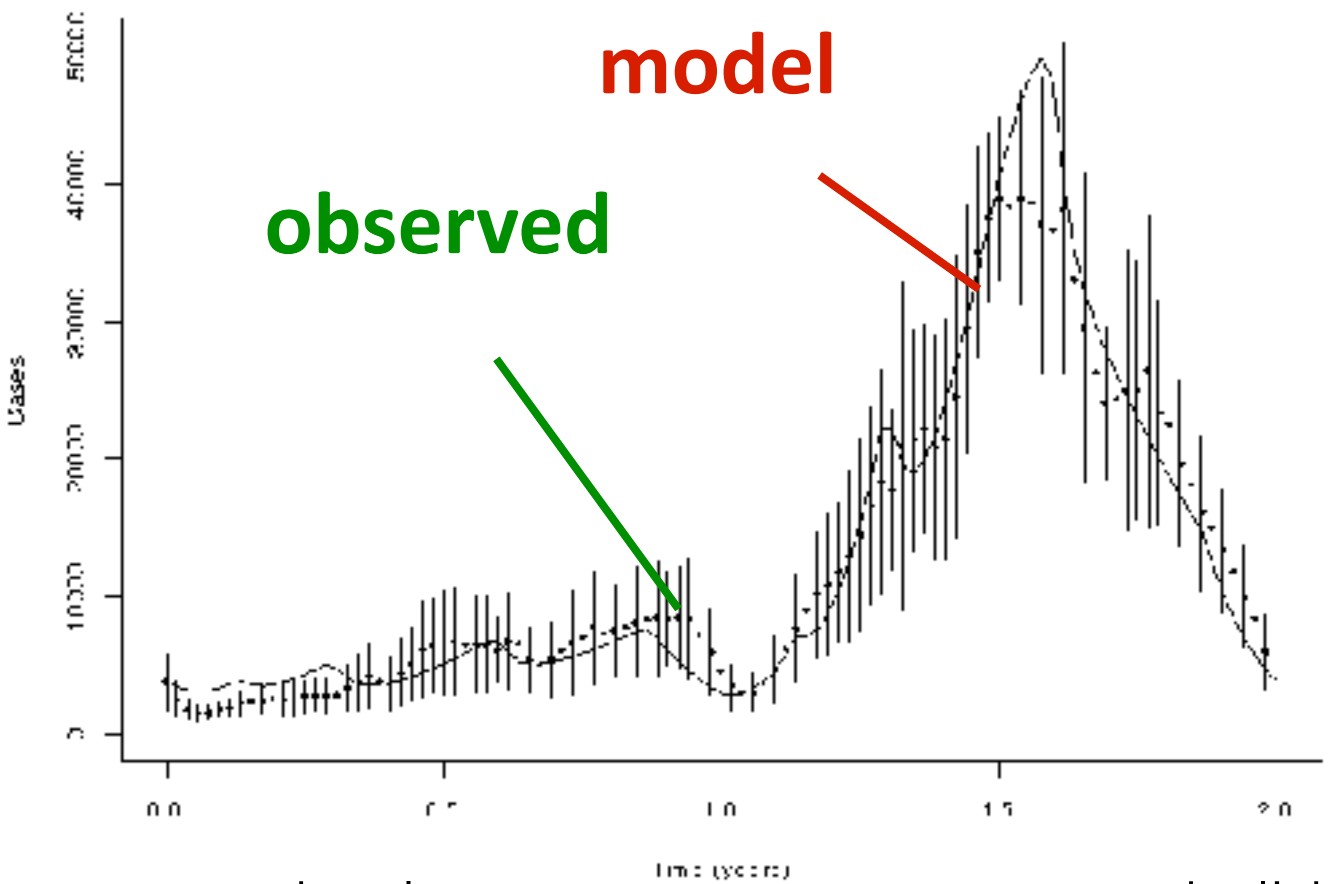
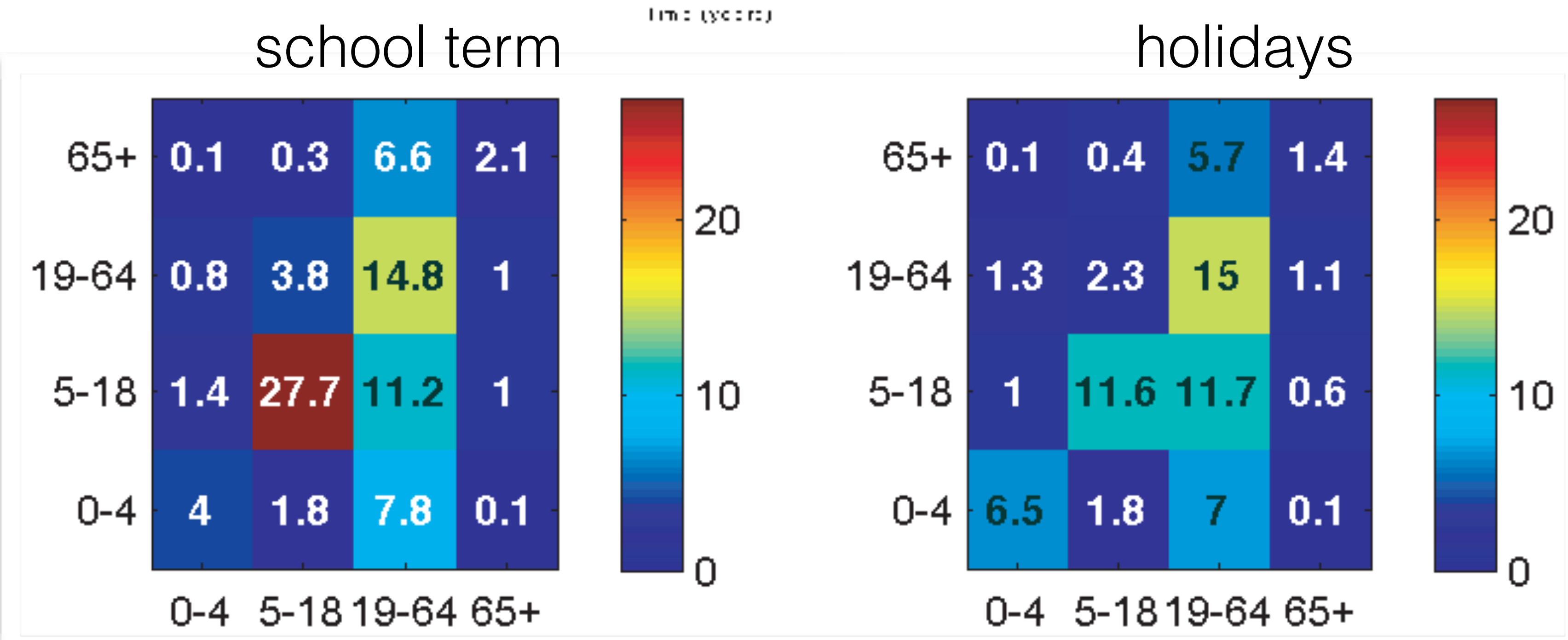
Measles Dynamics (London: 1950-1968)



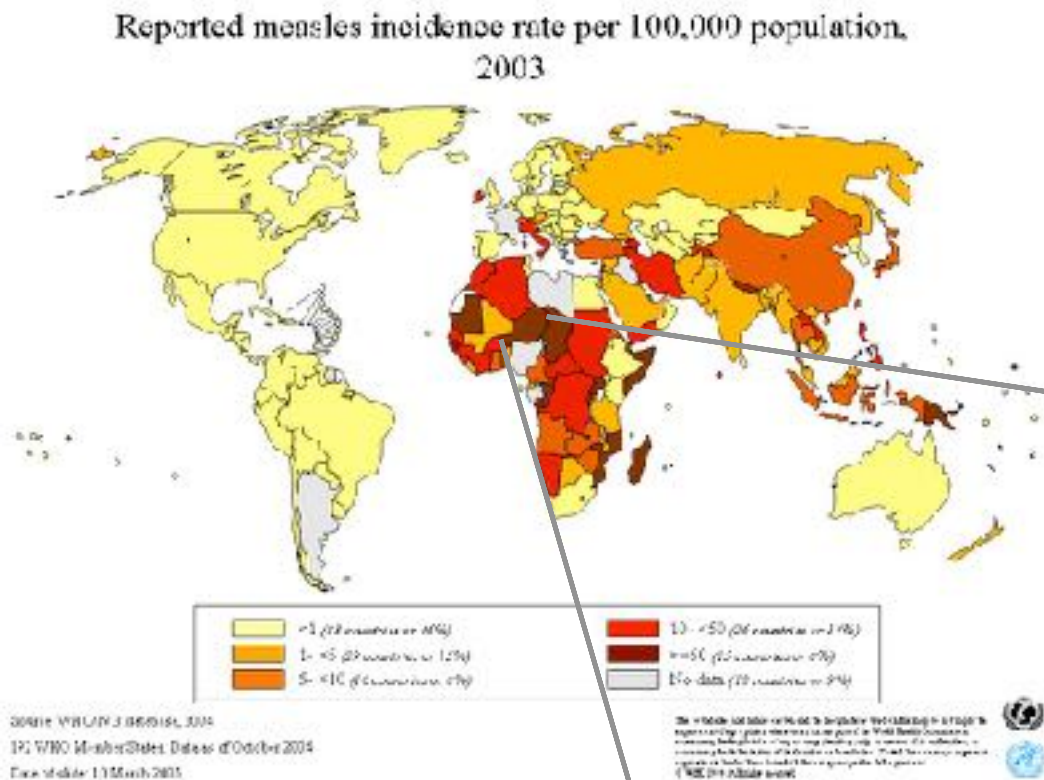
In England & Wales, changing contact patterns during year (driven by school terms) are responsible for seasonality in measles incidence

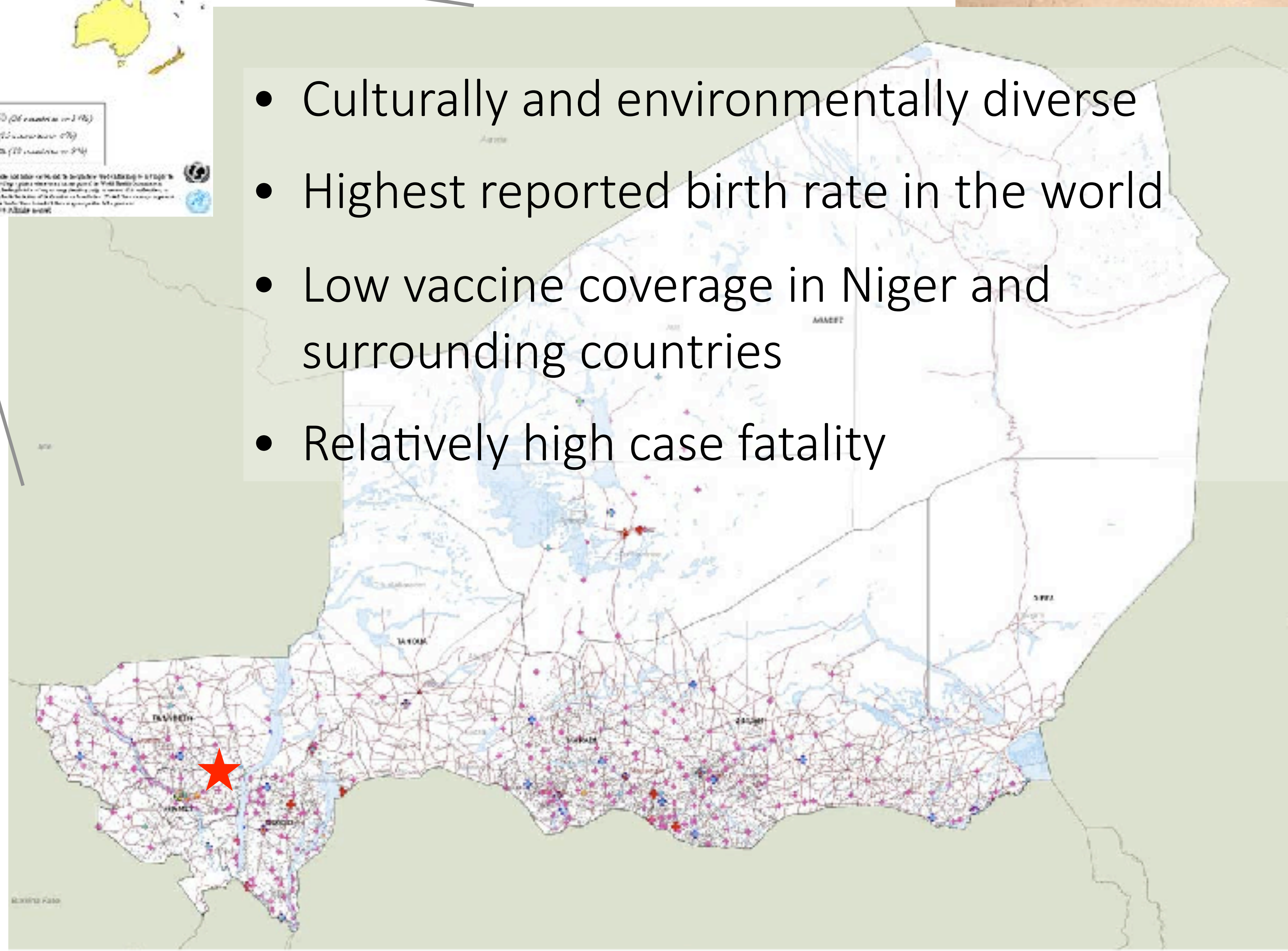


Social contact surveys confirm dynamic shifts in contacts though school year

Eames *et al.* (2012)

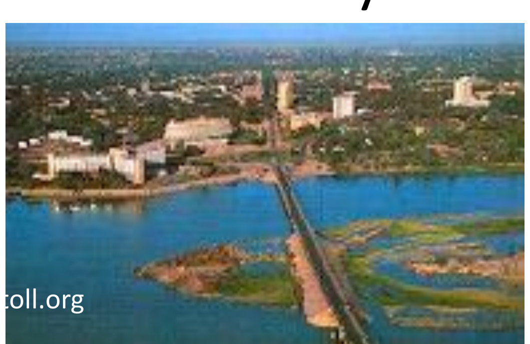
Niger





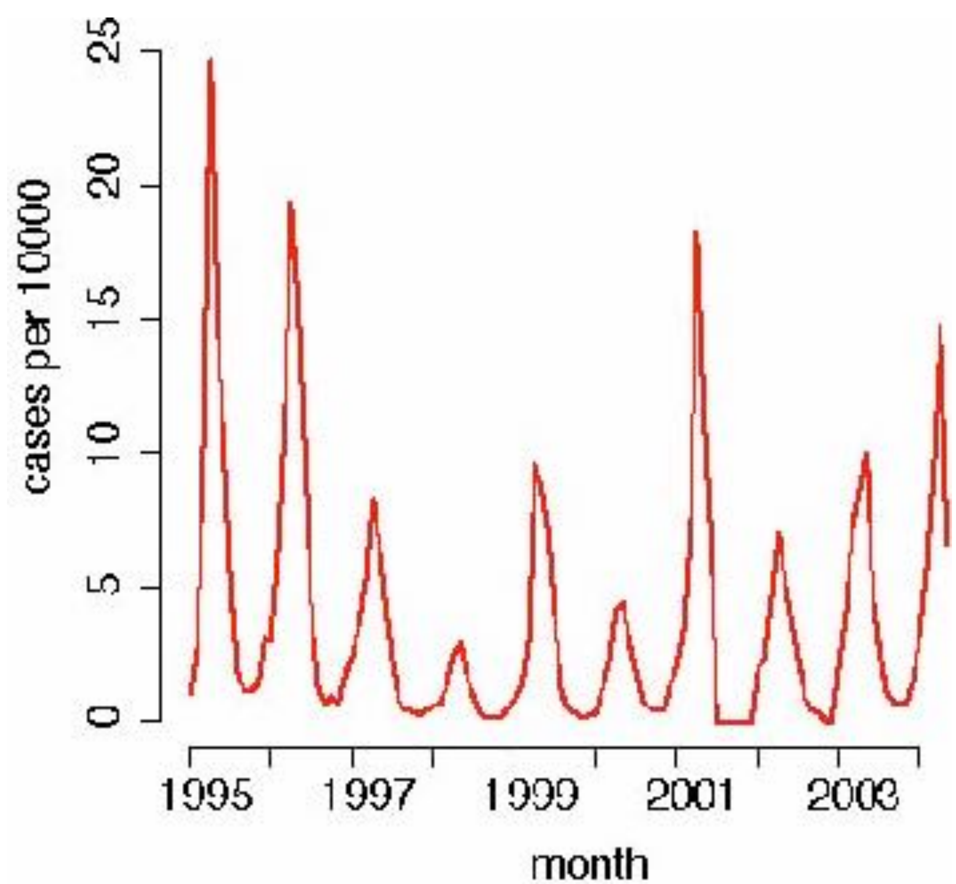
- Culturally and environmentally diverse
- Highest reported birth rate in the world
- Low vaccine coverage in Niger and surrounding countries
- Relatively high case fatality

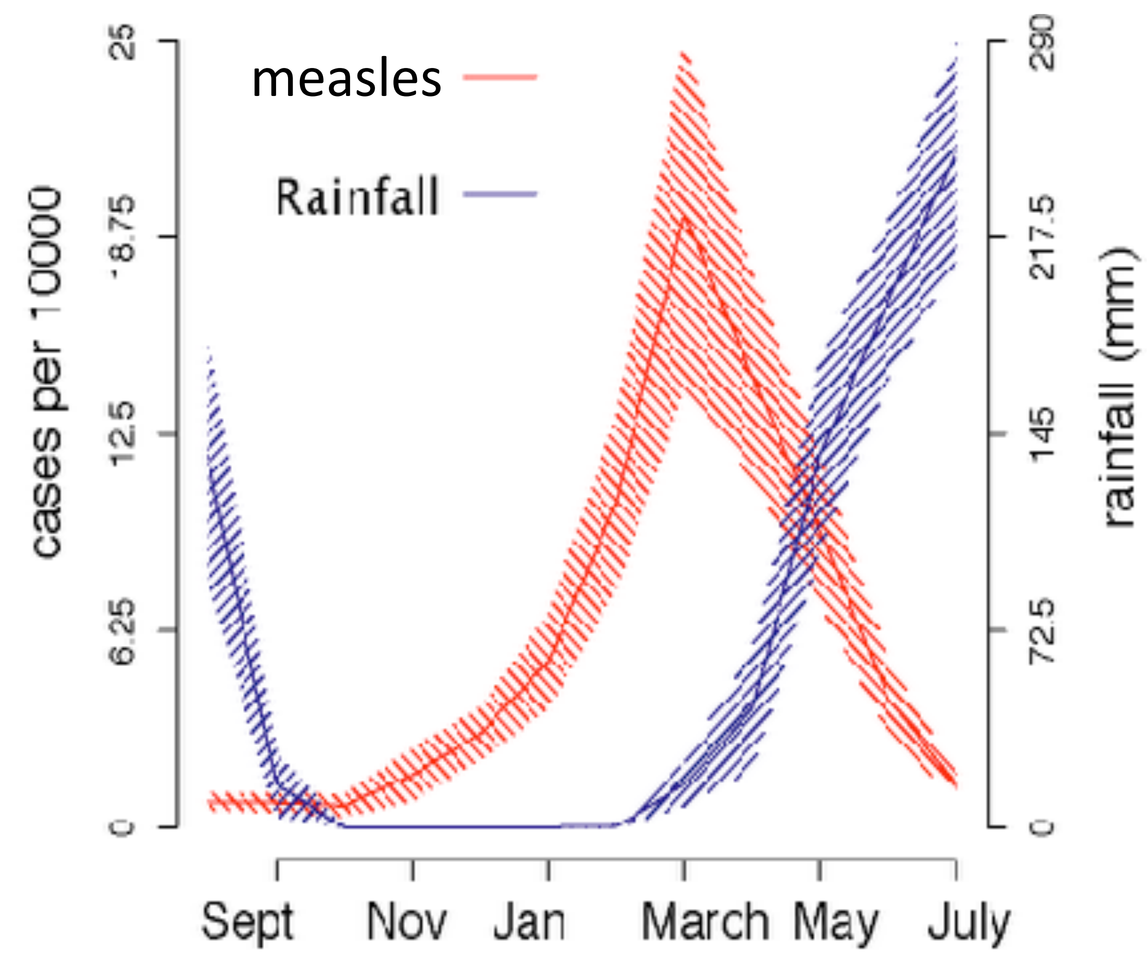
Niamey



Measles Dynamics in Niger

All Niger



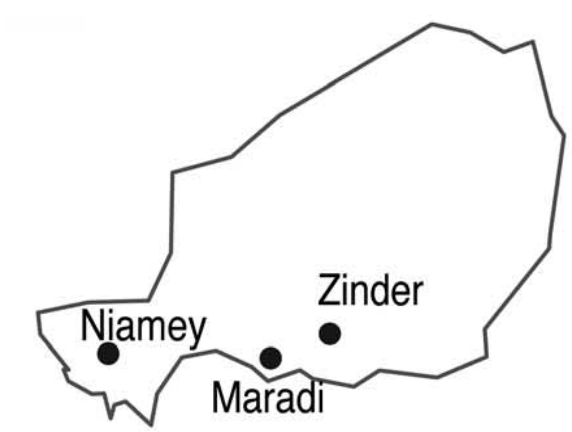


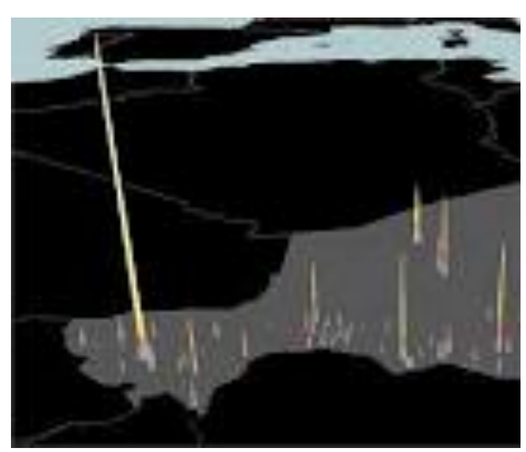
- Measles epidemic begin in the dry season

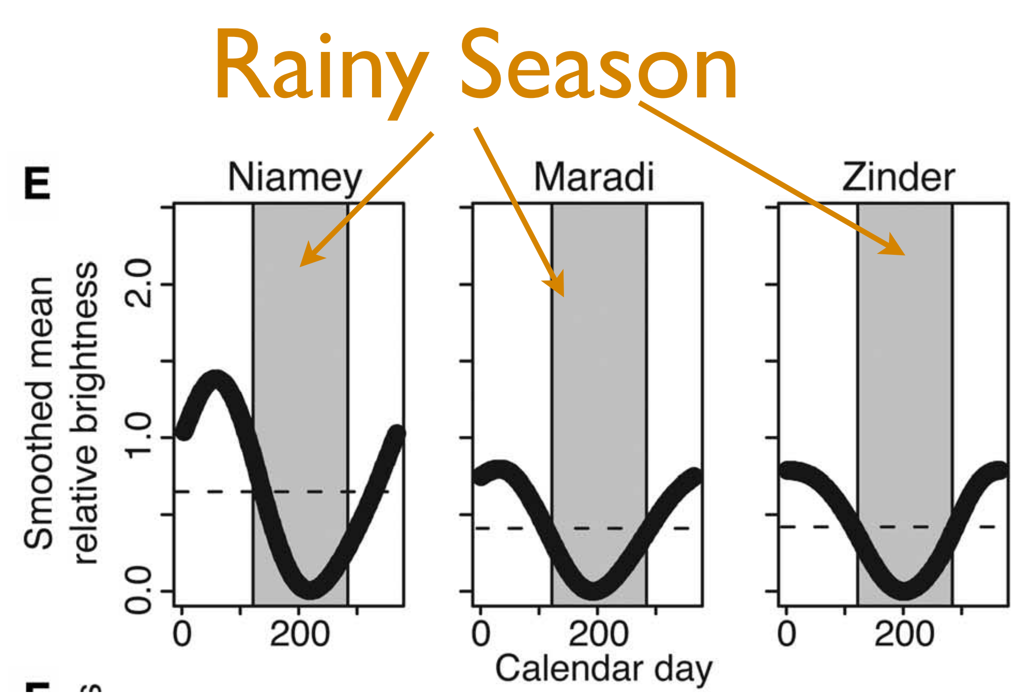
Ferrari et al. (2008; Nature)

Measles in Niger

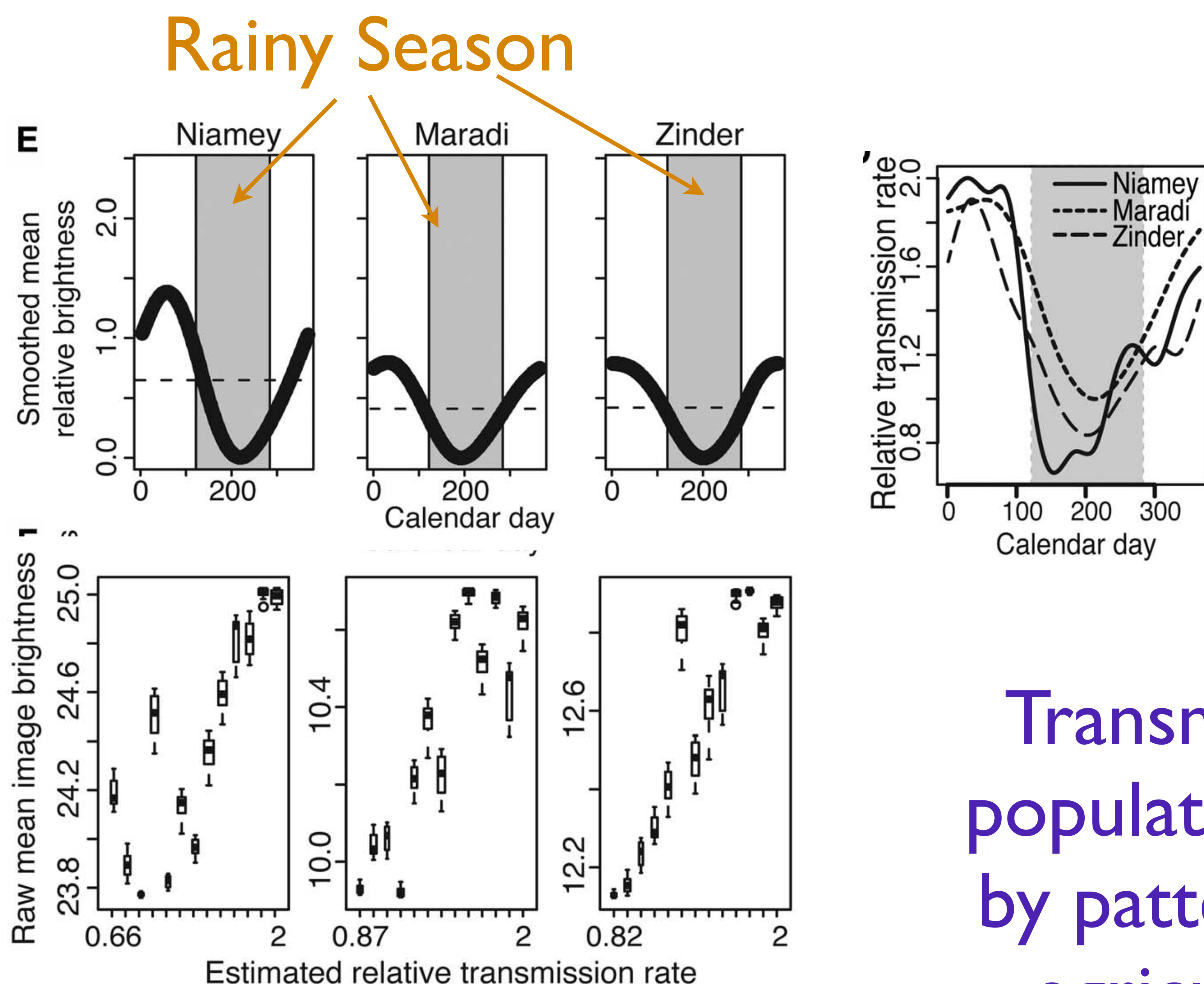
Bharti et al. (2011; *Science*) used intensity of nighttime lights from satellite imagery to estimate population density





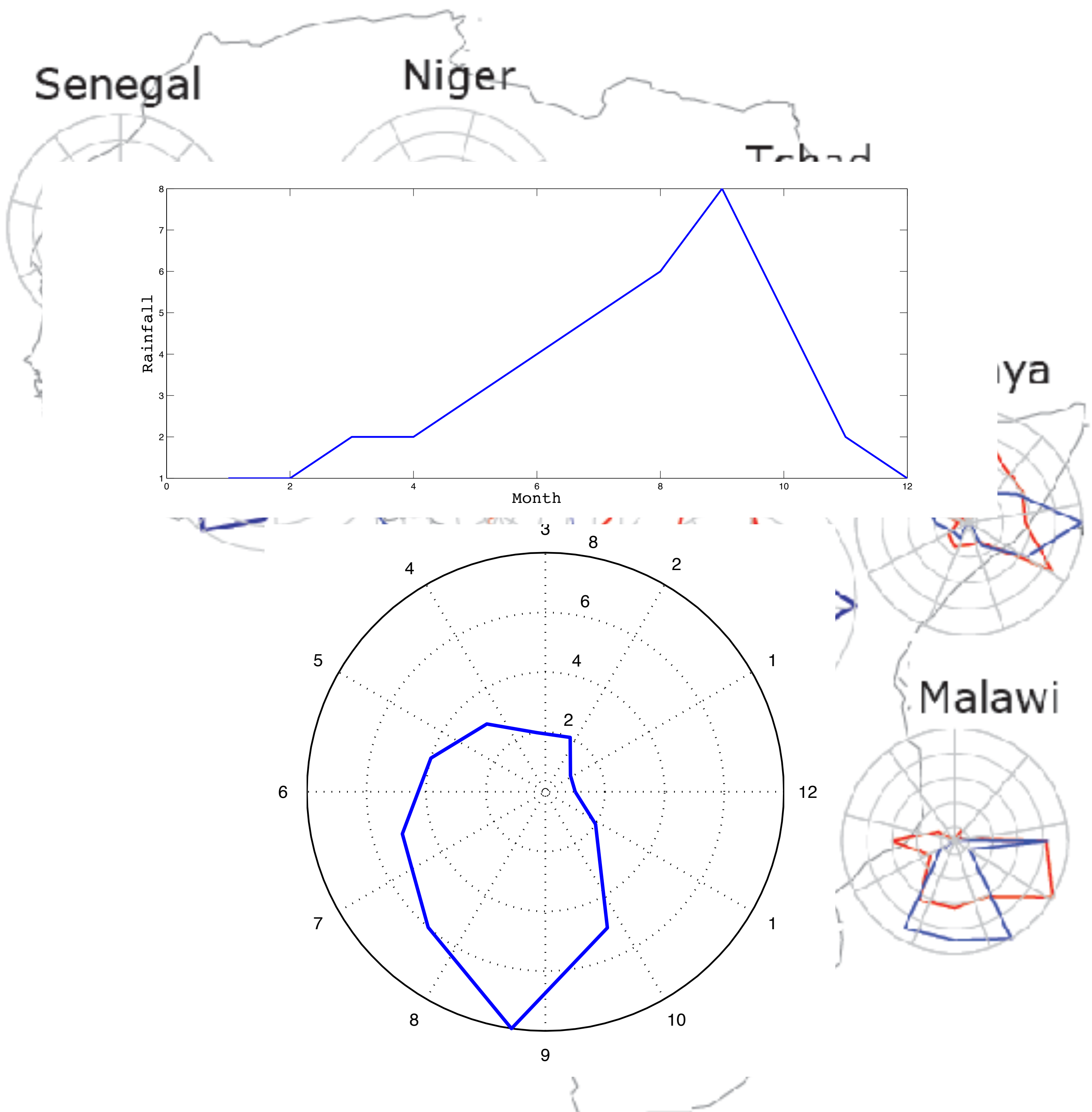


Measles in Niger



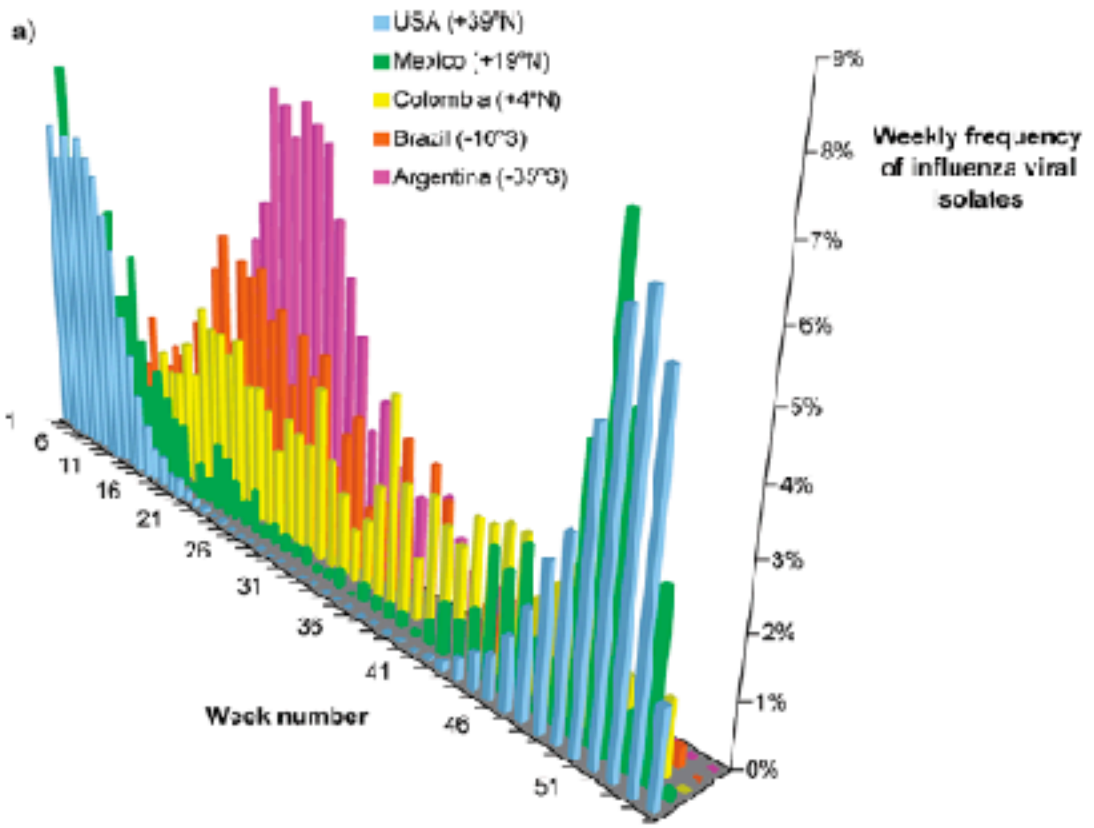
Transmission rates and population density driven by pattern of rainfall and agricultural practices

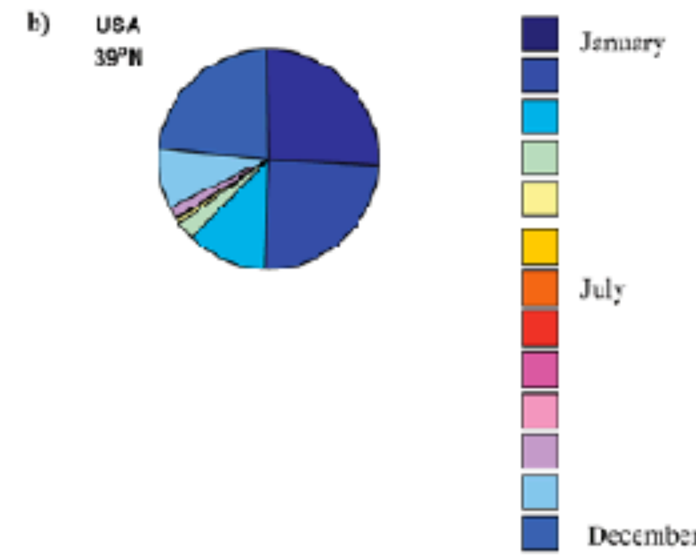
Measles in Africa



Seasonality differs regionally, driven by patterns of rainfall and agricultural practices

Latitudinal trends in Influenza transmission

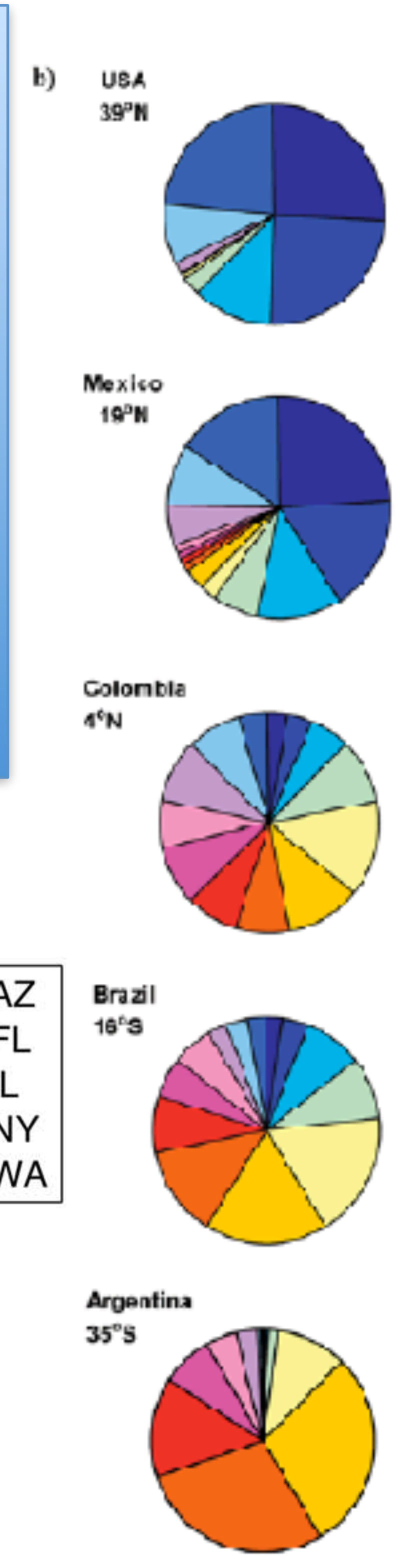


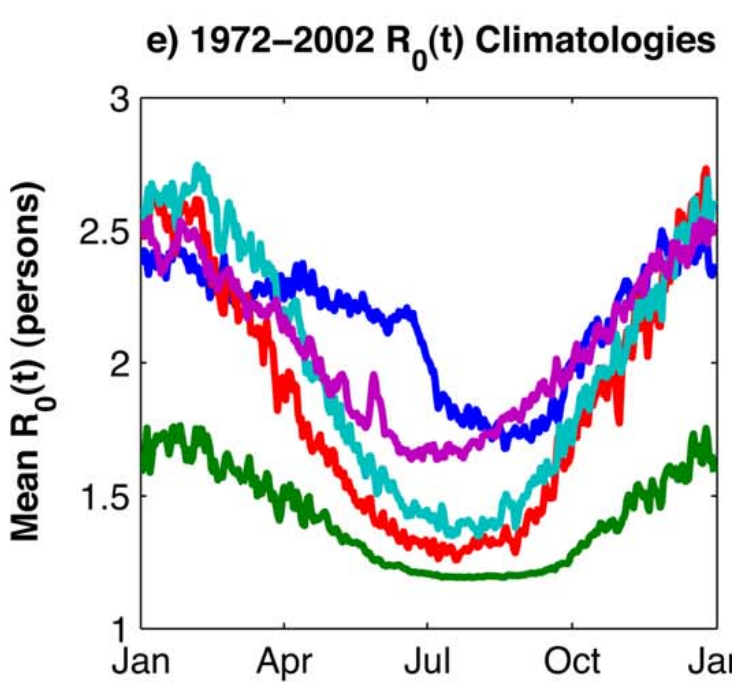


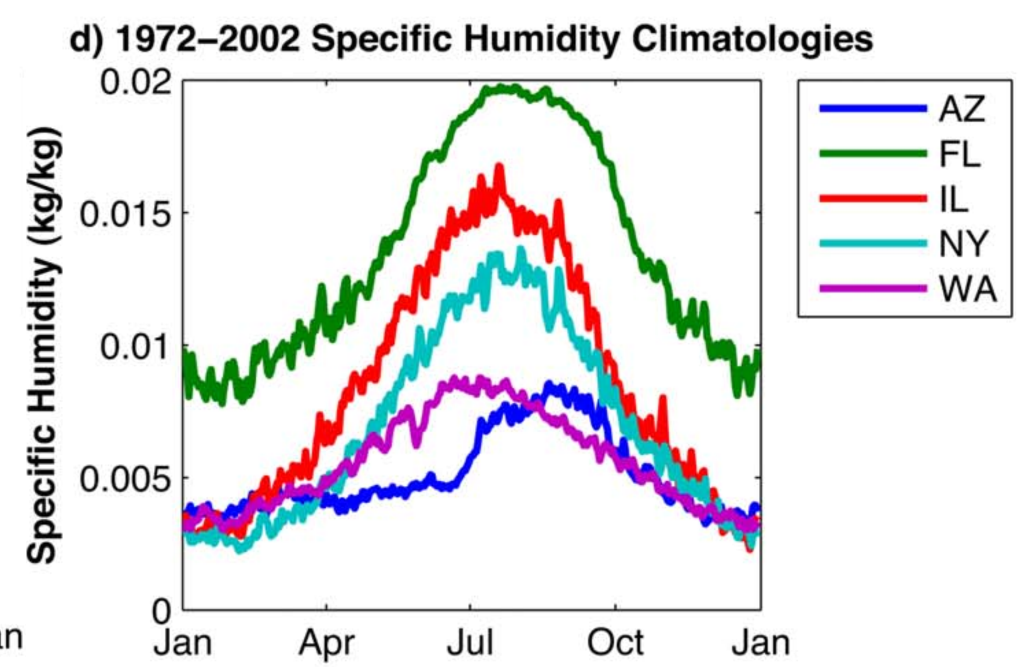
Viboud et al. (2006)

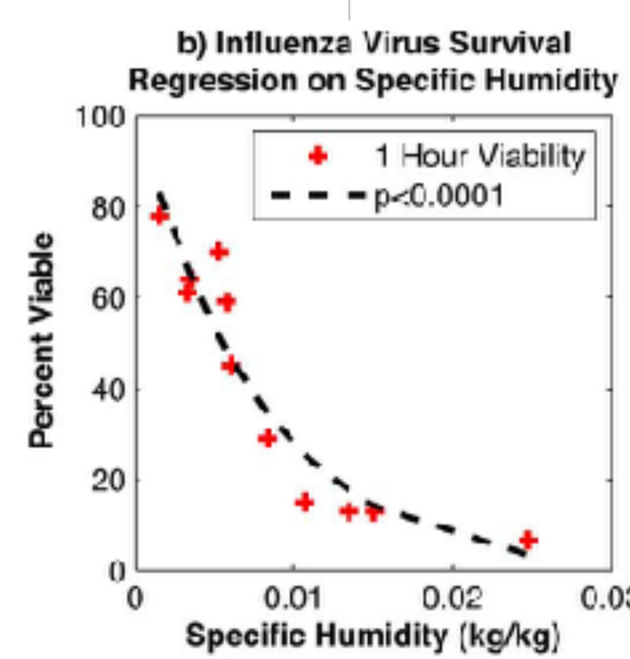
Latitudinal trends in Influenza transmission

- What are mechanisms causing these patterns?
  - Host aggregation (in winter)
  - Changes in host mucosal lining
  - Impact of humidity on aerosol transmission – environmental determinant of virus survival
- Open question, but best available evidence suggests absolute humidity is major explanatory variable for influenza viability through seasons

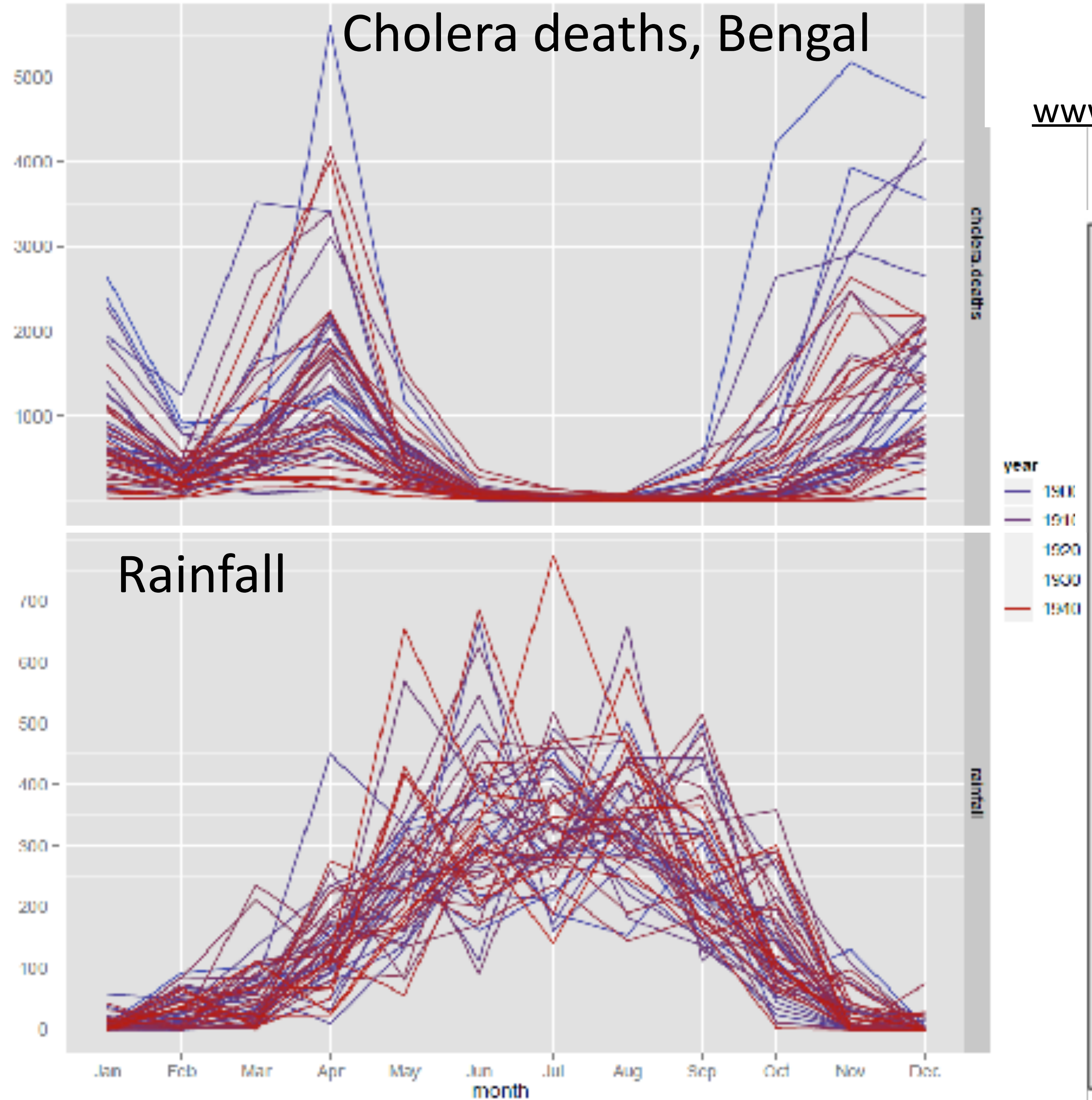




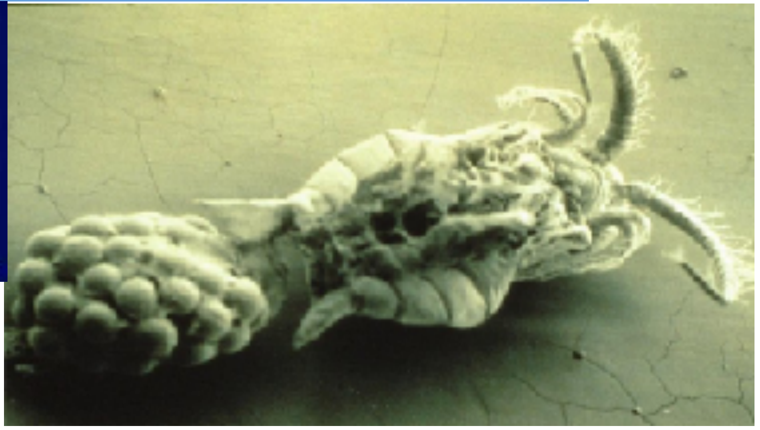




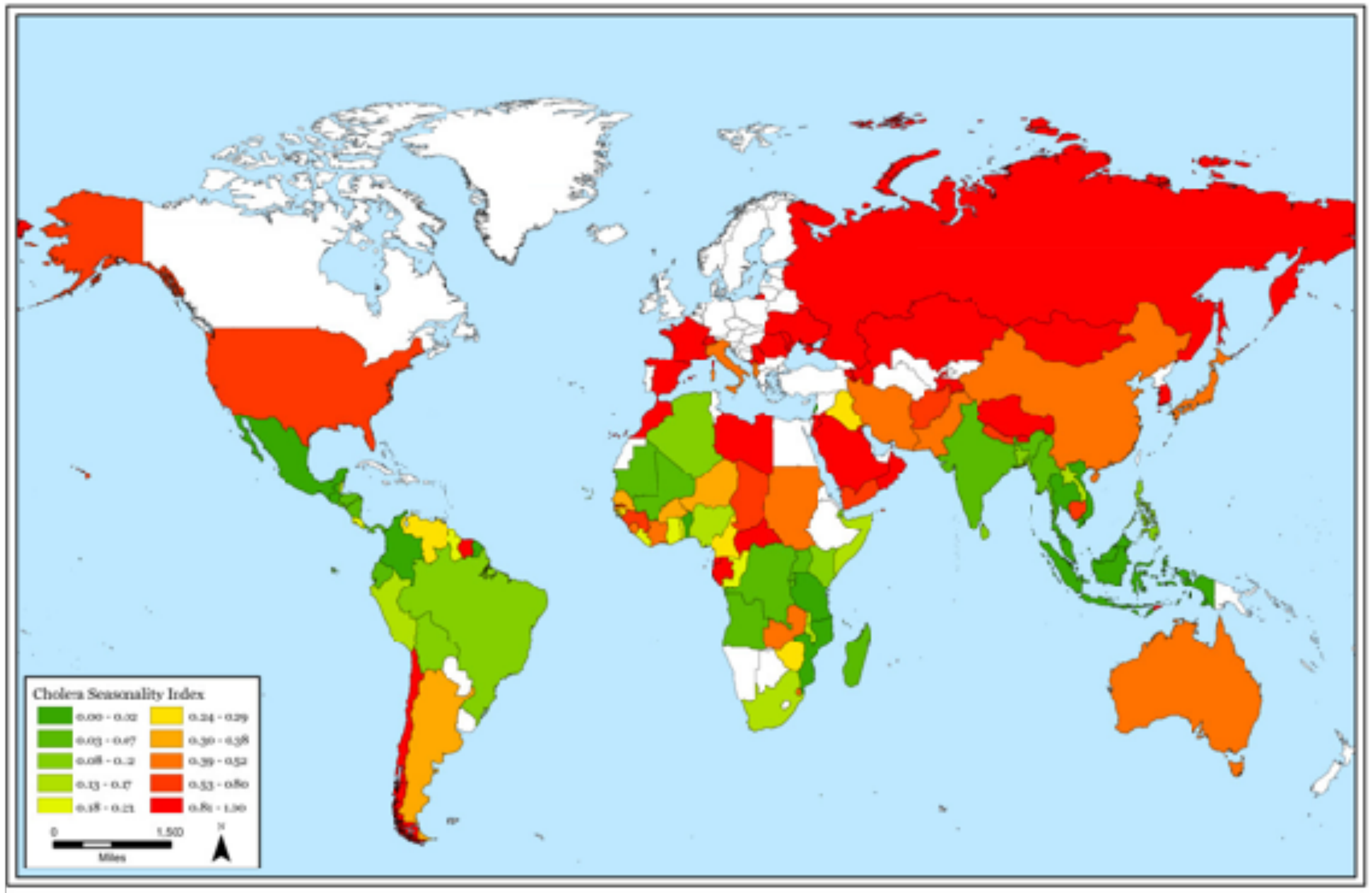
Cholera seasonality



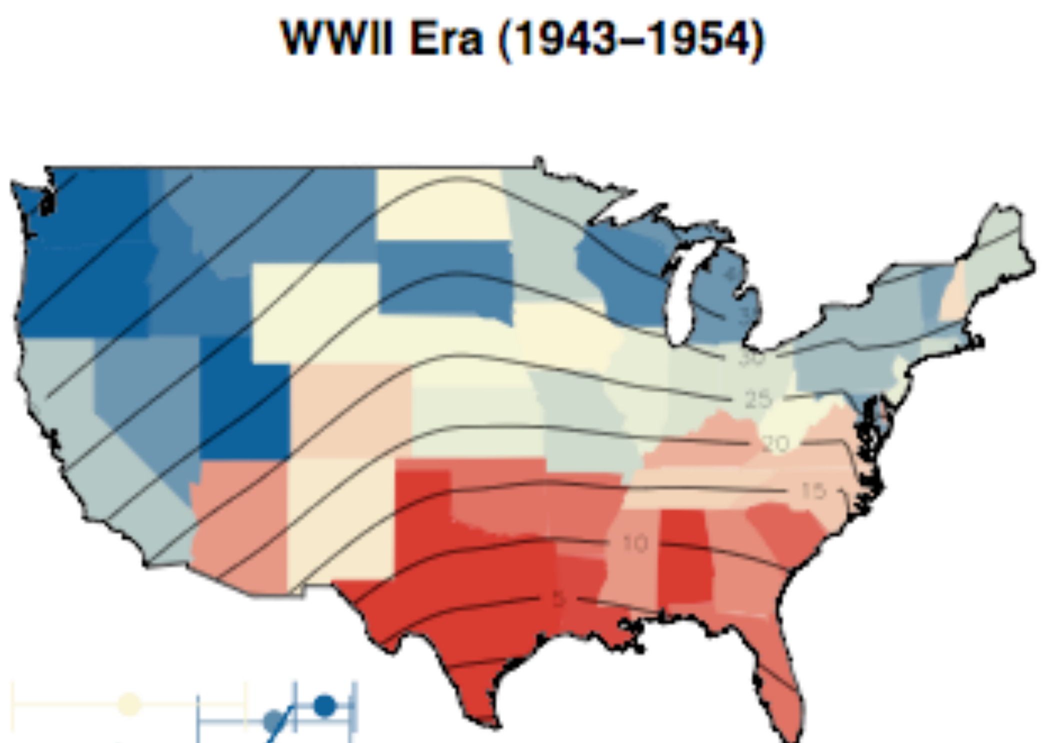
www.kawaiibuzz.com/

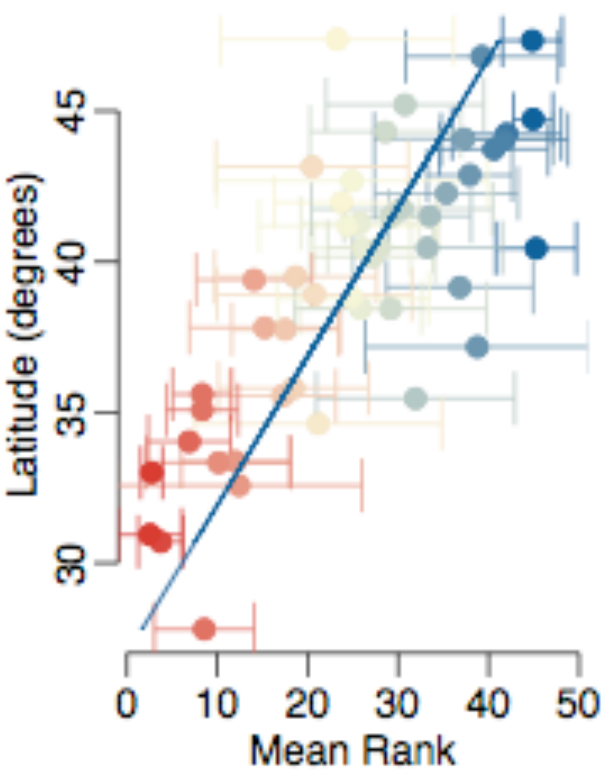


Copepods: a reservoir for *Vibrio cholerae*

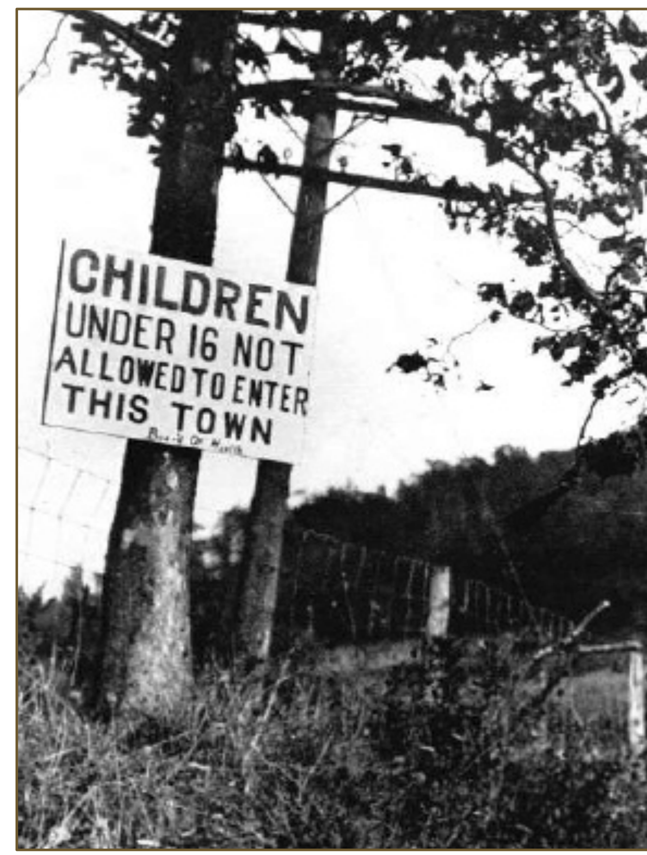


Polio

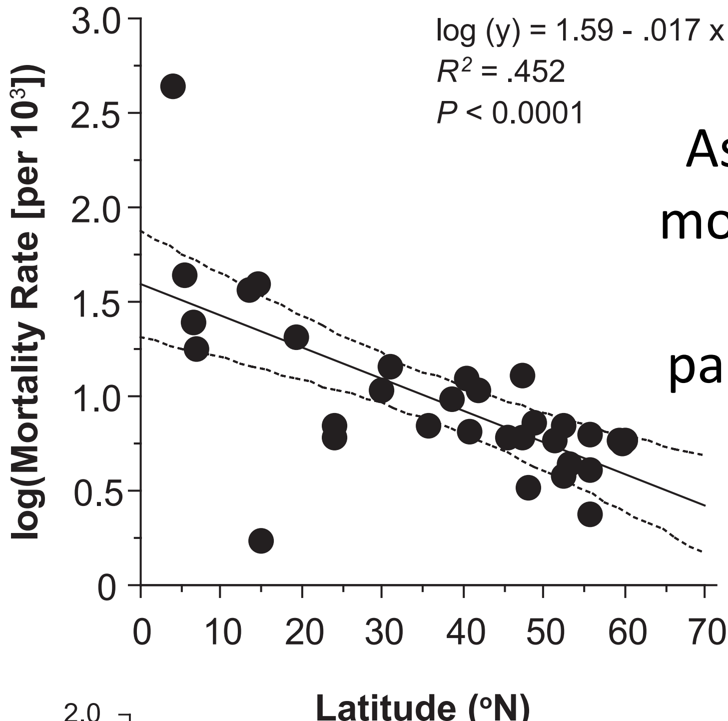




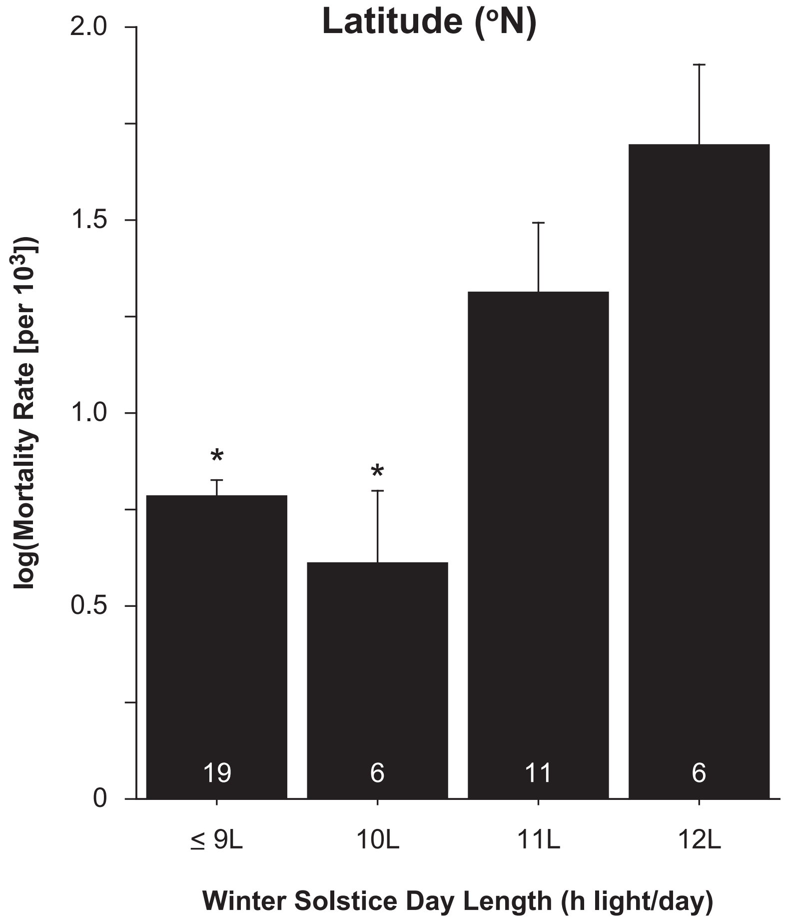
Timing of seasonal polio epidemics in US driven by latitude

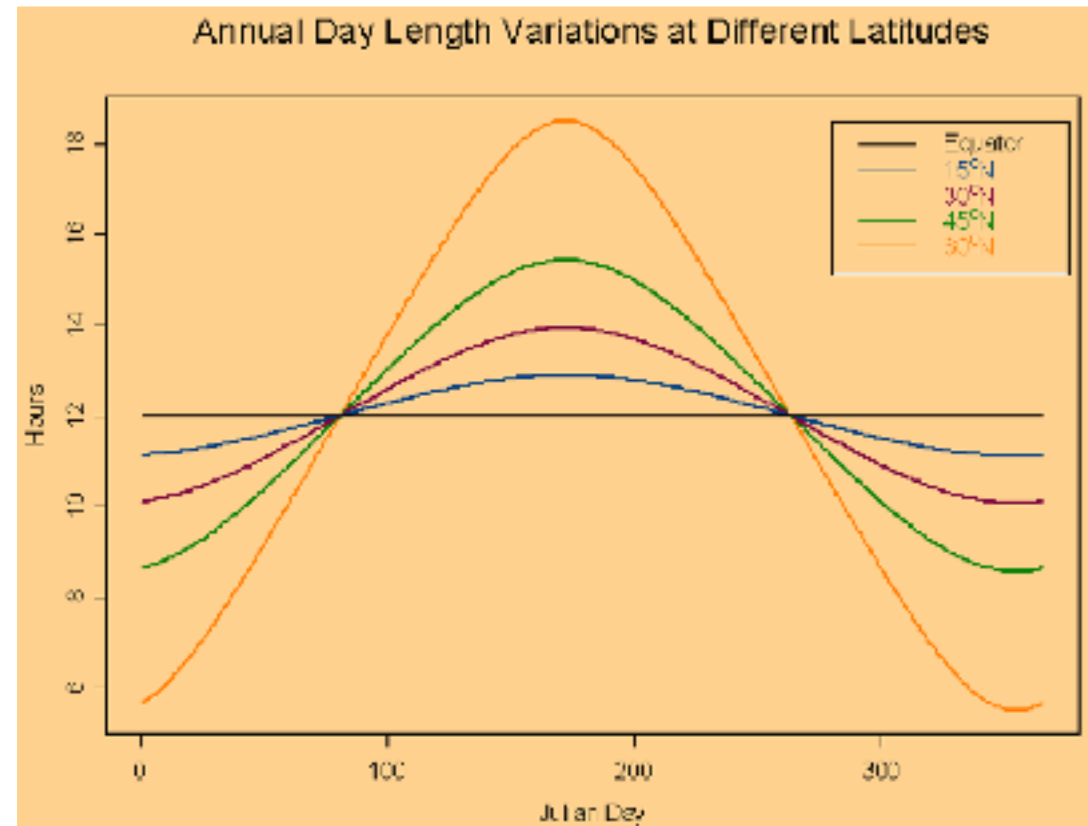


Photoperiodism



Association between mortality probability of 1918 influenza pandemic and latitude



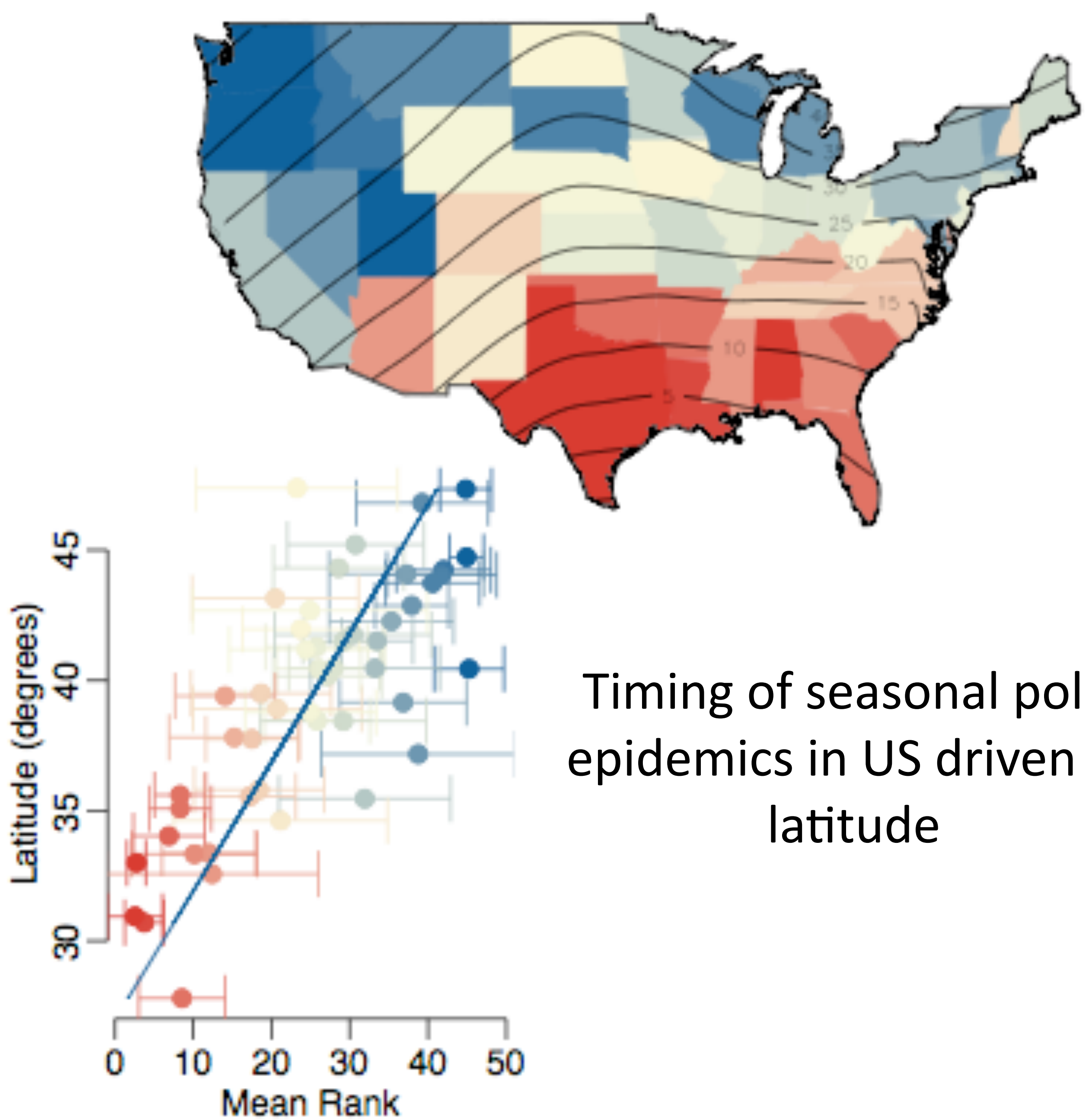


Photoperiodism: physiological response of animals/plants to changes in day length

In laboratory rodent experiments, exposure to short day lengths alone is sufficient to attenuate symptoms of simulated bacterial and viral infections

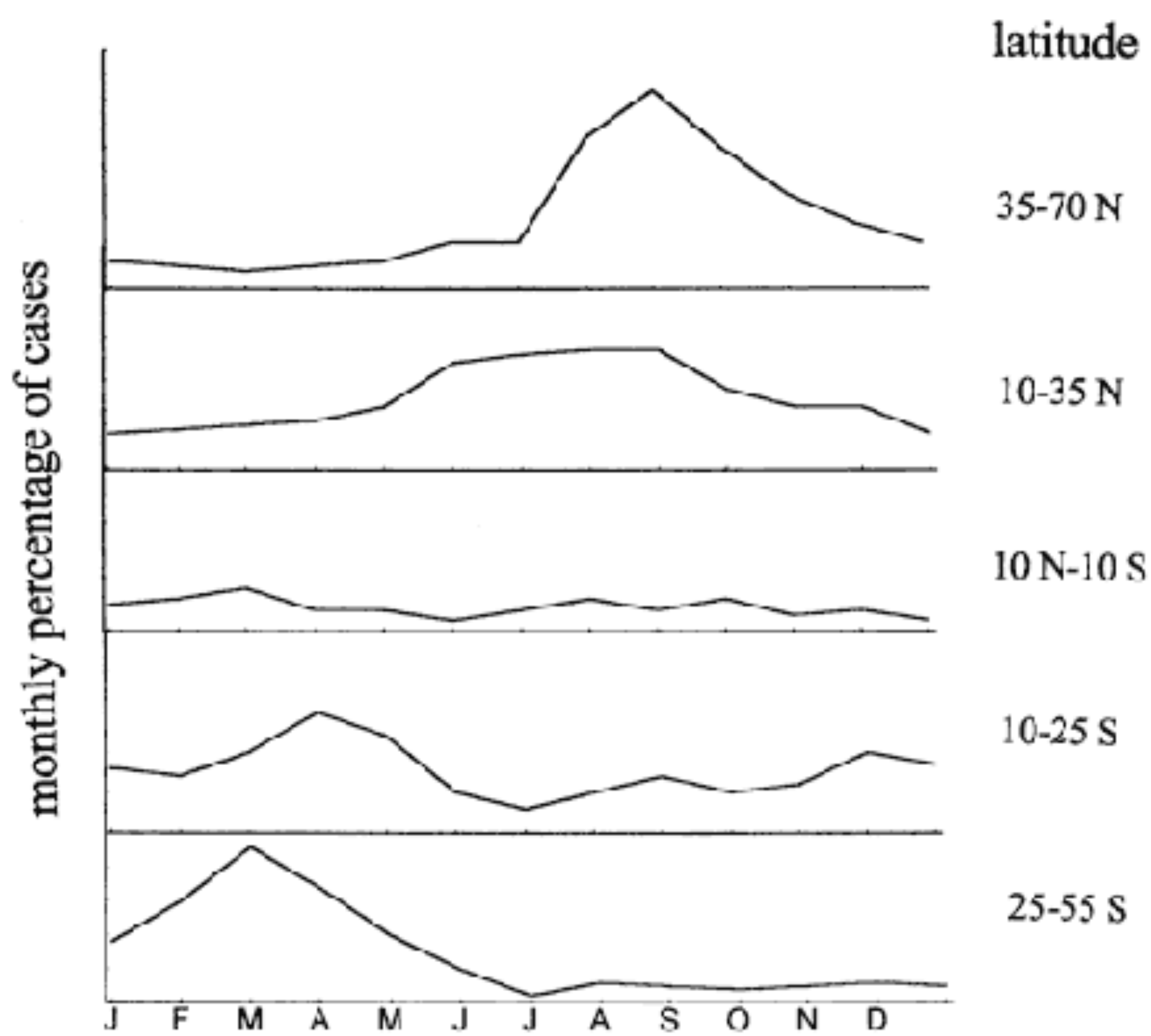
Polio

WWII Era (1943–1954)



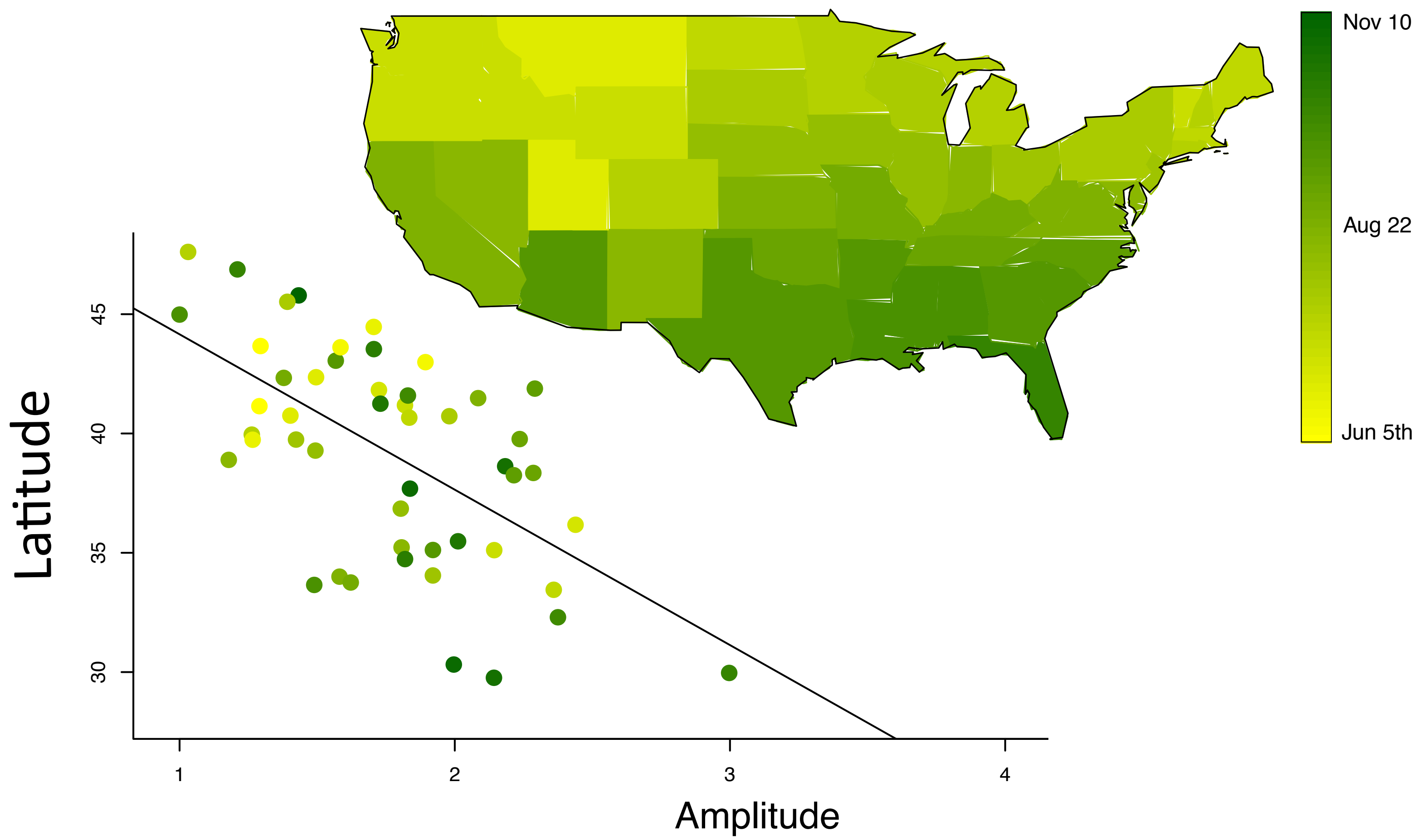
Timing of seasonal polio epidemics in US driven by latitude

Hypothesis I: Changes in susceptibility linked to light/dark cycle, typically mediated by changes in duration of daily melatonin pulse?

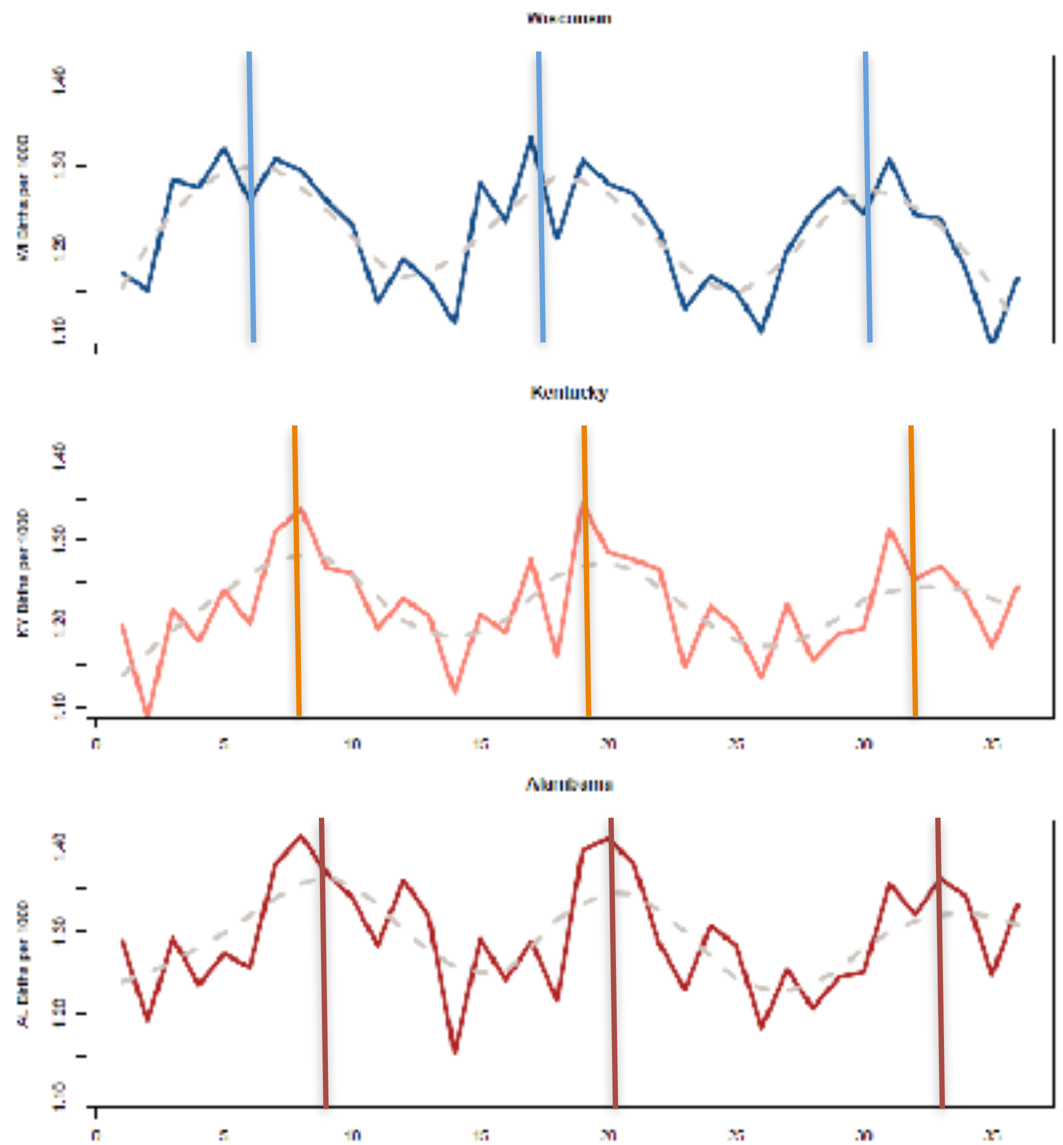


Dowell (2001; EID)

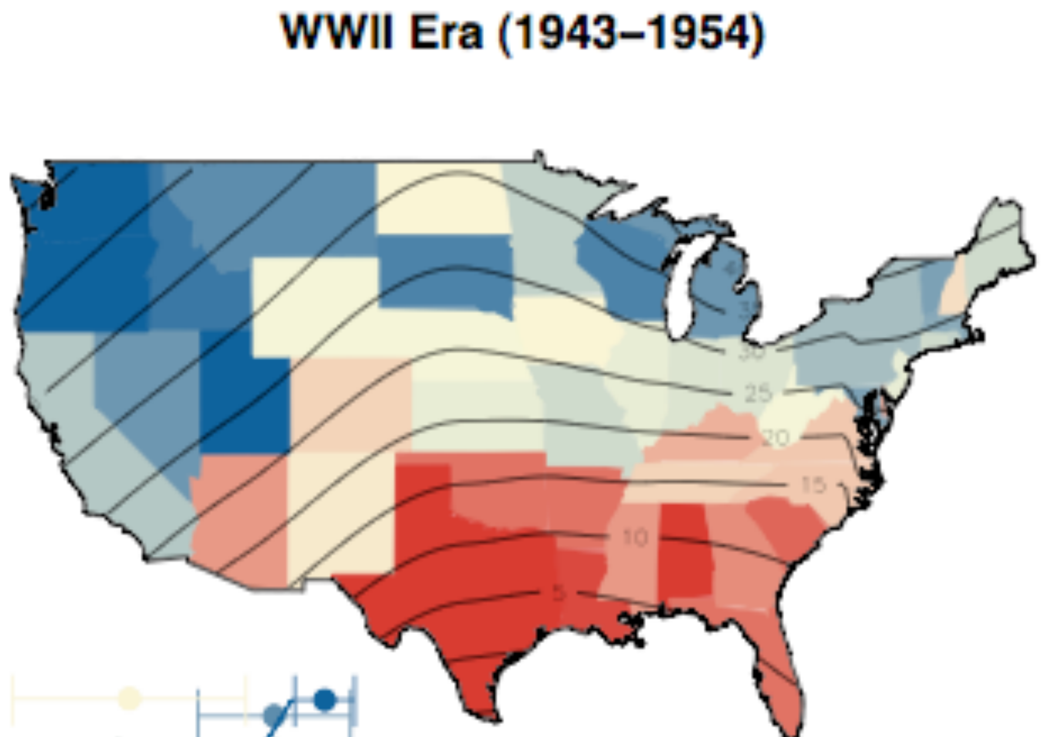
Seasonality in Births

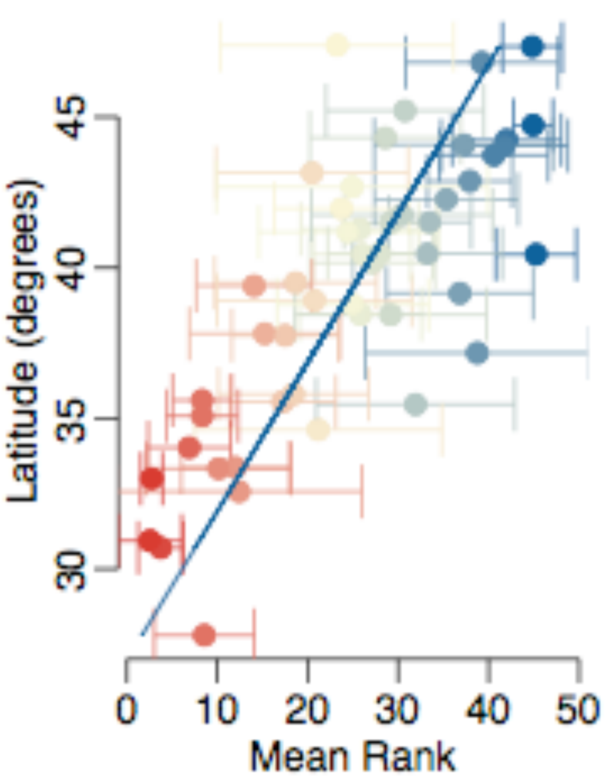


Timing and amplitude of seasonality varies according to latitude

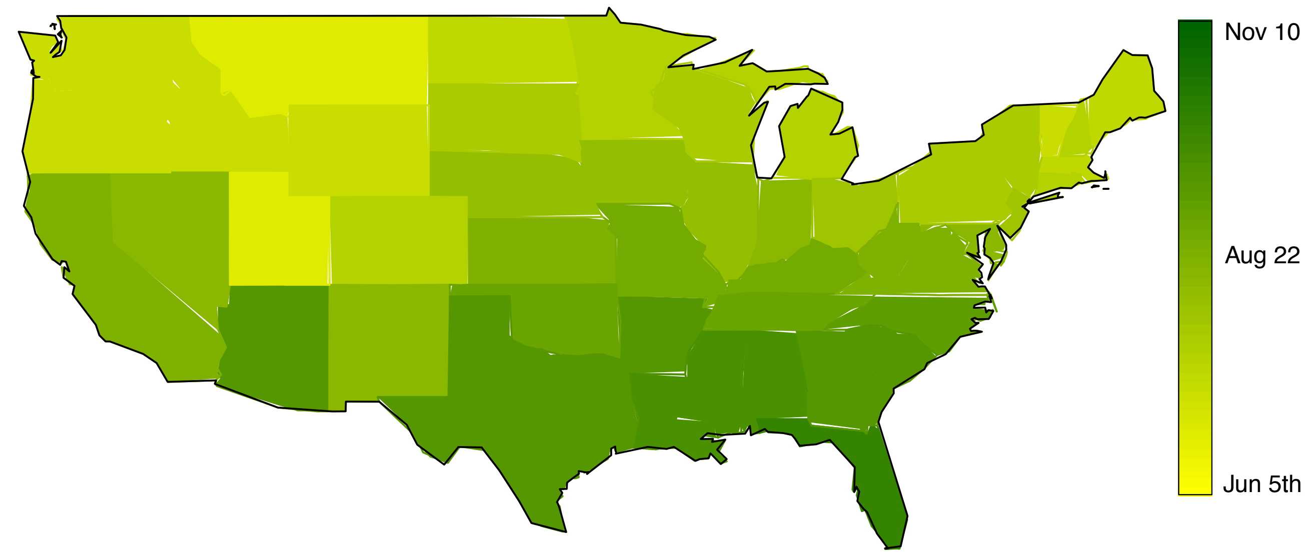


Polio



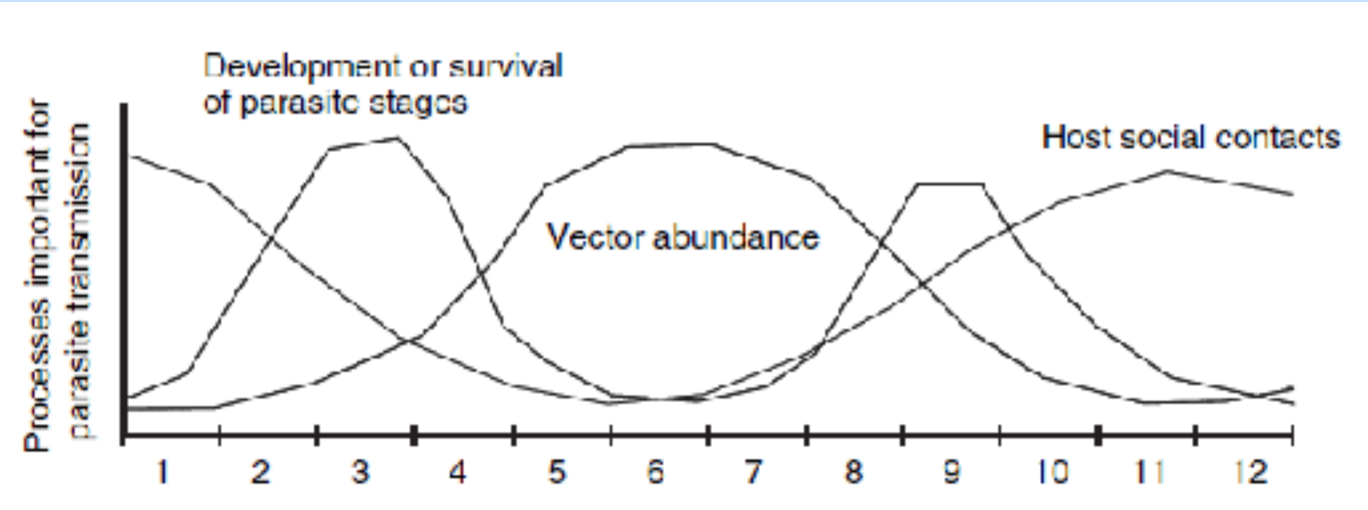


Timing of seasonal polio epidemics in US driven by latitude



Hypothesis II: State-specific difference in epidemic timing due to latitudinally driven demography and seasonality in births?

General mechanisms for seasonality

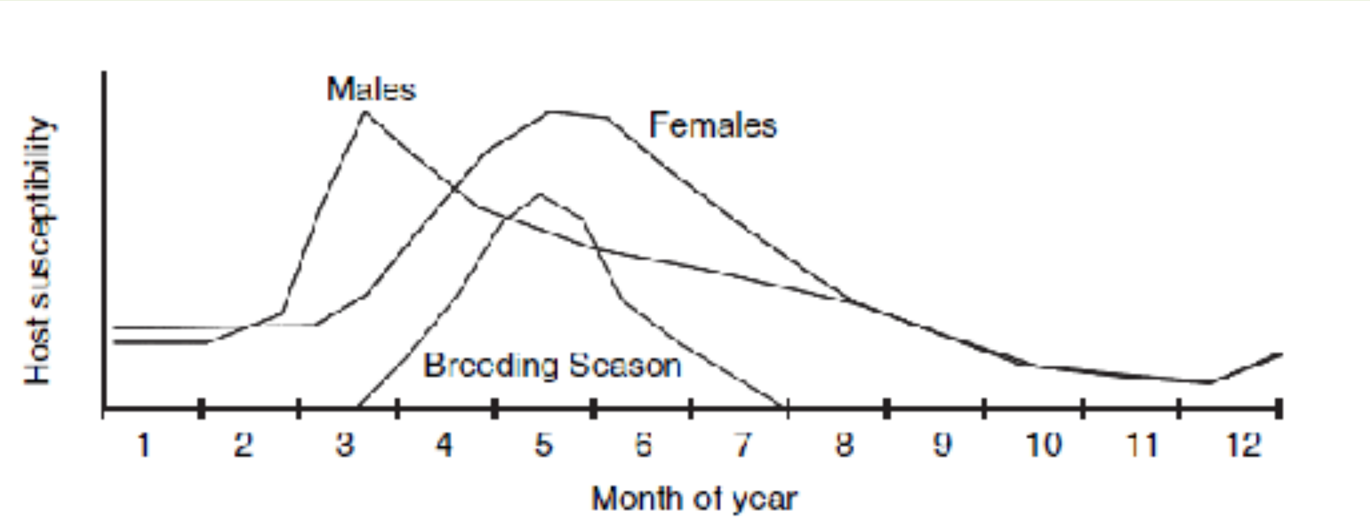


Host exposure

Host aggregation & increased contacts

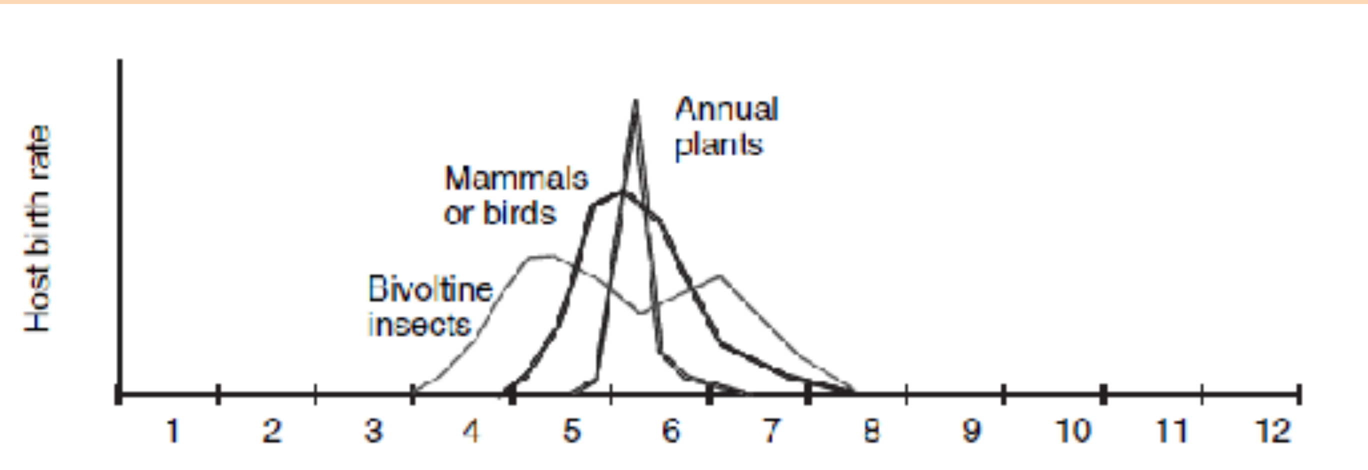
Vector abundance & biting rates

Development & survival of parasite



Host Susceptibility

Changes in host stress & immunity



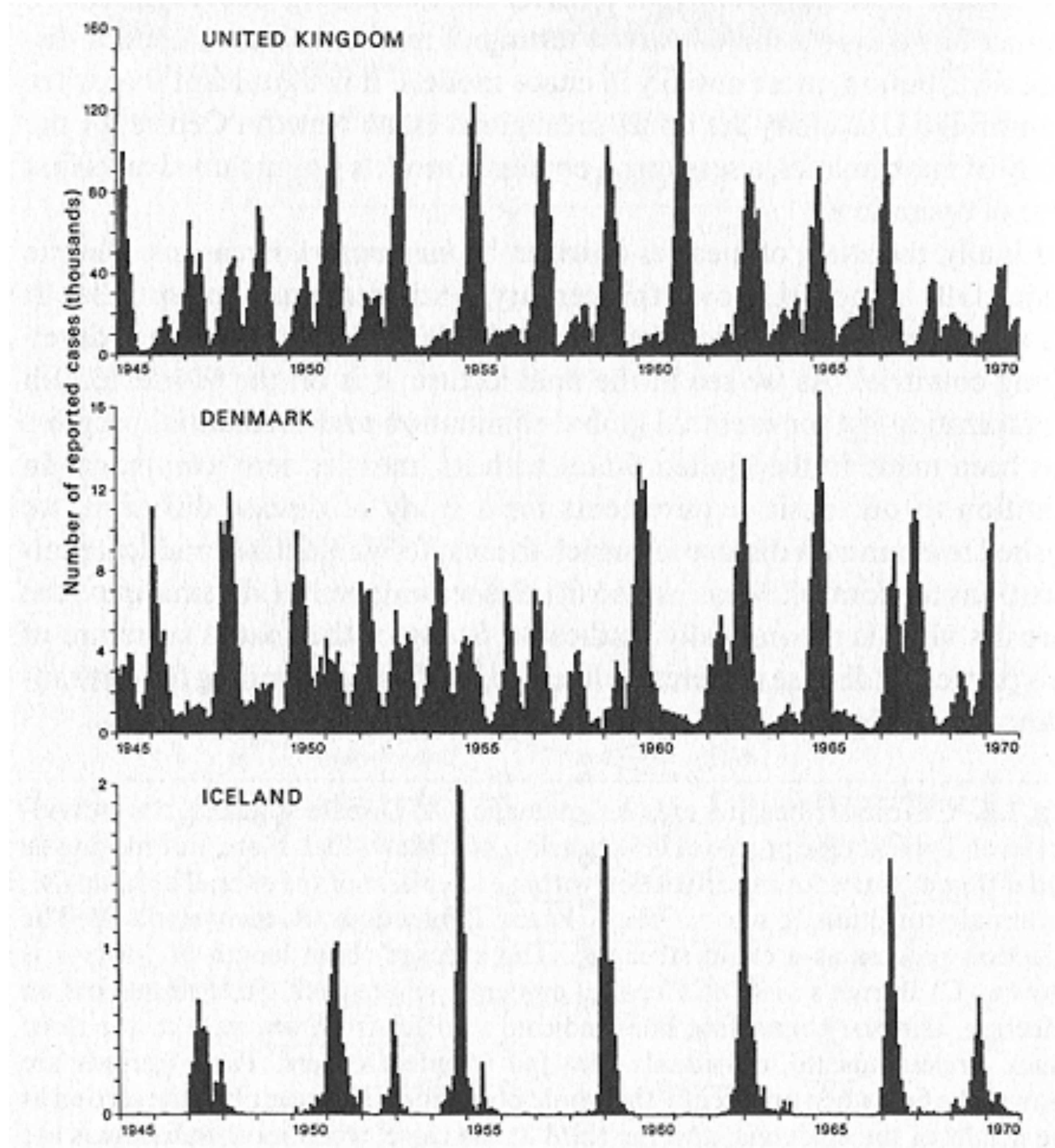
Host Population Size

Seasonally pulsed births

Measles in humans

Dramatic epidemic cycles and 'fade out'

- Reported monthly cases 1945-70
- Descending order of population size
- Dramatic cycles in cases
- Reduction in UK after 1968
- Extinction ("fade out") in Iceland between epidemics

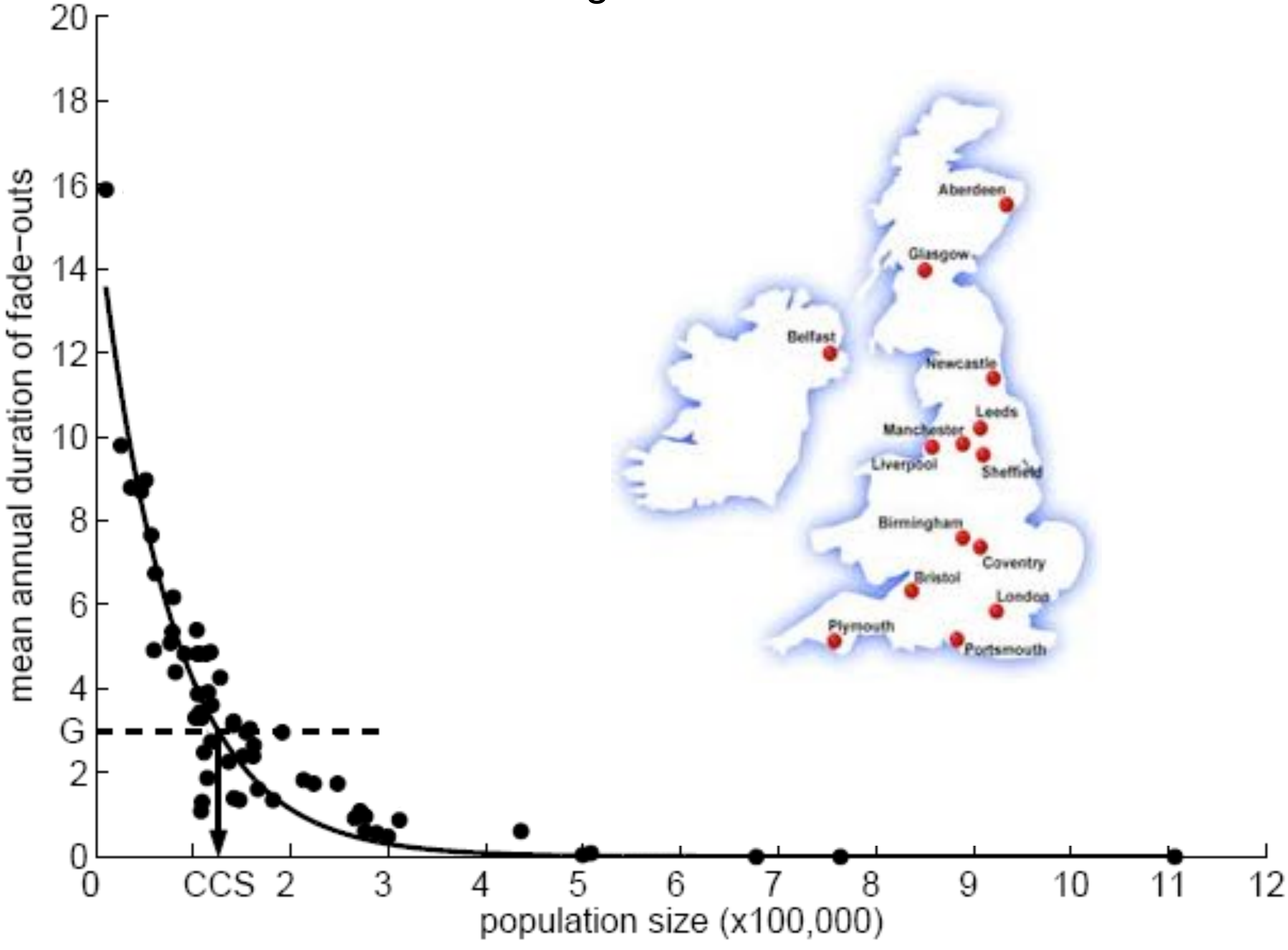


Critical community size (CCS)

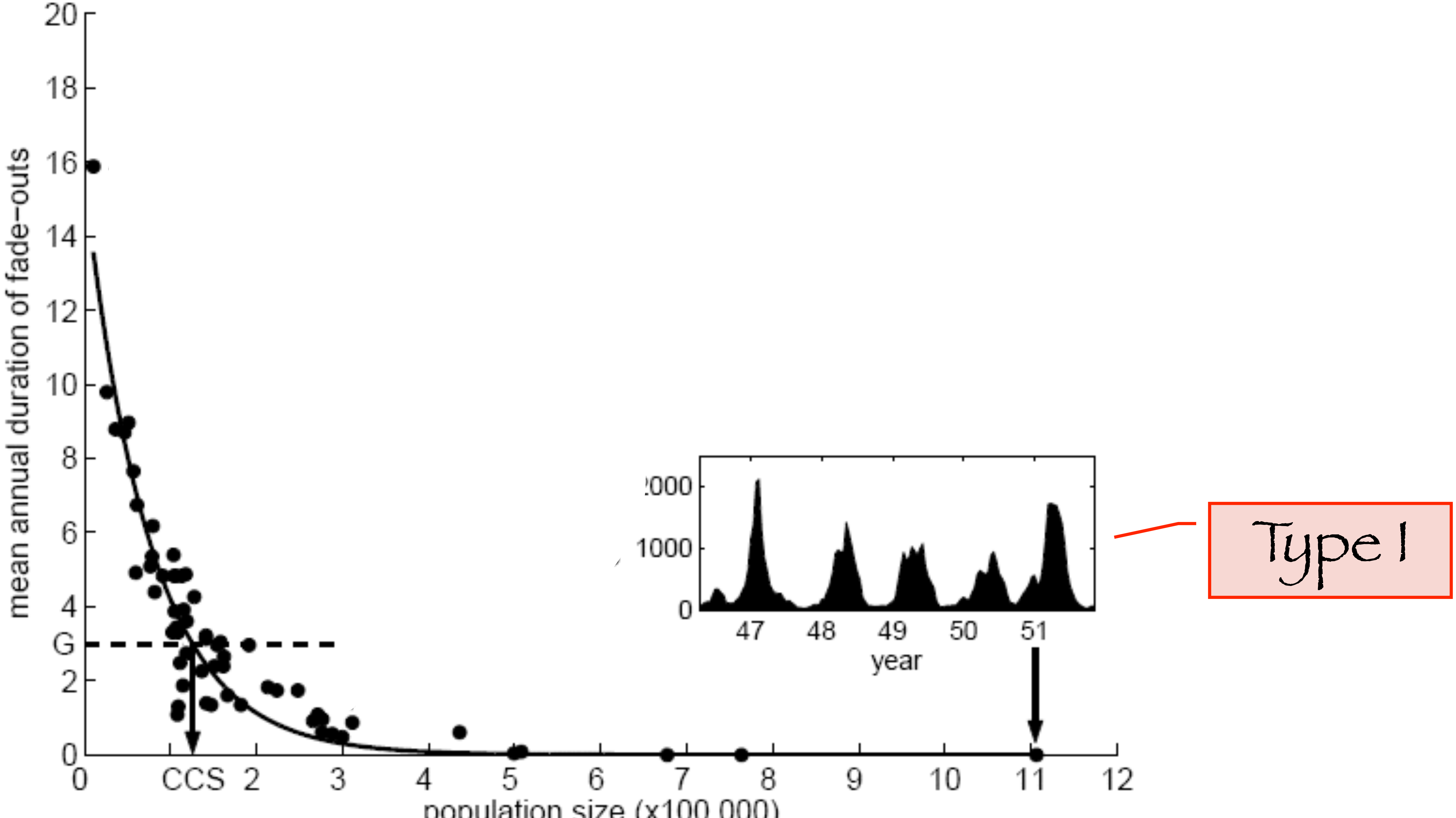
- Smallest population of susceptible hosts below which disease goes extinct, and above which disease persists
- Microparasitic infections, like measles, can persist in large cities but ‘fade out’ in smaller towns
- Influx of susceptibles in-between epidemics not sufficient in small places to maintain chain of transmission

Different kinds of epidemics

Measles outbreaks in England & Wales

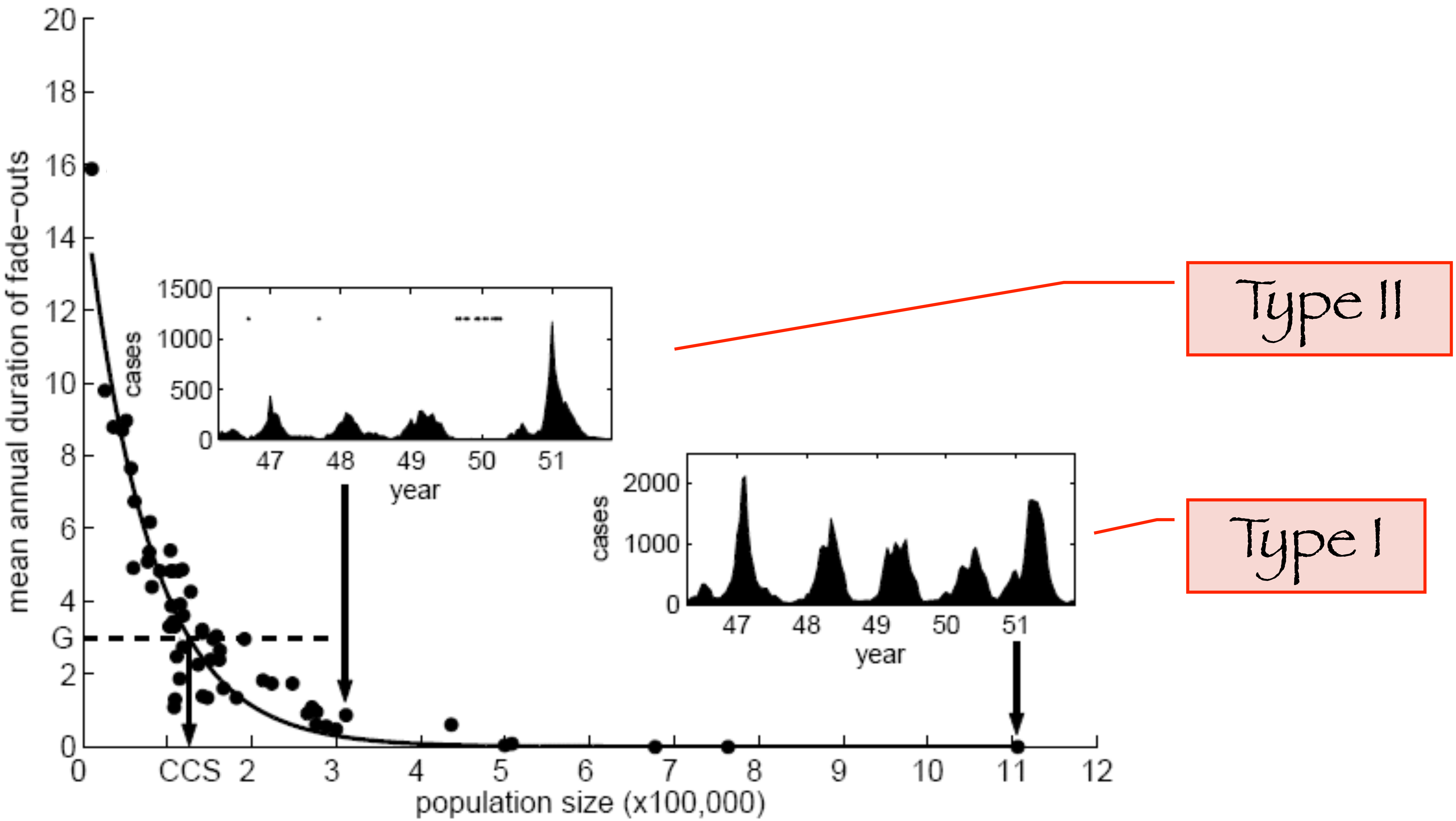


Different kinds of epidemics



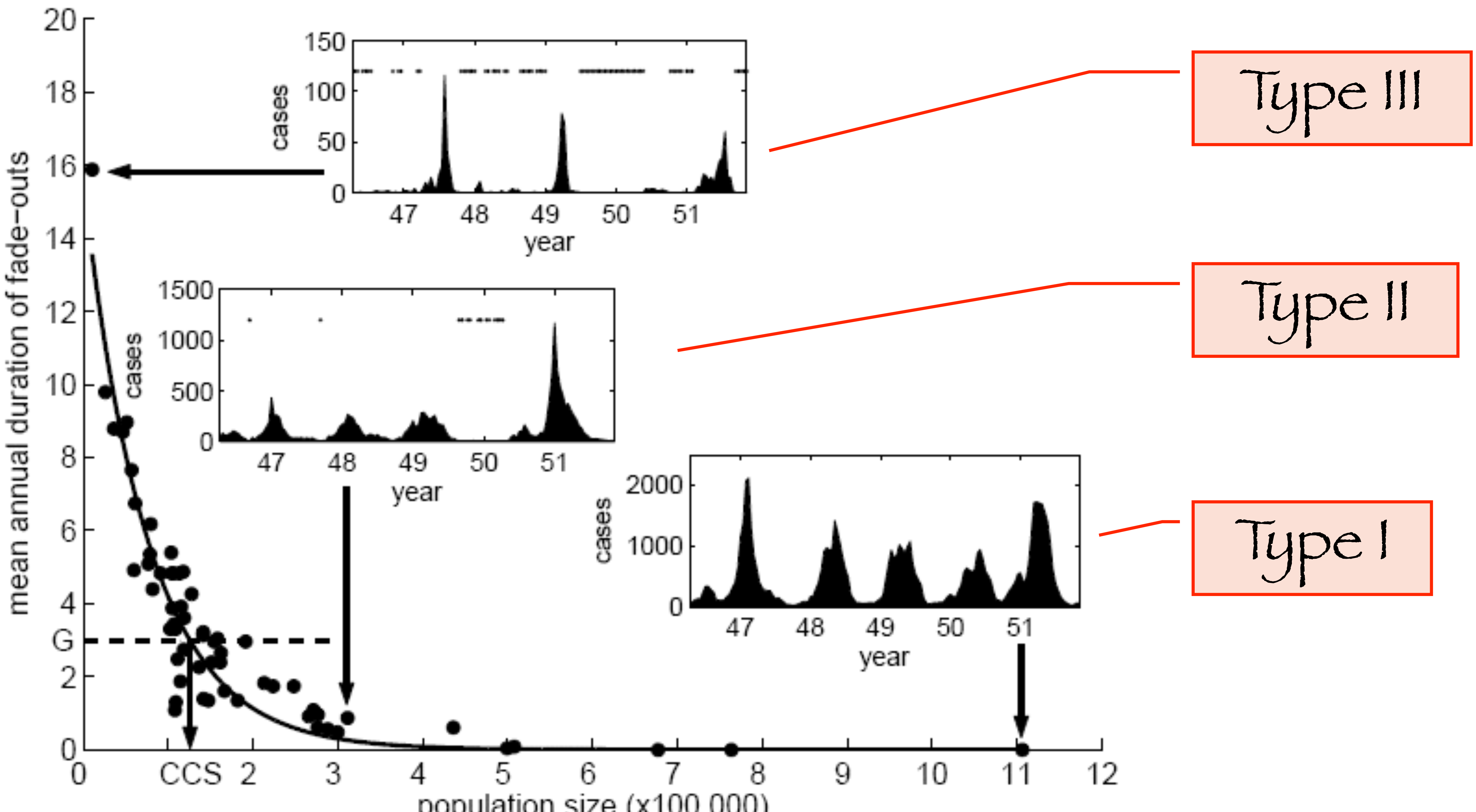
Bartlett (1956)

Different kinds of epidemics



Bartlett (1956)

Different kinds of epidemics



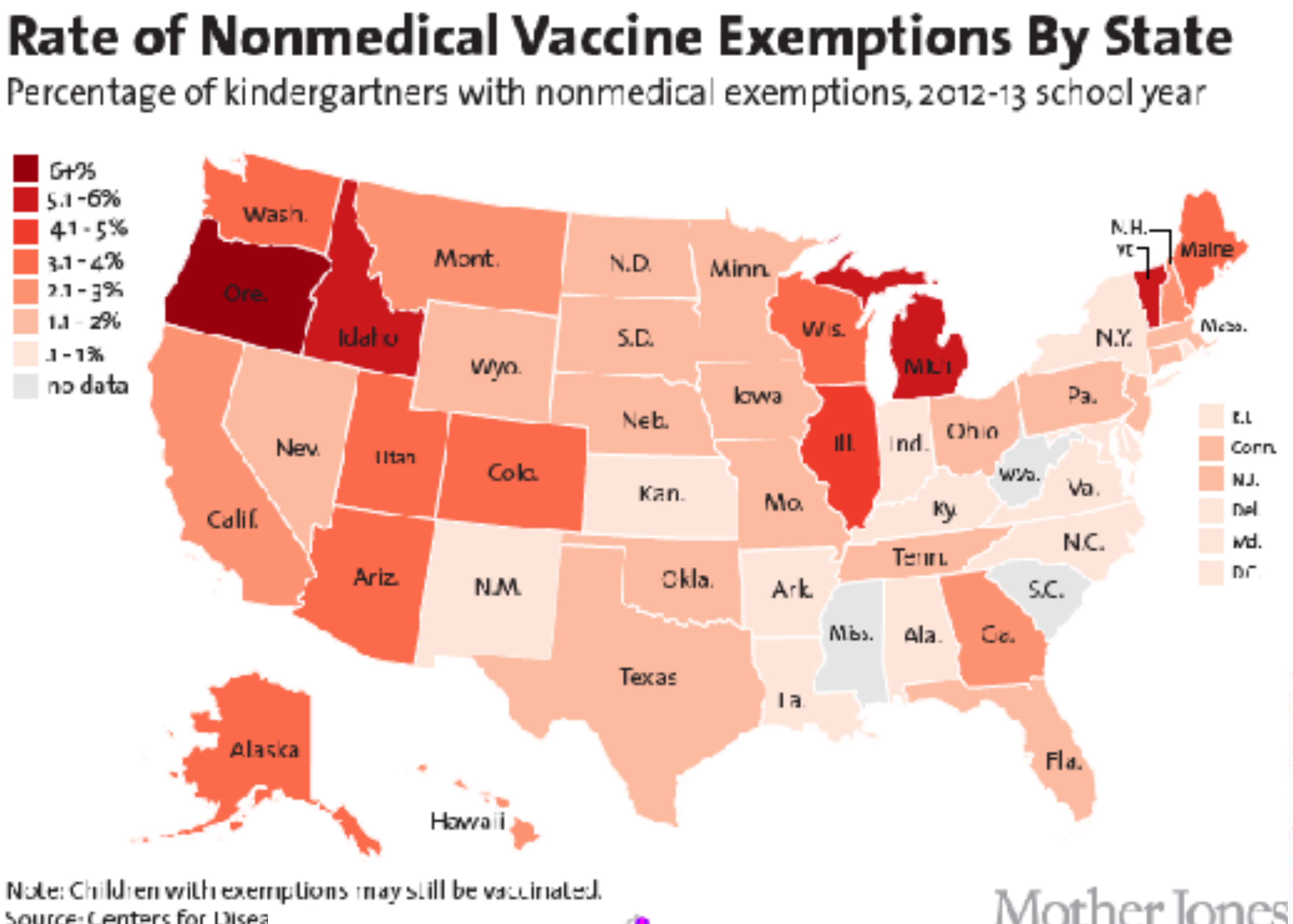
Bartlett (1956)

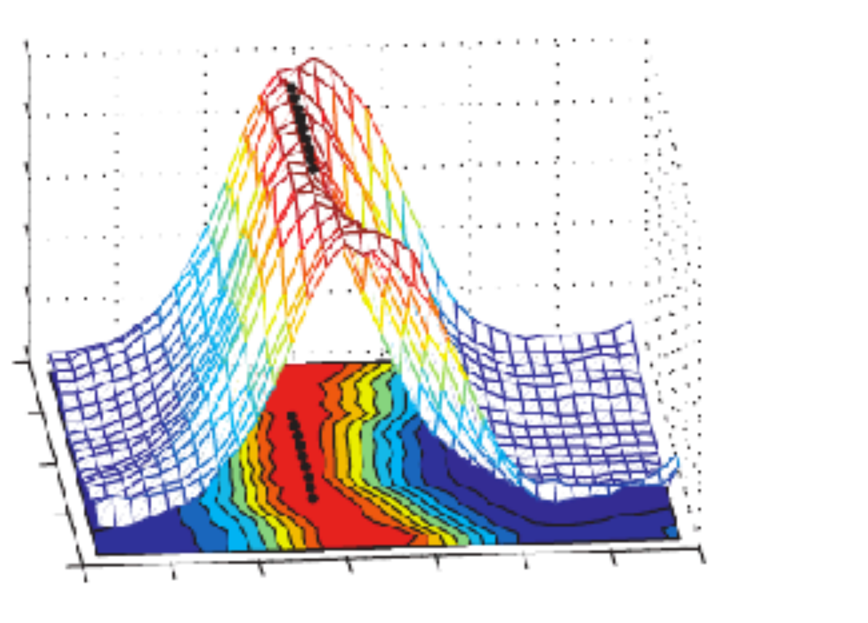
Lecture Summary

- Dynamics of epidemics
- Recurrent outbreaks
- Seasonal pathogens and the drivers of “seasonality”
  - Pulsed births
  - Changes in host susceptibility
  - Pattern of contacts, pathogen persistence, vector biology
- Fade-outs and Critical Community Size

- **Next**
- Metapopulations
- Within-host dynamics — Polymicrobial systems

Measles


Rate of Nonmedical Vaccine Exemptions By State
Percentage of kindergartners with nonmedical exemptions, 2012-13 school year
no data
Note: Children with exemptions may still be vaccinated.
Source: Centers for Disea
Mother Jones



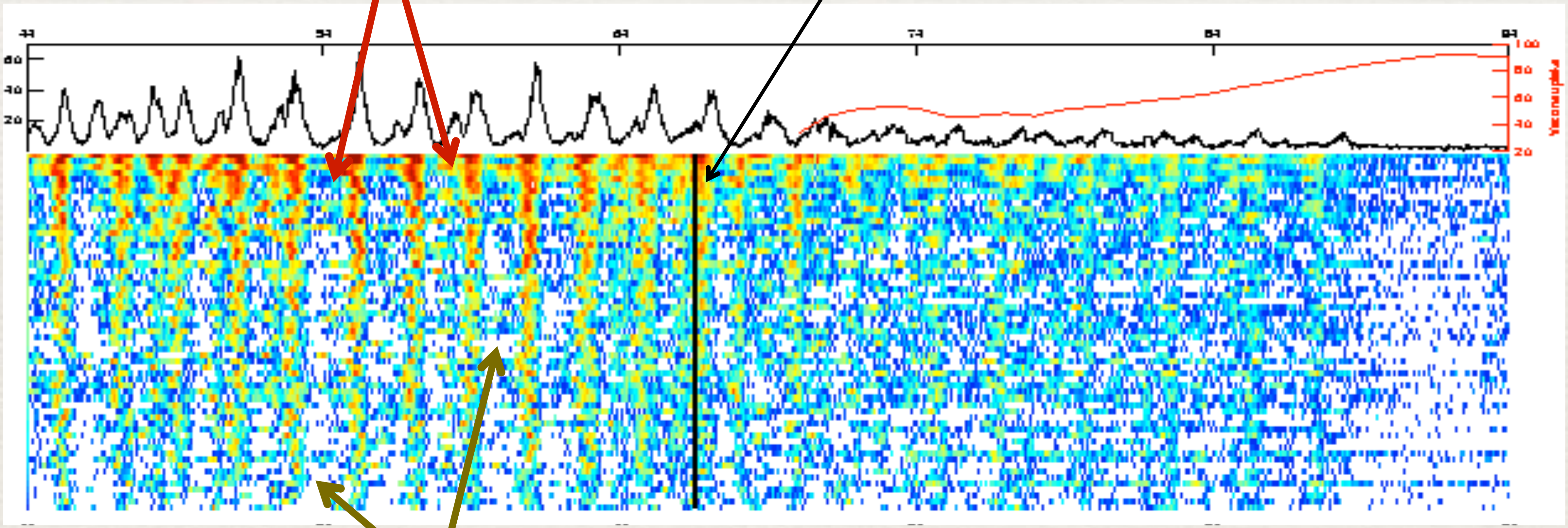

CALIFORNIA ADVENTURE
MEASLES

Measles in England & Wales

Measles persists well in large cities

Mass vaccination, 1968

Population Size



But “fades out” (goes locally extinct) in small populations

Rohani et al. (1999)

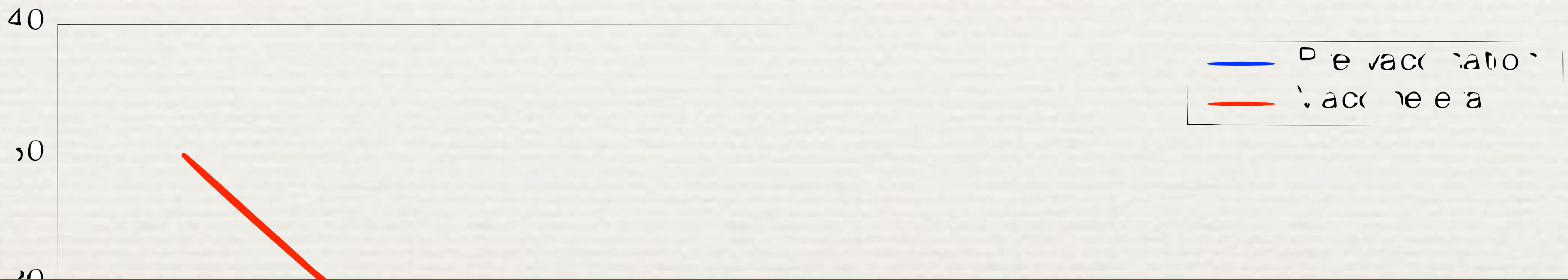
Long-term persistence:
Critical Community Size (CCS)

- Smallest population of hosts below which disease goes extinct, and above which disease persists (Bartlett 1956)

- Measles can persist in cities with 300,000-500,000 but 'fades out' in smaller towns

- How would vaccination affect CCS?

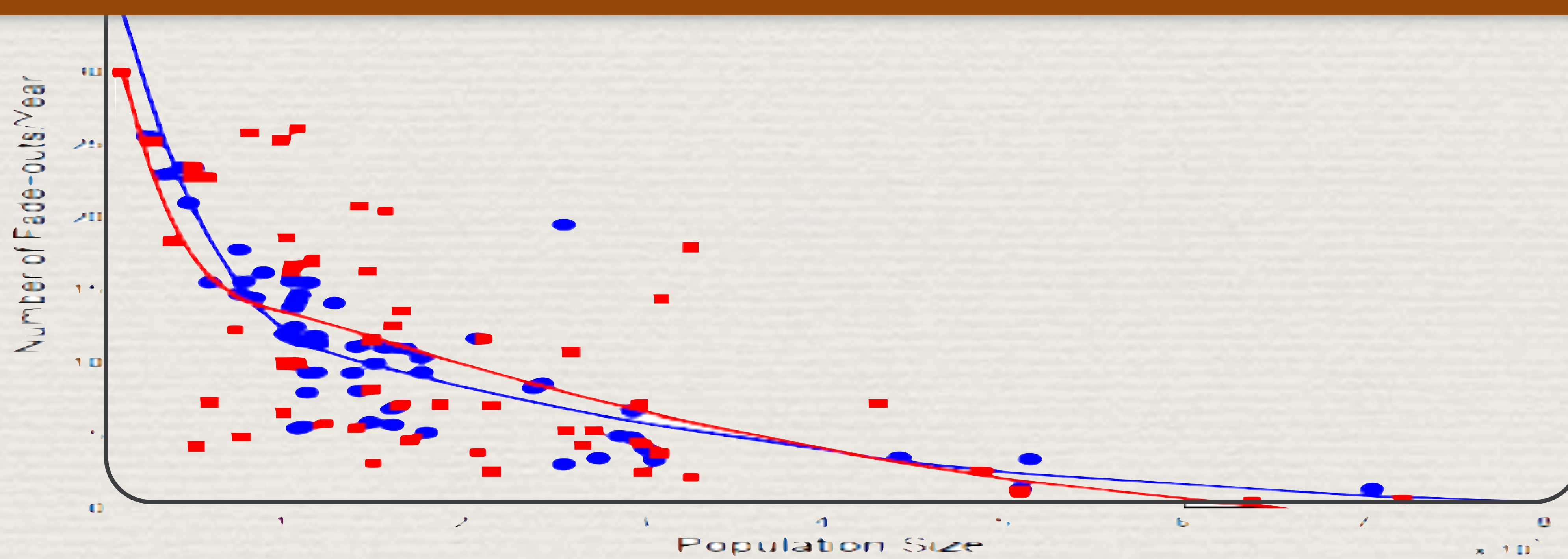
Measles CCS in Model Vs Data

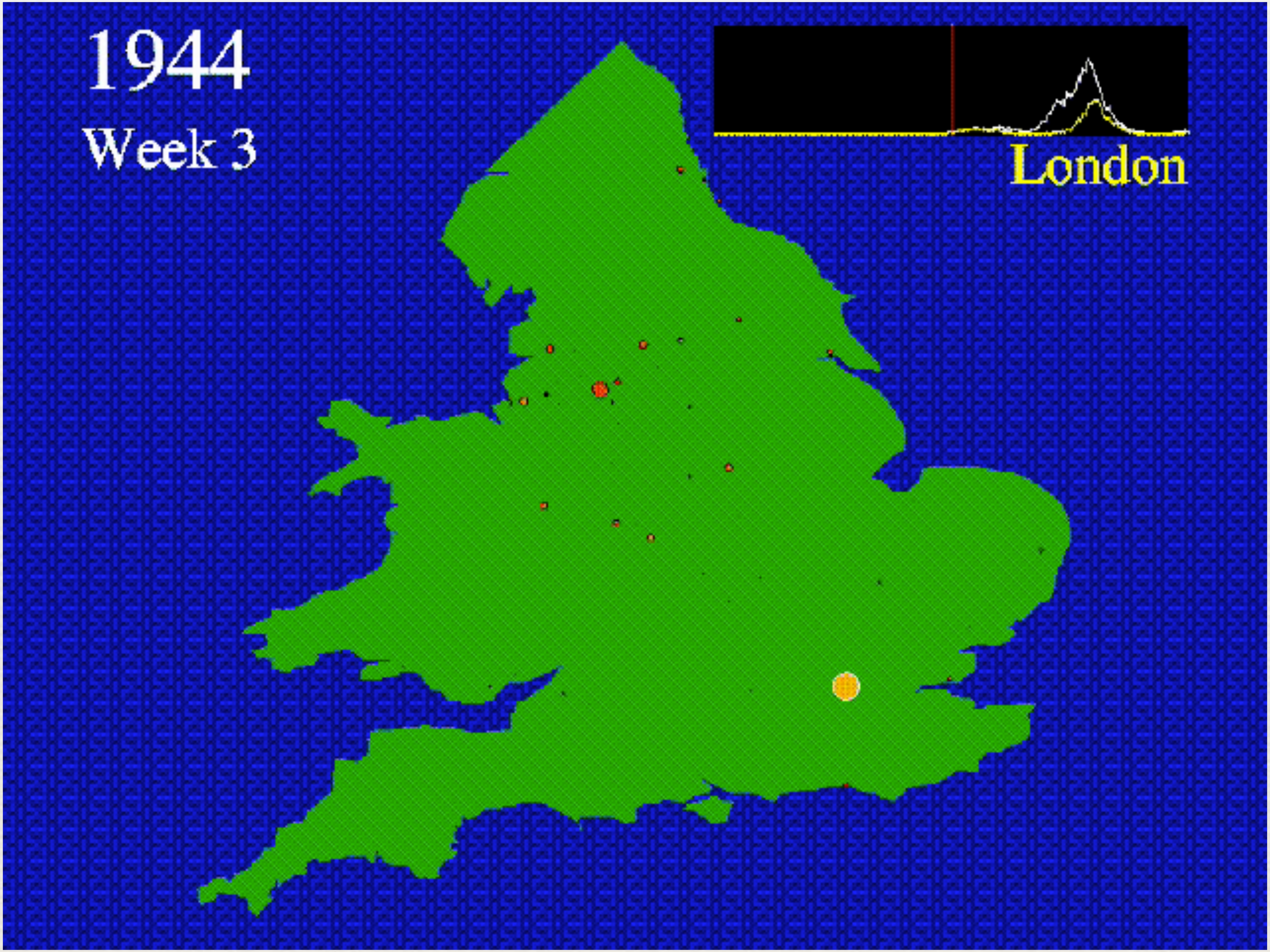


No increase in Critical Community Size!

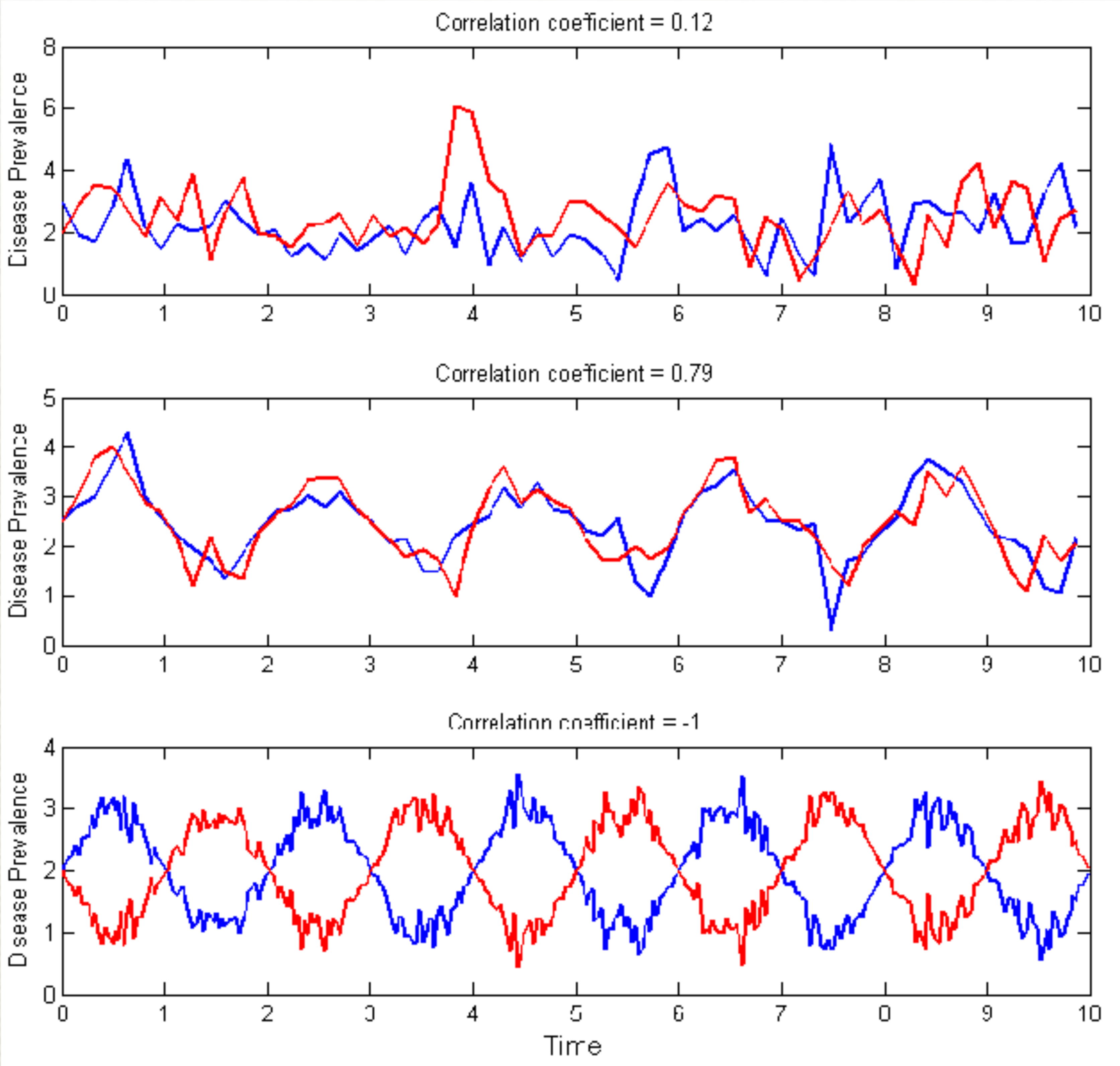
➔ vaccine doesn't work?

England & Wales Data




1944
Week 3
London

Spatial Synchrony & Correlation

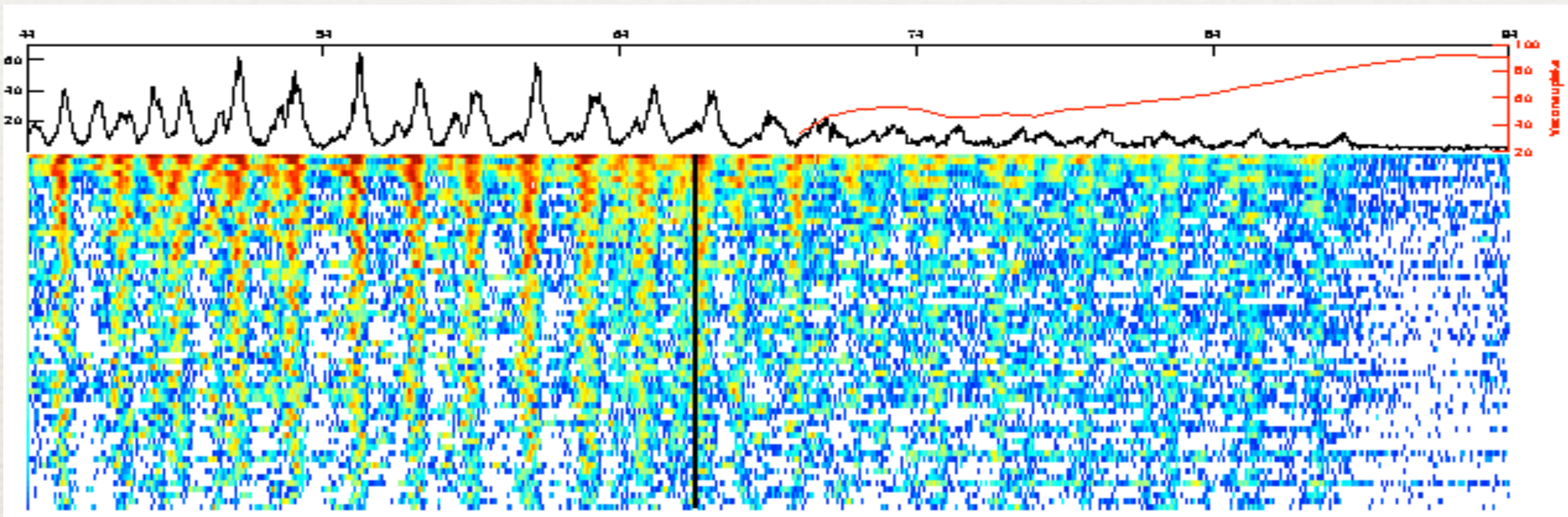


Spatially Uncorrelated

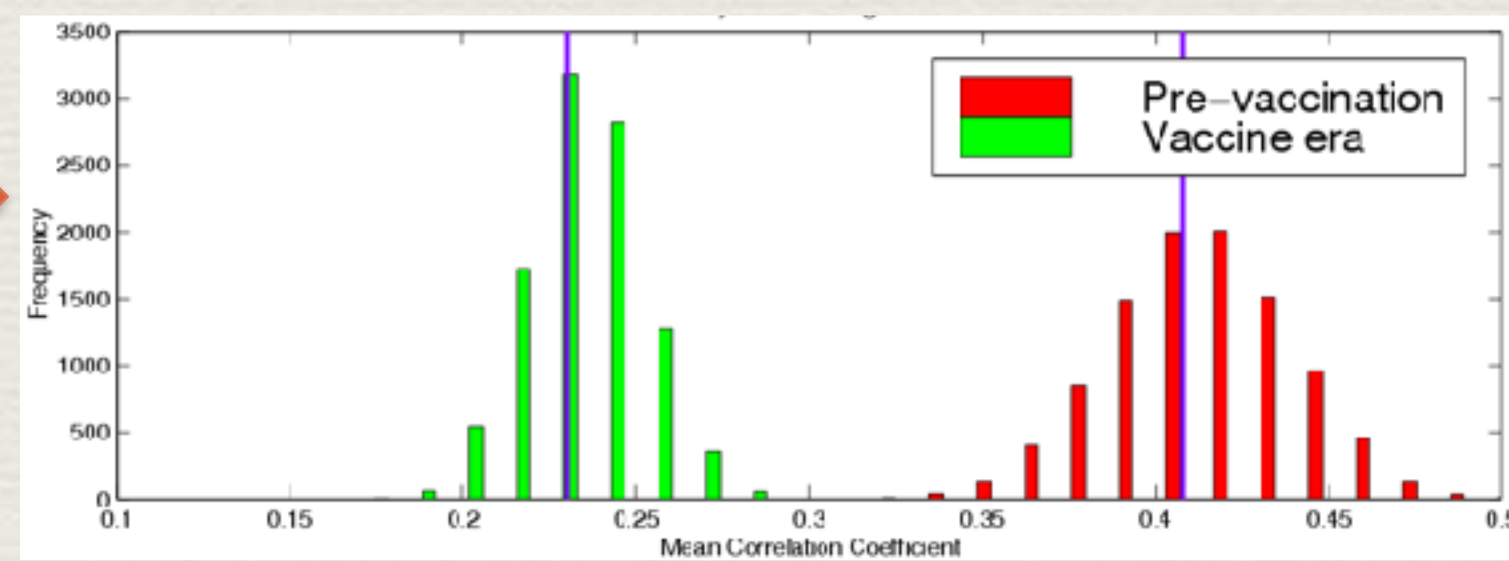
Strongly correlated

Negatively correlated

Measles in England & Wales

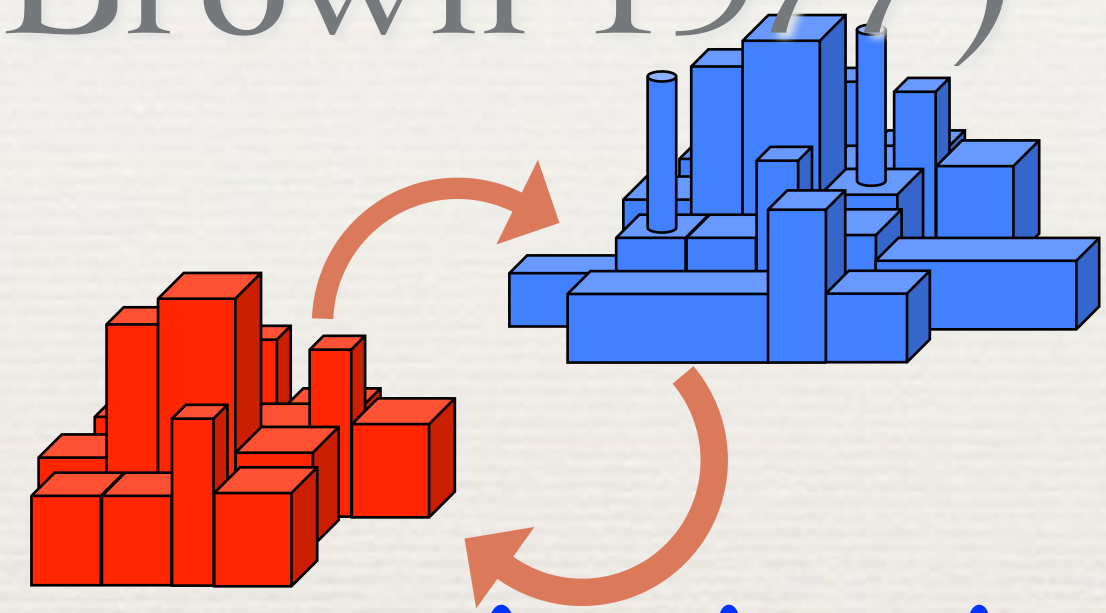


Pre-vaccine epidemics significantly more spatially synchronised than in vaccine era

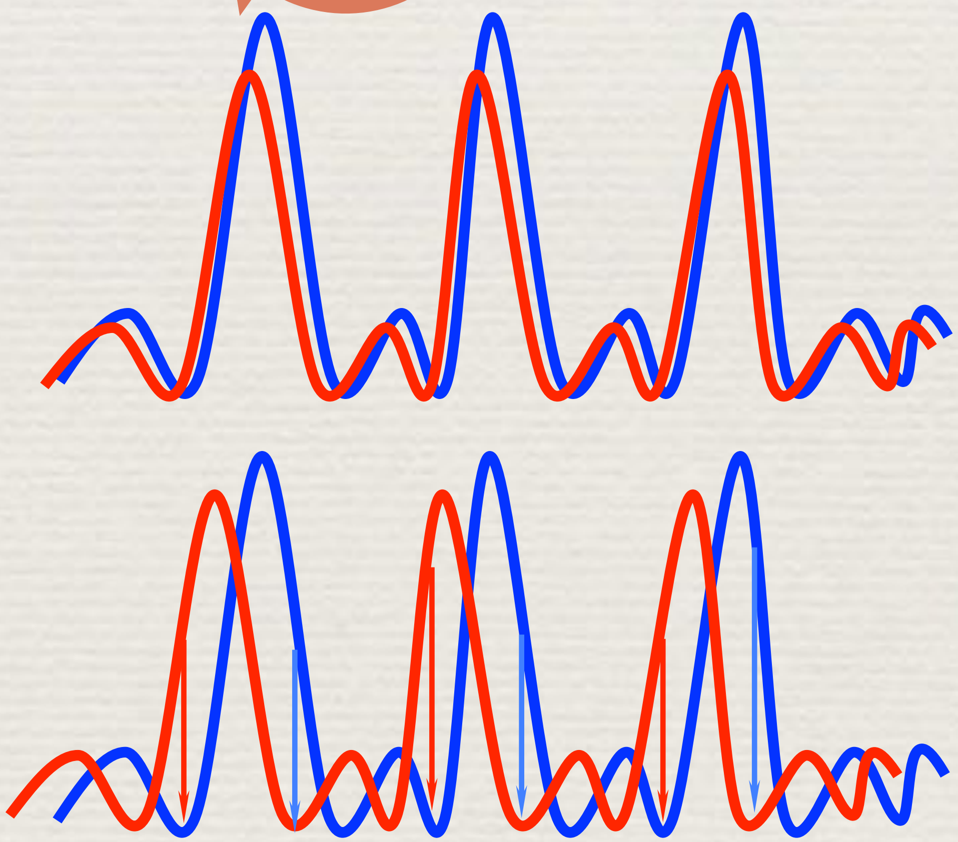


Rohani et al. (1999)

The 'Rescue Effect' (Brown & Kodric-Brown 1977)



Consider two towns linked by movement



With epidemics in phase, number of fadeouts remains largely unaffected

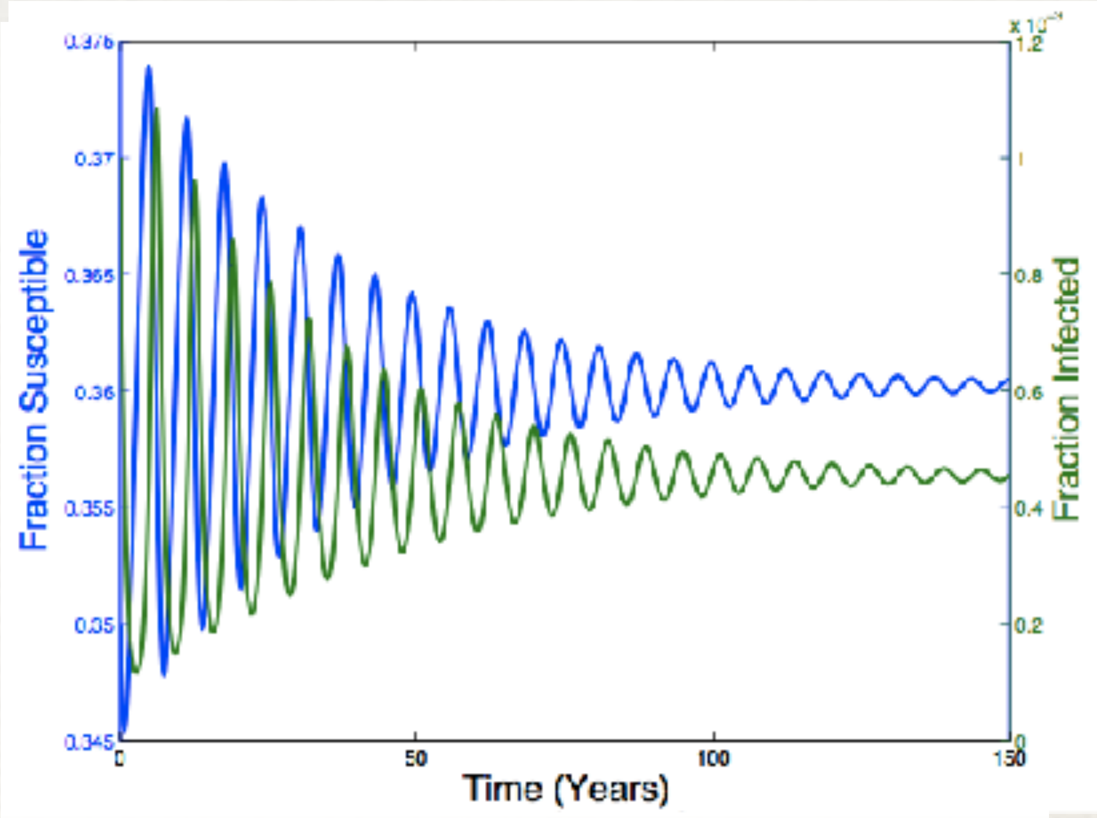
Out-of-phase towns may reduce fadeouts in epidemic troughs

So, spatial ecology of epidemics also important
May have significant vaccination consequences

Metapopulation Ecology

- What are metapopulations?
- Meta: "of a higher order"
- Metapopulation = a population of populations
- Any patchily distributed system where populations can go extinct and be recolonized
- Set of local populations with migration between patches

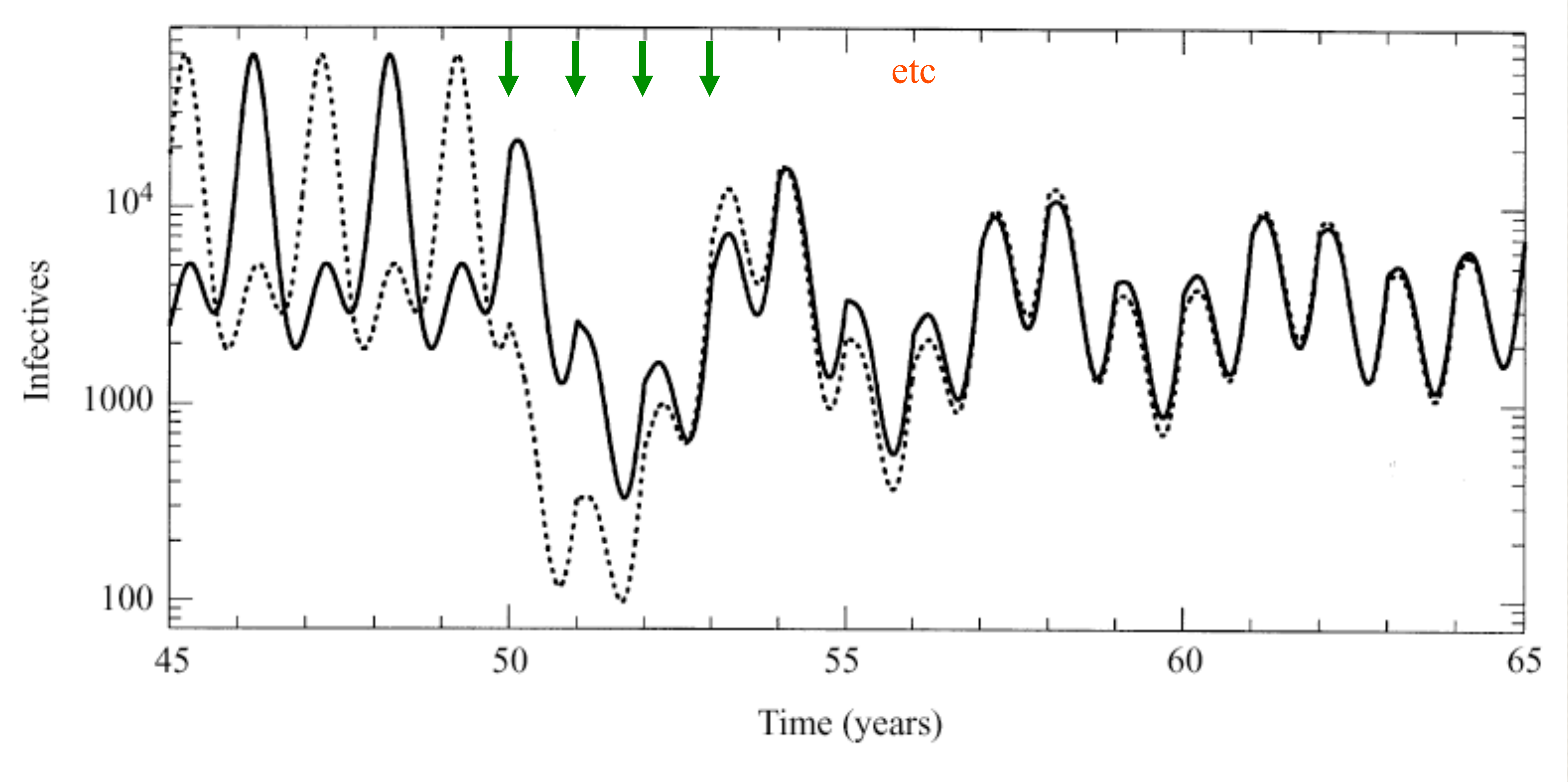
Spatial disease dynamics
Mechanism for parasite persistence



- Local persistence
  - Susceptible recruitment
    - Loss of immunity
    - New births
- Regional persistence
  - Spatial transmission between partly isolated host populations – *spatial spread*
  - Asynchronous epidemics: *epidemiological metapopulations*

The ‘Rescue Effect’ in Action?

Potential Role for Pulsed Vaccination?

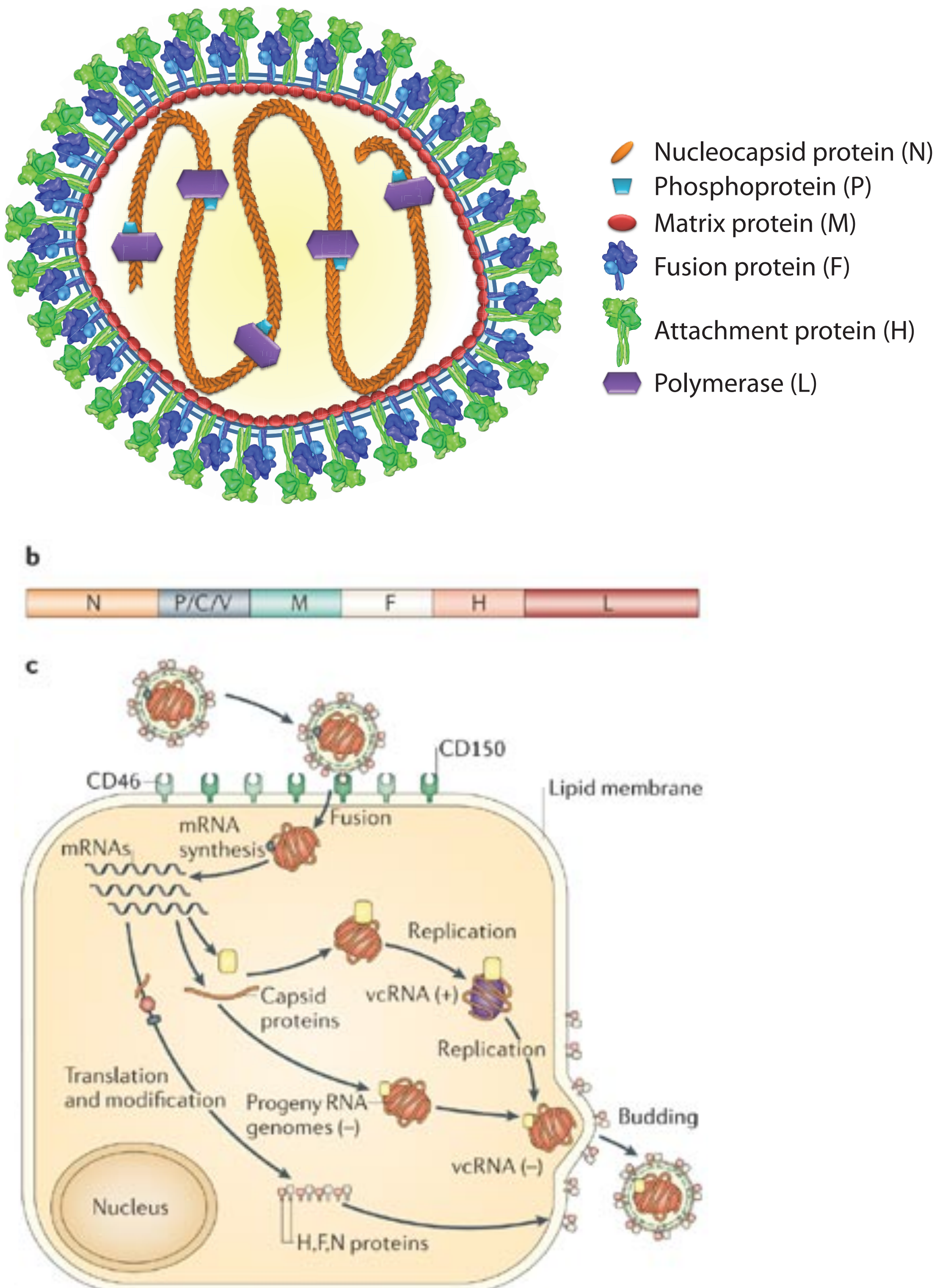


Vaccination at same time in two cities with out-of-phase dynamics can synchronise epidemics (Earn et al. 1998)

Summary

- Travelling waves from point source introductions
- "Metapopulation" concept also applicable in disease ecology
- Understanding patterns of spatial synchrony can explain persistence dynamics (measles)
- In E&W, measles transmission follows a spatial hierarchy, with core cities and satellite towns and villages
- Some cities/states play a bigger role in spatial transmission
  - Important for control or management strategies

Measles Virus

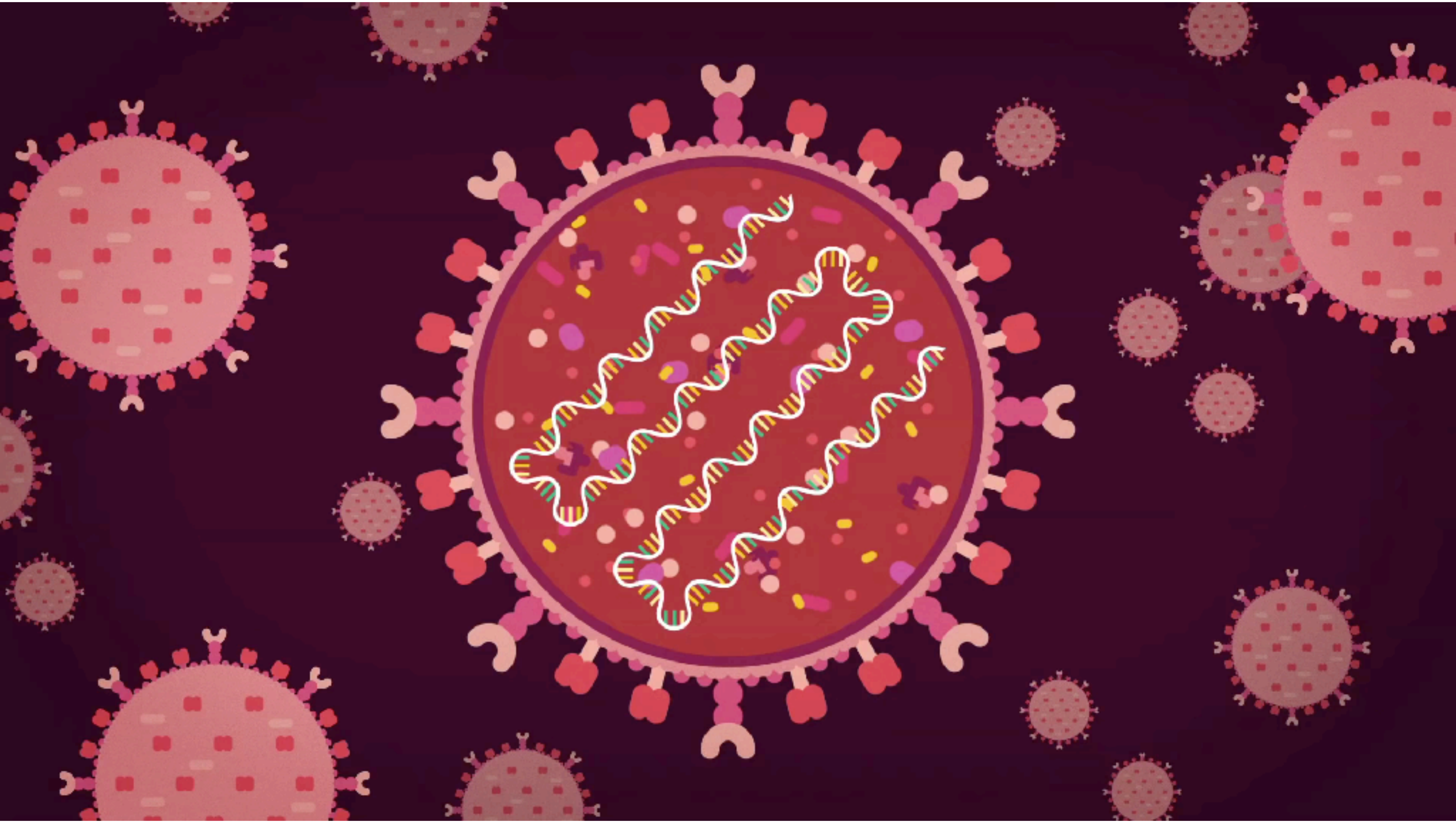


Moss & Griffin (2006, Nat. Rev. Micro)

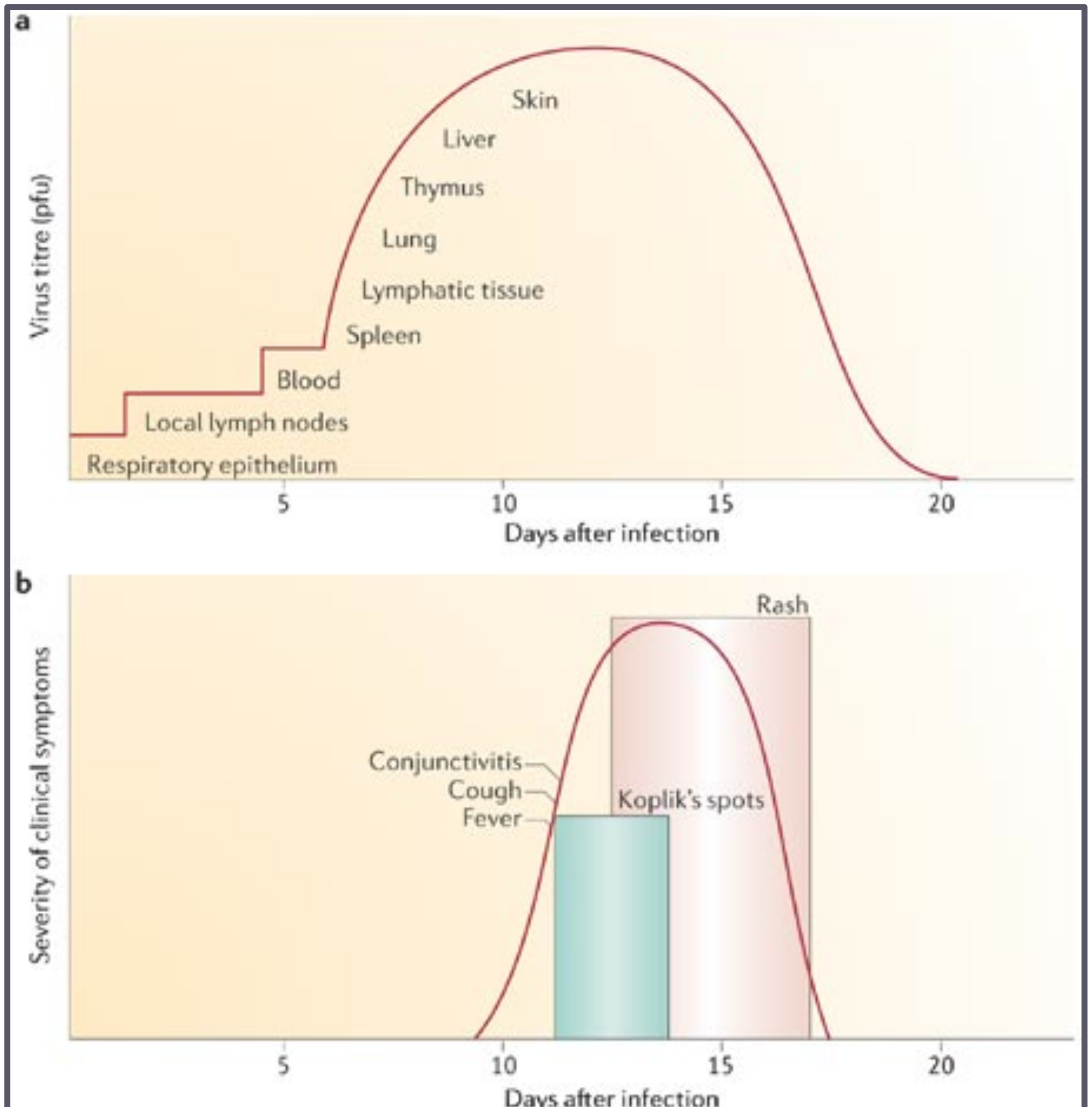
- Paramyxoviridae family, Morbillivirus genus
- Non-segmented, enveloped, single-stranded, negative sense RNA virus
- Genome: 16,000 nt, encodes 6 structural and 2 non-structural proteins
- Cellular receptors: CD46, CD150 & Nectin-4

youtu.be/y0opgc1WoS4

Measles Infection



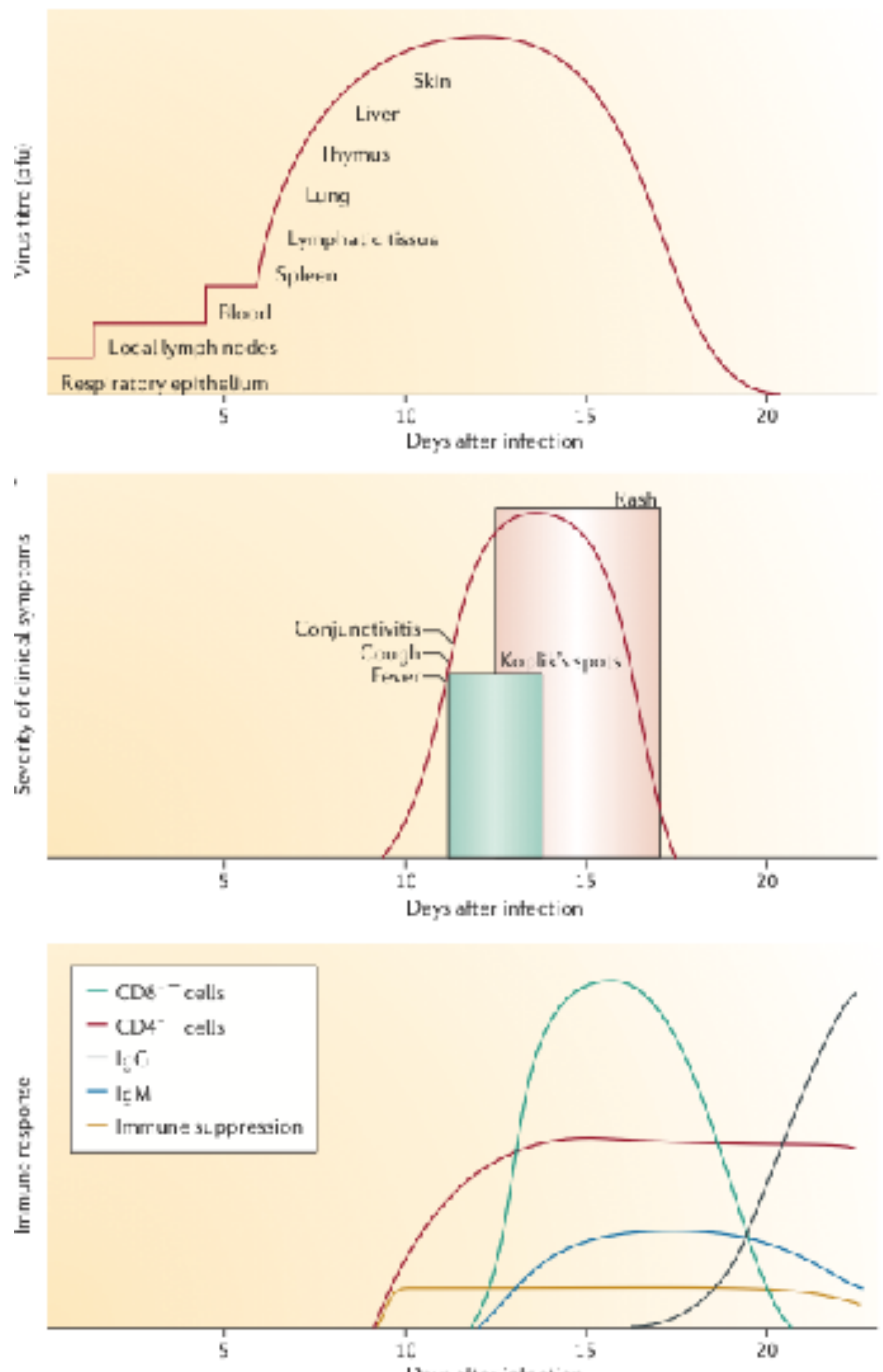
Time Course of Measles Infection



Moss & Griffin (2006, Nat. Rev. Micro)

- Measles is a disease with great complexity
- Systemic infection
- Targets broad range of cells: immune cells, epithelial & endothelial cells, …

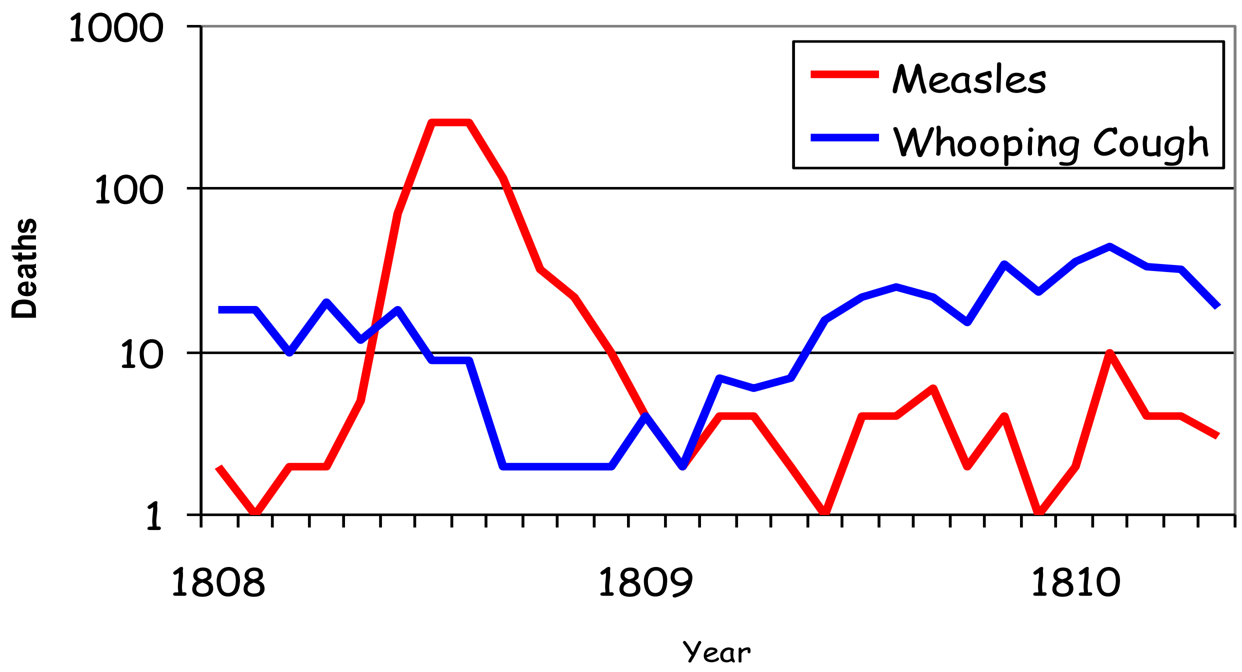
MV Infection and the Immune system



Moss & Griffin (2006, Nat. Rev. Micro)

- Early innate response
  - activation of NK cells
  - early production of INF-α & β
- Adaptive immune responses
  - Cellular immunity important for clearing virus
  - Antibody response protect from reinfection (long-lasting immunity)
    - immunity conferred to infants by maternal ABs
    - Unclear role of ABs in viral clearance

Charles Creighton (1894)



"... the great measles epidemic of 1808 in Glasgow was indeed followed by many deaths from whooping cough in 1809.

Whatever correspondence or relation there may be between measles and whooping-cough, (and it has been remarked by many in the ordinary way of experience), it eludes the method of statistics."

Immunosuppressive Effects of Measles

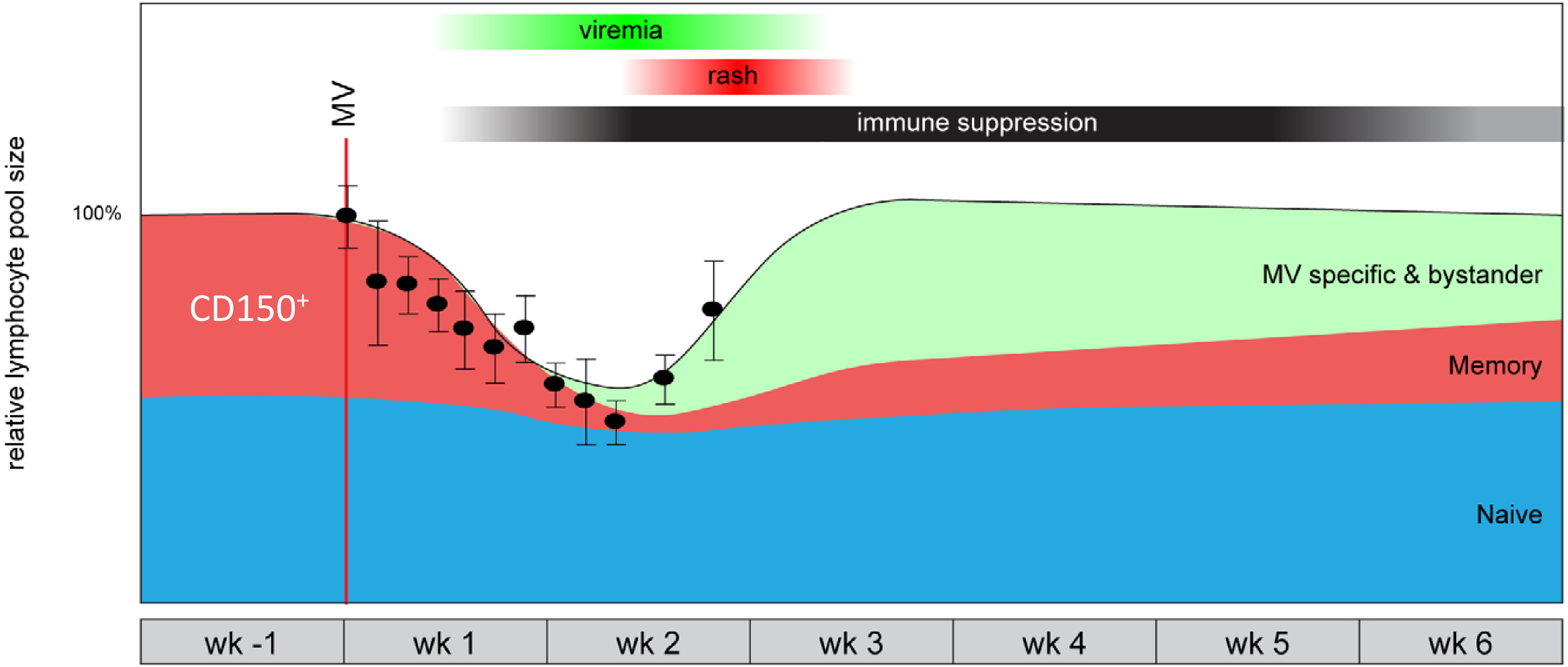
- “The immune responses induced by MV infection are paradoxically associated with **depressed responses to non-MV antigens**, and this effect continues for **several weeks to months after resolution of the acute illness**... delayed-type hypersensitivity (DTH) responses to recall antigens, such as tuberculin, are suppressed and cellular and humoral responses to new antigens are impaired.”
- “MV-induced **immune suppression renders individuals more susceptible to secondary bacterial and viral infections** that can cause pneumonia and diarrhoea, and is **responsible for much of the measles-related morbidity and mortality**. Pneumonia, the most common fatal complication of measles, occurs in 56–86% of measles-related deaths”

Griffin, D. in Fields Virology

The Measles Paradox

- “Hallmark of measles infection”: generalized immune suppression lasting several weeks to months after resolution of virus
  - increased susceptibility to opportunistic infections
- BUT measles is associated with immune activation and induces strong MV-specific immune responses that confer lifelong immunity

Measles infection in macaques



de Vries et al. 2012, PLOS Pathogen

- Depletion of pre-existing CD150+ memory lymphocytes
- Whether depletion is mediated by necrosis, apoptosis, pyroptosis, or cytotoxic T-cells remains to be determined

Polymicrobial systems

What are effects of measles immune suppression on other infectious diseases?

Polymicrobial diseases: transmission and pathogenicity involve interactions among distinct pathogens

Examine by quantifying consequences of measles vaccination

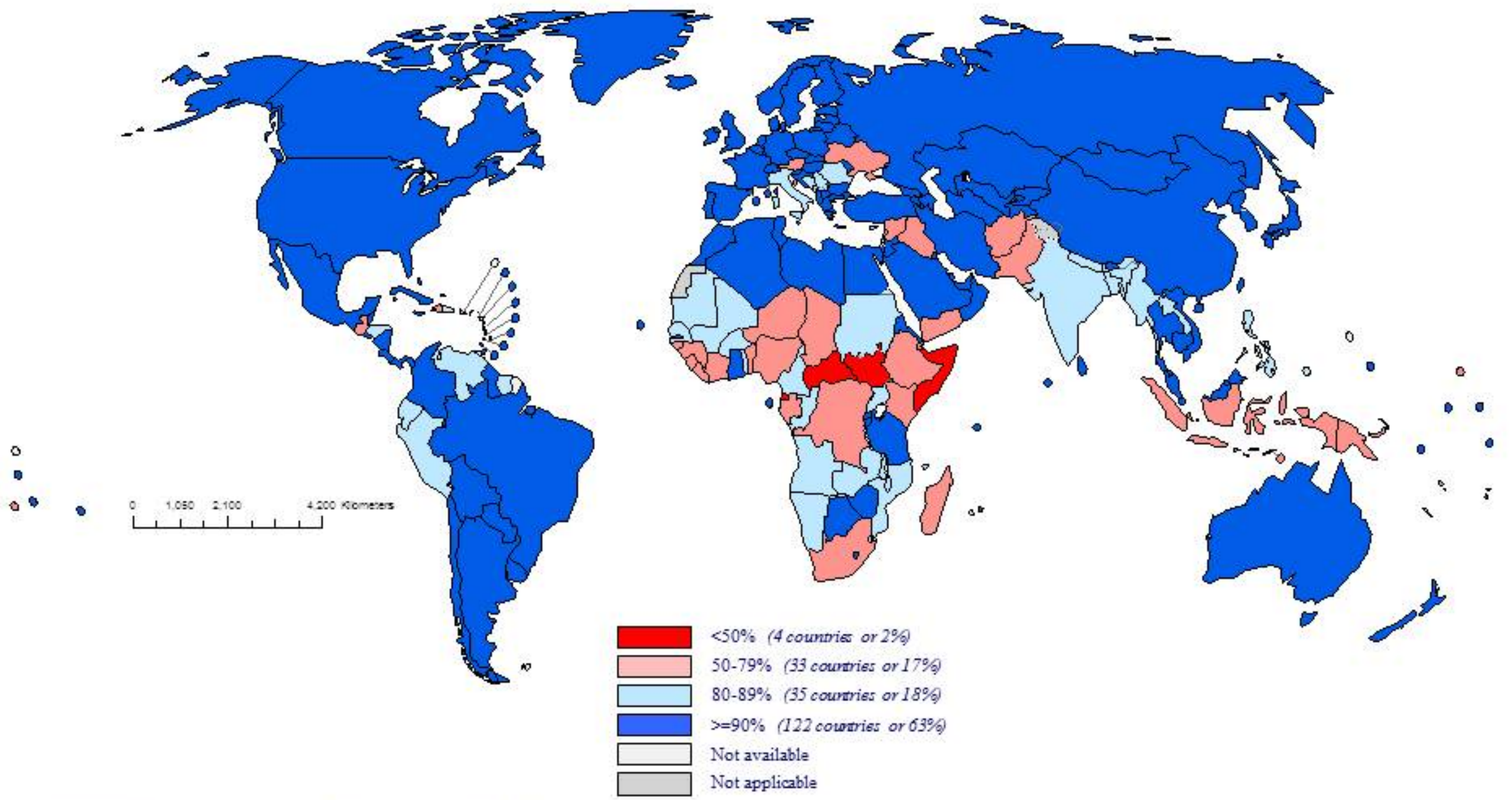
RESEARCH | *REPORTS*

VACCINES

Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality

Michael J. Mina,[1,2]* C. Jessica E. Metcalf,[1,3] Rik L. de Swart,[4] A. D. M. E. Osterhaus,[4] Bryan T. Grenfell[1,3]

Measles vaccine coverage



Source: WHO/UNICEF coverage estimates 2014 revision. July 2015. Map production: Immunization Vaccines and Biologicals, (IVB). World Health Organization
Date of slide: 16 July 2015

WHO

Mina *et al*. (2015) evidential requirements

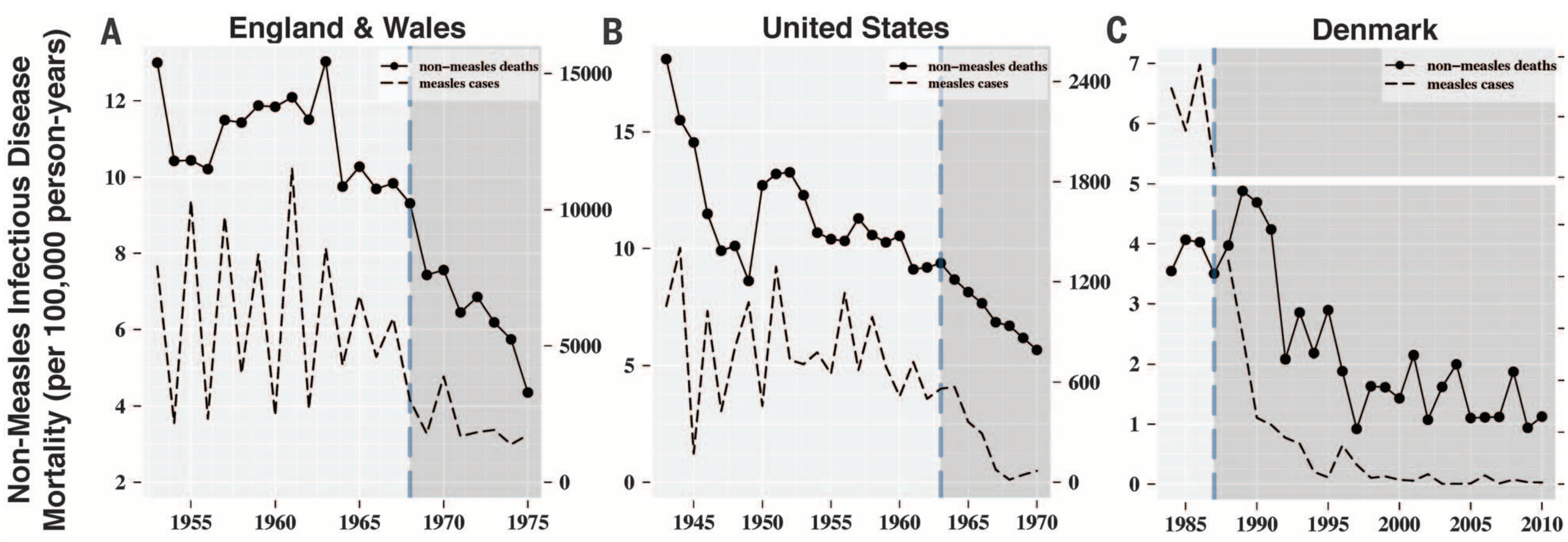
I. Non-measles mortality should be correlated with measles incidence data

II. Immune memory loss mechanism should present as a strengthening of this association when measles incidence data are appropriately accumulated (a measles “shadow”)

III. Strength of association should be greatest when mean duration over which cases are accumulated matches mean duration required to restore immunological memory after MV infection

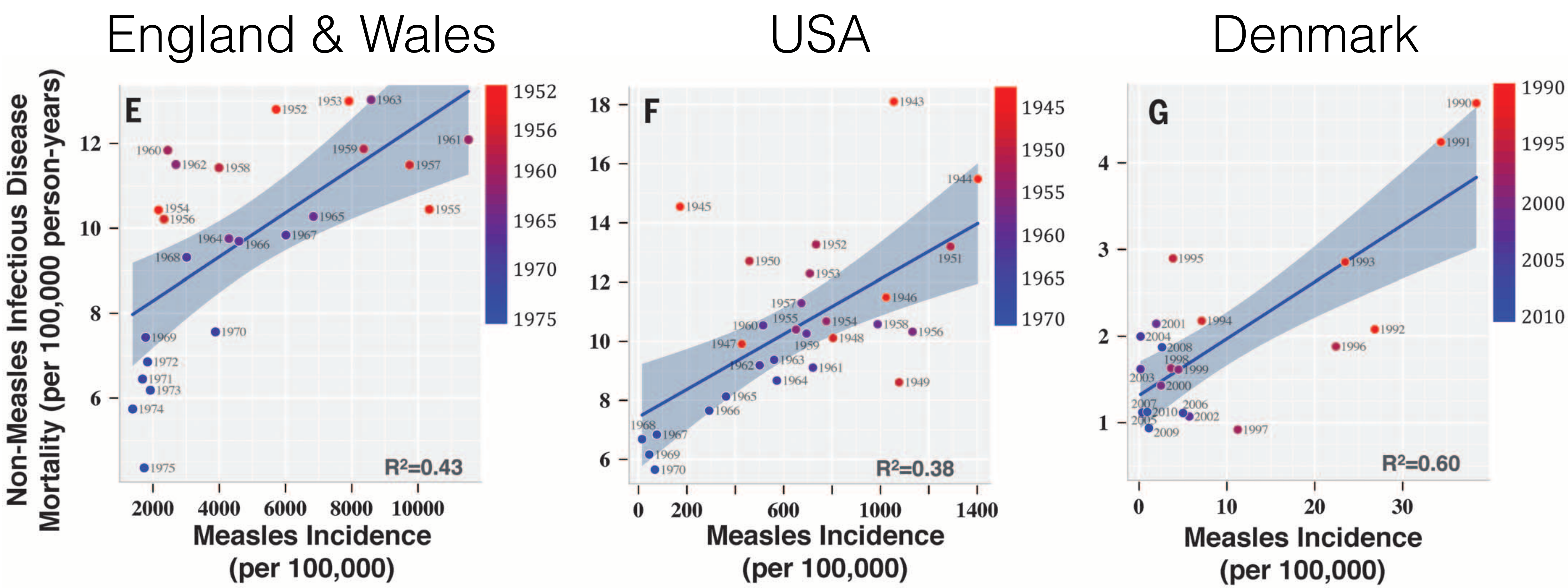
IV. Estimated duration should be consistent both with available evidence of increased risk of mortality after MV, compared with uninfected children, and with time required to build a protective immune repertoire in early life

Mina *et al.* (2015)



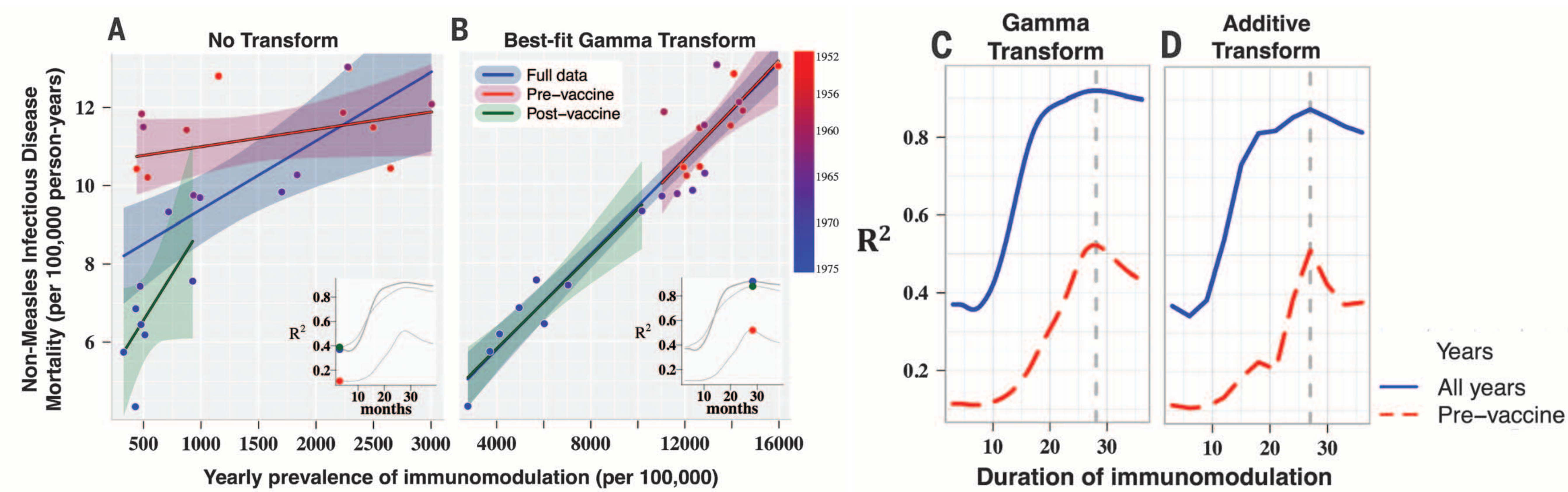
Rollout of national measles routine immunization programs associated with drop in non-measles infectious disease deaths – a measles "shadow"?

Mina *et al.* (2015)

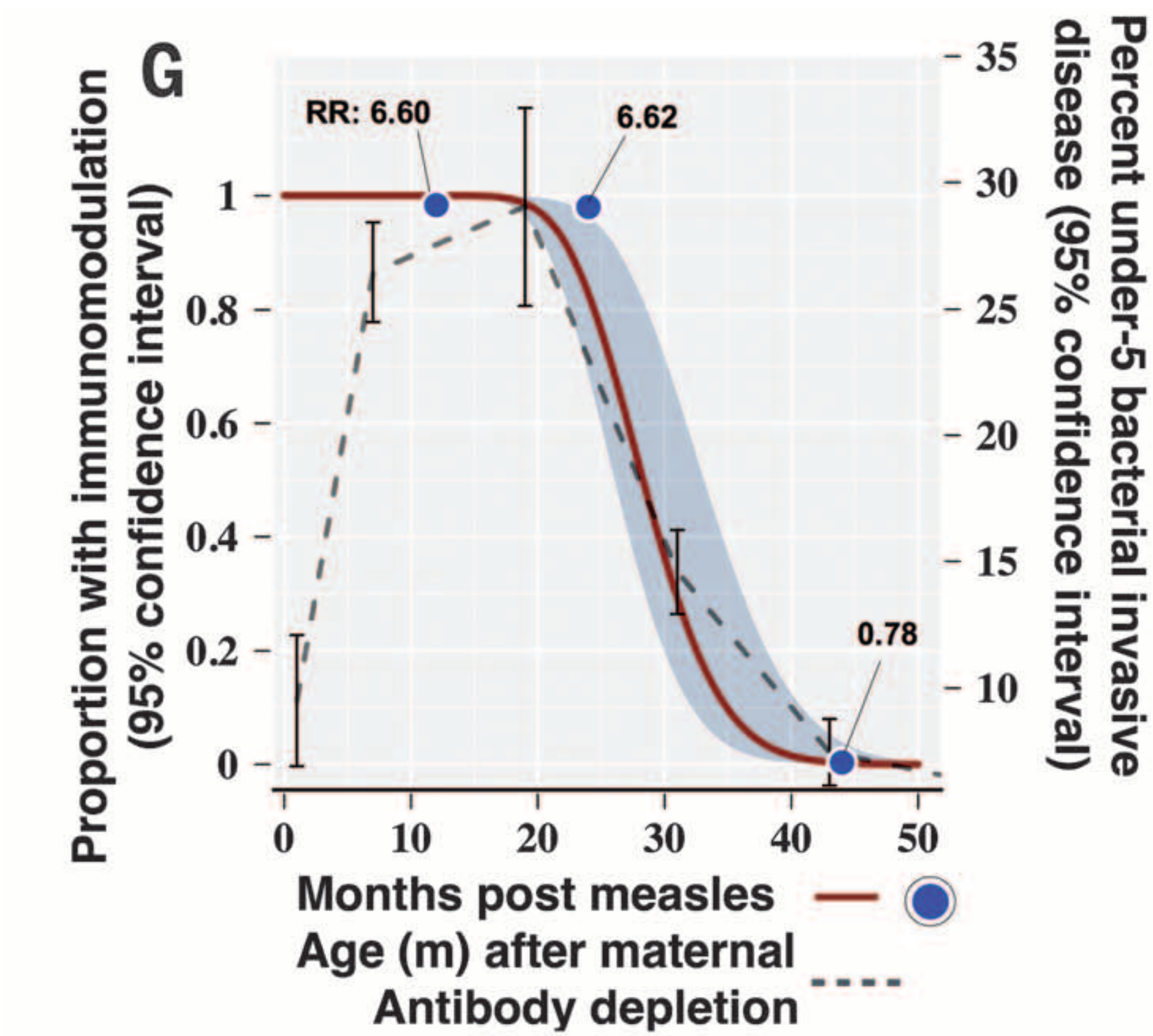


How long is the ‘shadow’?

England & Wales

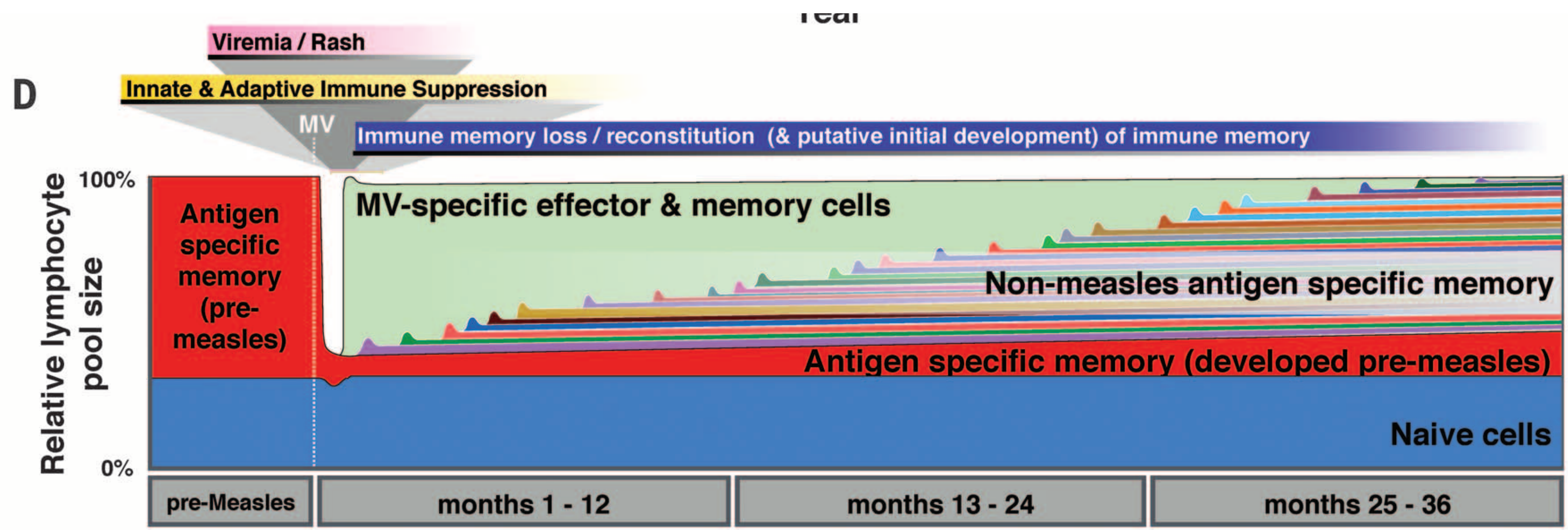


Polymicrobial effects



Both elevated RR of all-cause mortality after measles exposure and declines from peak rates of bacterial disease, indicating development of sufficiently protective immunity, fell precisely along gamma curve

How long is the ‘shadow’?



Conclusions

- Population evidence for prolonged (~2- to 3-yr) impact of measles infection on subsequent mortality from other pathogens
- MV infection and vaccination generate herd immunity against subsequent measles epidemics
- MV infections could also reduce population immunity against other infections via measles-induced immune amnesia
- Measles vaccination cost-effective intervention against measles
  - Mina *et al*. suggest extra bonus — additional immunological dividends: mortality (and probably morbidity) reductions linked to measles vaccination might be much greater than previously considered
  - "polymicrobial herd protection"