Spillover and emergence of zoonotic pathogens

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Goals of this talk

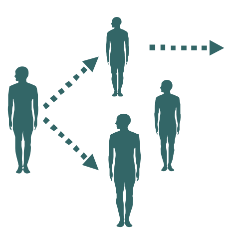
Summarize progress and challenges in understanding emergence of zoonotic pathogens.

*Modeler/quantitative ecologist/epidemiologist perspective

*Focus on directly-transmitted pathogens

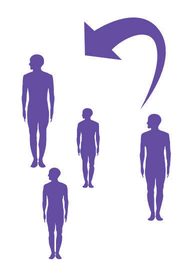
The reproductive number, *R*, is the average number of secondary cases infected by a typical case.

***R* > 1** is threshold for **sustained transmission.**

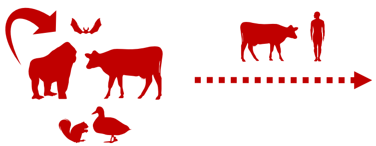


Subcritical transmission (*R* < 1)

Supercritical → epidemic or pandemic threat (*R* > 1)



Factors governing emergence risk



Spillover transmission

Human-to-human transmissibility

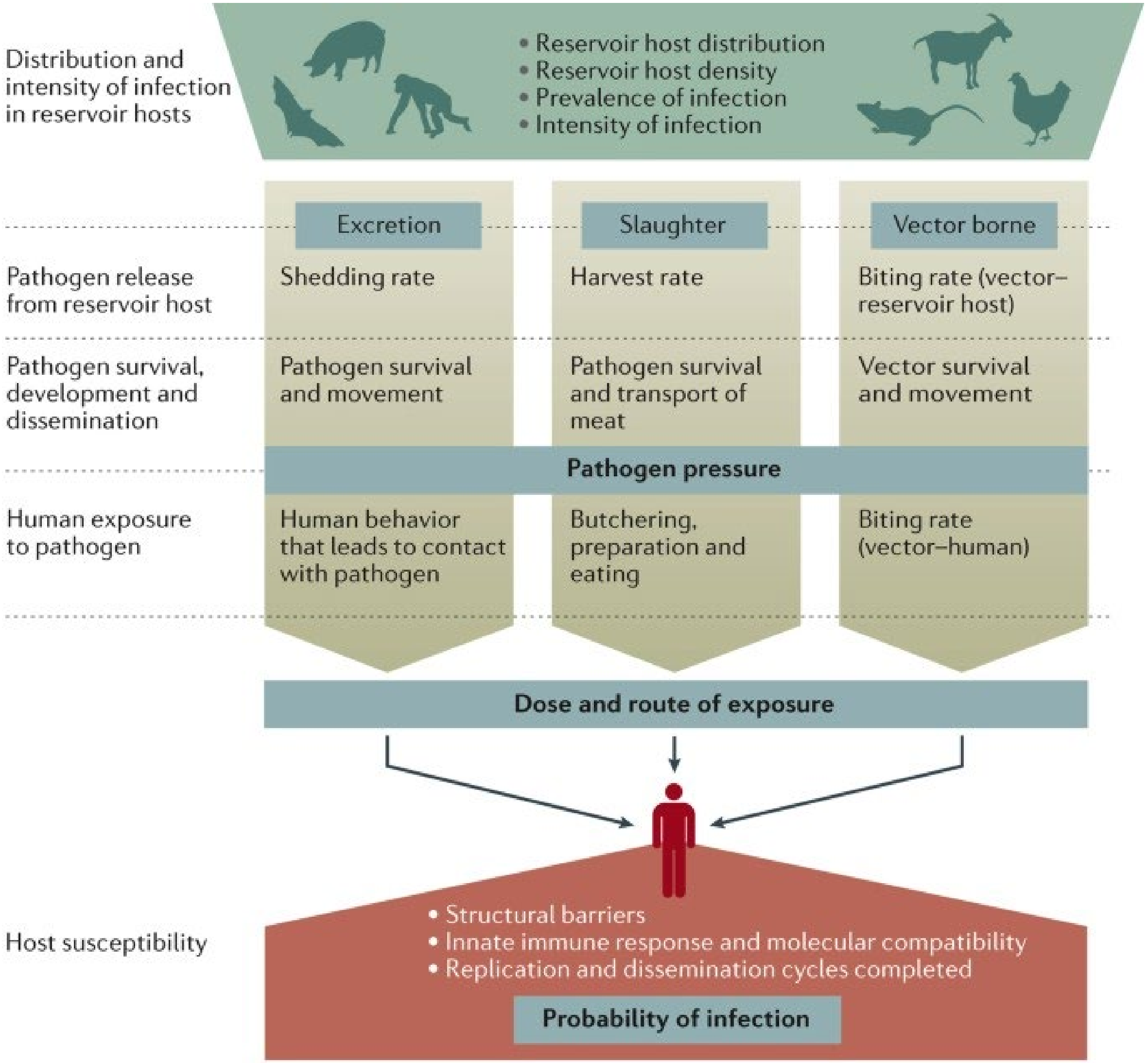
Susceptibility of the human population

Onward spread and connectivity

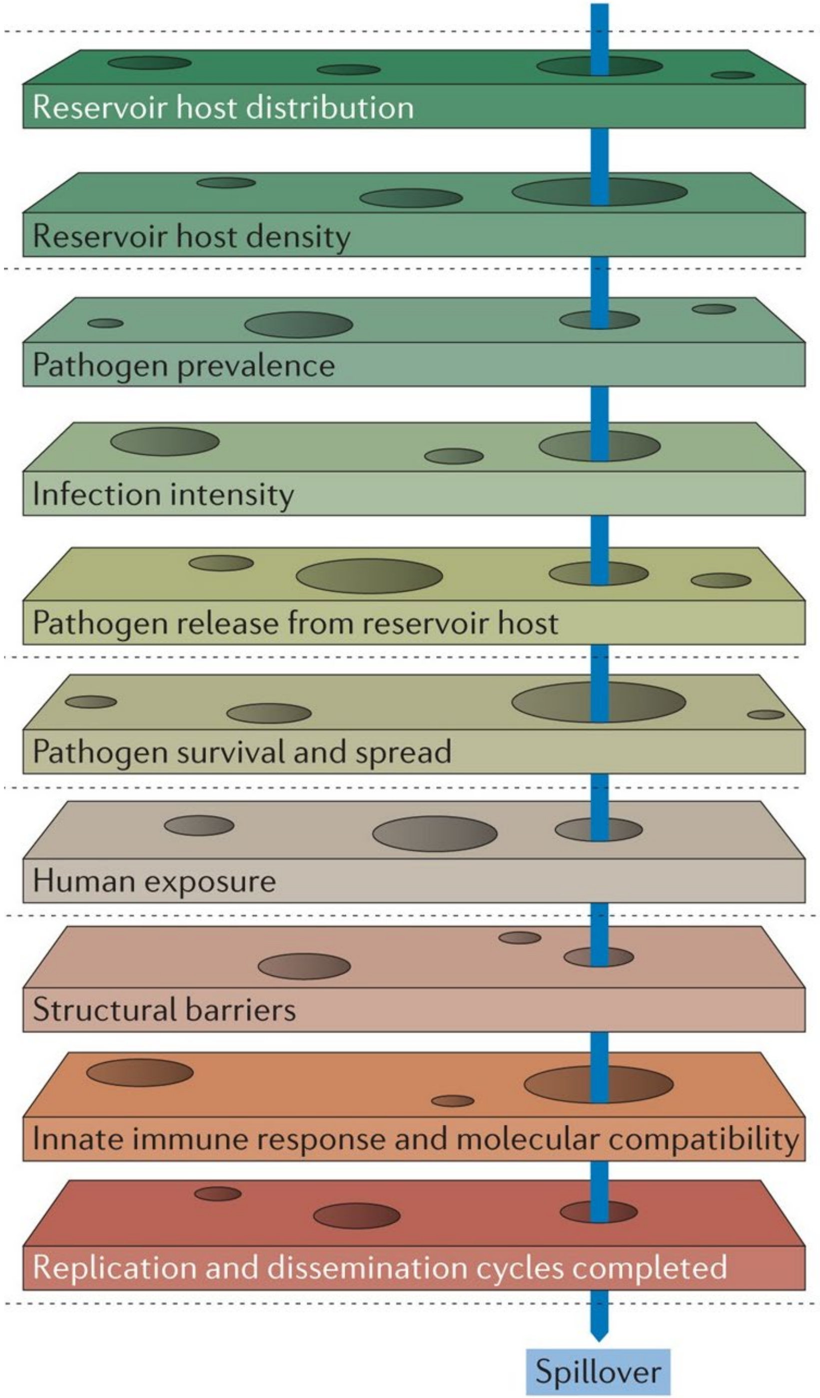
Zoonotic spillover

General model for animal-to-human spillover

- Linking scales from reservoir ecology to human behavior to within-host
- Different modes of transmission



Plowright et al, Nature Rev Microbiol (2015)



All factors changing in time and space!

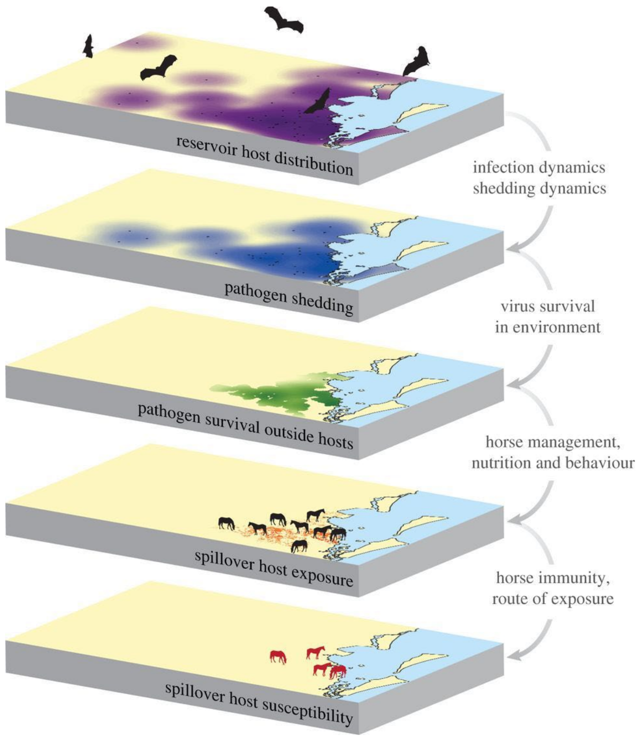
When do the openings line up to create spillover events?

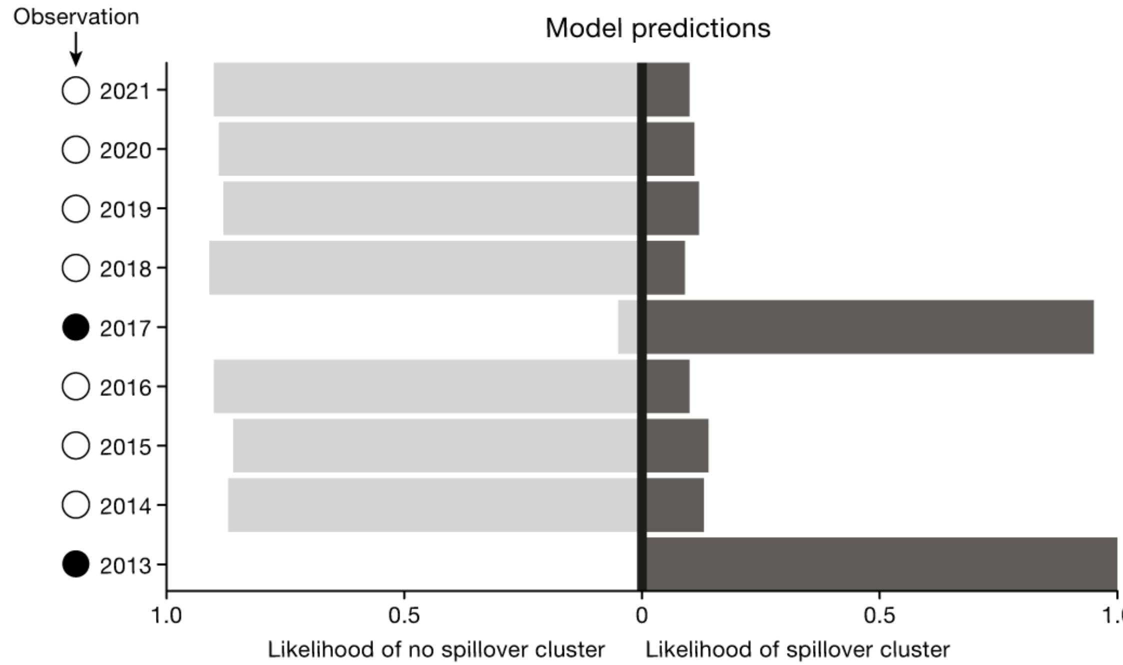
→ apparent 'stochasticity' of spillover.

But by studying the layers, we can understand risk.

Plowright et al, Nature Rev Microbiol (2015) nature

Pathogen spillover driven by rapid changes in bat ecology





Plowright et al, Proc Royal Soc B (2015); Eby et al, Nature (2023)

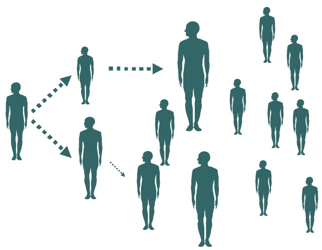
THE LANCET
PREVENTING PANDEMICS AT THE SOURCE

The *Lancet*–PPATS Commission on Prevention of Viral Spillover: reducing the risk of pandemics through primary prevention

Vora et al, Lancet (2023)

Factors governing emergence risk

Spillover transmission



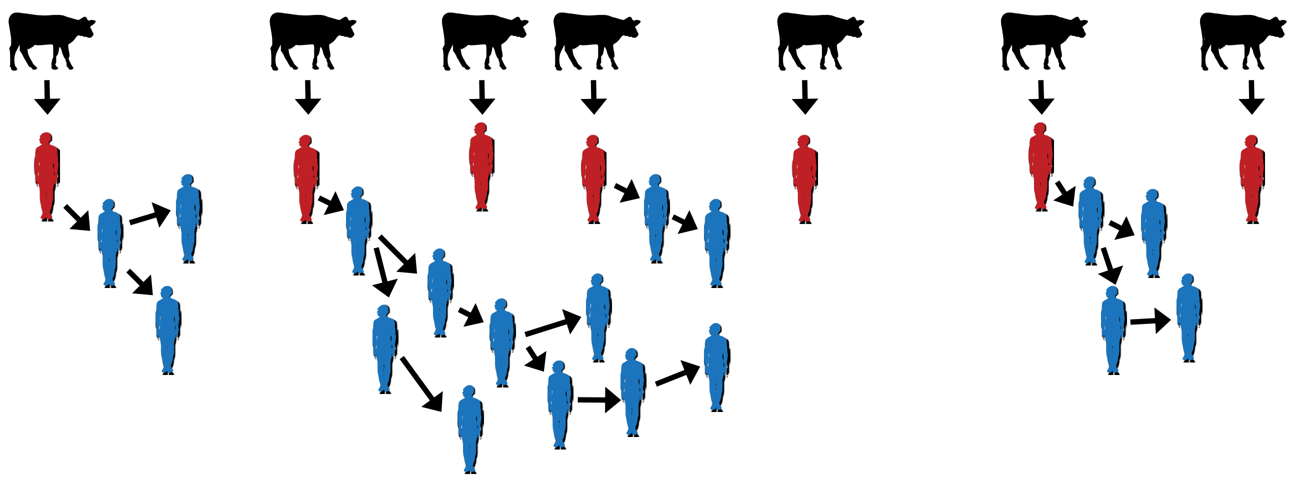
Human-to-human transmissibility

Susceptibility of the human population

Onward spread and connectivity

Estimating transmissibility from human case data

Key challenge: To disentangle contributions of zoonotic spillover versus human-to-human transmission.



Developed model-based methods using
attainable data (case onset dates or cluster sizes) and addressing
common challenges (imperfect case detection, missing data)
→ estimate human-to-human R from real-world data.

Blumberg & Lloyd-Smith, PLoS Comp Biol (2013)
Blumberg & Lloyd-Smith, Epidemics (2013)
Blumberg et al, Am J Epi (2014)
Ambrose et al, bioRxiv

Assessing transmissibility from lab experiments

Can we learn more from animal transmission studies?

<u>Meta-analysis of ferret model for influenza transmission</u>

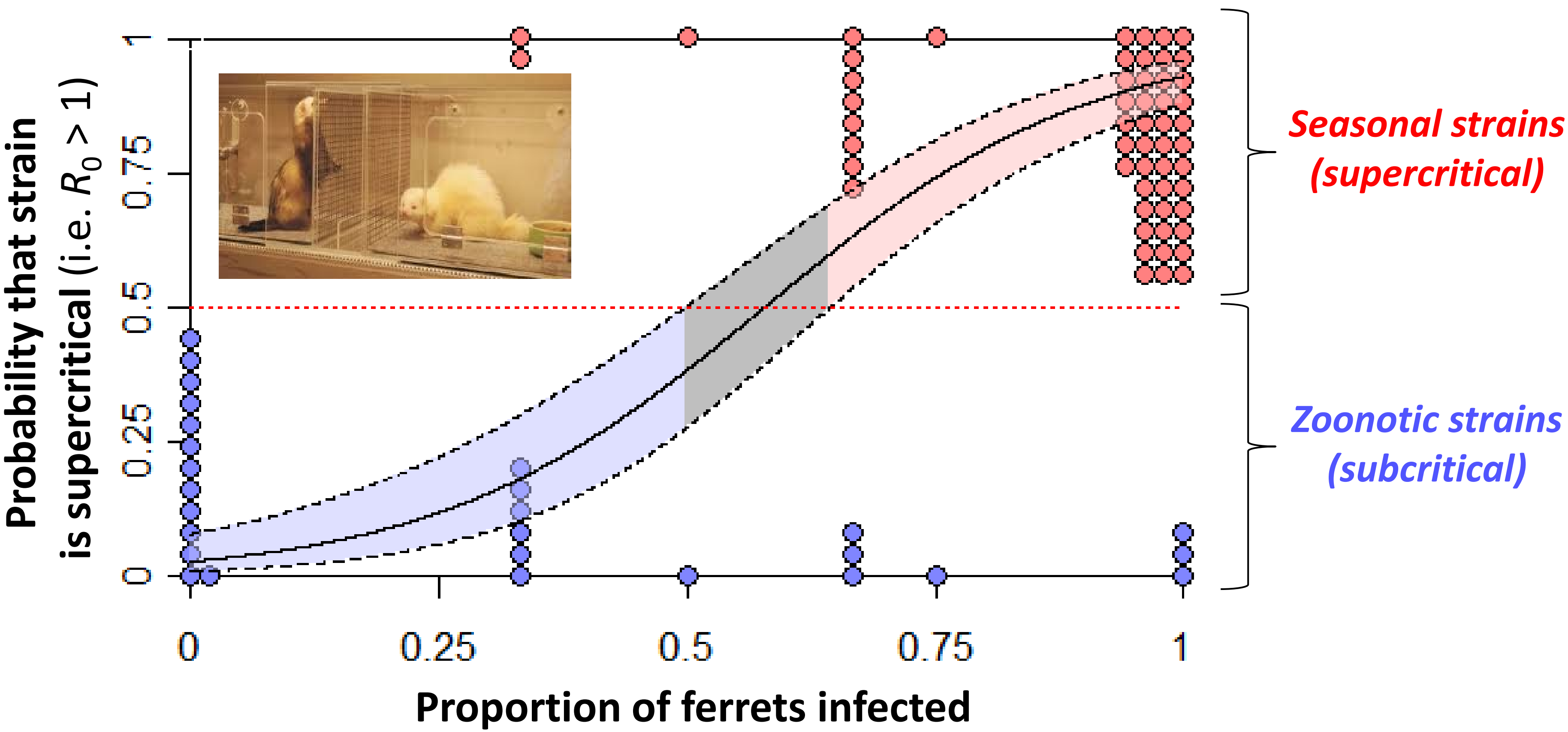
Can we identify strains as likely to be **supercritical in humans** (i.e. $R_0 > 1$) from ferret data?

Buhnerkempe et al, eLife (2015)

Assessing transmissibility from lab experiments

Gathered data:

- All ferret transmission experiments using influenza strains isolated from humans. 10 subtypes represented, 4 seasonal and 6 zoonotic.

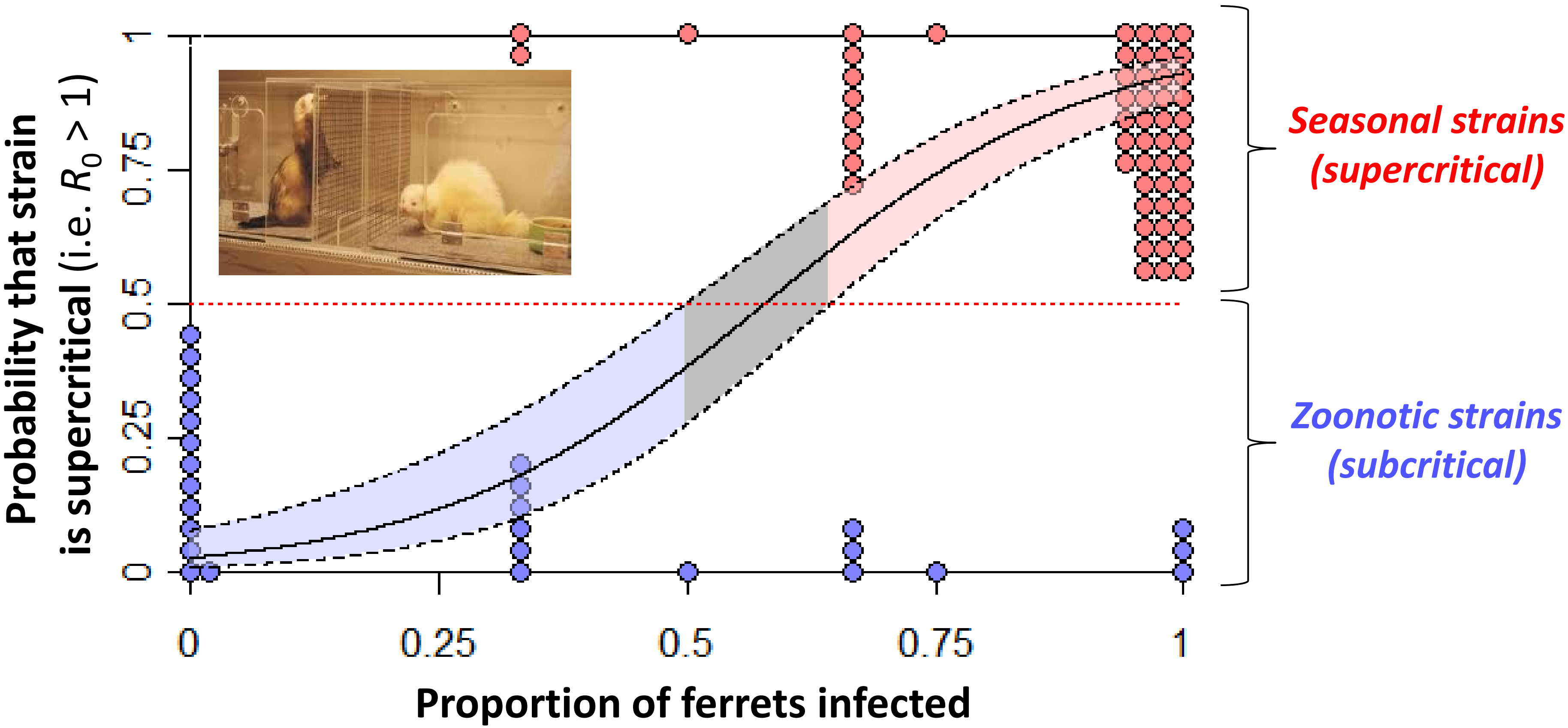


Buhnerkempe et al, eLife (2015)

Assessing transmissibility from lab experiments

Statistically speaking:

if more than 2/3 of ferrets infected via airborne spread, the strain is likely to be supercritical.



Buhnerkempe et al, eLife (2015)

Assessing transmissibility from lab experiments

Vincent Munster
NIH

Hector Aguilar
Cornell

Airborne shedding

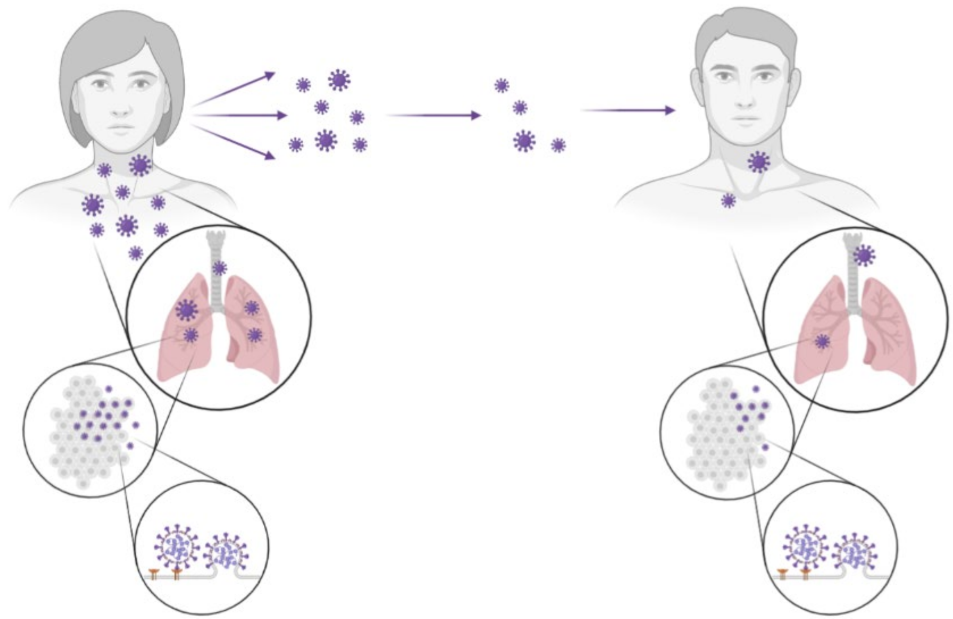
Virus stability

Tissue tropism

Dose-response

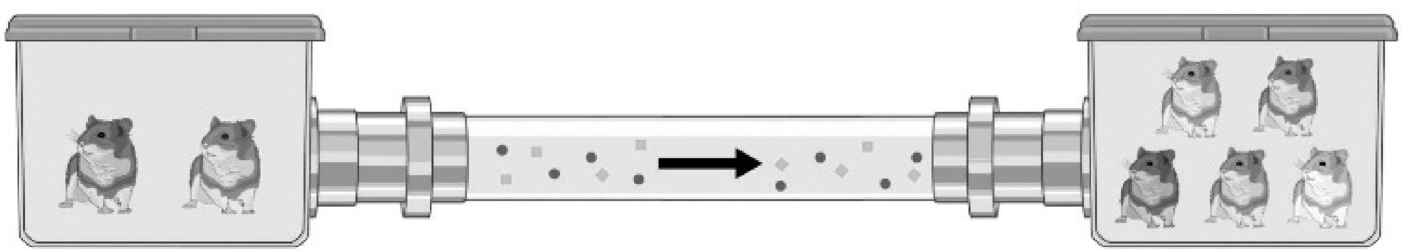
Within-host drivers of infectious virus load

Immunity and breakthrough



→ mechanistic model to estimate transmission risk using virological data

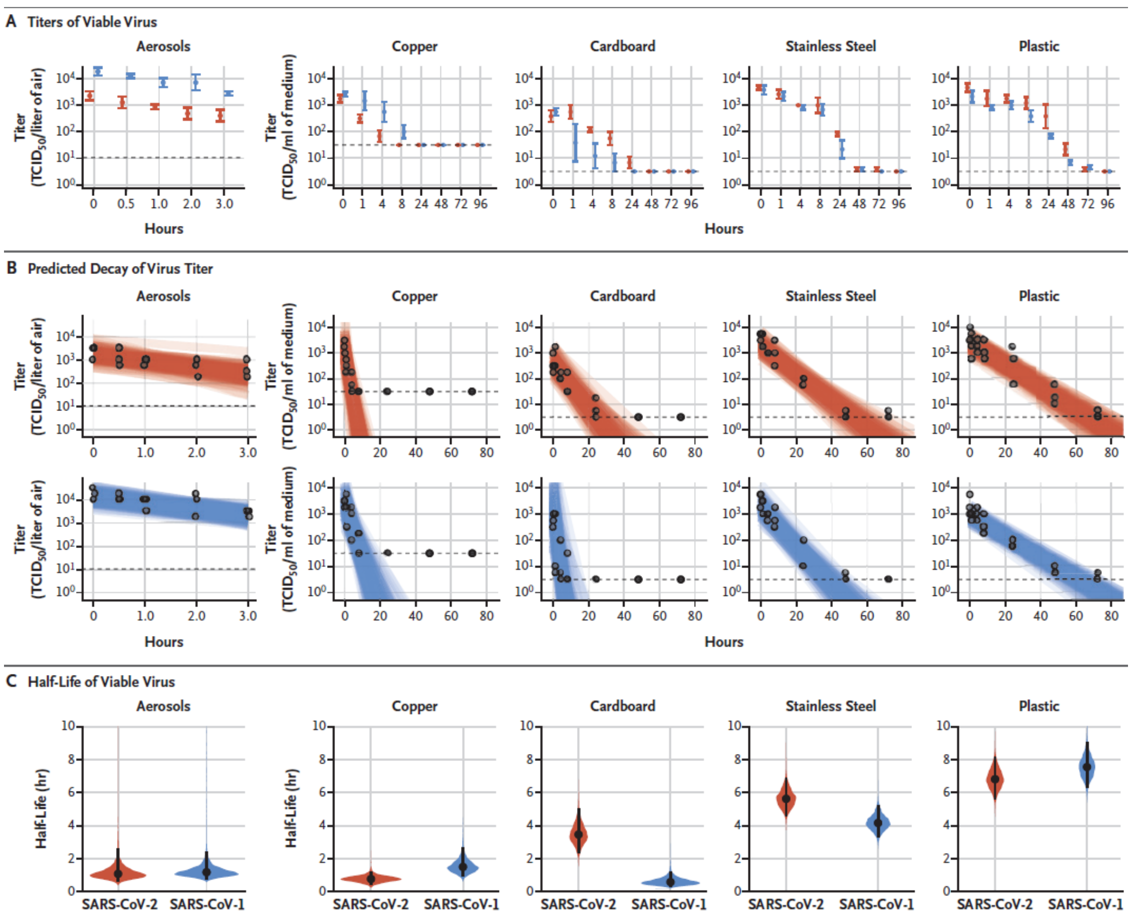
(and elements of aerosol physics, dose-response theory, etc)



Assessing transmissibility from lab experiments

The NEW ENGLAND JOURNAL of MEDICINE

Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1



Lab data

+

Model-based analysis

+

Comparative epidemiology

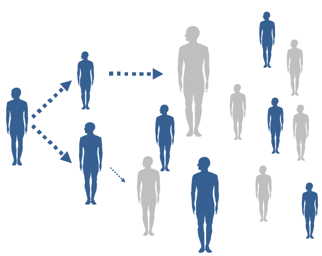
Predicted potential for airborne transmission and superspreading in March 2020.

Van Doremalen et al. 2020, NEJM

Factors governing emergence risk

Spillover transmission

Human-to-human transmissibility



Susceptibility of the human population

Effective $R = R_0 \times$ susceptibility

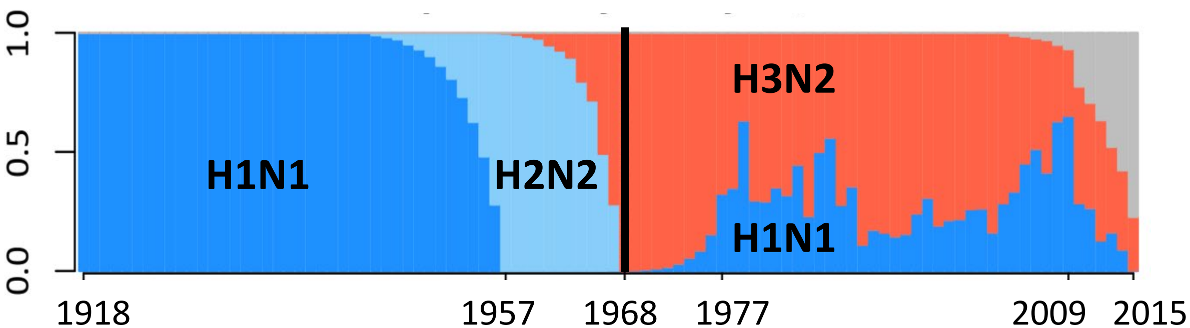
Onward spread and connectivity

Prior immunity against 'novel' pathogens: avian influenza

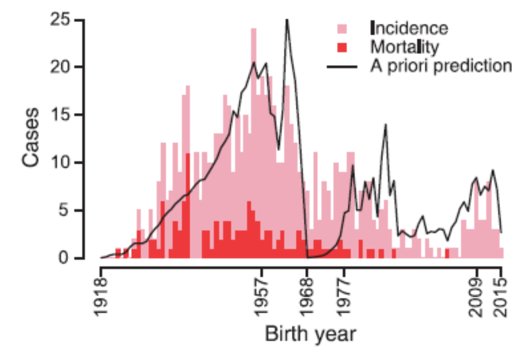
Potent protection against H5N1 and H7N9 influenza via childhood hemagglutinin imprinting

Katelyn M. Gostic,[1] Monique Ambrose,[1] Michael Worobey,[2*] James O. Lloyd-Smith[1,3*]

Initial exposures to influenza A, by birth year – China 2015



H7N9 cases



Immunological imprinting to first infection with seasonal flu

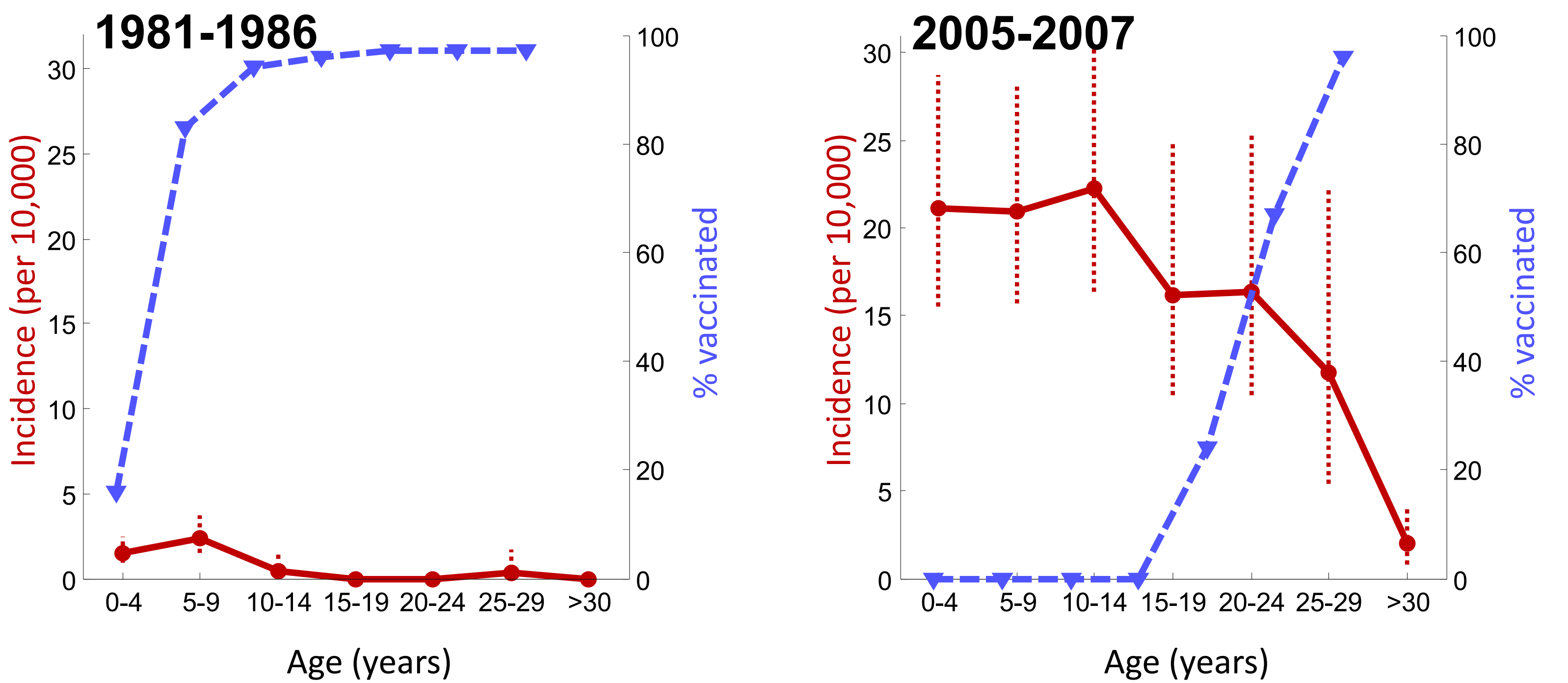
→ lifelong protection against avian flu viruses from same HA group

Pandemic shifts in seasonal flu subtypes → predictable waves of susceptibility.

Gostic et al, Science (2016)

Prior immunity against 'novel' pathogens: mpox

Human mpox incidence in DRC is shaped by past vaccination against smallpox...



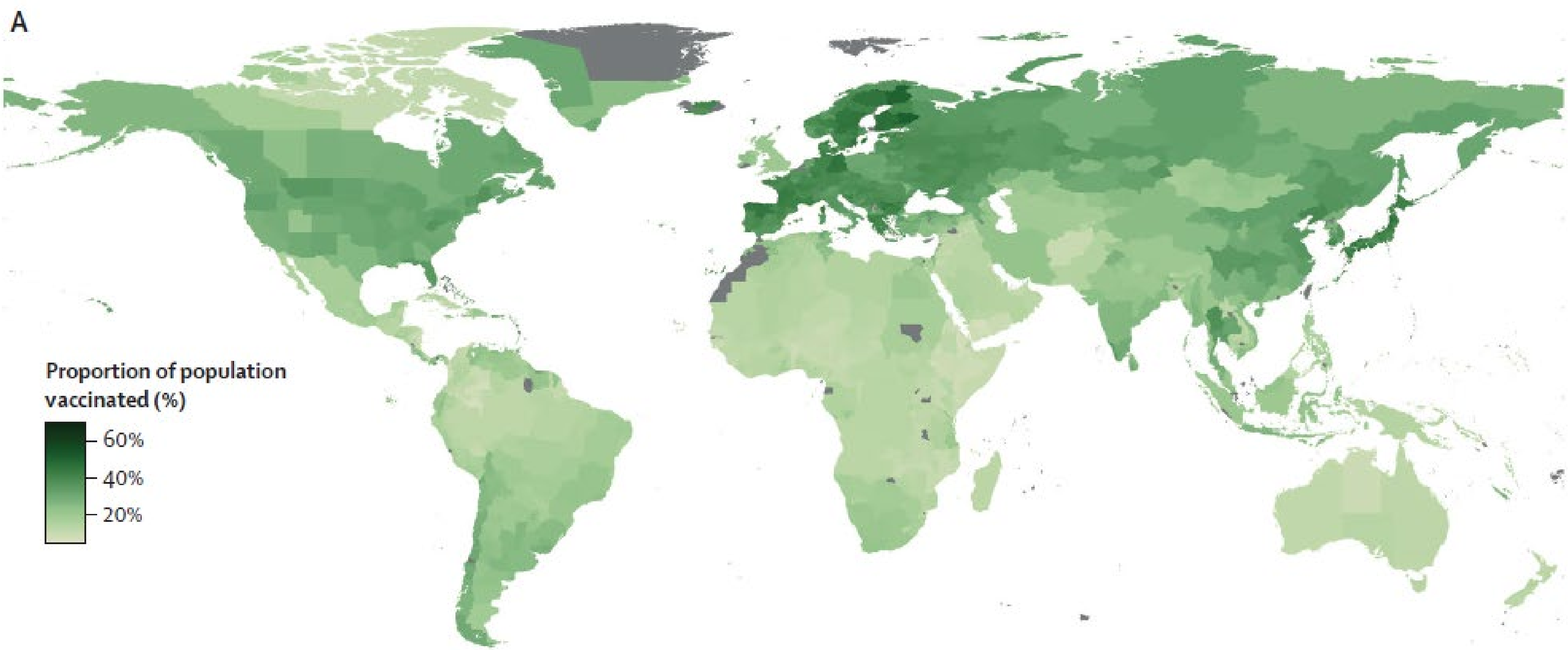
In aftermath of smallpox eradication in 1980.

Rimoin et al, PNAS (2010)
Lloyd-Smith, Phil Trans B (2013)

Prior immunity against 'novel' pathogens: mpox

Human mpox incidence in DRC is shaped by past vaccination against smallpox...

… which can be mapped globally and projected through time.



In aftermath of smallpox eradication in 1980.

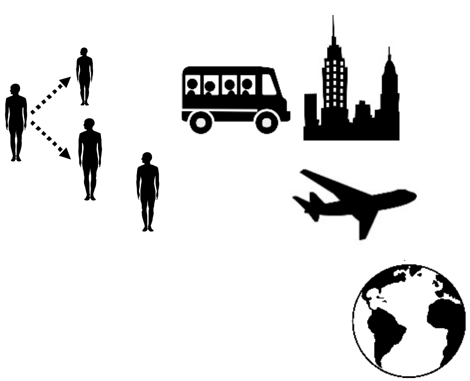
Taube et al, Lancet Infectious Disease (2023)

Factors governing emergence risk

Spillover transmission

Human-to-human transmissibility

Susceptibility of the human population

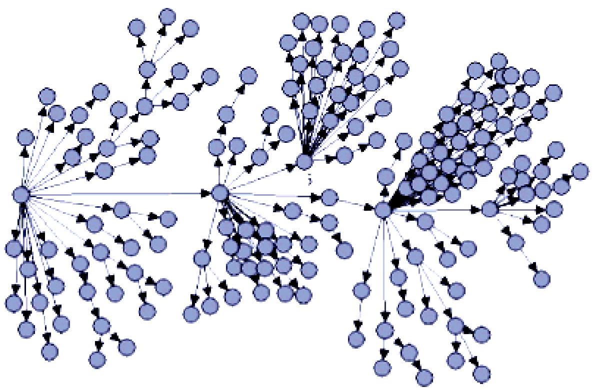


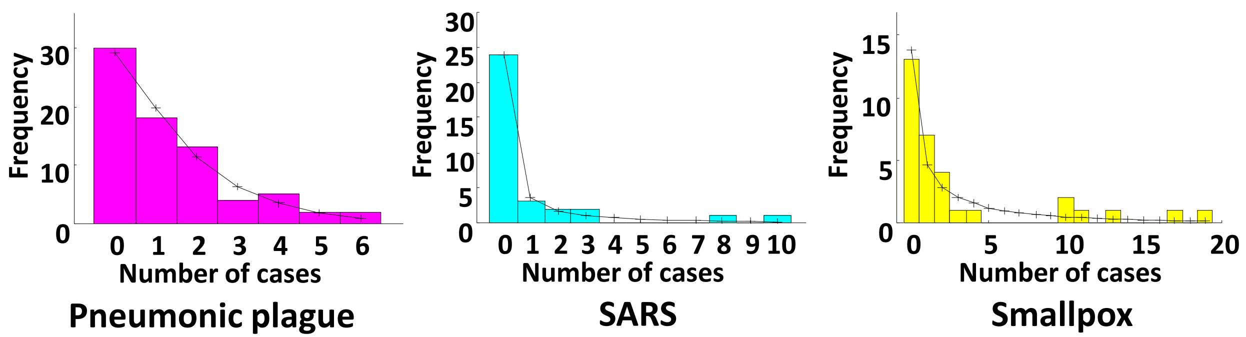
Onward spread and connectivity

Initial spread: superspreading and extinction risk

Following spillover to index case, virus must **establish transmission chain**.

Viruses with R_0>1 often die out by chance.





'Superspreading' (i.e. substantial individual variation in transmission) is ubiquitous in infectious diseases – just a matter of degree.

Greater individual variation

→ Major outbreaks are **explosive**.

→ Introductions **more likely to die out**.

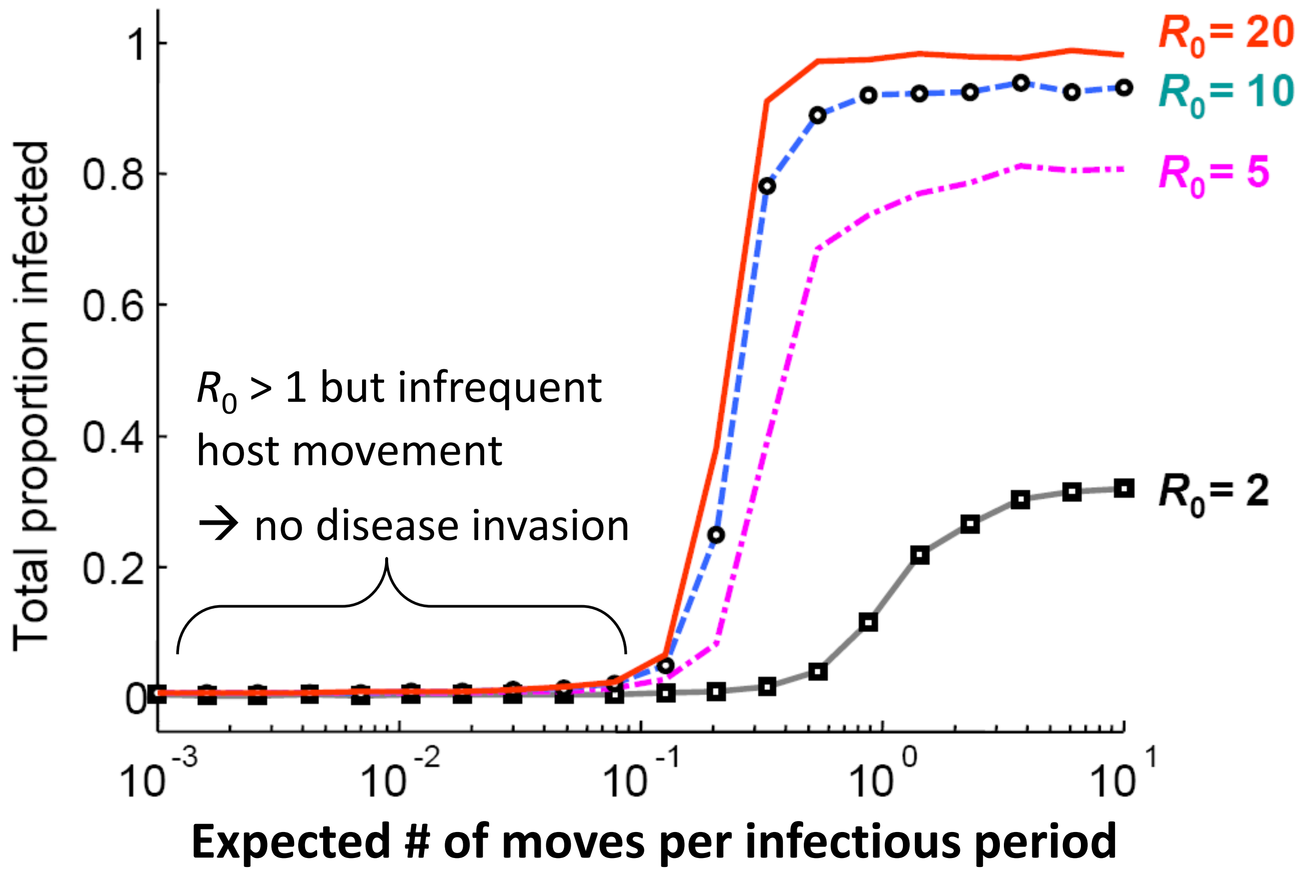
e.g. SARS-CoV predicted to die out 75% of time (despite $R_0 \approx 3$)

Lloyd-Smith et al, Nature (2005)

Onward transmission: host population structure

To cause a generalized epidemic,
an outbreak must **jump from its initial location to other regions**.
Frequency of host movements and infectious period are crucial.

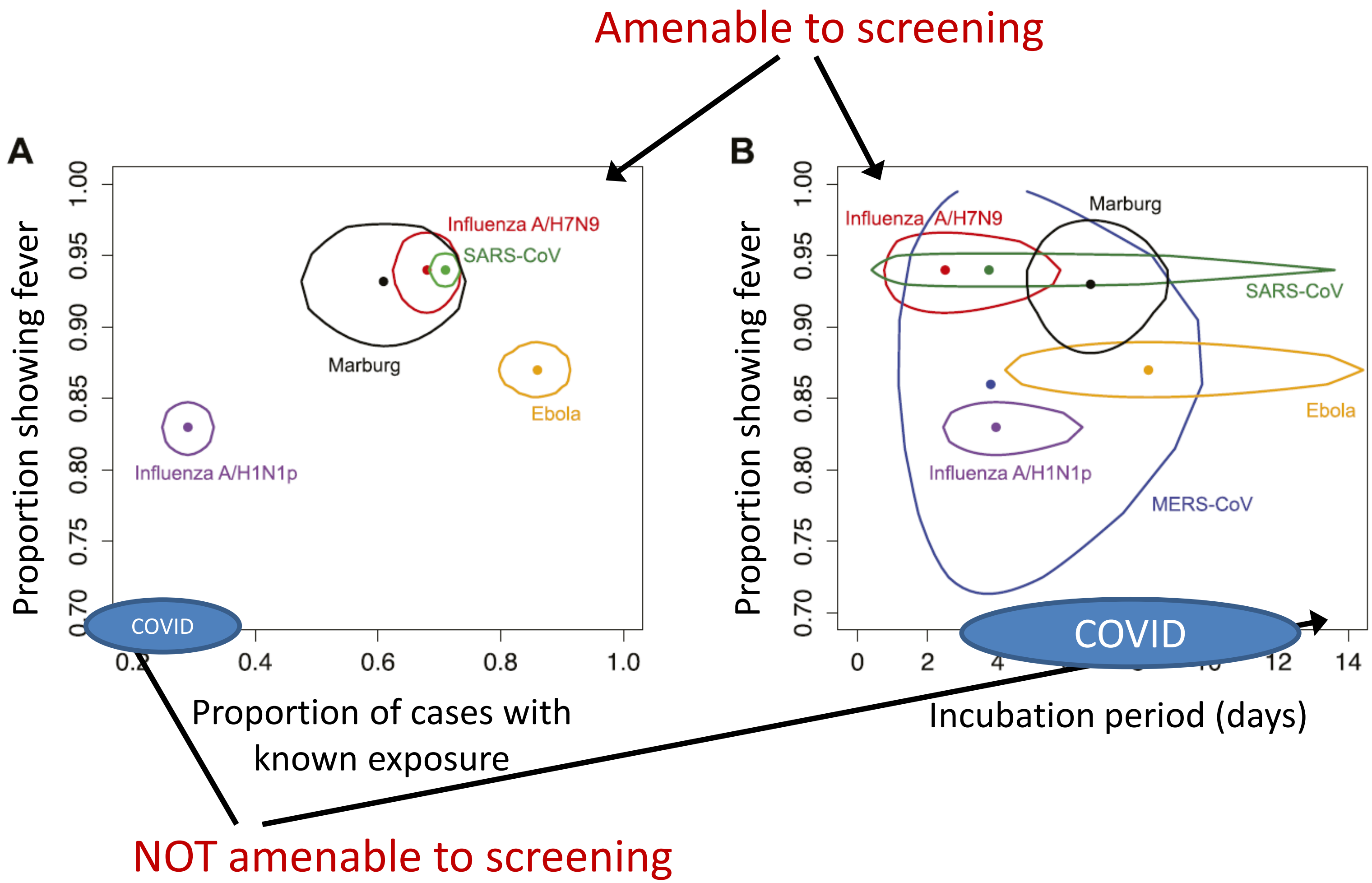
Simulation study: stochastic epidemic in a network of villages



Cross et al, Ecology Letters (2005)

Control: traveler screening

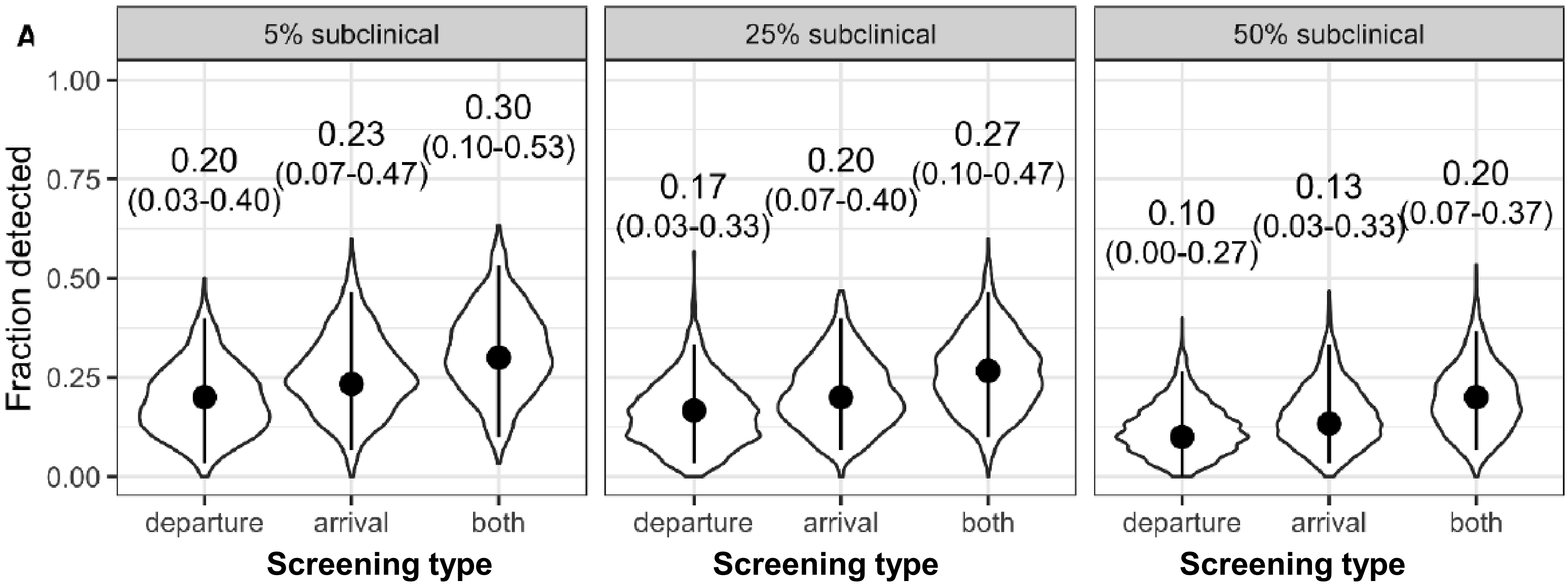
Effectiveness of traveler screening programs depends on natural history of infection and knowledge of risk factors.



Gostic et al, eLife (2015)

Control: symptom screening for COVID-19

Symptom screening will **detect less than half** of infected people, maybe as few as **1 in 10** → **Not a viable standalone strategy**.



Captured early knowledge to guide policy (despite uncertainty).

Submitted **Jan 29, 2020 –** leveraged existing model framework.

Gostic et al, eLife (2020)

Summary

Spillover: broke into mechanistic steps → study, predict, intervene.

Transmissibility: model-based approaches to analyze field and lab data.

Susceptibility: even novel viruses face landscapes of acquired immunity.

Onward spread: superspreading and population connectivity can cause early extinction or explosive outbreaks.

Control: life history of infections → effectiveness of interventions.

Take-home principles

- Breaking complex processes into constituent steps enables research progress and practical findings.
- Mechanistic models can integrate diverse data sources, synthesize knowledge and identify gaps.
- Investing in modeling platforms or data+modeling pipelines, trained on case studies, can build rapid response capabilities for new events.
- Rational risk assessment can guide longer-term investment in prevention and response. (e.g. WHO R&D Pipeline, Lancet Commission)

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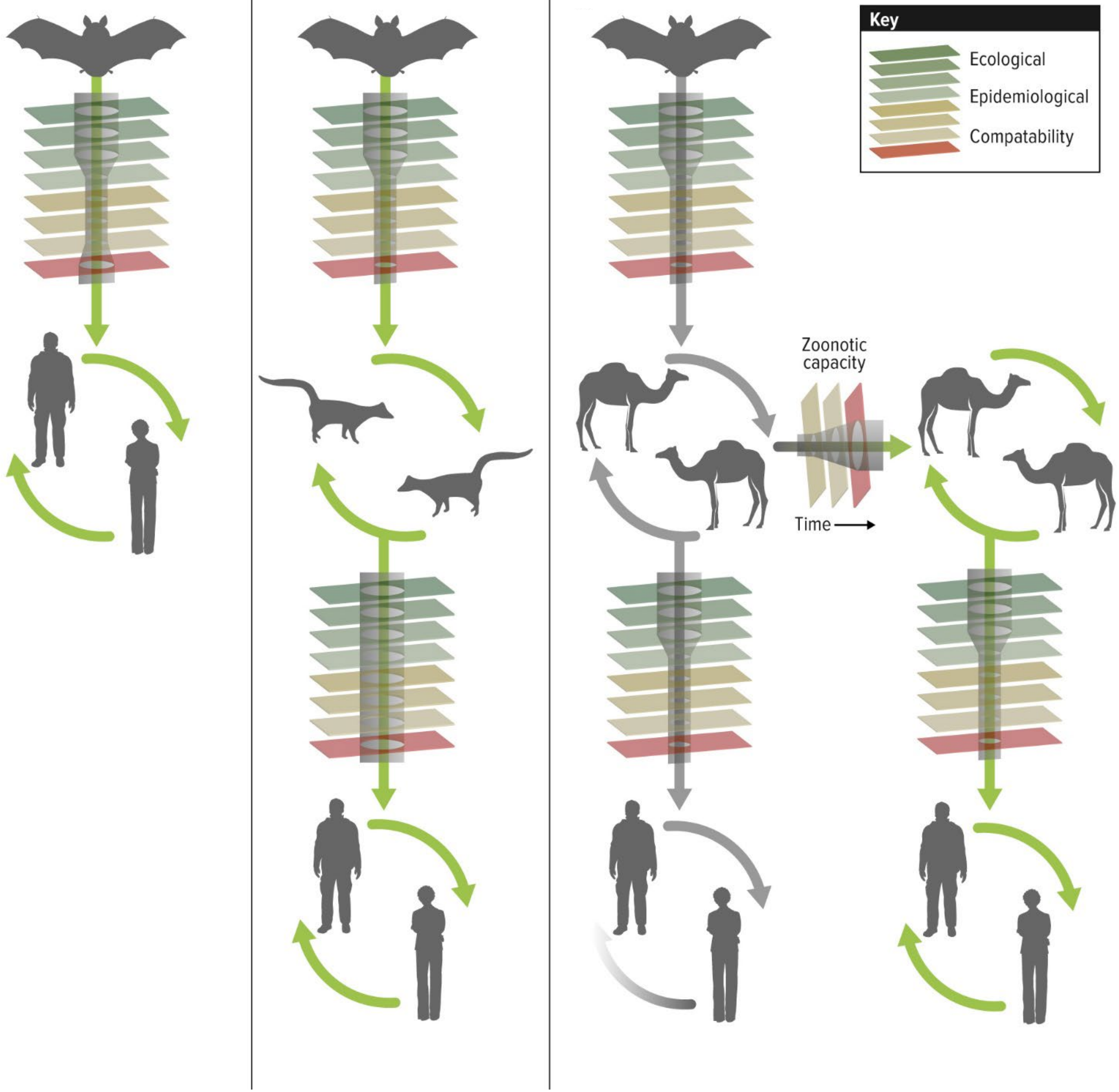


Ruiz Arevano et al, Nature Rev Microbiol (2022)

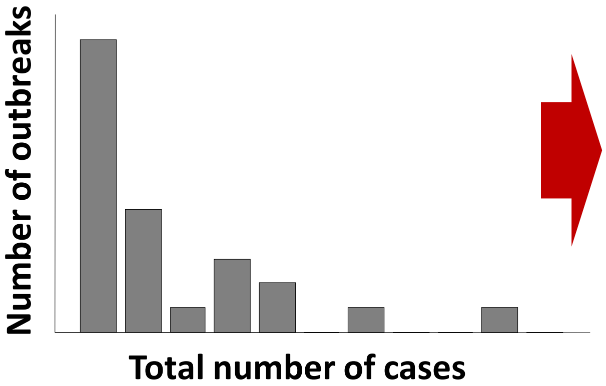
Estimating transmissibility of subcritical pathogens

From contact tracing data

Easy analysis but data are rare!

Lloyd-Smith et al, Nature (2005)

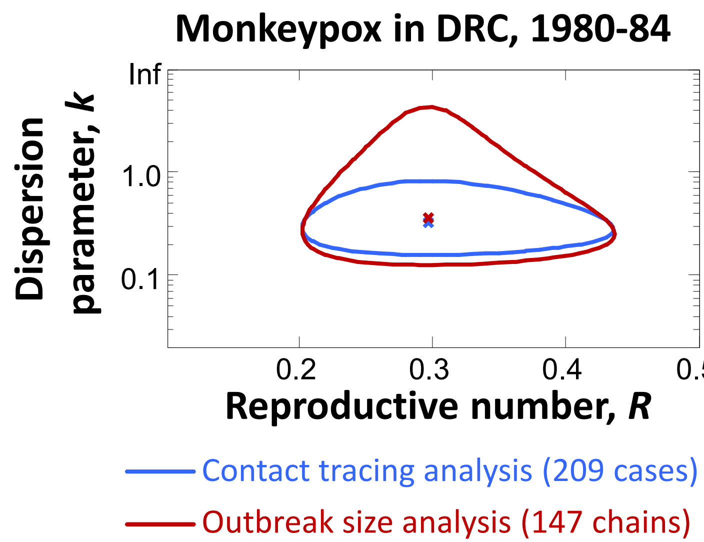
From the distribution of outbreak/cluster sizes



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

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

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



Blumberg & Lloyd-Smith, PLoS Comp Biol (2013)
Blumberg & Lloyd-Smith, Epidemics (2013)

From the proportion of cases infected by animals

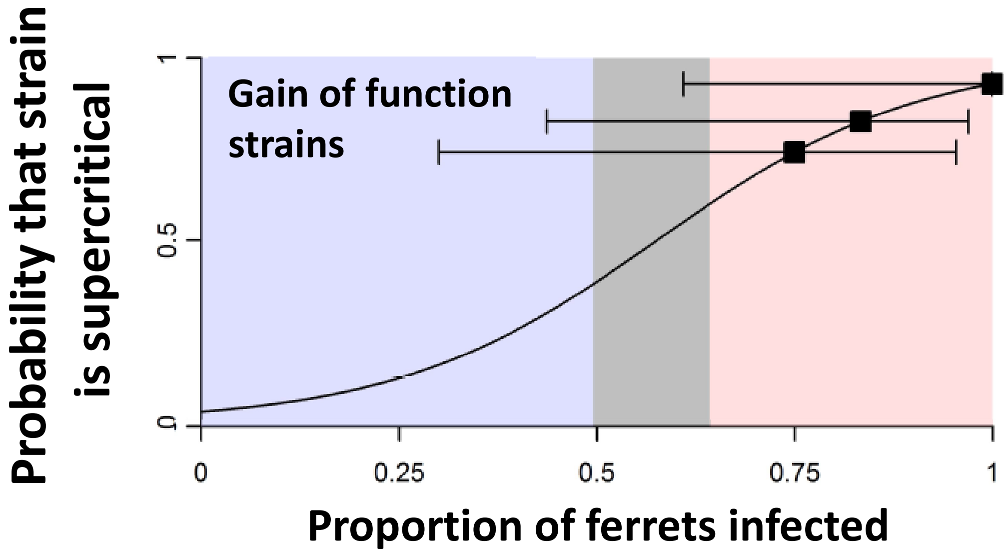
Handles under-ascertainment well but you need to know sources of infection.

Cauchemez et al, PLoS Med (2013)

From viral genetic data (perhaps mixed with epi data)

New approaches, look powerful, but need viral isolates for sequencing.

Assessing transmissibility without data from humans



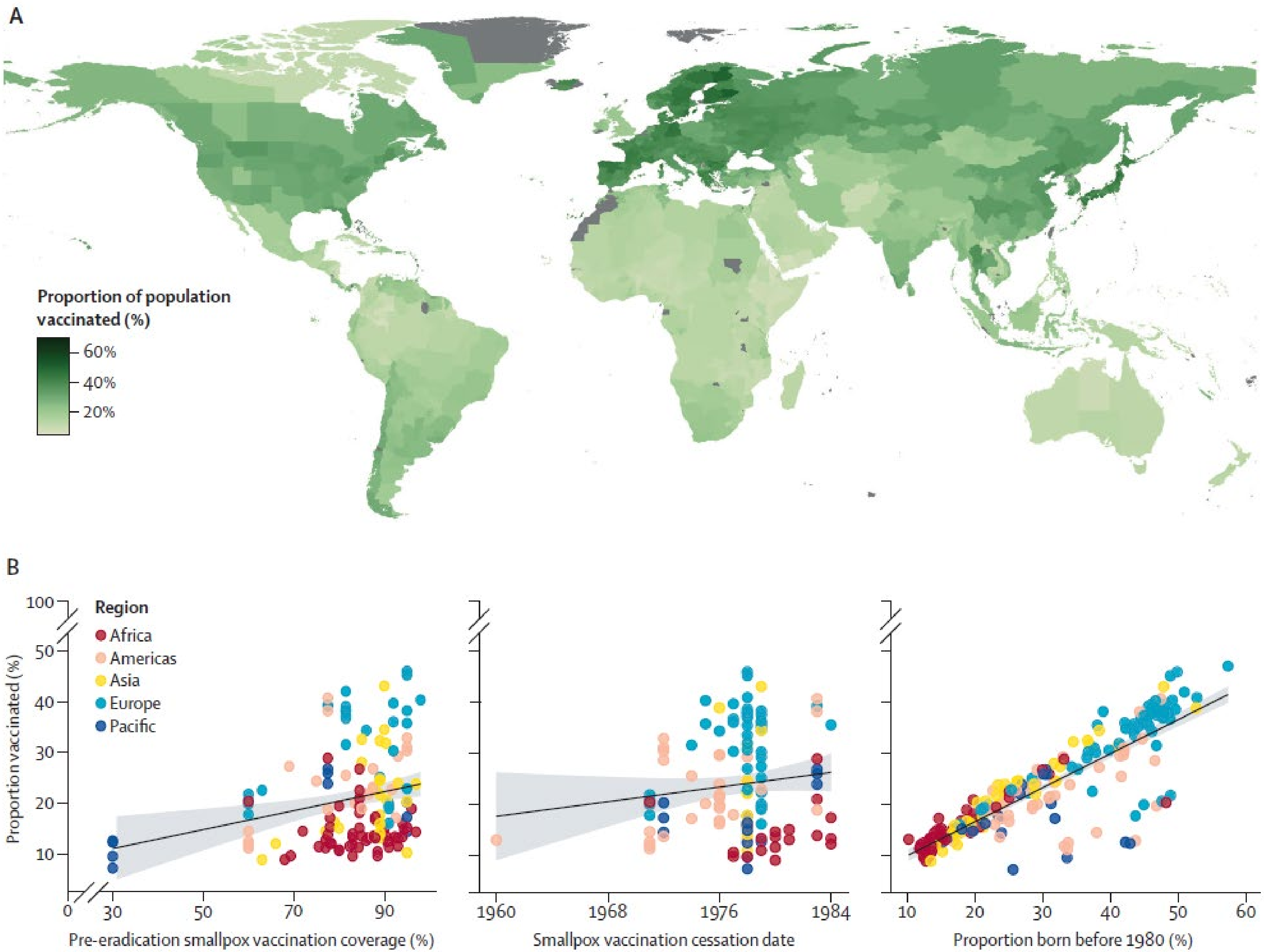
Caveats

- Binomial uncertainty is a huge problem.
- Out-of-sample prediction is inherently risky.

Conclusion: ferret studies are a valid approach to screening novel influenza strains for pandemic potential, but corroborating evidence is needed.

Buhnerkempe et al, eLife (2015)

Prior immunity against 'novel' pathogens

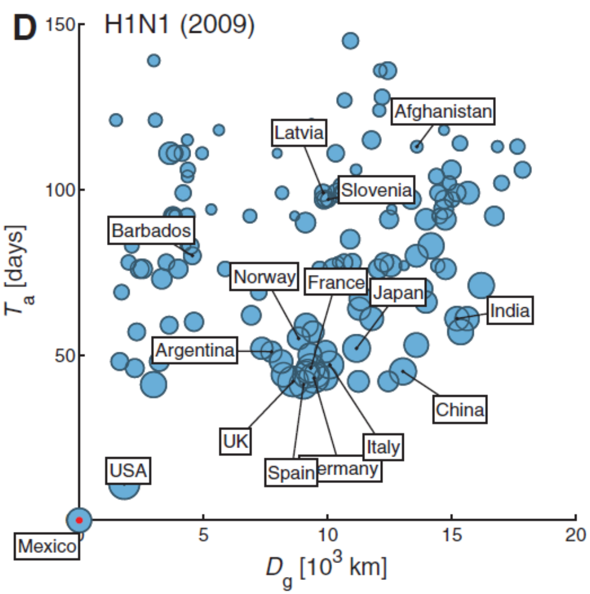


Taube et al, Lancet Infectious Disease (2023)

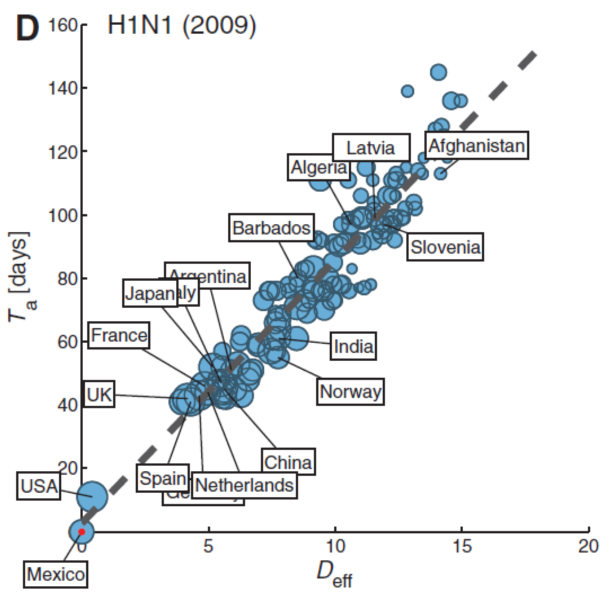
Global spread: air travel networks and rescaling space

Global spread patterns can be predicted by rescaling space
according to human mobility patterns.

Global air passenger flows



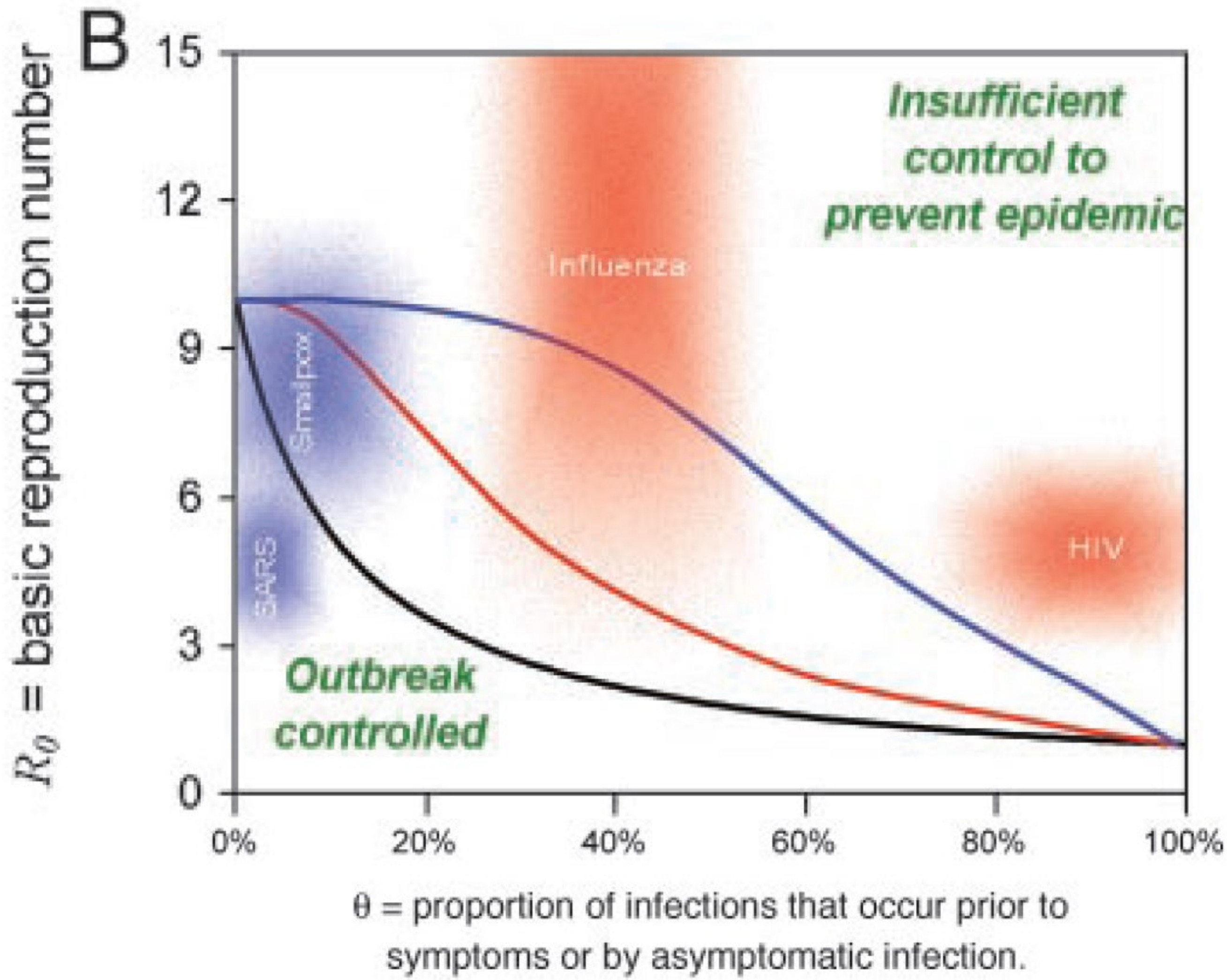
Rescale distance



Brockmann & Helbing, Science (2013)

Control: case isolation, contact tracing and quarantine

Transmission by asymptomatic cases has huge influence on ability to control epidemics by targeted measures.



Fraser et al, PNAS (2004)