For further information please contact Seth Blumberg (sblumberg@ucla.edu).

Disentangling the transmission dynamics of human monkeypox and other emerging zoonoses

Seth Blumberg

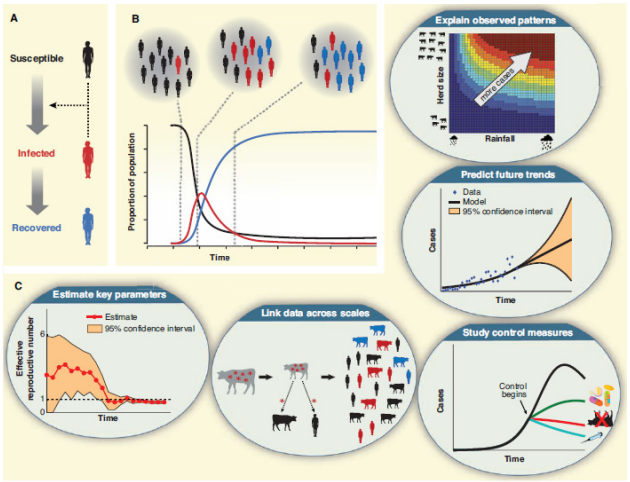
RAPIDD Postdoctoral Fellow

NIH Fogarty / UC Los Angeles

FOGARTY

My Background

University of Michigan Health System



Lloyd-Smith et al, Science (2009)

Infections disease dynamics

Lloyd-Smith lab
UCLA

Zoonotic pathogens

Zoonoses are infections of vertebrate animals that transmit naturally to humans.

e.g. ‘swine flu’, SARS, HIV, plague, West Nile virus, rabies, etc.

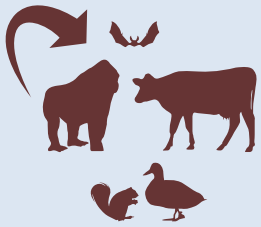
Major impact on human health

- 58% of all human pathogens are zoonotic (*Woolhouse & Gowtage-Sequeria 2005*)
- 60-76% of recent emerging infectious diseases (*Taylor et al 2001; Jones et al 2008*)
- Biggest epidemics in history: Black Death, Spanish influenza, HIV/AIDS

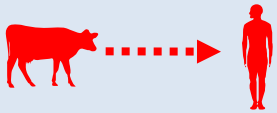
Fascinating and challenging population dynamics

- Complex multi-species interaction with frequent ‘invasion’ events.
- Disease dynamics arise from transmission within and among host species.

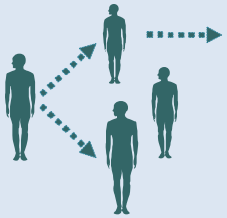
Key processes in zoonotic dynamics



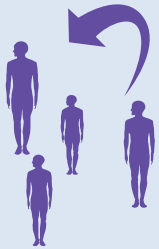
Circulation in reservoir



Cross-species spillover



Stuttering chains (R_0<1)



Epidemics and persistence (R_0>1)

Stage II pathogens, e.g. rabies

- The basic reproductive number, R_0, is the average number of secondary cases infected by a typical case in a wholly susceptible population.
- $R_0 > 1$ is threshold for sustained transmission.

Stage IV pathogens, e.g. pandemic influenza

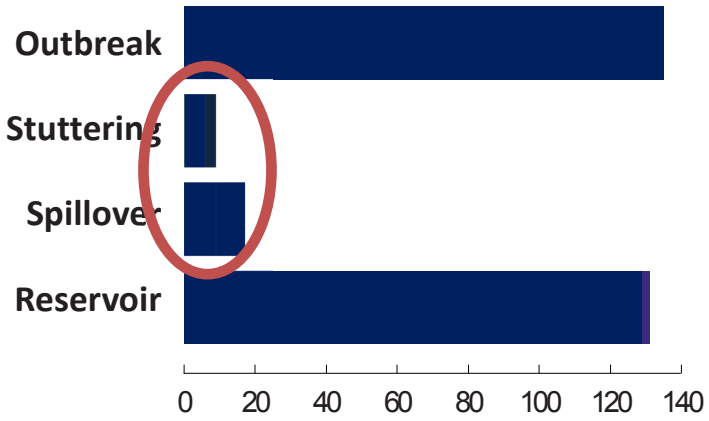
Epidemic Dynamics at the Human-Animal Interface

James O. Lloyd-Smith,[1,2]† Dylan George,[2,3]* Kim M. Pepin,[4]* Virginia E. Pitzer,[2,4]*
Juliet R. C. Pulliam,[2]* Andrew P. Dobson,[5] Peter J. Hudson,[2,4] Bryan T. Grenfell[2,4,5]

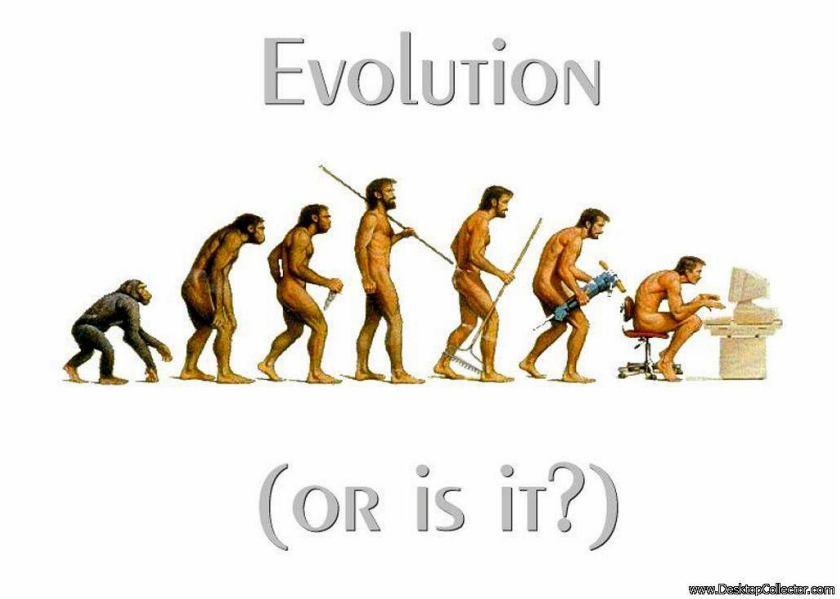
Reviewed 442 modeling papers on 85 zoonotic pathogens.

AIMS:

- Identify strengths, weaknesses, crucial gaps.
- Set priorities for research.



Summary: Evolution questions



- How can one determine if evolution or ecology is a stronger regulator of emergence?
- How should one think about effective population size and fitness in the presence of cross-species transmission and within-species population structure?
- How do genetic bottlenecks and population structure affect phylogenetic inference of between-host transmission?
- For constant fitness, when is there an evolutioanry advantage of supershedding?

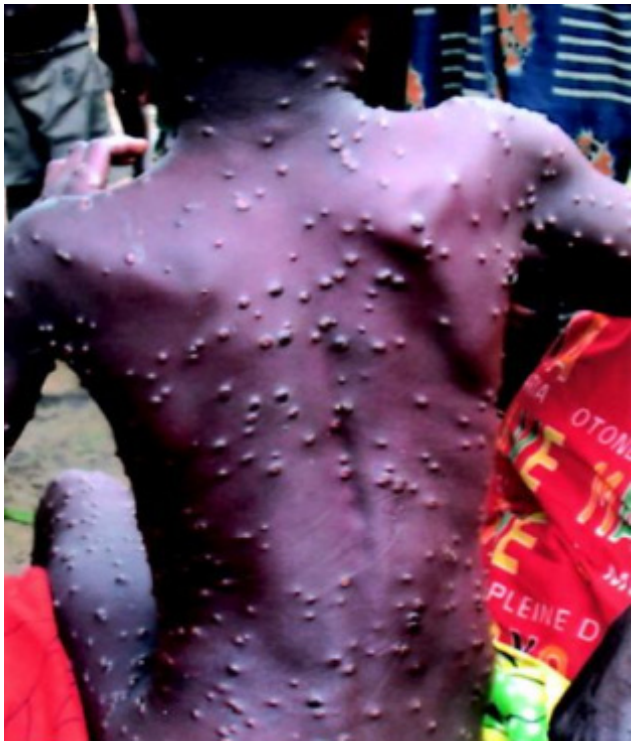
Acknowledgements

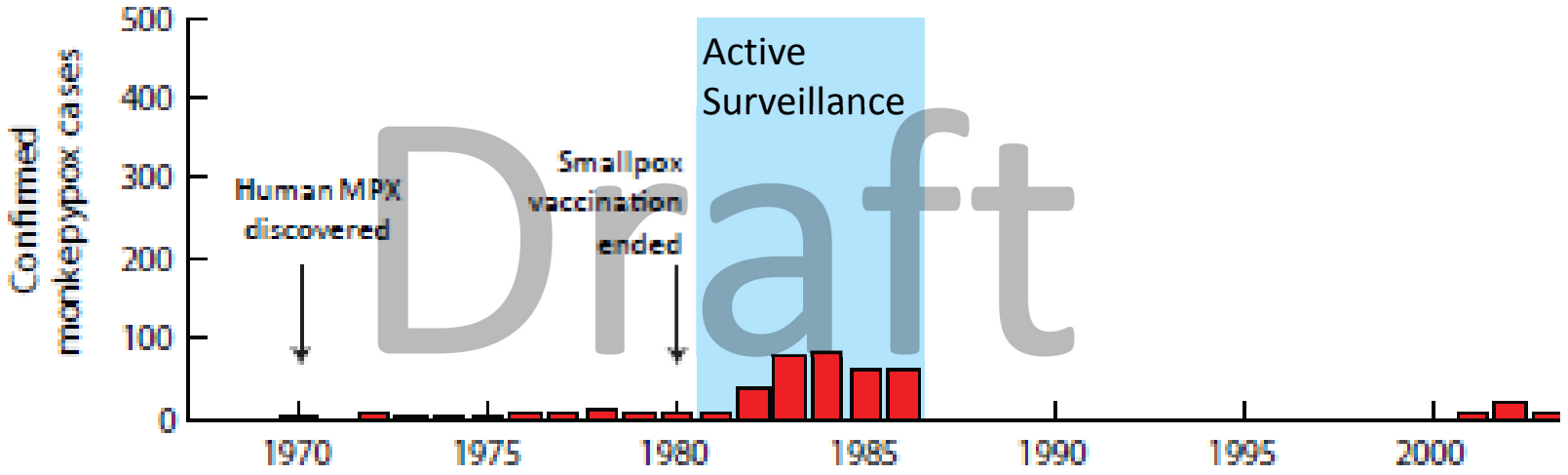
Principal Investigator: Jamie Lloyd-Smith , UCLA Dept of Epidemiology

Collaboration with Anne Rimoin, UCLA Dept of Epidemiology, and her team: Prime Mulembakani, Neville Kisalu, Henri Thomassen, Trevon Fuller and many more in the field and lab.

FOGARTY

Human Monkeypox





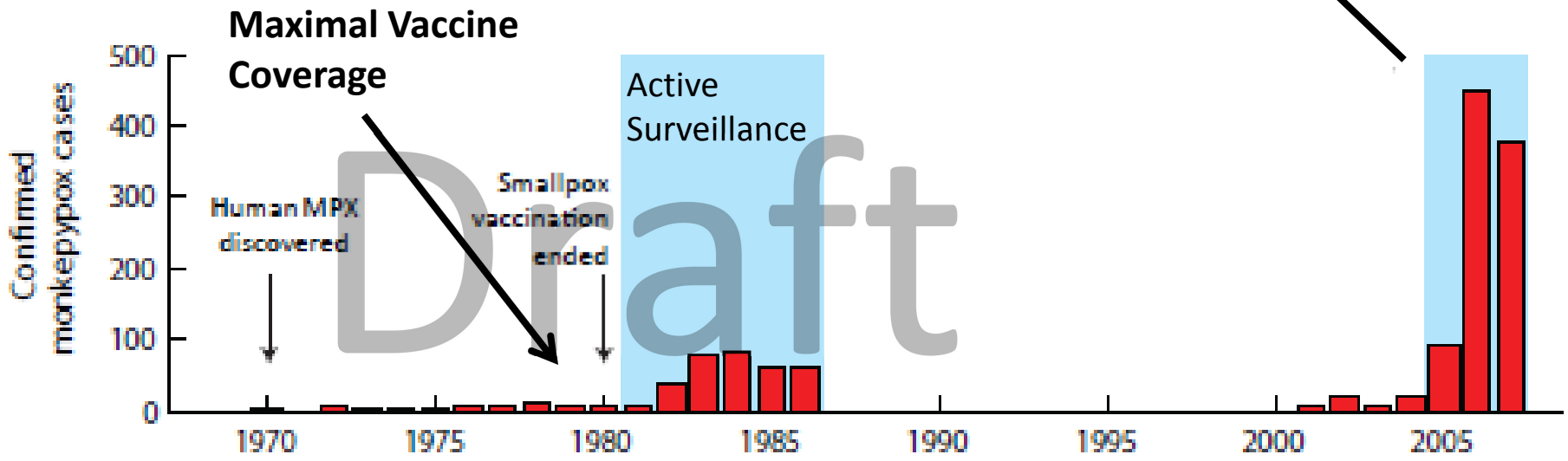
Human Monkeypox

PNAS

Major increase in human monkeypox incidence 30 years after smallpox vaccination campaigns cease in the Democratic Republic of Congo

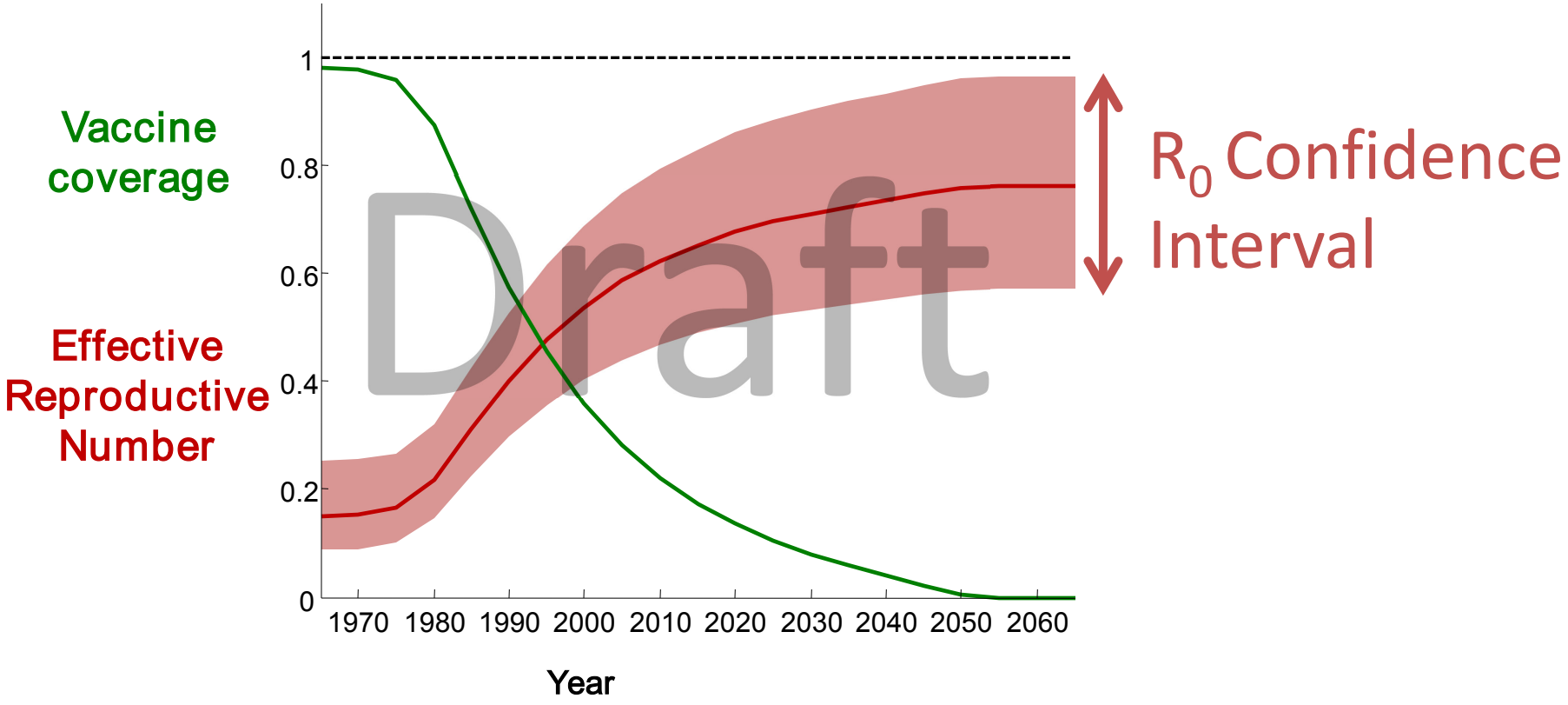
Anne W. Rimoin[a,b,1], Prime M. Mulembakani[c], Sara C. Johnston[d], James O. Lloyd Smith[b,e], Neville K. Kisalu[f], Timothee L. Kinkela[c], Seth Blumberg[b,e], Henri A. Thomassen[g], Brian L. Pike[h], Joseph N. Fair[h], Nathan D. Wolfe[h], Robert L. Shongo[i], Barney S. Graham[j], Pierre Formenty[k], Emile Okitolonda[c], Lisa E. Hensley[d], Hermann Meyer[l], Linda L. Wright[m], and Jean-Jacques Muyembe[n]

per capita incidence increased by factor of 20 (95% CI, 14-29) between 1981-86 and 2005-07.

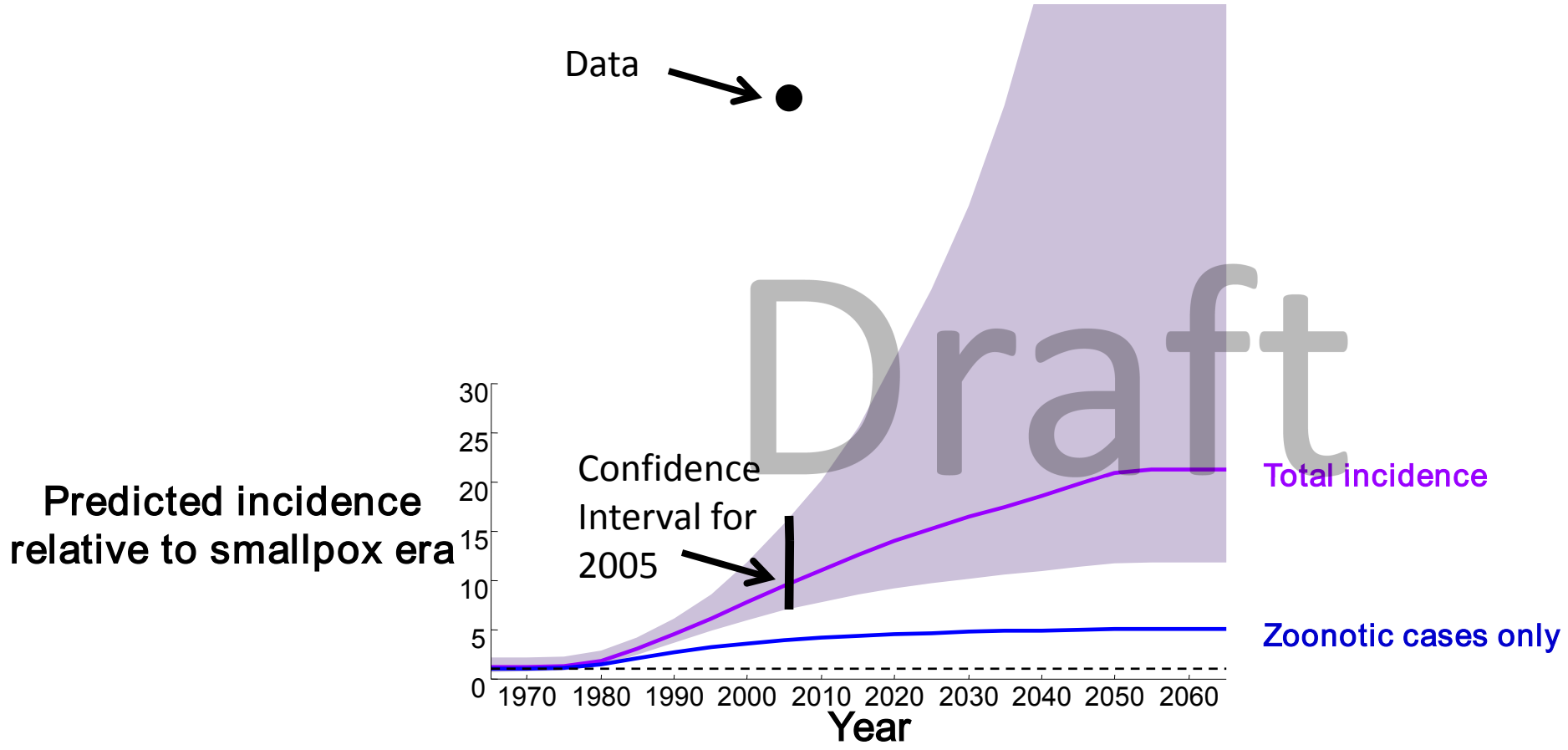


Deterministic emergence of human monkeypox?

- Is the population still protected by immunity to smallpox?
- What will happen when this immunity is gone?



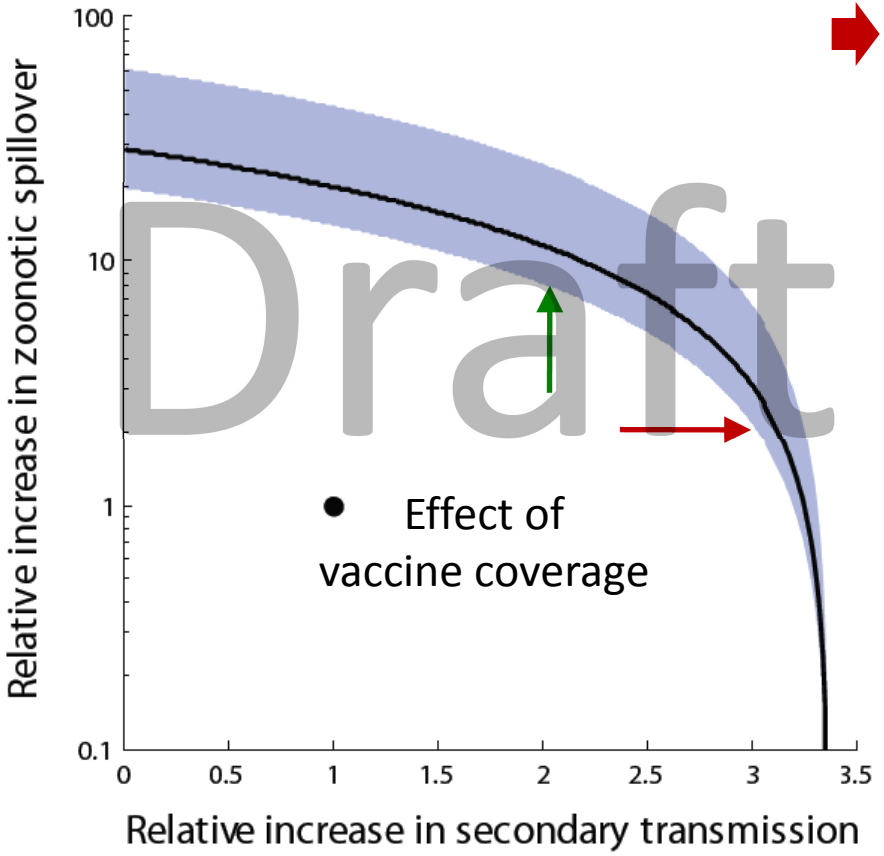
Does declining vaccine coverage explain observed increase in monkeypox incidence?



Possible causes of increased incidence

Total incidence rate = **Rate of zoonotic spillover events** × **Mean number of cases per spillover event**

= λ_{sp} × $1/(1-R_0)$



- Calculate changes in spillover or human-to-human transmission needed to observe a 20-fold increase.

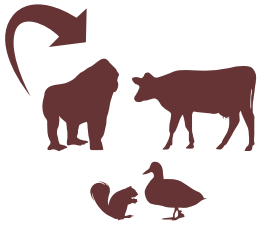
After accounting for vaccine coverage, still requires a further

50-60% increase in R_0

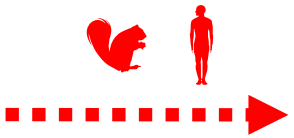
or

250-700% increase in spillover.

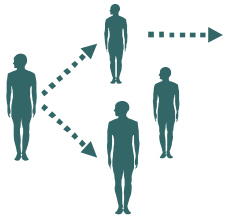
What else has changed?



Circulation in reservoir

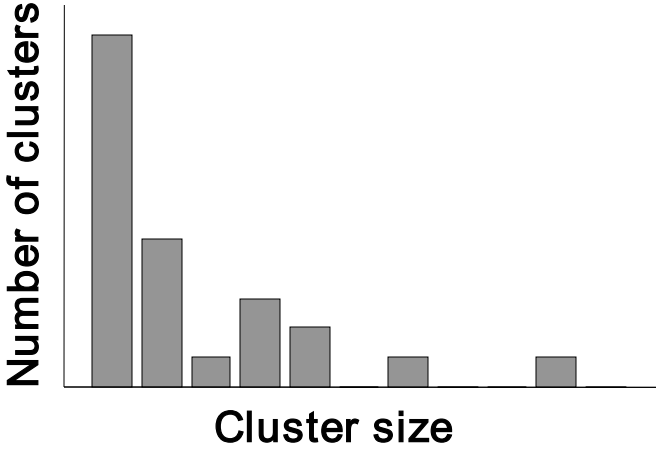


Cross-species spillover



Stuttering chains (R_{eff}<1)

R_{eff} Inference

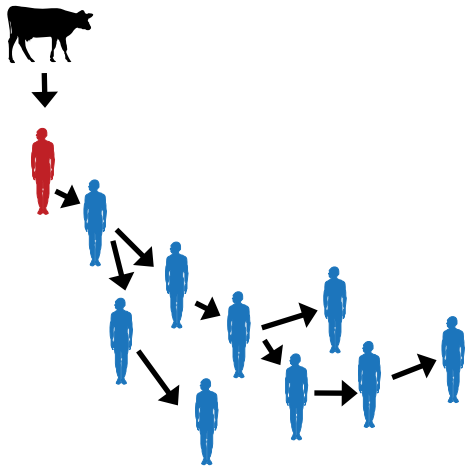


Mean cluster size:

$1+R_0 + R_0^2 + \ldots$

$= 1/(1-R_0)$

$$R_{eff} = 1 - \frac{\text{\# of clusters}}{\text{\# of cases}}$$



R_{eff} = Fraction of cases due to secondary transmission

Maximum Likelihood estimation of R_{eff}

$$P(Model \mid Data) = \frac{P(Data \mid Model)\ P(Model)}{P(Data)}$$

Transforming progeny distribution into a cluster size distribution

$$T_j(s) = [Q(s)]^j \qquad r_j = \frac{1}{j!} T_j^{(j-1)}|_{s=0}$$

Generating Function for a negative binomial distribution

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

Cluster size distribution when the progeny distribution is a negative binomial

$$r_j = \frac{\Gamma(kj+j-1)}{\Gamma(kj)\Gamma(j+1)} \frac{\left(\frac{R_0}{k}\right)^{j-1}}{\left(1+\frac{R_0}{k}\right)^{kj+j-1}}$$

Likelihood Calculation

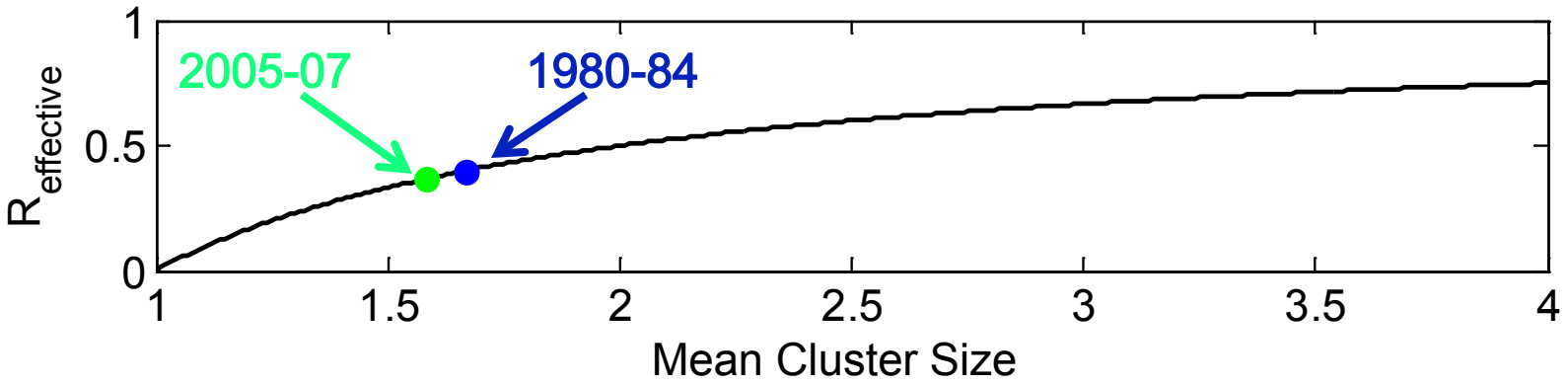
$$L = \prod_{j=1}^{\infty} r_j^{n_j}$$

Does additional data help?

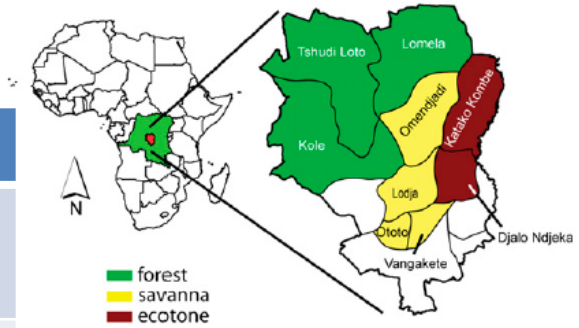
$$R_0 = 1 - \frac{\text{\# of clusters}}{\text{\# of cases}}$$

- ~~Incorporation of full cluster size distribution assuming a negative binomial offspring distribution~~
- ~~Utilization of the number of generations in each cluster~~
- ~~Utilization of contact tracing data~~

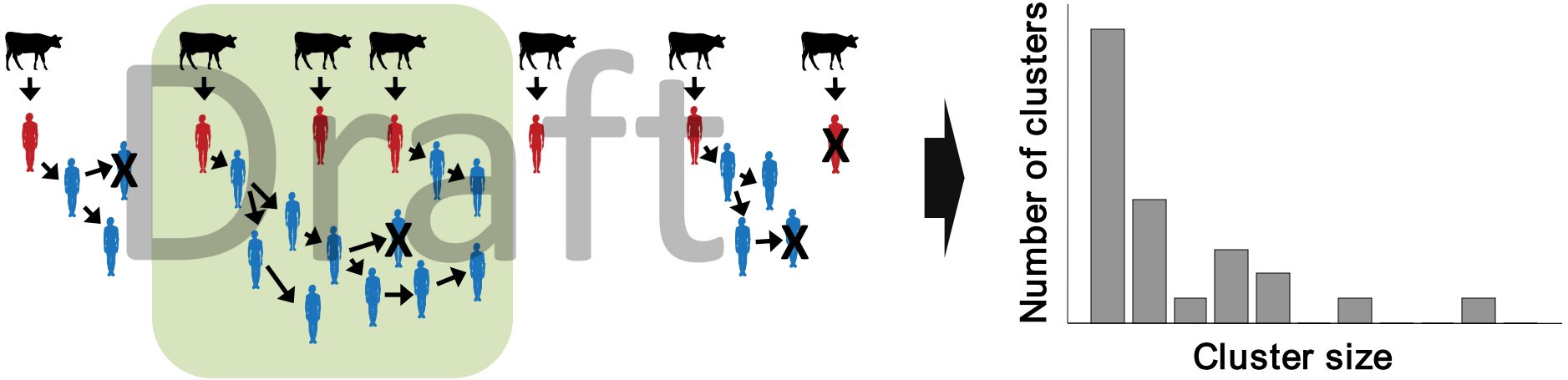
Cluster sizes are a marker of human transmissibility



1980-1984	2005-2007
Experienced, well-trained field teams	Relatively Inexperienced field team
Well Funded	Limited Resources
Monetary rewards for case identification	No financial rewards
Retrospective case identification by contact tracing and serology	Case identification required sampling during active infection



Inferring R_{eff} - our measure of human transmissibility

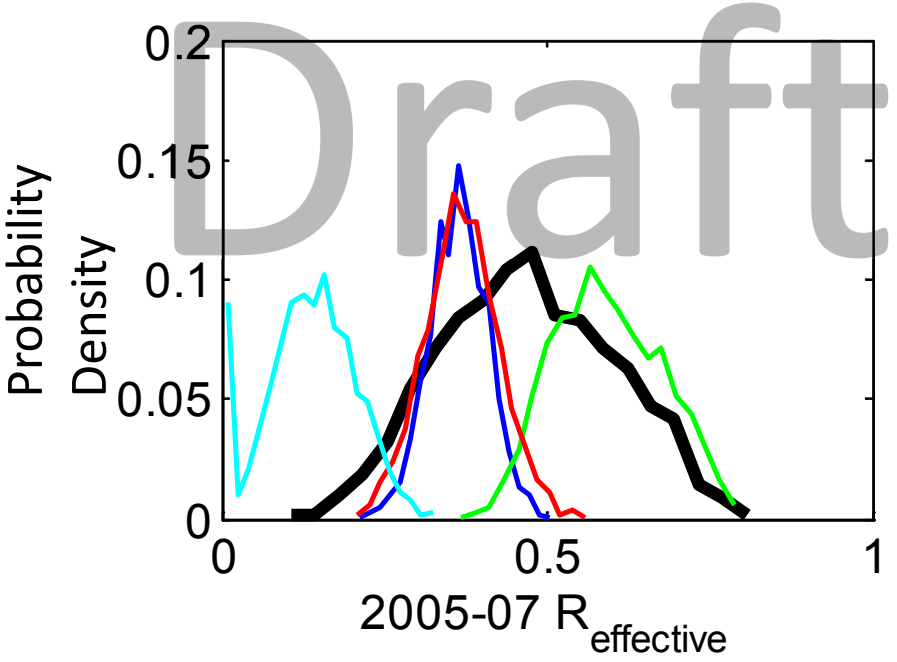


Extend model to account for complexities in surveillance data:

- imperfect case detection
- multiple primary cases in some clusters
- possibility of false positives

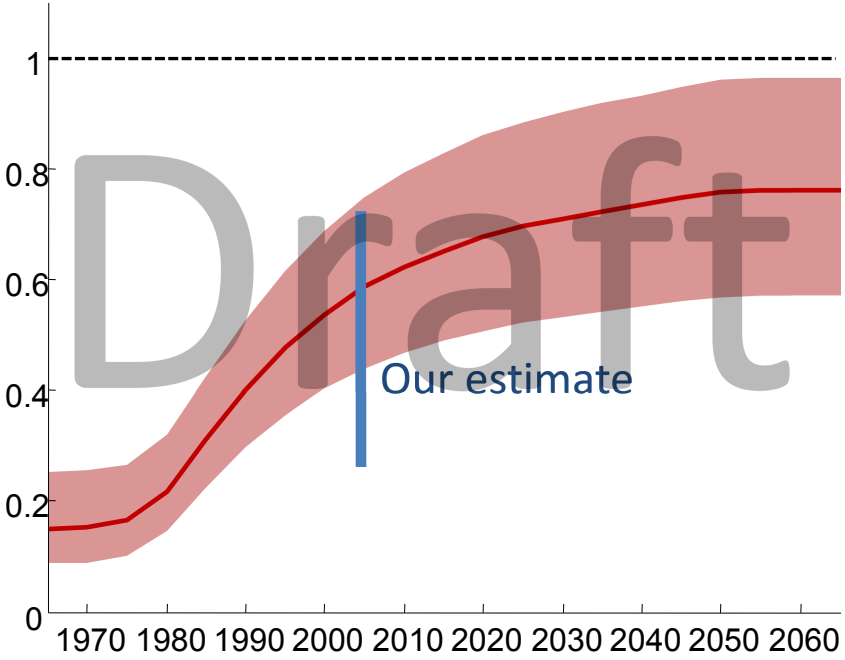
For given surveillance parameters, we can correct our R_{eff} estimate.

Bias-corrected Results



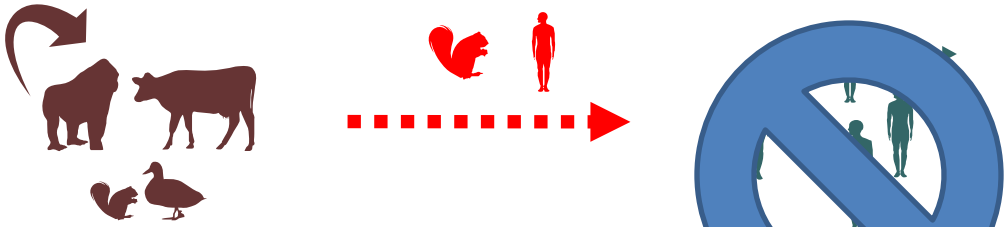
Correcting for:

- Sampling variance only
- Imperfect detection
- False positives
- Multiple primary infections
- All sources of bias



Effective Reproductive Number

What else has changed?



Circulation in reservoir

Cross-species spillover

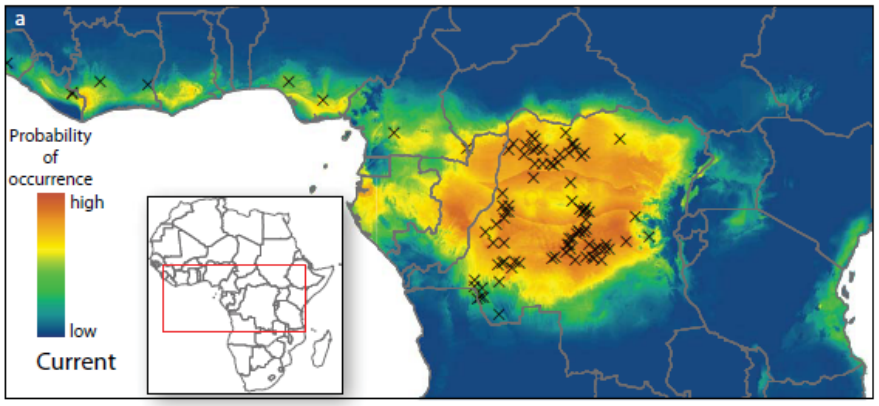
Sustaining chains (R_{eff}<1)

Studying animal-to-human spillover

- Case-control analysis of risk factors for monkeypox infection
  → contact with squirrels and terrestrial rodents was most important factor (after vaccine status).

Rimoin et al. (In review)

- Spatial modeling of monkeypox risk, using environmental variables and distribution of candidate reservoirs
  → forested zones and rope squirrel habitat.



H. Thomassen , T. Fuller et al, (Ecohealth 2010)

Future work: field studies to assay prevalence in rope squirrels and other candidate reservoir hosts.

→Understand ecological basis for zoonotic risk, and test hypotheses about increased spillover since 1980s.

Human Monkeypox in the United States

5-week outbreak highlighted need for preparedness

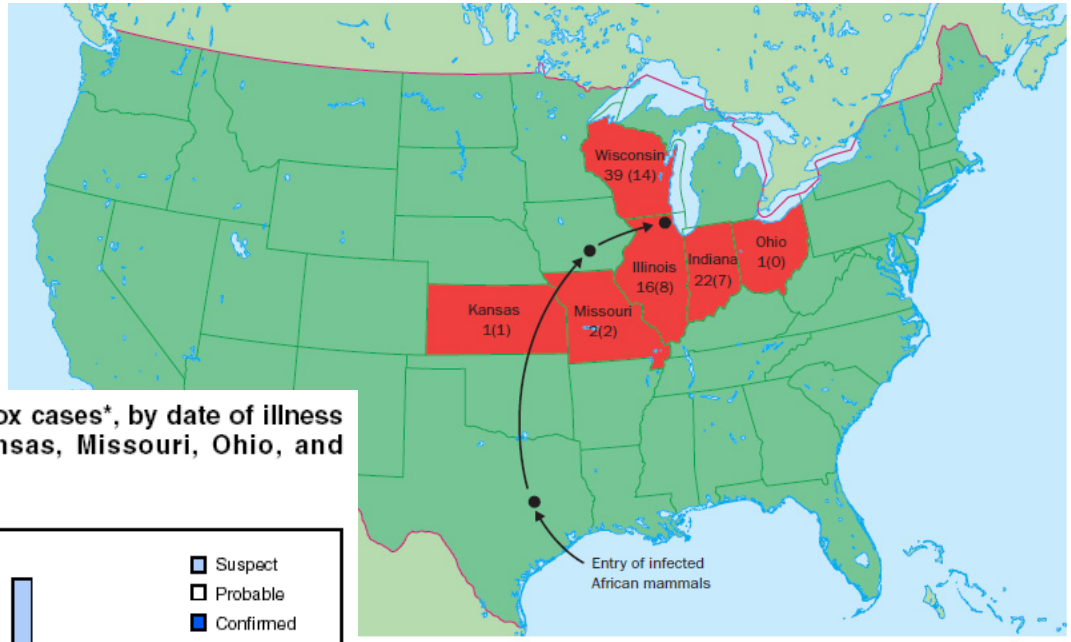
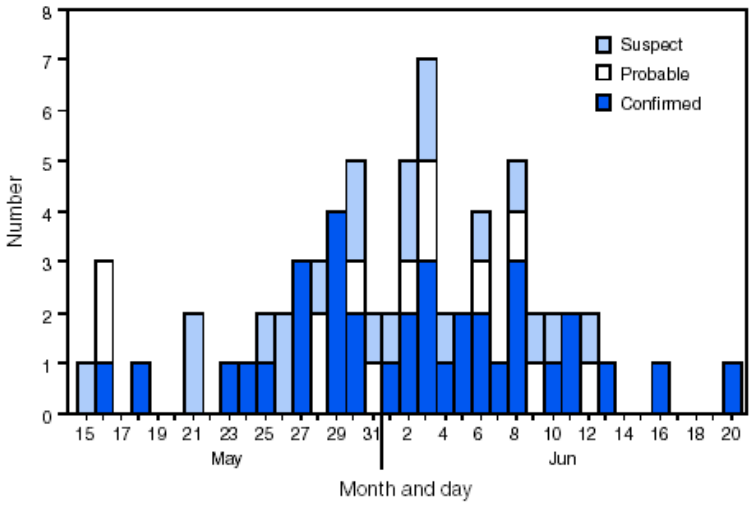


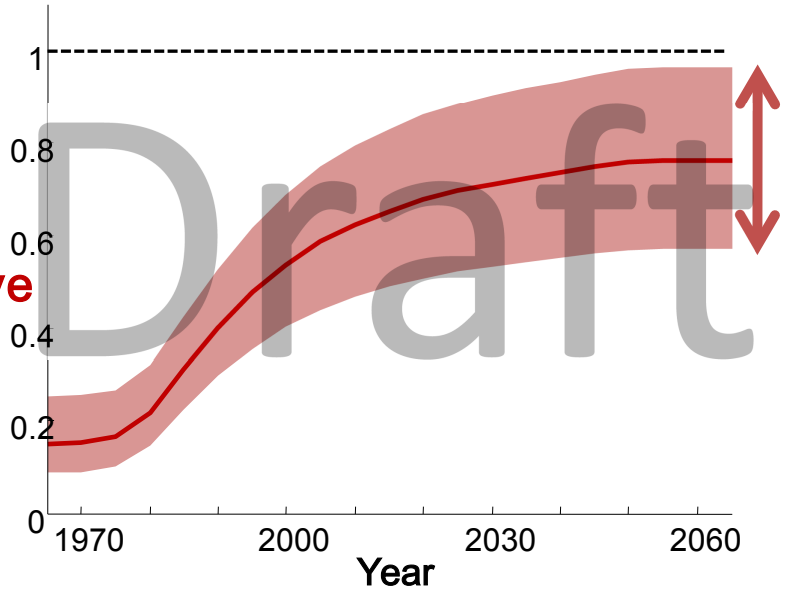
FIGURE 1. Number of monkeypox cases*, by date of illness onset — Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, 2003†



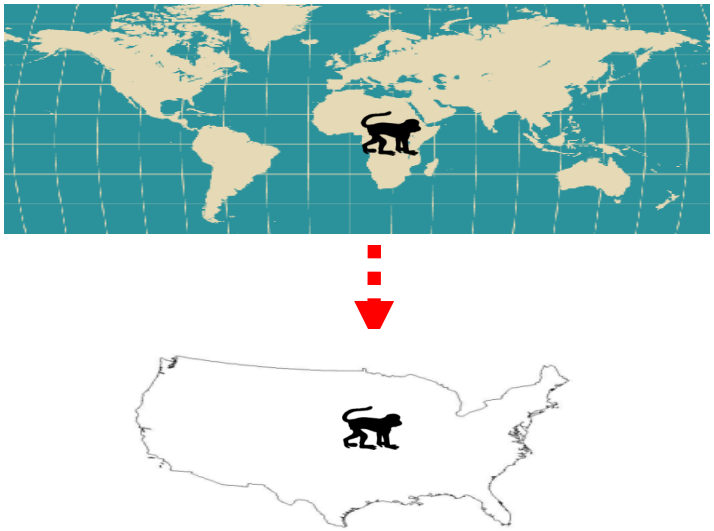
* N = 69 of 71 cases with known date of illness onset.
† As of July 8, 2003.

This kind of advertising = millions for Monkeypox research!

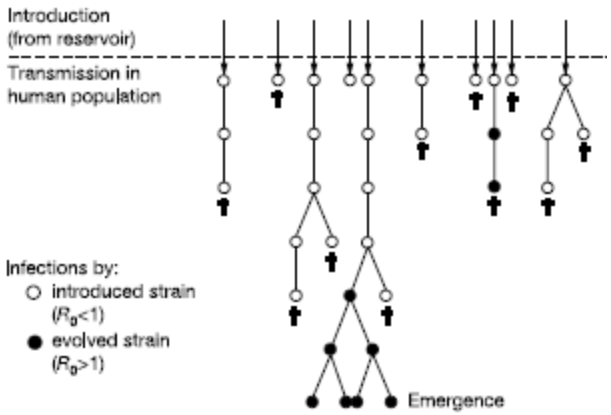
Is monkeypox a global threat?



Ecological driver

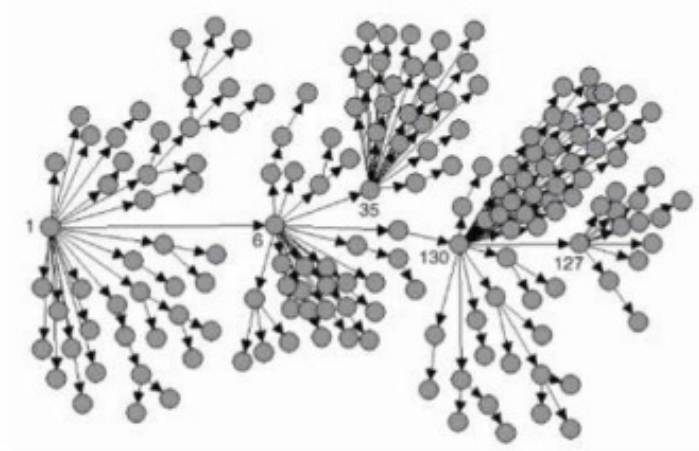


Evolutionary driver



Antia et al. Nature 2003

Mechanisms of transmission heterogeneity



Super-Shedder
$R_1=R_0$

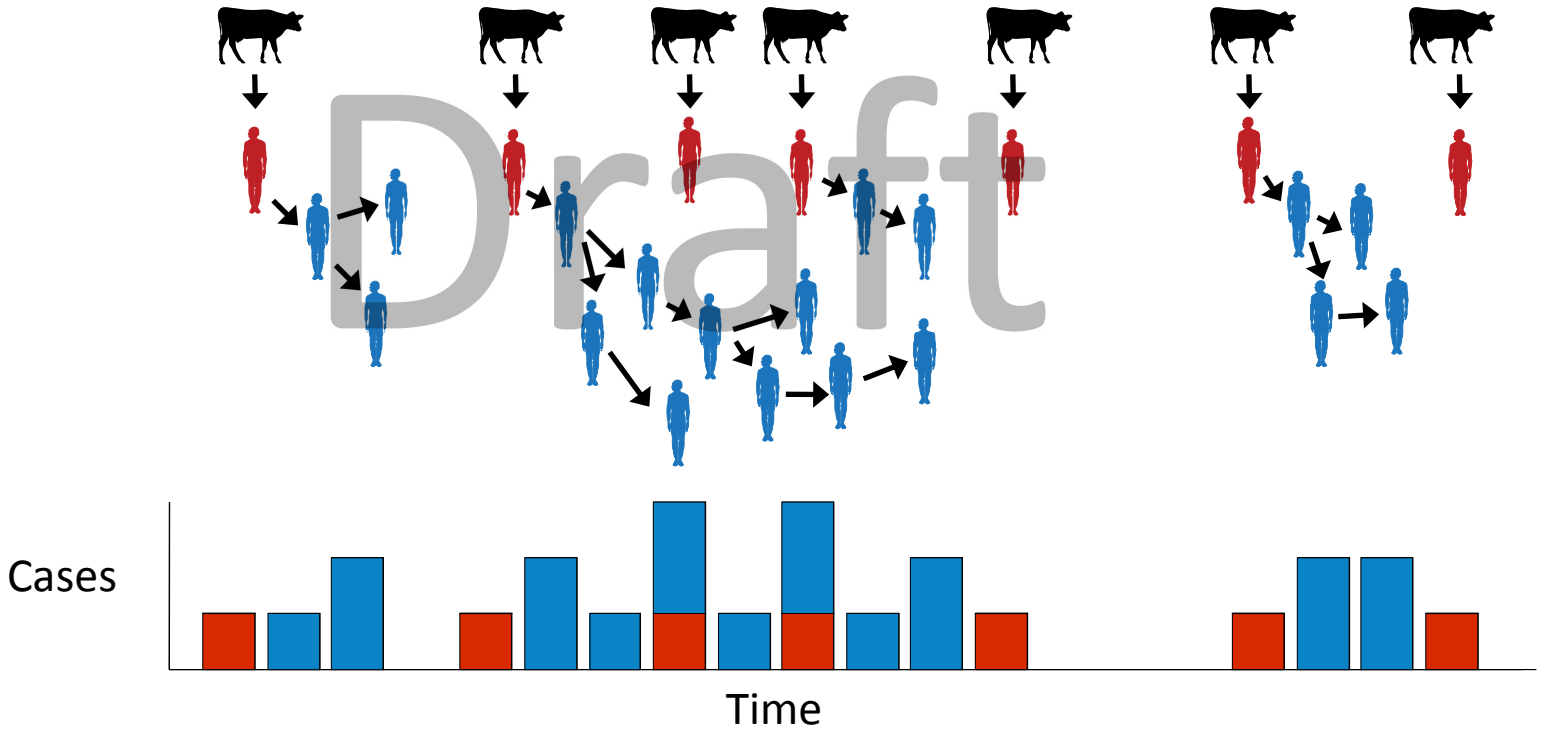
Super-Friendly
$R_1=R_0*(1+1/k)$

R_0=Reproductive number of index case
R_1=Reproductive number for subsequent human-human transmission

Upcoming challenges in zoonotic modeling

With Julie Pulliam

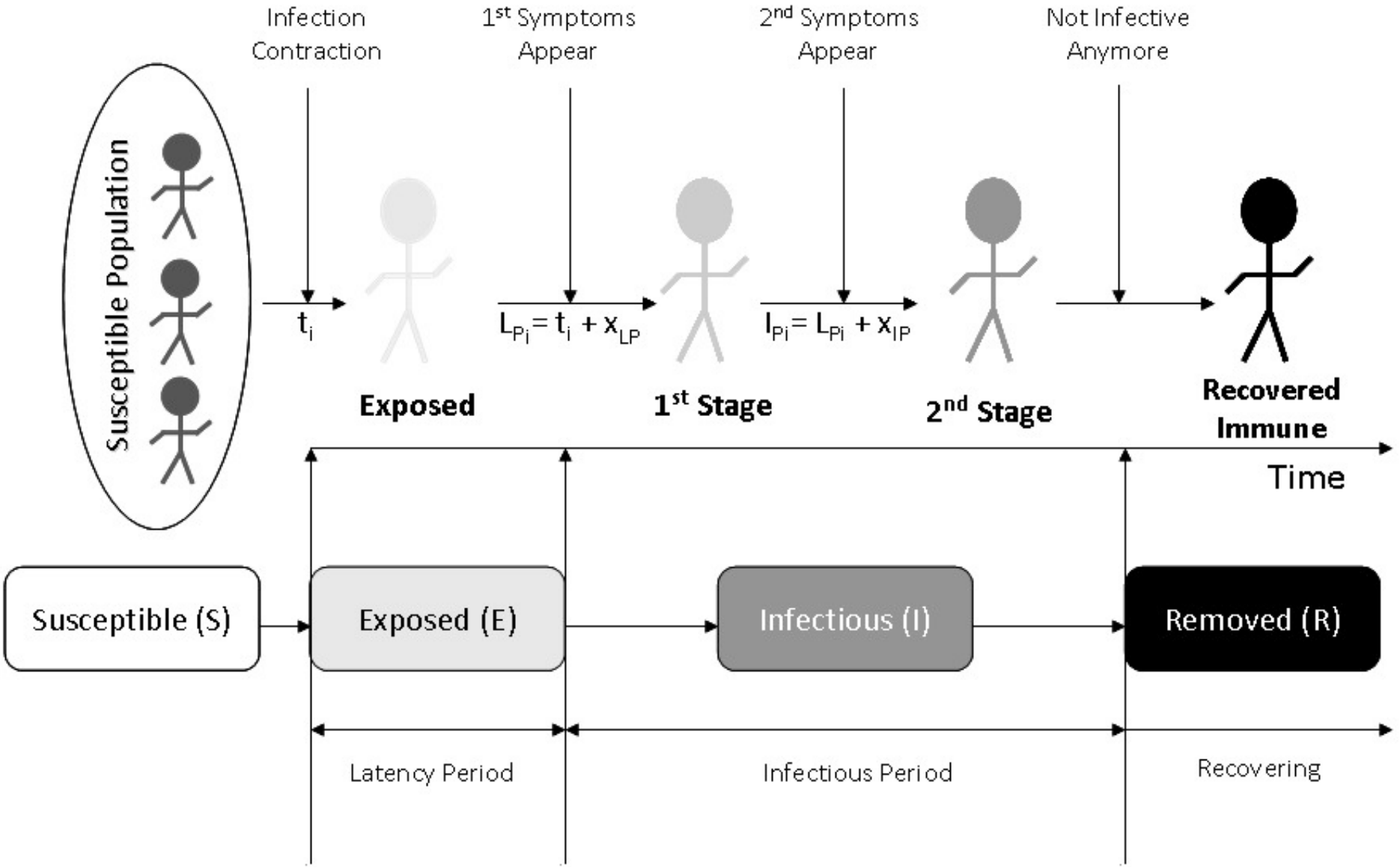
Discriminate contributions of zoonotic spillover
vs human-to-human transmission



Essential in order to:

- Assess pandemic risk of emerging pathogens
- Determine risk factors for pimary and secondary transmission
- Quantify spillover in order to study and control

SEIR Model


Infection Contraction
1st Symptoms Appear
2nd Symptoms Appear
Not Infective Anymore
Susceptible Population
t_i
$L_{Pi} = t_i + x_{LP}$
$I_{Pi} = L_{Pi} + x_{IP}$
Exposed
1st Stage
2nd Stage
Recovered Immune
Time
Susceptible (S)
Exposed (E)
Infectious (I)
Removed (R)
Latency Period
Infectious Period
Recovering

Method: likelihood of the data

The probability of the time series of cases
(for given structure and parameters):

$$P(t_1, t_2 \ldots, t_n) = P(t_1)P(t_2|t_1)P(t_3|t_1, t_2) \cdots P(t_n|t_1, t_2 \ldots, t_{n-1})$$

Case onset dates

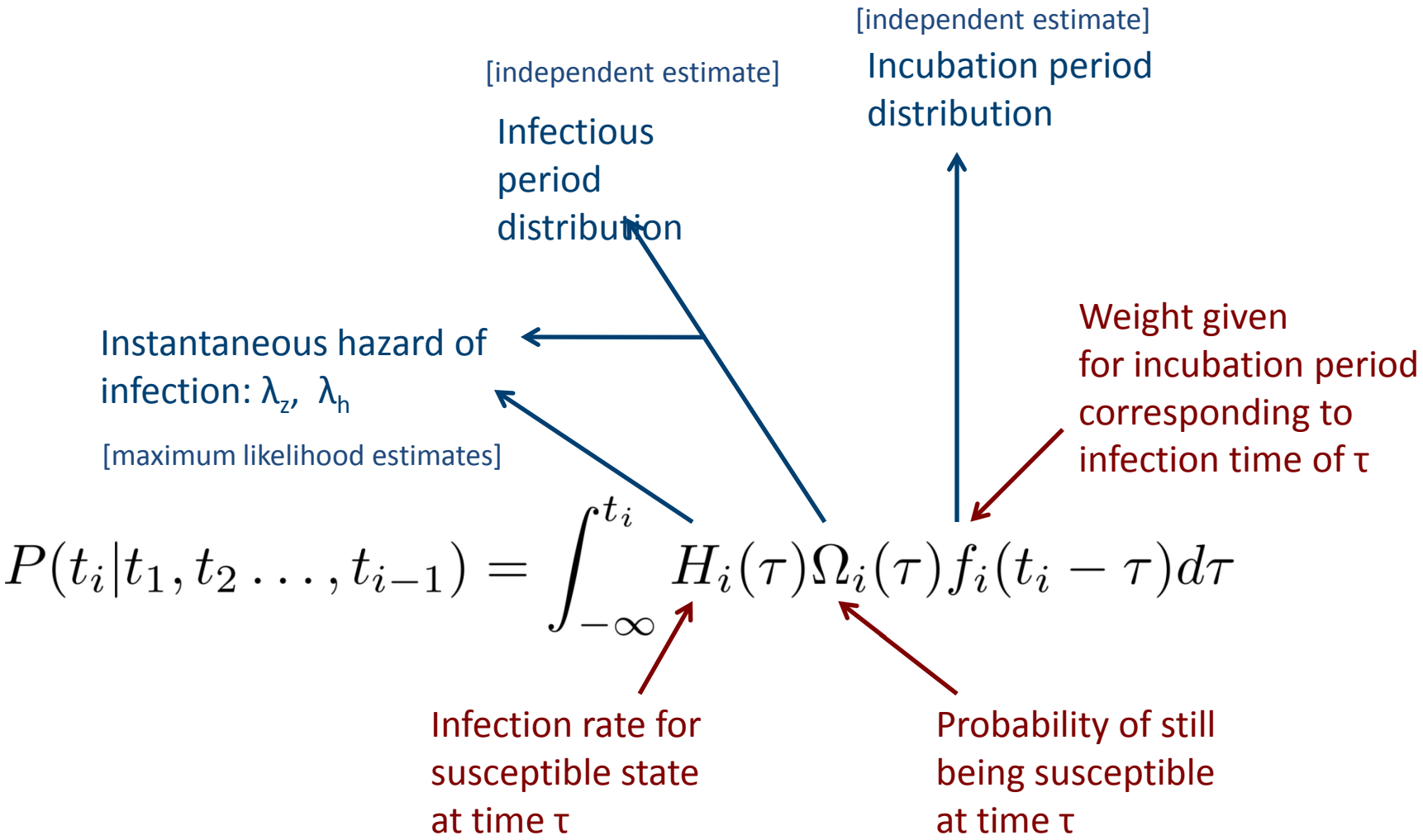
Weight given
for incubation period
corresponding to
infection time of τ

$$P(t_i|t_1, t_2 \ldots, t_{i-1}) = \int_{-\infty}^{t_i} H_i(\tau)\Omega_i(\tau)f_i(t_i - \tau)d\tau$$

Infection rate for
susceptible state
at time τ

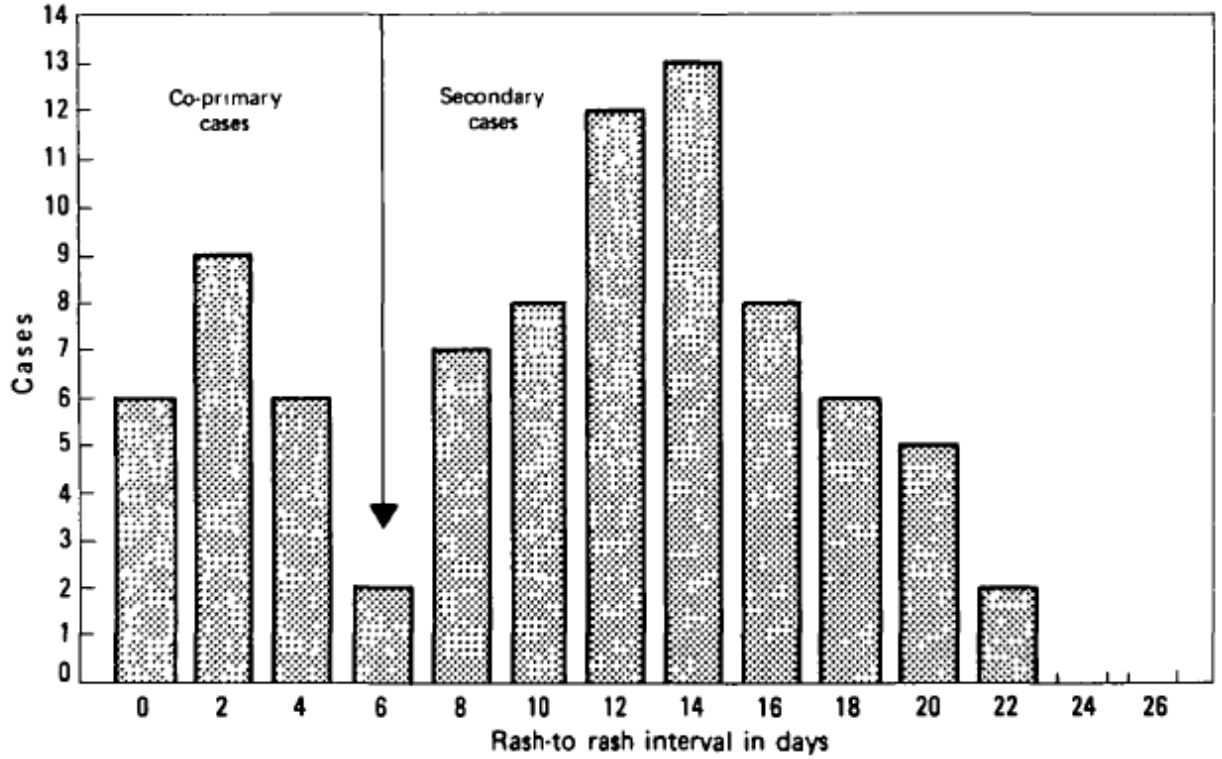
Probability of still
being susceptible
at time τ

Method: likelihood parameters



Under development: tools for determining infection source

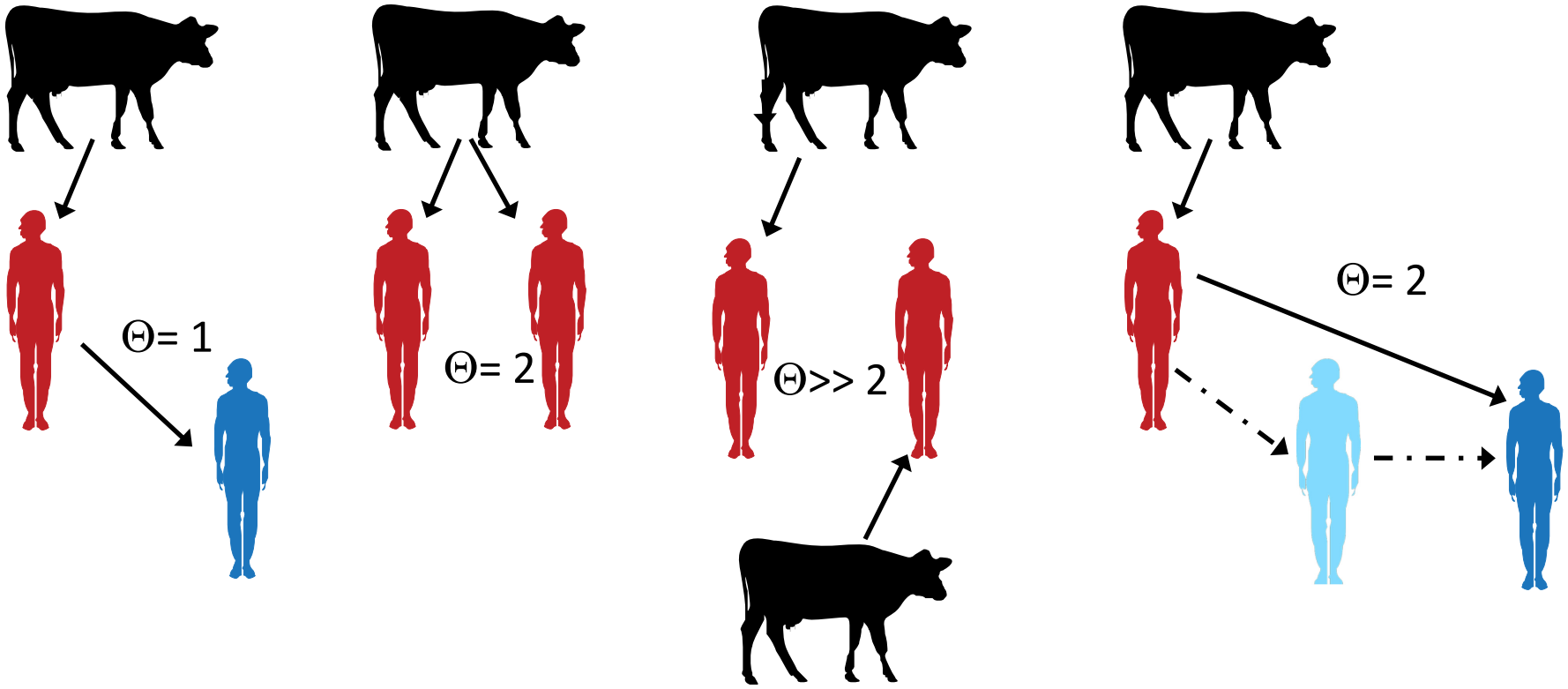
- Symptom onset intervals



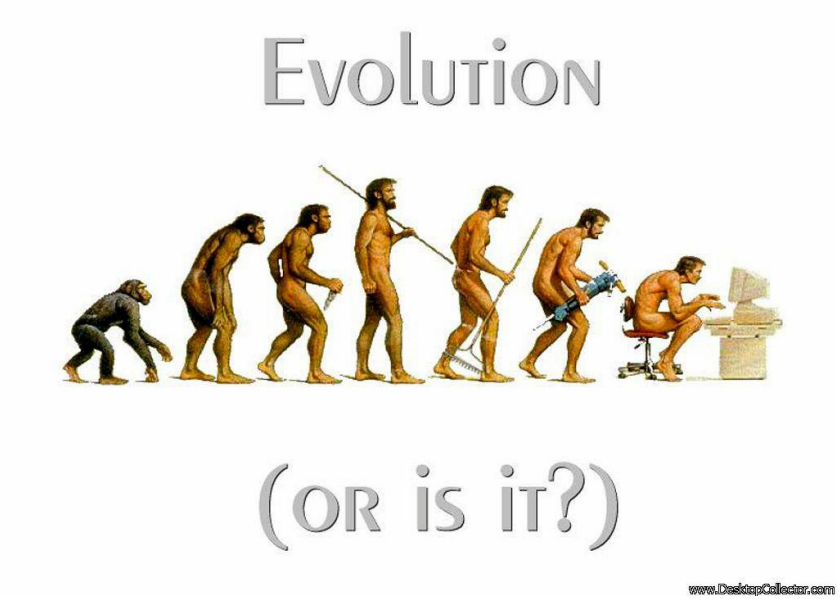
Z. Jezek et al, (Am J of Epi 1987)

Under development: tools for determining infection source

- Symptom onset intervals
- Sequencing



Summary: Evolution questions



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