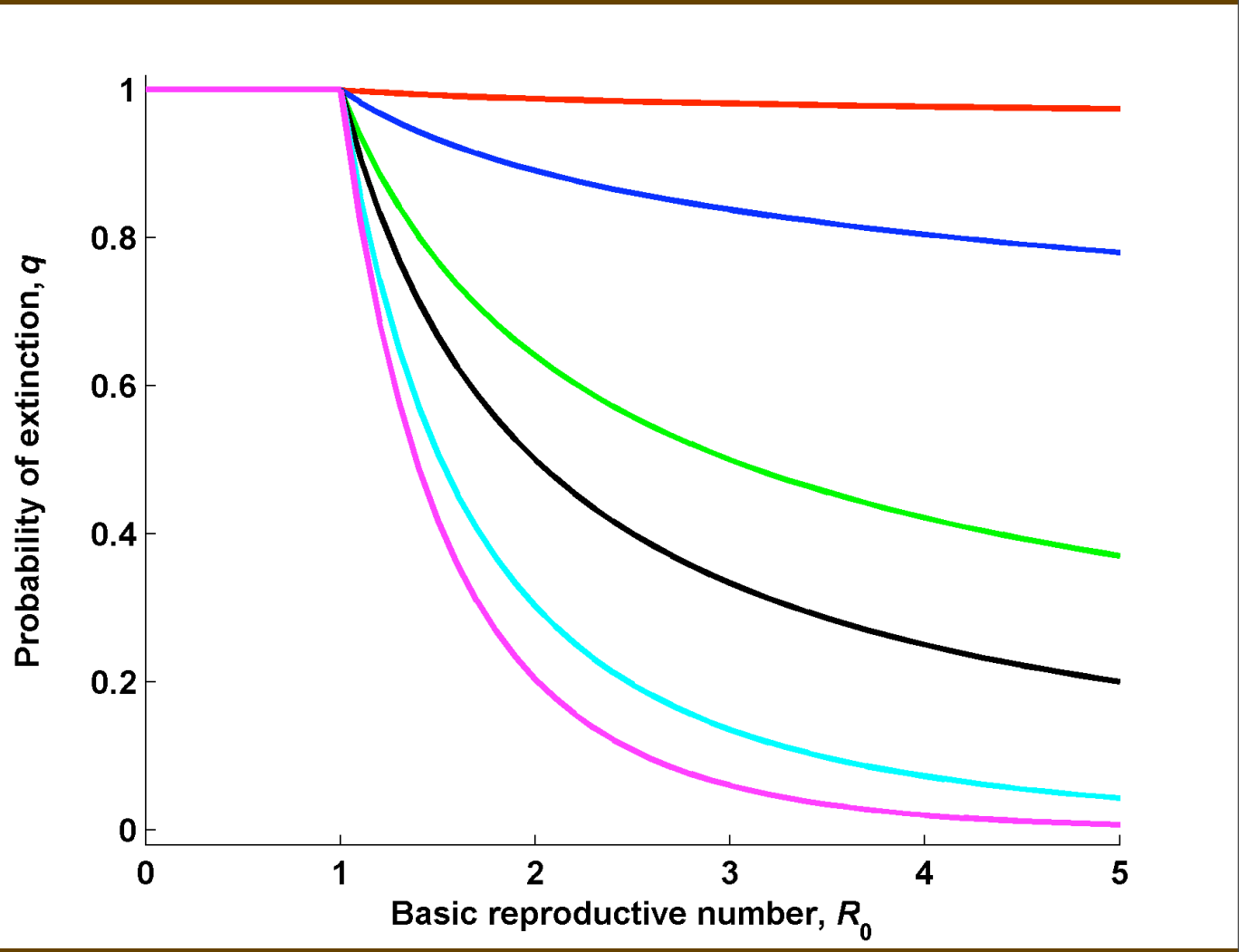
k=infty constant ν: Poisson offspring dist.

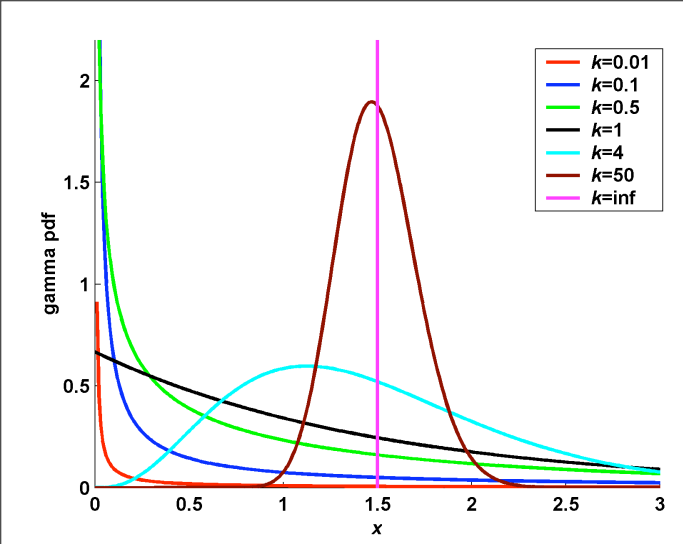
smaller k greater variance in ν: Neg Biomial offspring dist. more aggregated



Probability of disease extinction

Greater variation in ν favors stochastic extinction, due to higher $\Pr(Z=0)$.

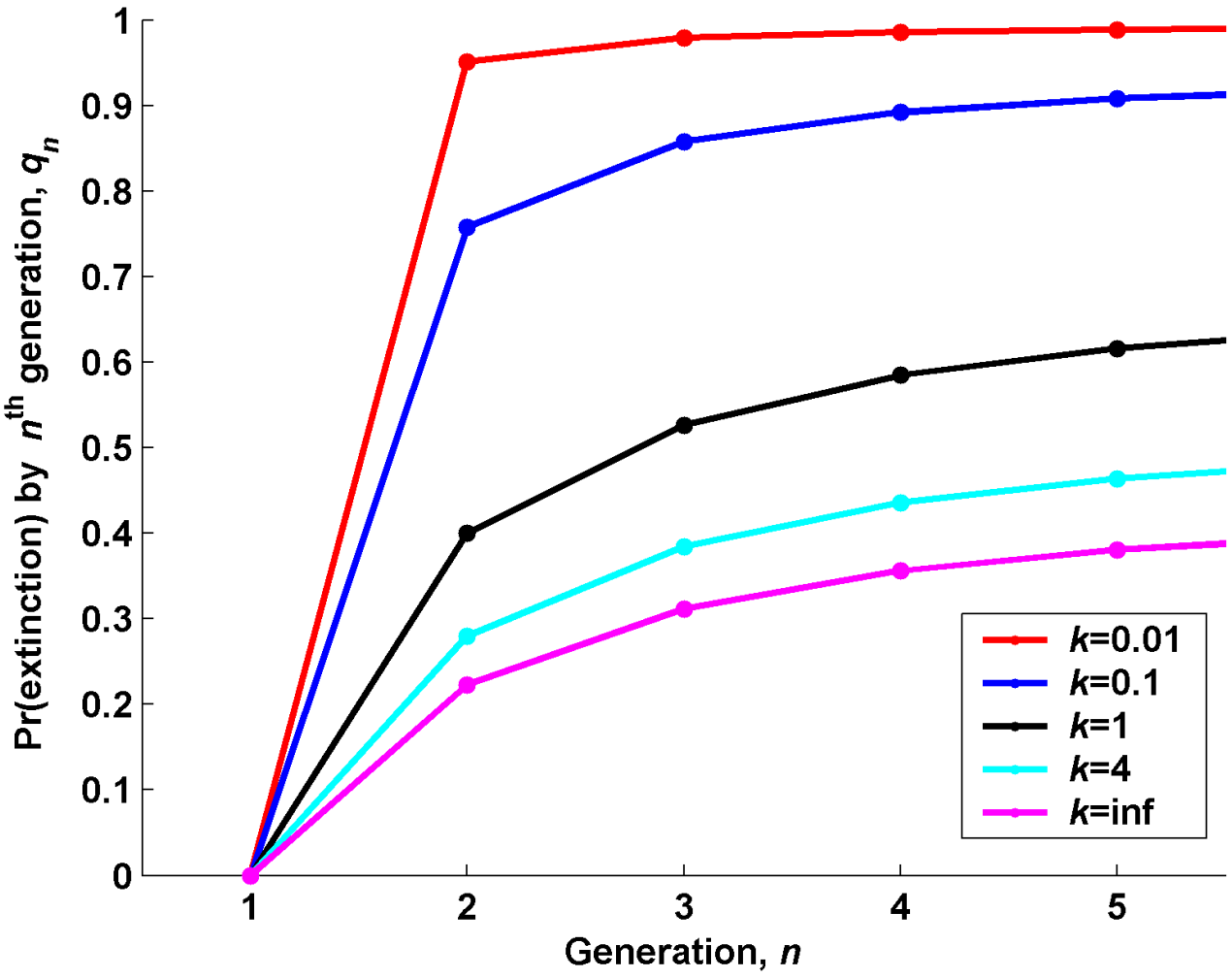




Time to stochastic extinction

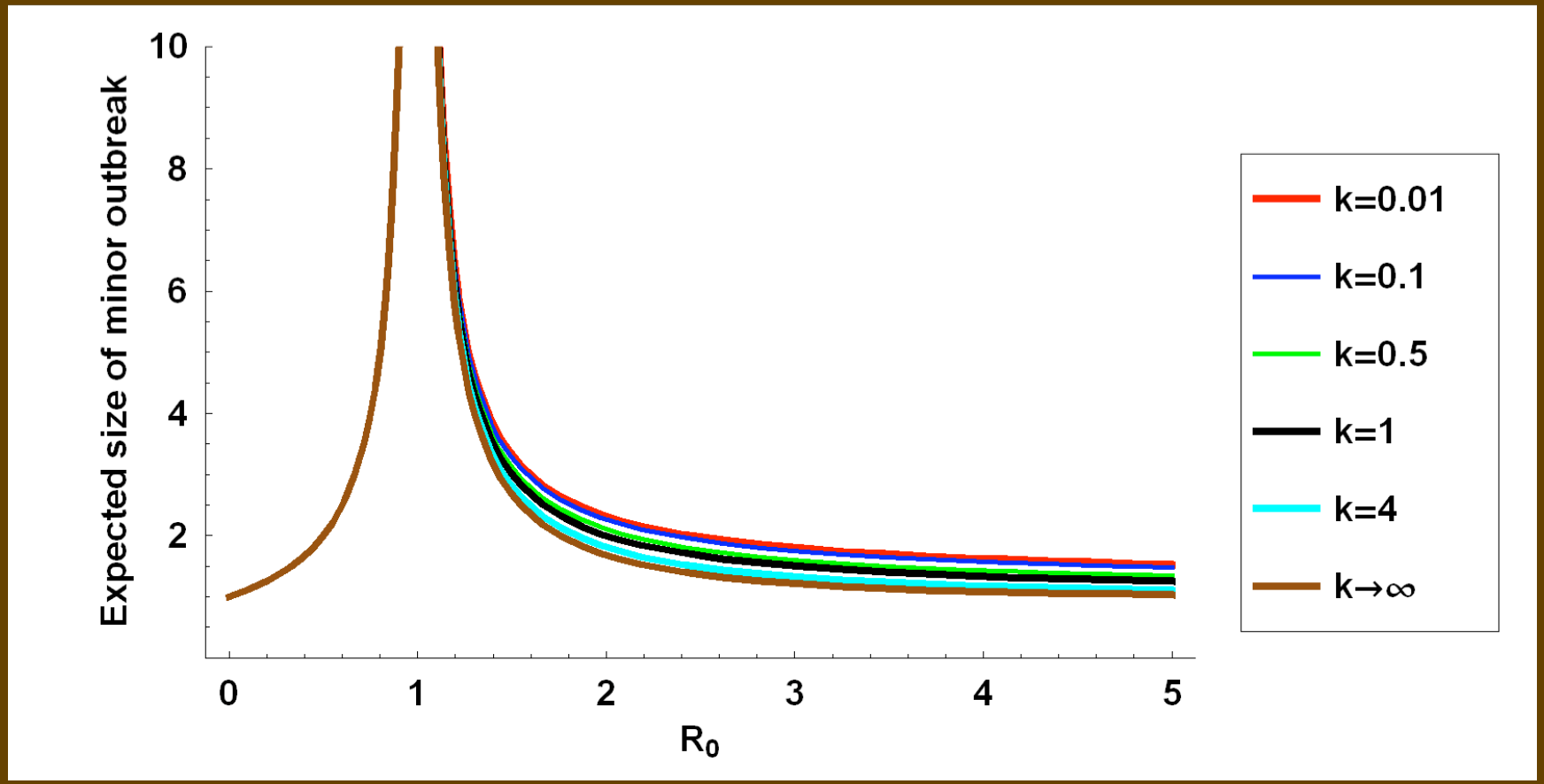
High variability in ν (small k) ⇒ extinction happens fast or not at all.

Implications for detection of emerging pathogens



Expected size of minor outbreak

(i.e. epidemic in infinite pop goes extinct)



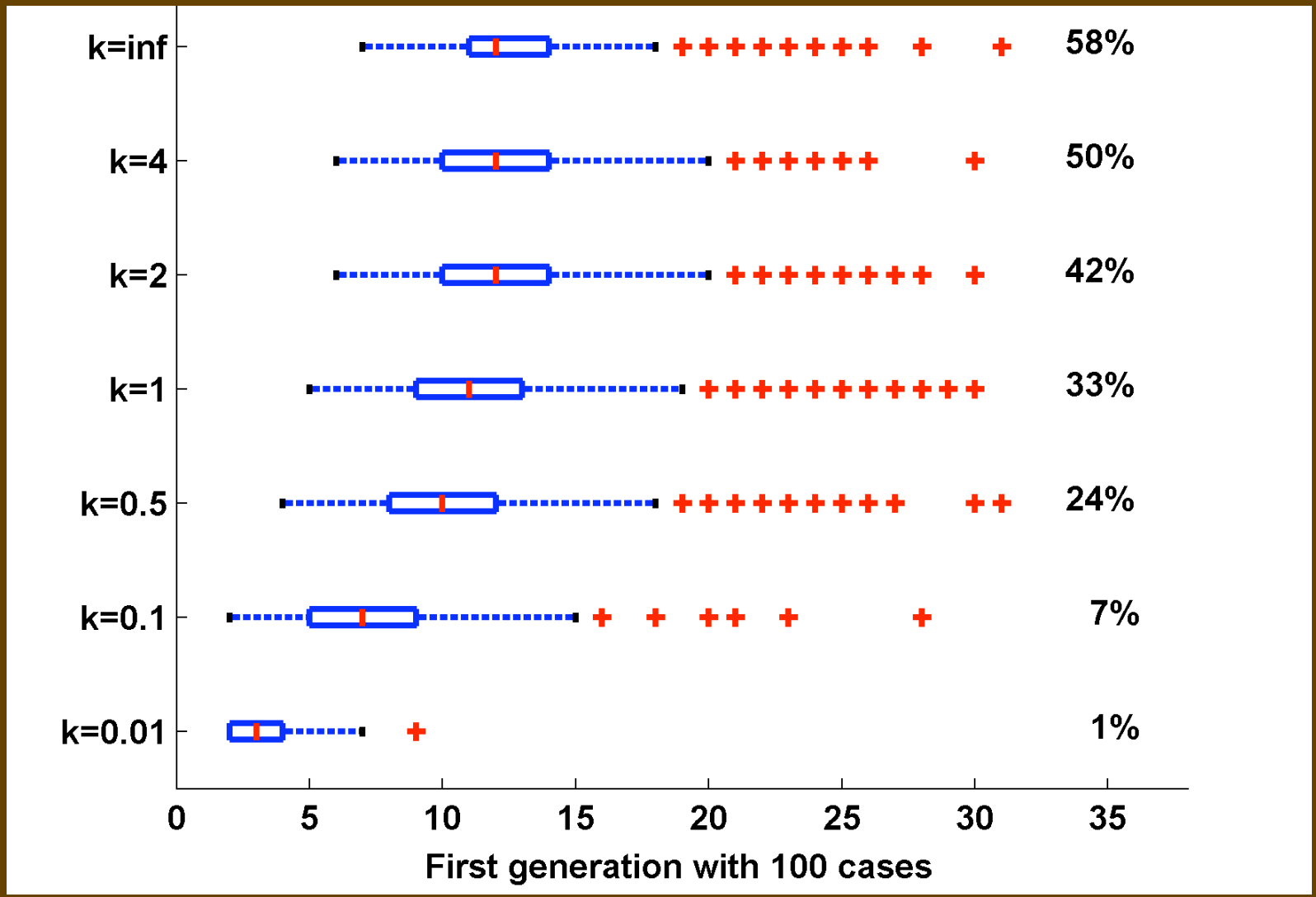
$R_0 < 1$ E(total # cases) = $1/(1-R_0)$

i.e. independent of k

$R_0 > 1$ E(total # cases)

depends very weakly on k

Rate of growth of major epidemic



Greater variability ⇒ major outbreaks are rare but explosive!

Conclusion

- Data imply considerable heterogeneity in epidemics
- Heterogeneity needed to explain rare explosive outbreaks, as in SARS
- To estimate level of heterogeneity we need *BOTH* R_0 and p_0 (proportion of cases *NOT* transmitting) or SSL statistic
- Control measures should target individuals in tails of parent distribution and hence reduce probability of explosive outbreaks

How to do this an important area of research?

Thanks!

The End

This research is supported by the US NIH, NSF,
and James S. McDonnell Foundation