

Infectious diseases: time, space and control

Marc Choisy

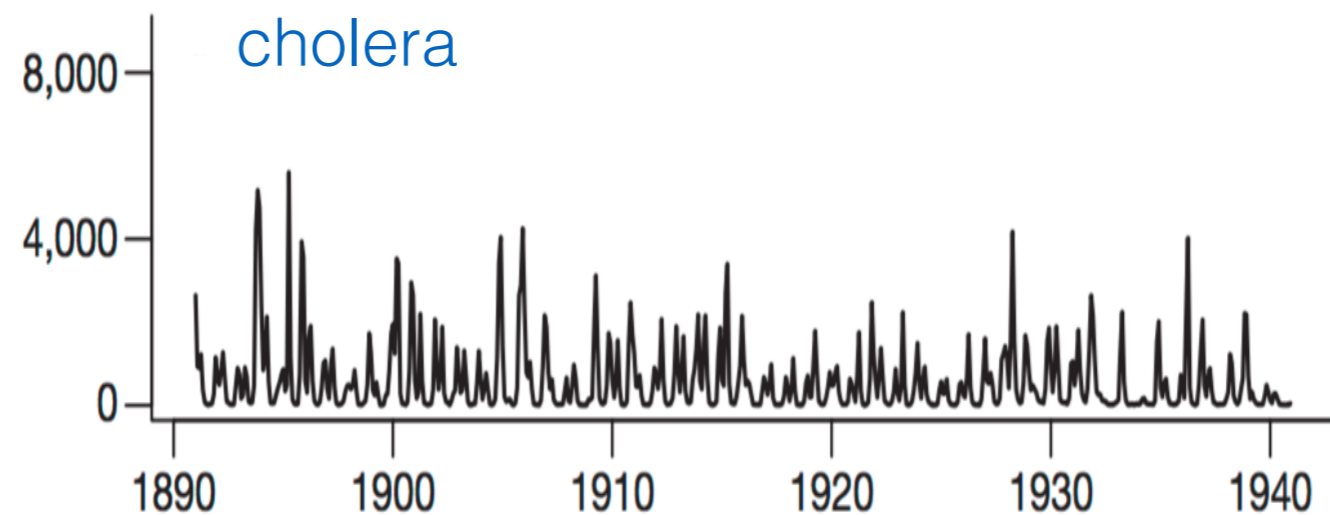
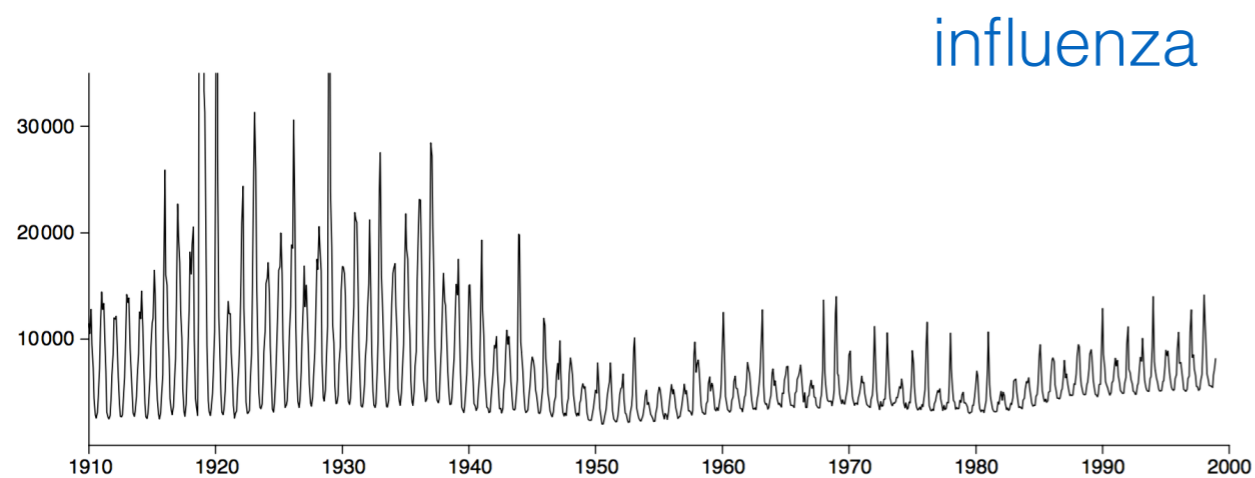
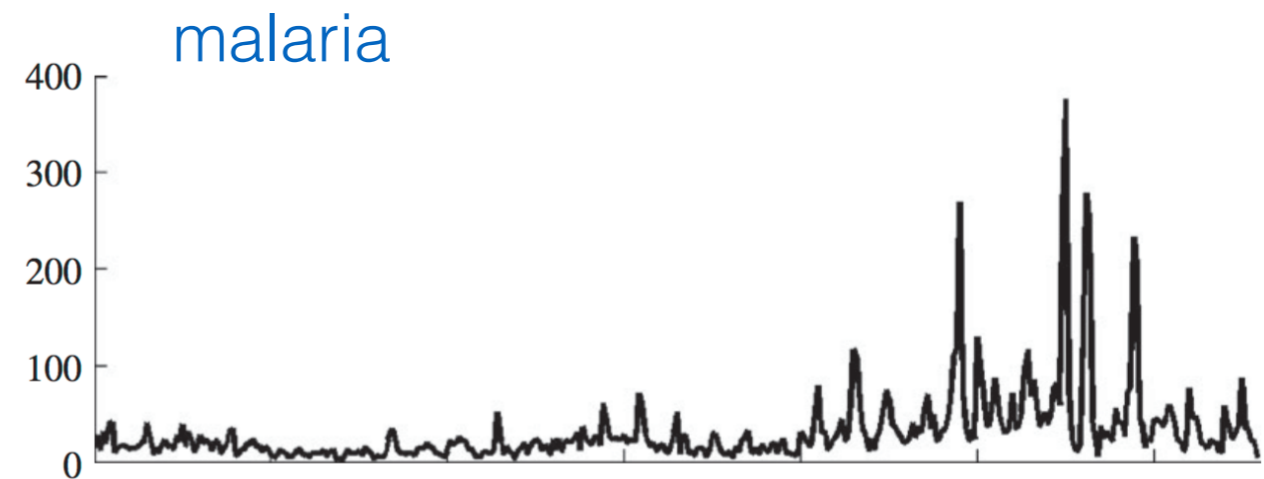
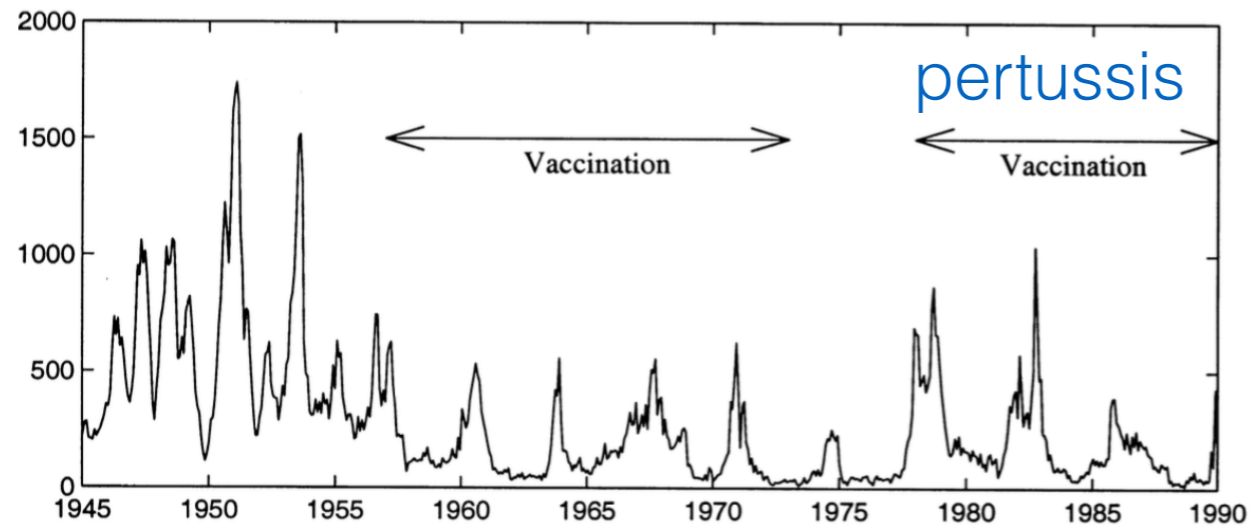
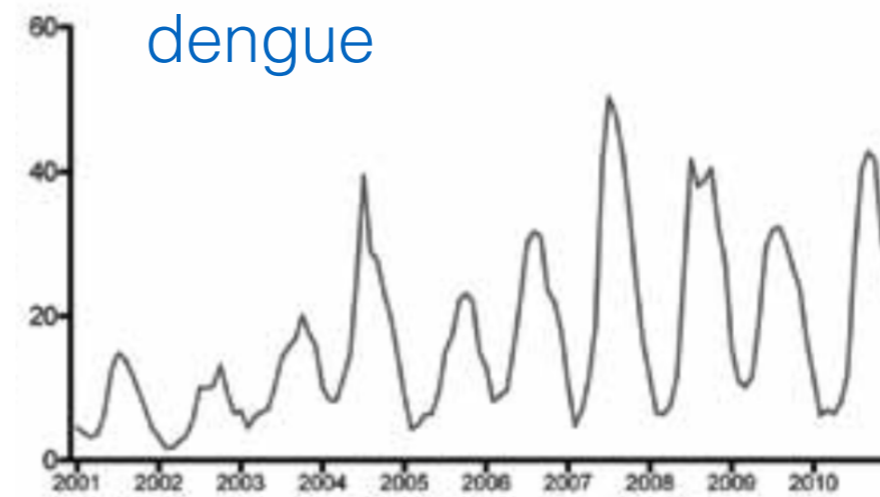
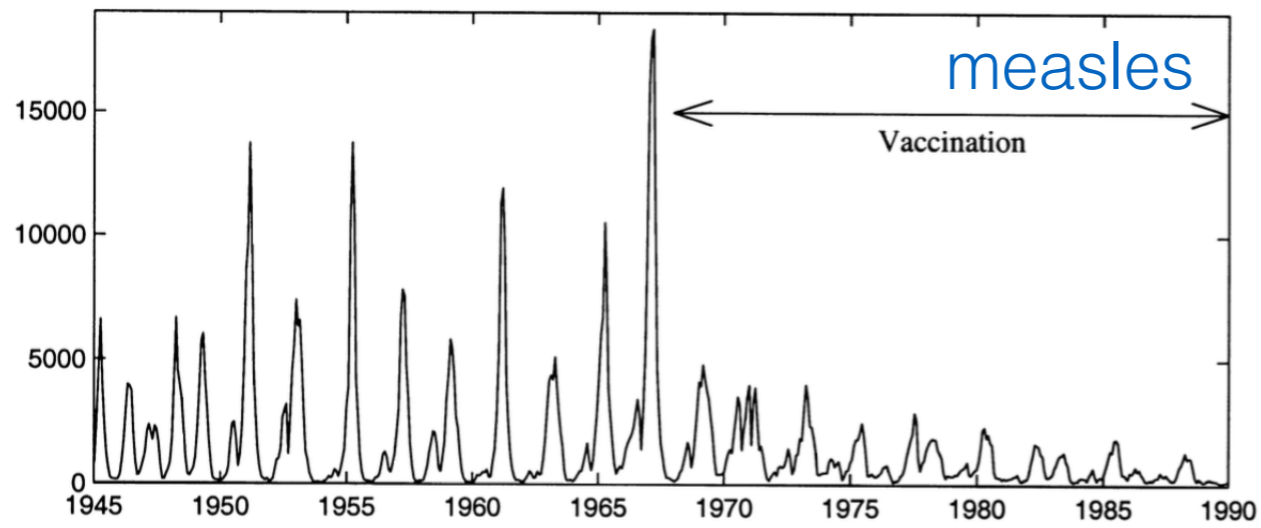


Seasonality

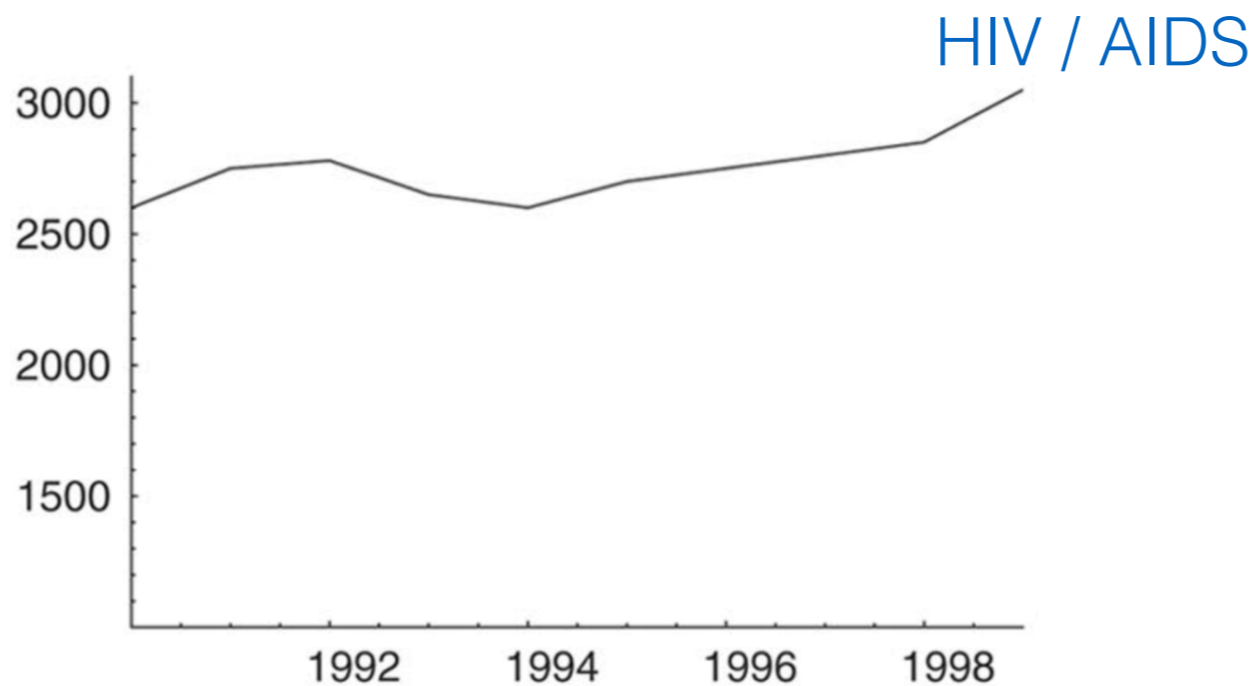
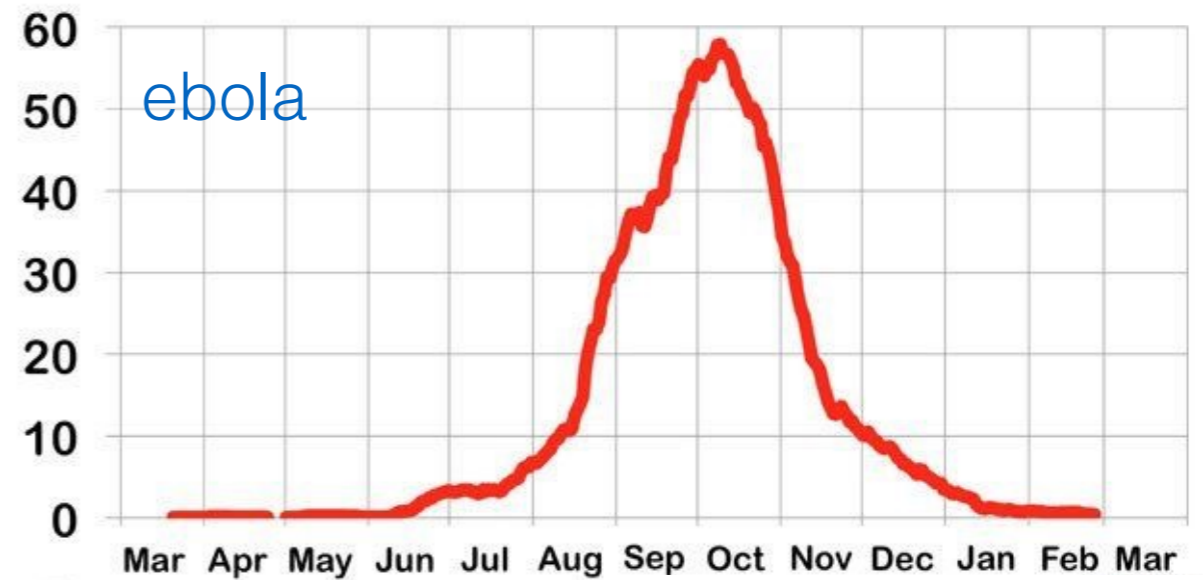
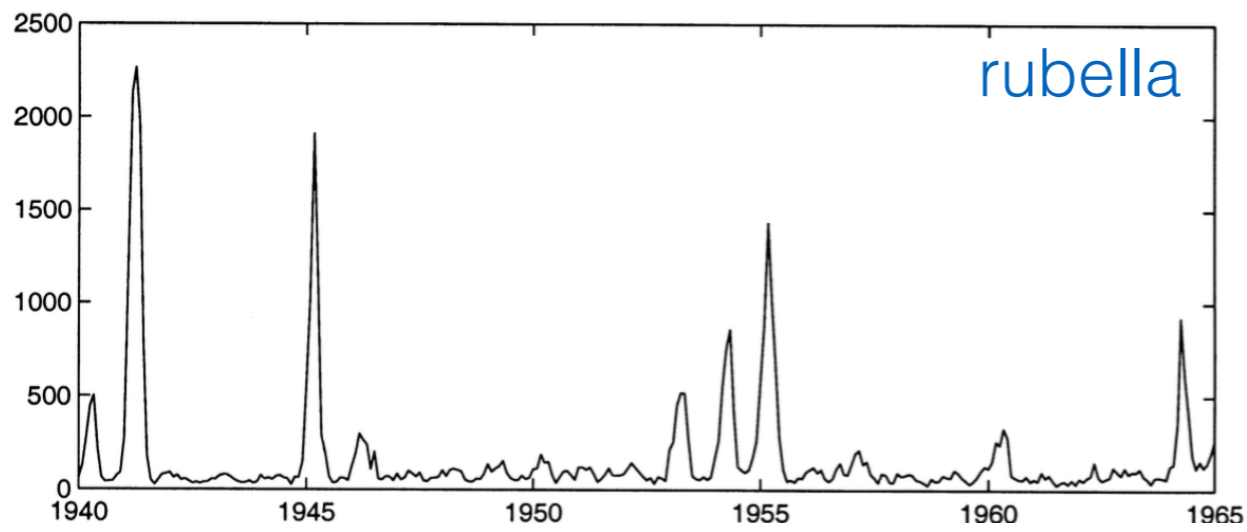
Spatial dynamics

Optimal control

Seasonality of infectious diseases



Seasonality of infectious diseases



Seasonality of infectious diseases

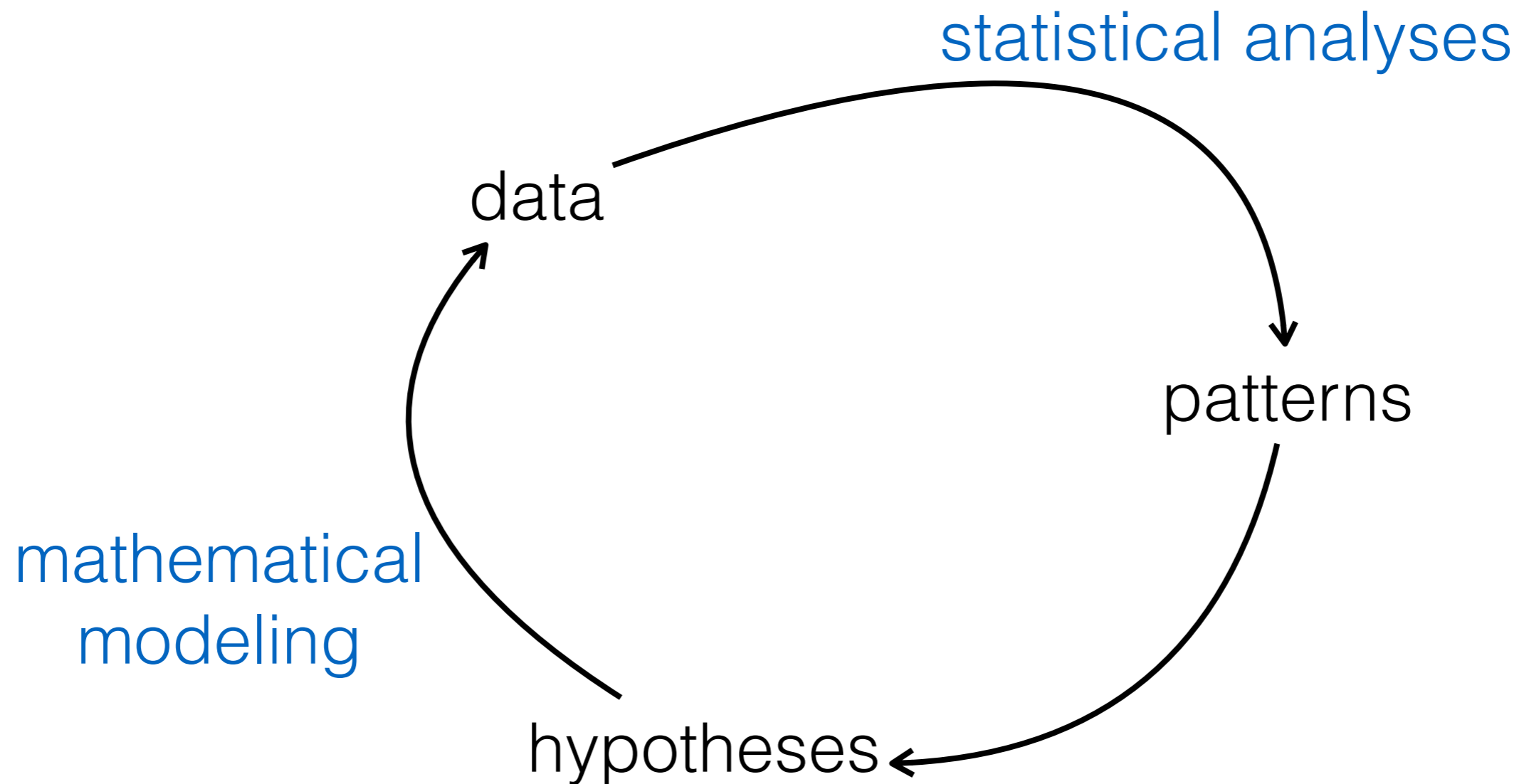
Why studying seasonality?

- can help forecasting
- can affect persistence

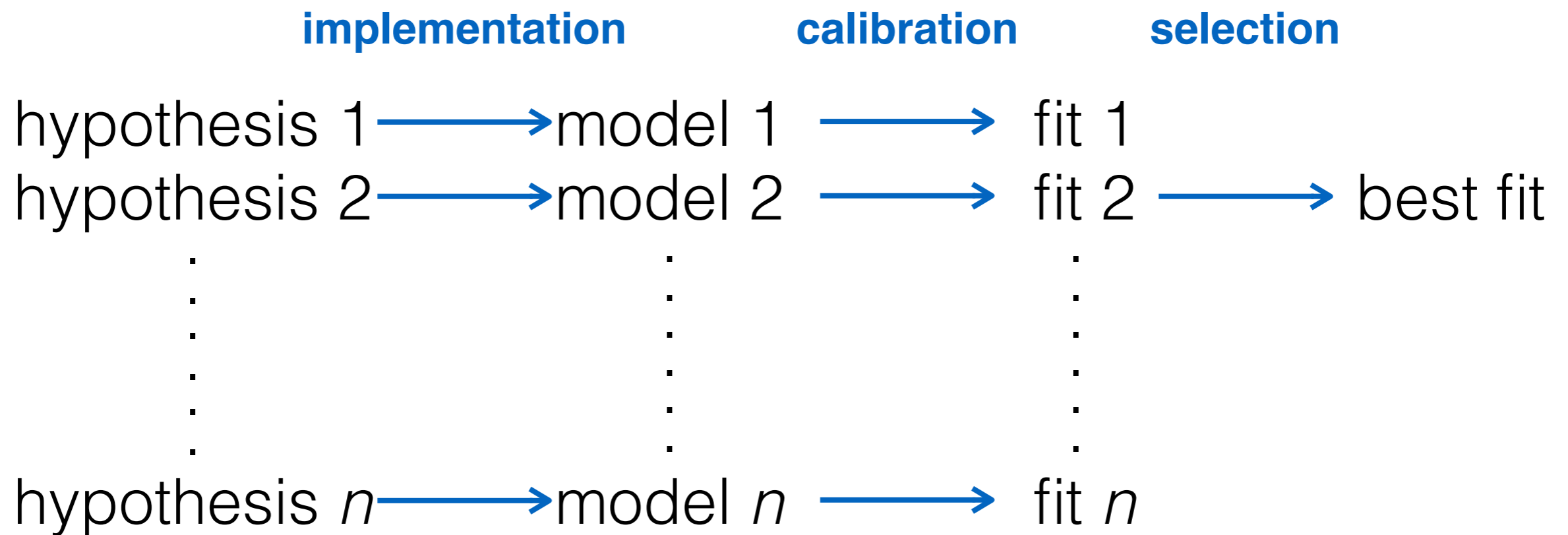
How to study seasonality?

- signal processing to unravel patterns
- testing hypotheses on mechanisms
 - natural experiments
 - competing hypotheses

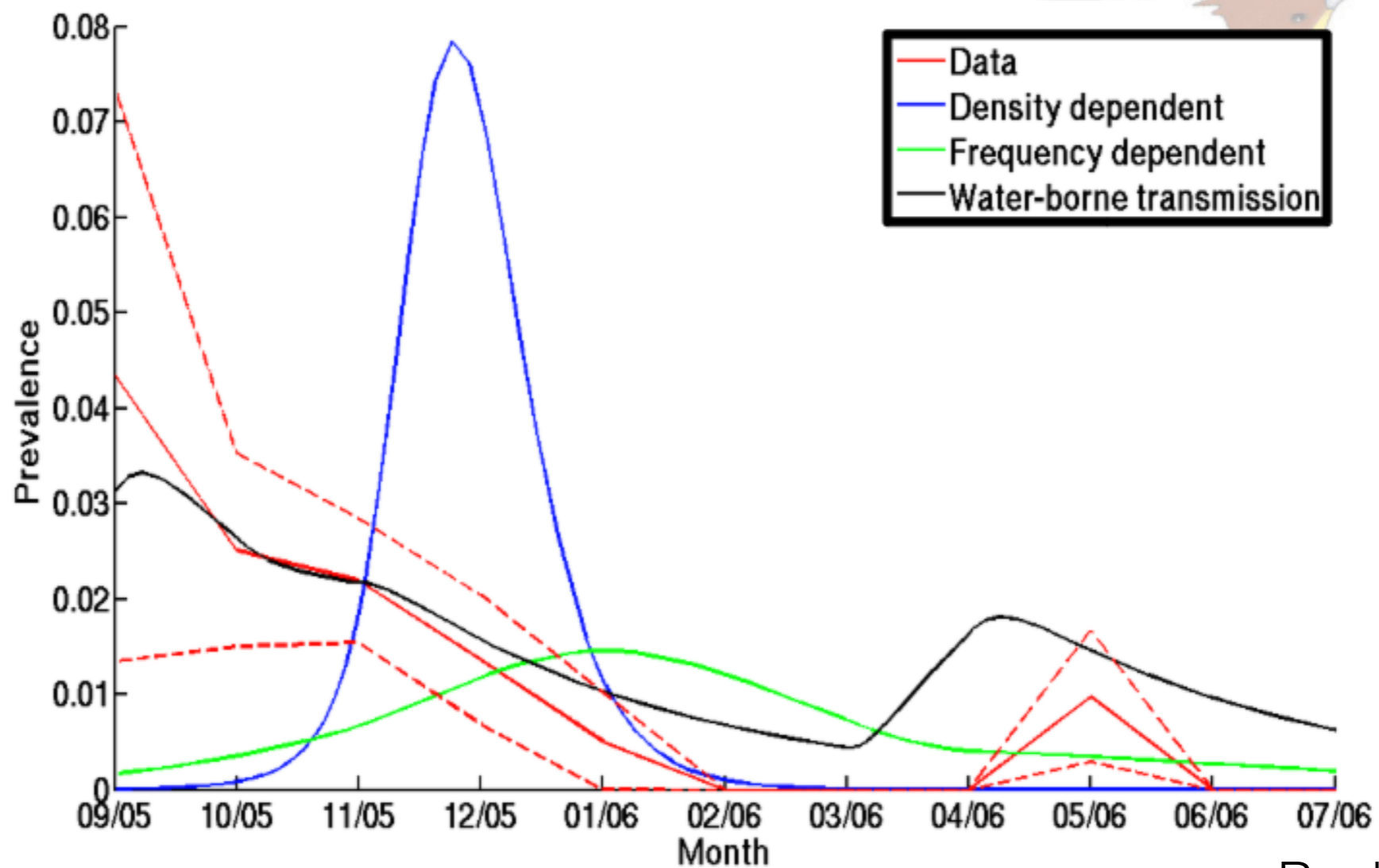
Seasonality of infectious diseases



Testing hypotheses: Competing models

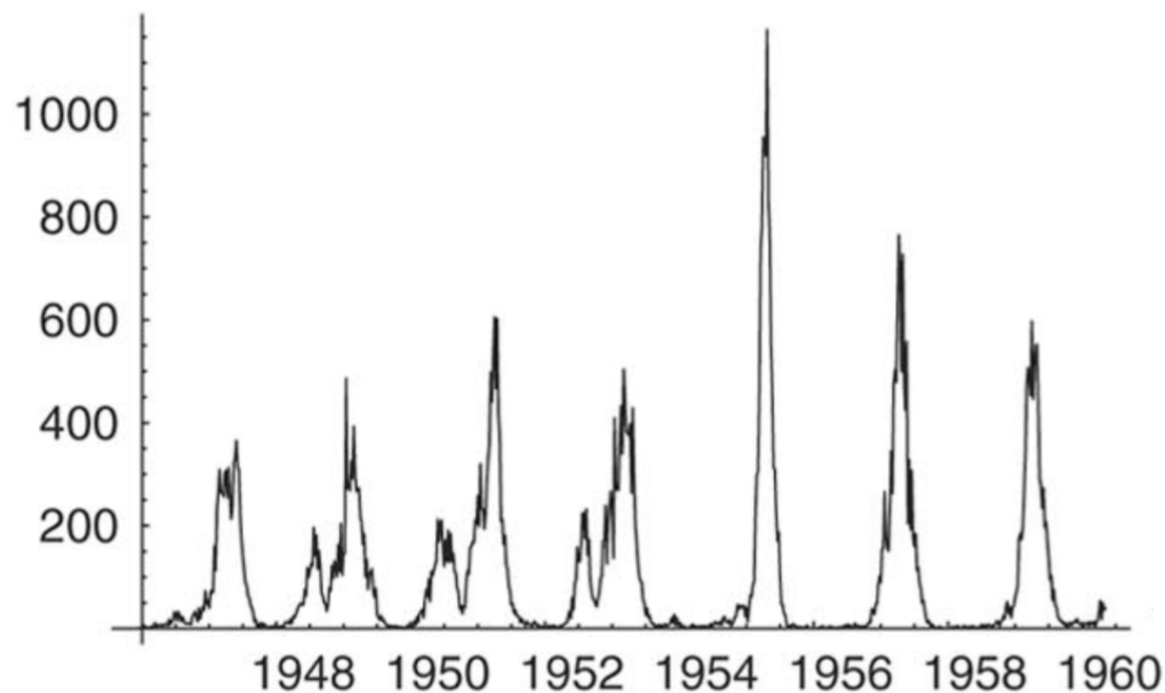


Testing hypotheses: Competing models

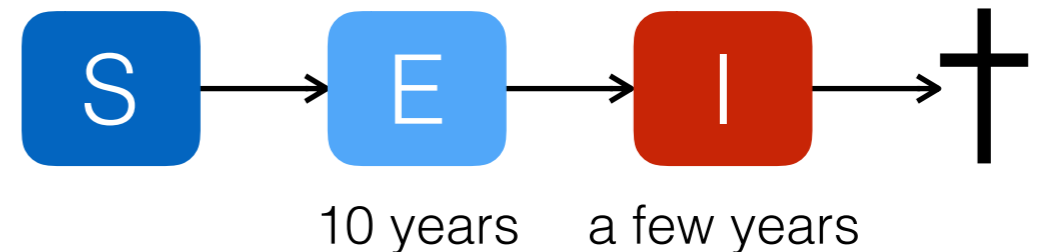
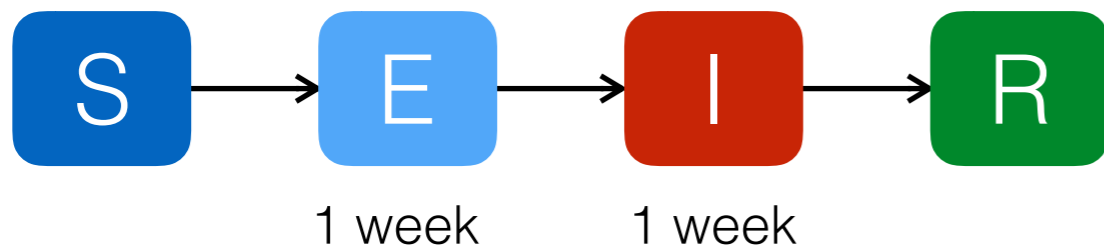
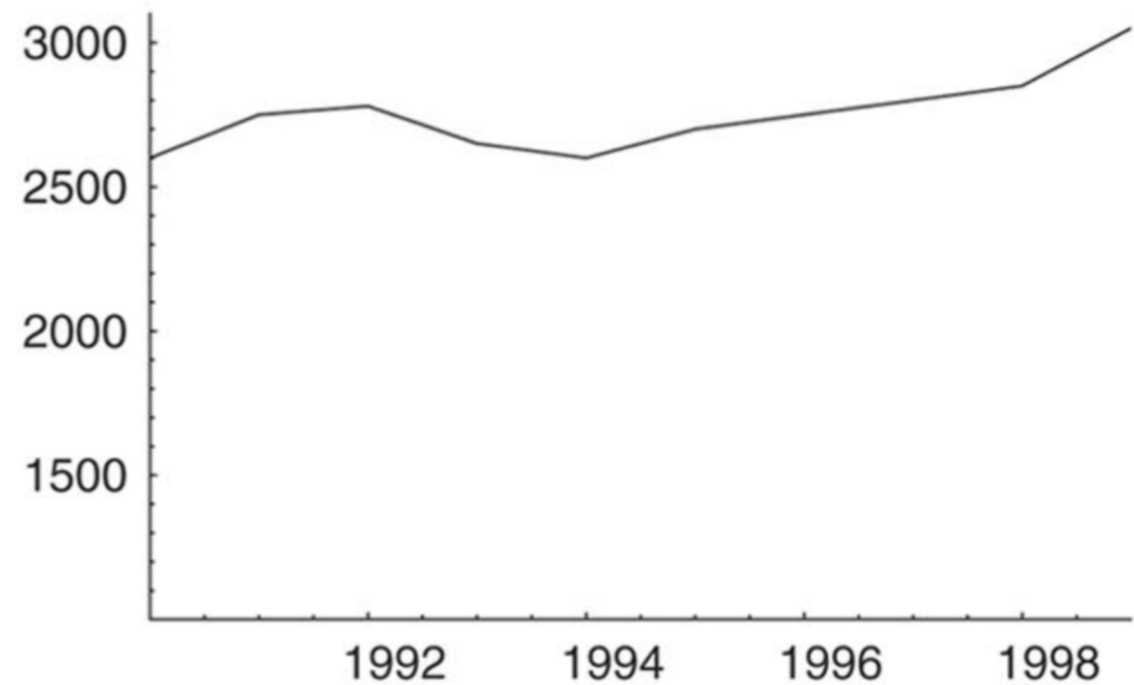


Causes of seasonality: Intrinsic epidemiological dynamics

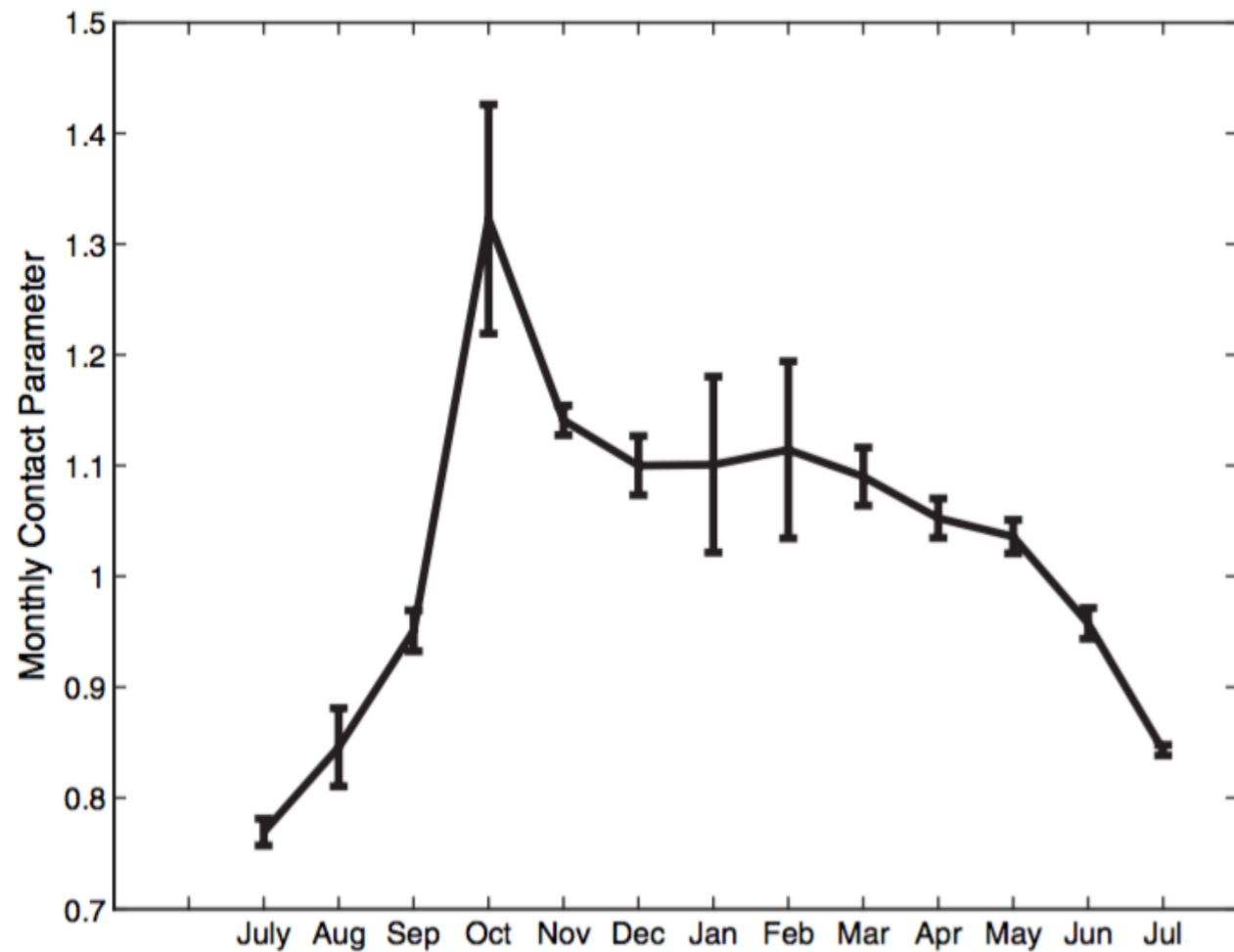
measles



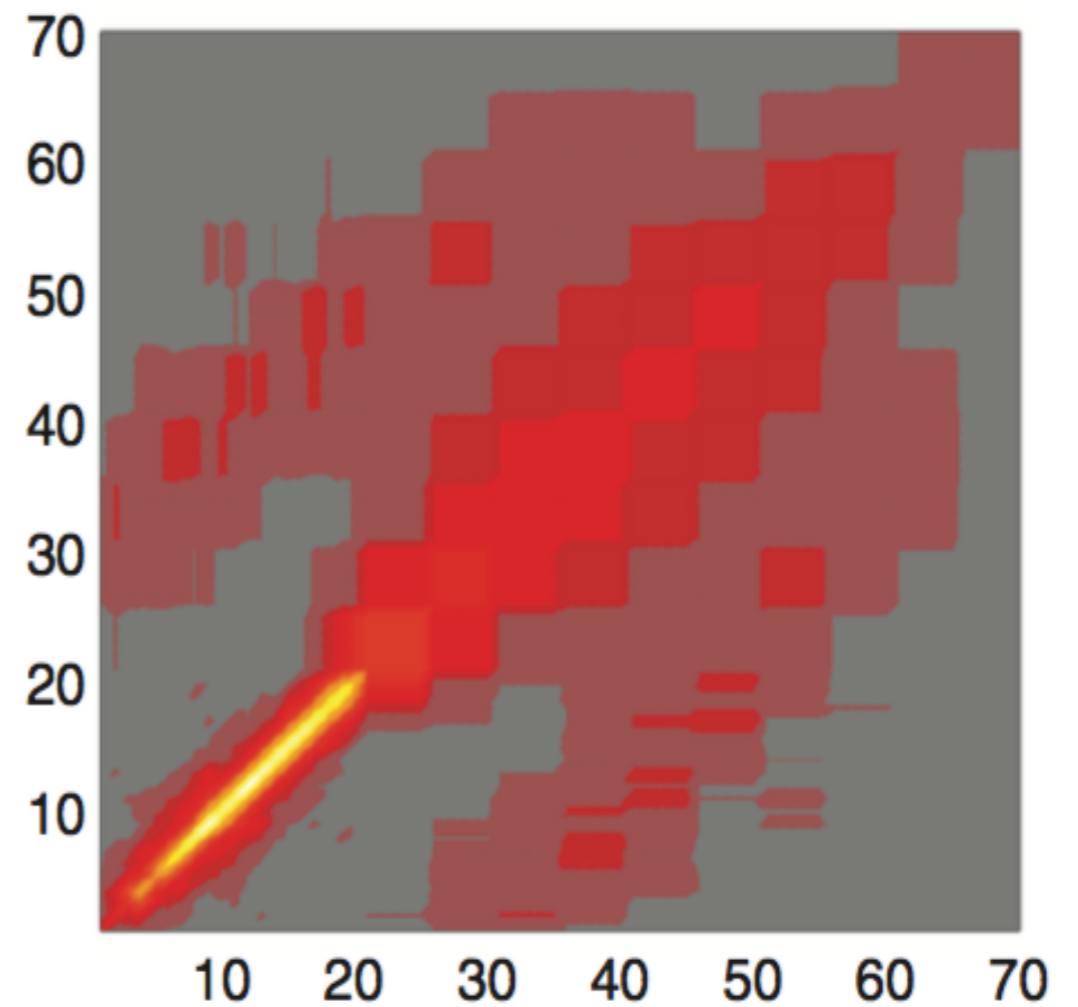
HIV / AIDS



Causes of seasonality: sociology

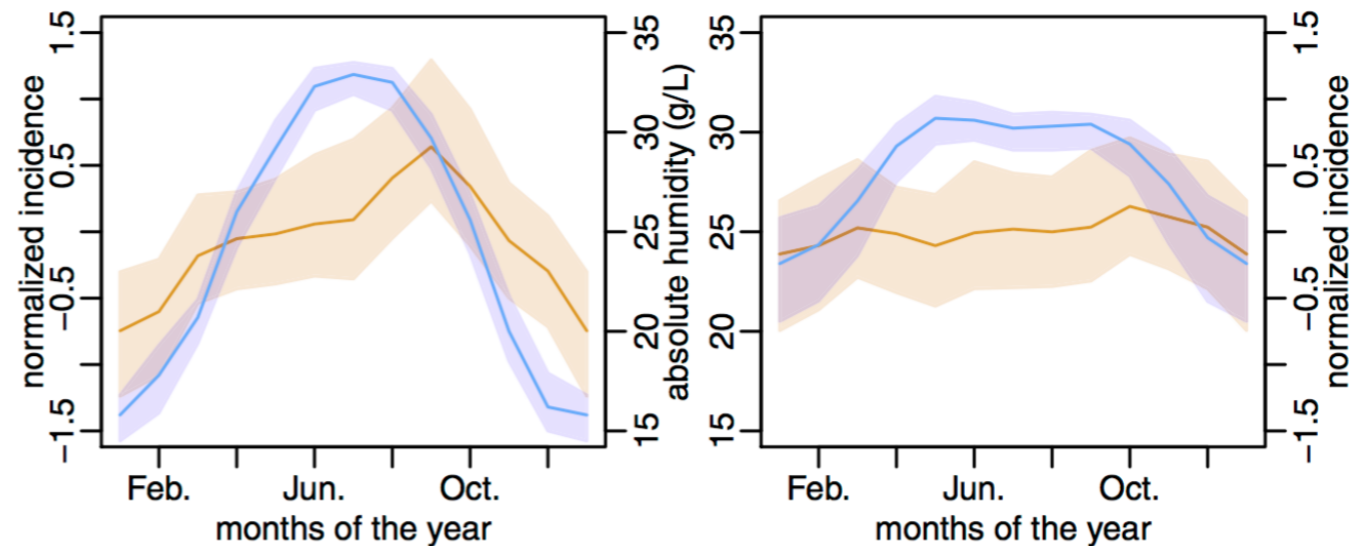
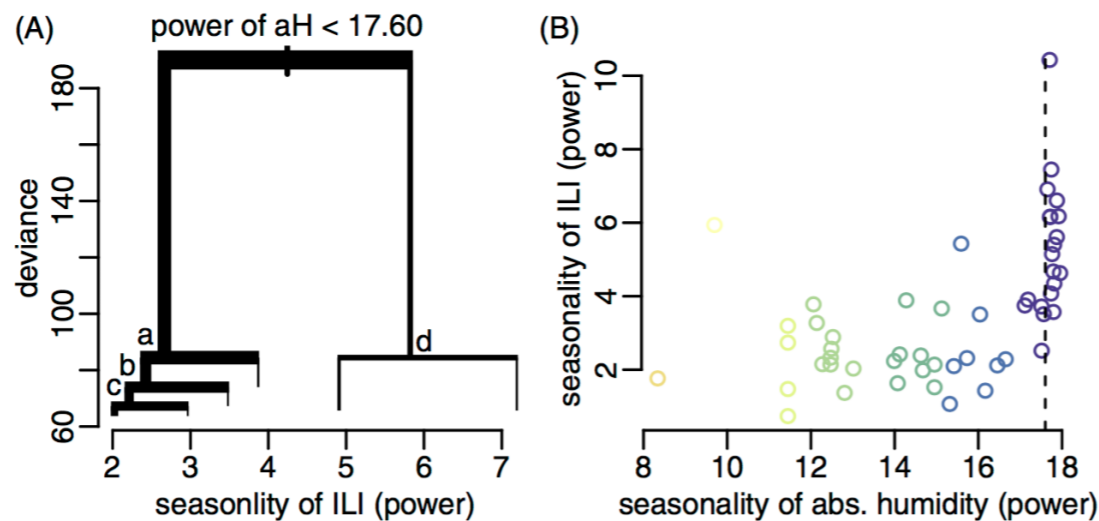
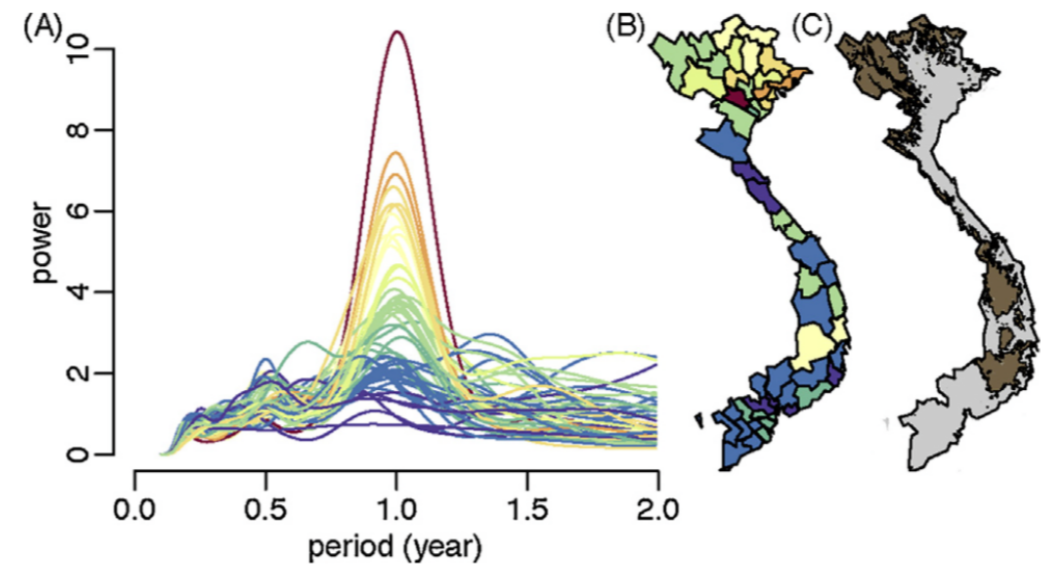
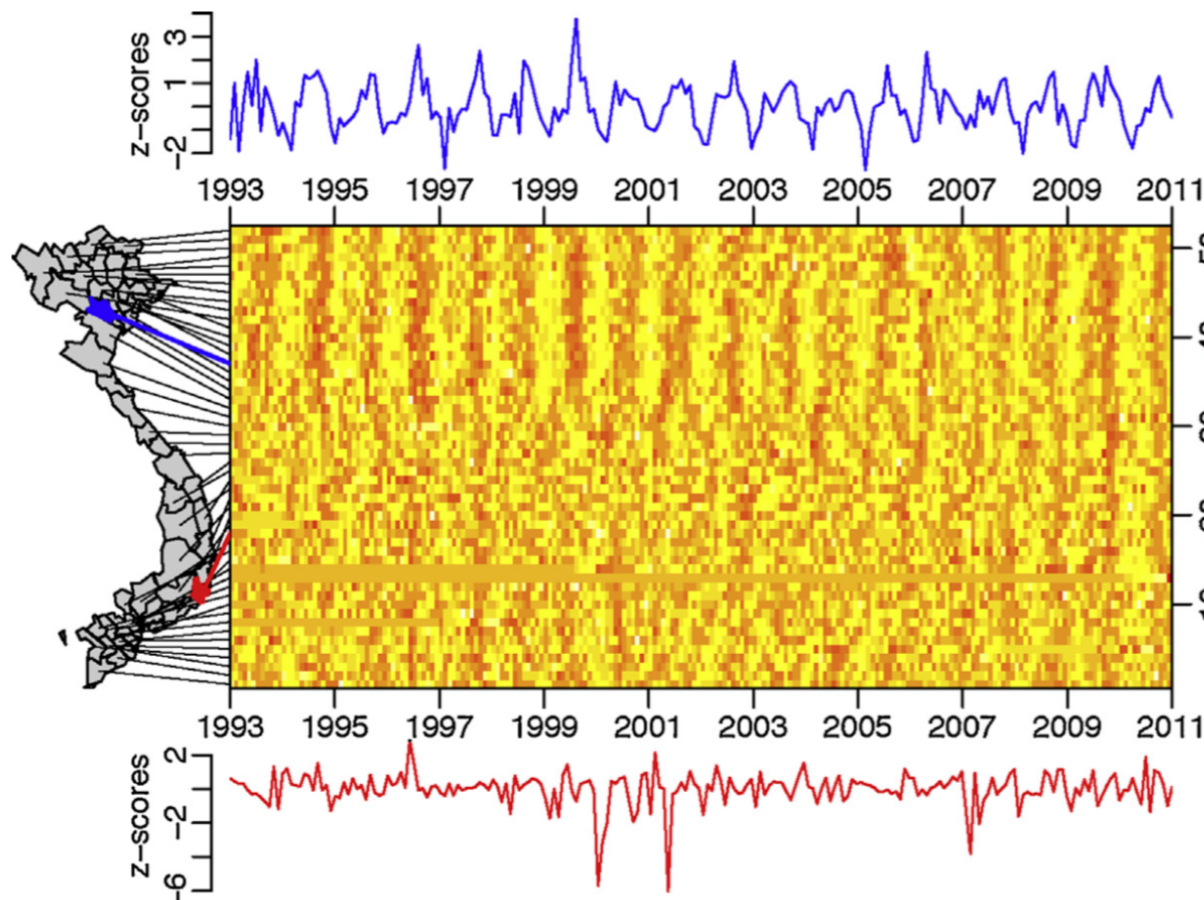


Soper 1929

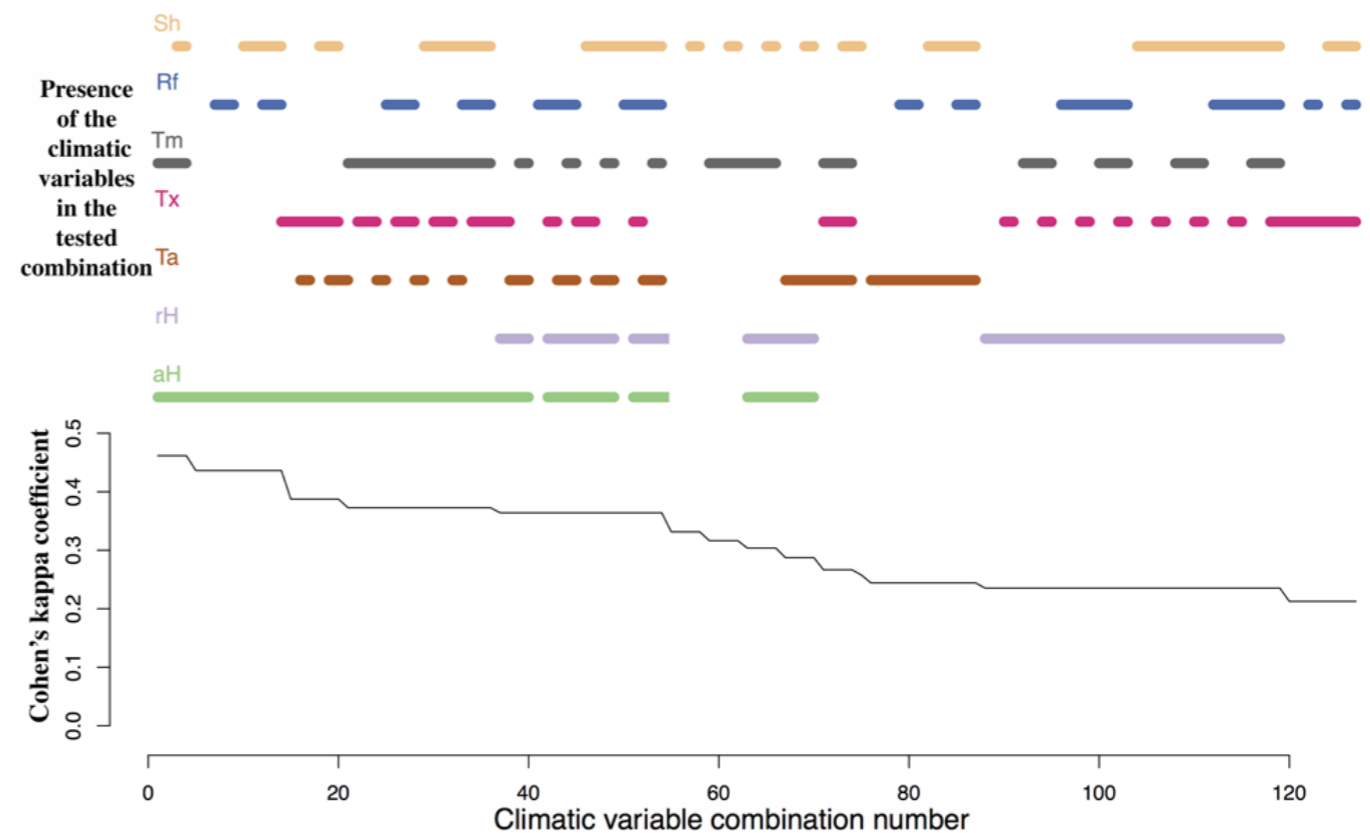
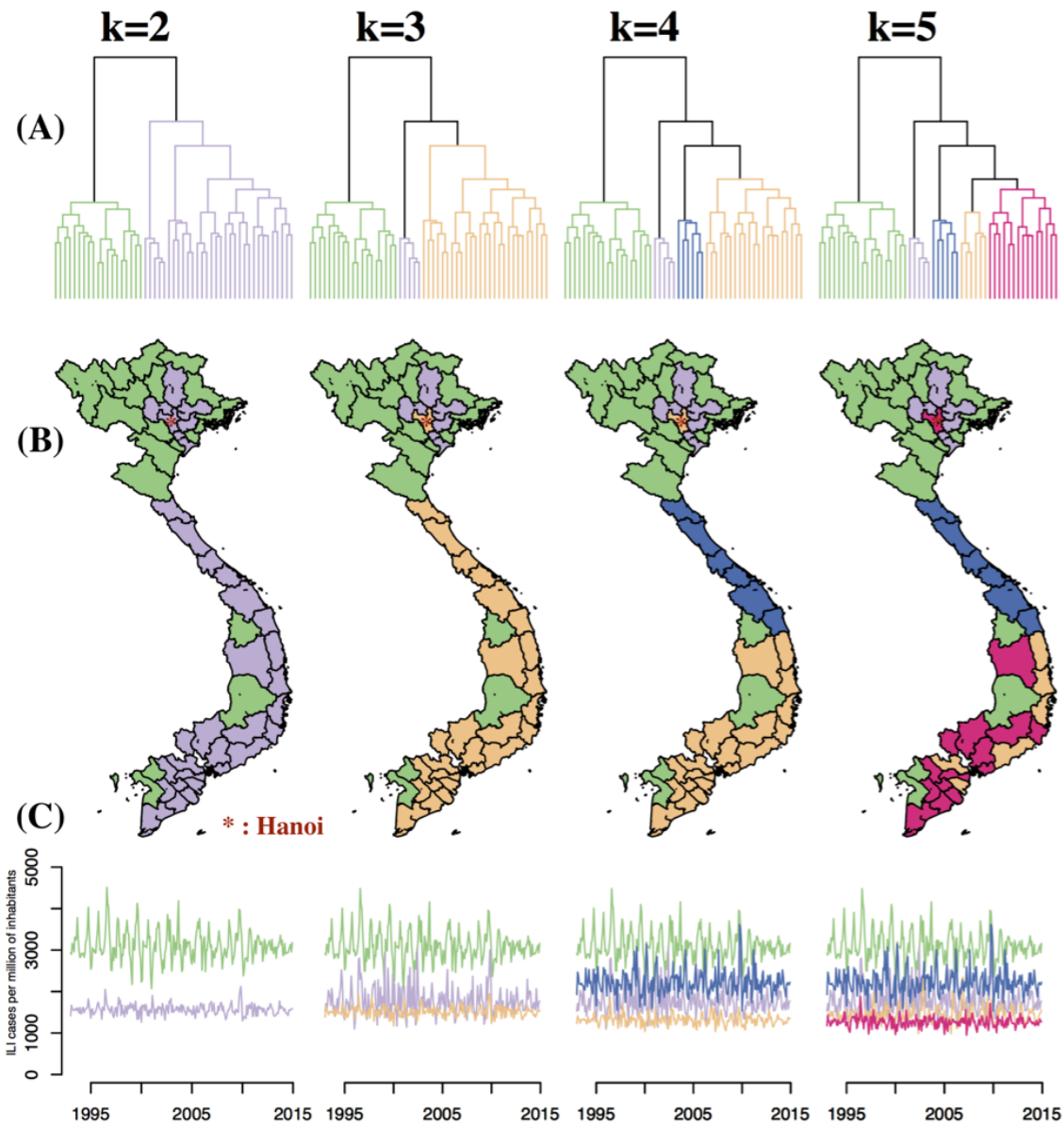


Rohani et al. 2010

Causes of seasonality: meteorology



Causes of seasonality: meteorology



Seasonality of infectious diseases

Why cause seasonality?

- intrinsic epidemiological dynamics
- demography
- sociology / behaviors
- immunology / evolution
- meteorology
- entomology
- etc...

Seasonality of infectious diseases

Climate

Nonstationary Influence of El Niño on the Synchronous Dengue Epidemics in Thailand

Bernard Cazelles^{1,2*}, Mario Chavez³, Anthony J. McMichael⁴, Simon Hales⁴

1 CNRS UMR 7625, Ecole Normale Supérieure, Paris, France, **2** IRD UR GEDDES, Bondy, France, **3** LENA-CNRS UPR 640, CHU Pitié-Salpêtrière, Paris, France, **4** National Centre for Epidemiology and Population Health, Australian National University, Canberra, Australian Capital Territory, Australia

Competing Interests: The authors have declared that no competing interests exist.

Author Contributions: BC and SH designed the study. MC and BC analyzed the data. BC, AJM, and SH contributed to the writing of the paper.

Academic Editor: Mercedes Pascual, University of Michigan, United States of America.

Citation: Cazelles B, Chavez M, McMichael AJ, Hales S (2005) Nonstationary influence of El Niño on the synchronous dengue epidemics in Thailand. *PLoS Med* 2(10): e106.

Received: November 10, 2004
Accepted: March 1, 2005
Published: April 26, 2005

DOI: 10.1371/journal.pmed.0020106

Copyright: © 2005 Cazelles et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abbreviations: DHF, dengue hemorrhagic fever

* To whom correspondence should be addressed. E-mail: cazelles@biologie.ens.fr



PLOS Medicine | www.plosmedicine.org

Open access, freely available online PLOS MEDICINE

OPEN ACCESS Freely available online

The Impact of the Demographic Transition on Dengue in Thailand: Insights from a Statistical Analysis and Mathematical Modeling

Derek A. T. Cummings^{1*}, Sophon Iamsrithaworn², Justin T. Lessler¹, Aidan McDermott³, Rungnapa Prasanthong², Ananda Nisalak⁴, Richard G. Jarman⁵, Donald S. Burke⁵, Robert V. Gibbons⁴

1 Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America, **2** Bureau of Epidemiology, Ministry of Public Health, Nonthaburi, Thailand, **3** Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America, **4** Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand, **5** Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America

Abstract

Background: An increase in the average age of dengue hemorrhagic fever (DHF) cases has been reported in Thailand. The cause of this increase is not known. Possible explanations include a reduction in transmission due to declining mosquito populations, declining contact between human and mosquito, and changes in reporting. We propose that a demographic shift toward lower birth and death rates has reduced dengue transmission and lengthened the interval between large epidemics.

Methods and Findings: Using data from each of the 72 provinces of Thailand, we looked for associations between force of infection (a measure of hazard, defined as the rate per capita at which susceptible individuals become infected) and demographic and climatic variables. We estimated the force of infection from the age distribution of cases from 1985 to 2005. We find that the force of infection has declined by 2% each year since a peak in the late 1970s and early 1980s. Contrary to recent findings suggesting that the incidence of DHF has increased in Thailand, we find a small but statistically significant decline in DHF incidence since 1985 in a majority of provinces. The strongest predictor of the change in force of infection and the mean force of infection is the median age of the population. Using mathematical simulations of dengue transmission we show that a reduced birth rate and a shift in the population's age structure can explain the shift in the age distribution of cases, reduction of the force of infection, and increase in the periodicity of multiannual oscillations of DHF incidence in the absence of other changes.

Conclusions: Lower birth and death rates decrease the flow of susceptible individuals into the population and increase the longevity of immune individuals. The increase in the proportion of the population that is immune increases the likelihood that an infectious mosquito will feed on an immune individual, reducing the force of infection. Though the force of infection has decreased by half, we find that the critical vaccination fraction has not changed significantly, declining from an average of 85% to 80%. Clinical guidelines should consider the impact of continued increases in the age of dengue cases in Thailand. Countries in the region lagging behind Thailand in the demographic transition may experience the same increase as their population ages. The impact of demographic changes on the force of infection has been hypothesized for other diseases, but, to our knowledge, this is the first observation of this phenomenon.

Please see later in the article for the Editors' Summary.

Citation: Cummings DAT, Iamsrithaworn S, Lessler JT, McDermott A, Prasanthong R, et al. (2008) The Impact of the Demographic Transition on Dengue in Thailand: Insights from a Statistical Analysis and Mathematical Modeling. *PLoS Med* 5(9): e1000139. doi:10.1371/journal.pmed.1000139

Academic Editor: Jeremy Farrar, Oxford University Clinical Research Unit, Viet Nam

Received: July 30, 2008; **Accepted:** July 17, 2009; **Published:** September 1, 2009

This is an open-access article distributed under the terms of the Creative Commons Attribution License, which stipulates that, once placed in the public domain, this work may be freely reproduced, distributed, transmitted, modified, built upon, or otherwise used by anyone for any lawful purpose.

Funding: This work was supported by the National Institute of General Medical Sciences MIDAS (Grant R01-GM07009) and the National Science Foundation Career Award at the Scientific Interface from the Burroughs Wellcome Fund. The study sponsor had no role in the study design, collection, analysis and interpretation of data, writing of the paper, and decision to submit it for publication.

Competing Interests: The authors have declared that no competing interests exist.

Abbreviations: CI, confidence interval; DF, dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome

* E-mail: dcummings@jhsp.edu

PLOS Medicine | www.plosmedicine.org

September 2009 | Volume 6 | Issue 9 | e1000139

Ecological and immunological determinants of dengue epidemics

Helen J. Wearing^{1*} and Pejman Rohani^{1*}

1 Institute of Ecology and **2** Center for Tropical and Emerging Global Diseases, University of Georgia, Athens, GA 30602-2202

New Mexico, Albuquerque, NM, and approved June 13, 2006 (received for review April 12, 2006)

Dengue is an increasingly important disease, the precise mechanisms responsible for generating these dynamics are unclear. We use a combination of empirical data and mathematical modeling to tease apart the relative roles of ecological and immunological determinants in dengue transmission. We demonstrate that dengue epidemics are driven by a combination of ecological and immunological factors. We show that the interaction of dengue serotypes in human hosts is mediated, in part, by the immune system's antibody response to infection. Although the exact nature of this response is not fully understood, results from experiments on human volunteers suggest there is a relatively short period (2–9 months) during which cross-reactive antibody levels are elevated and confer cross-immunity to other serotypes (homologous immunity appears to be lifelong; refs. 10 and 11). This period of temporary cross-immunity is analogous to the convalescent period in models of interaction between sympatric childhood diseases (12). Transient strain-transcending immunity has also been found to be essential to explain key aspects of influenza dynamics (13), whereas short-lived partially cross-reactive immune responses are thought to play a significant role in generating antigenic variation in malaria (14). After the period of transient cross-protection, a second episode of infection with a heterotypic dengue virus may then lead to a process known as antibody-dependent enhancement (ADE; refs. 15–17). ADE occurs when cross-reactive antibodies stimulated by a prior infection wane to levels that no longer neutralize the heterotypic virus. Instead of preventing infection, the binding of antibody to virus at subneutralizing concentrations can result in enhanced viral replication by increased infection of cells bearing the IgG receptor (11). The presence of subneutralizing antibody levels is also thought to be temporary, although how long such levels persist is unknown. Epidemiological evidence in support of ADE is provided by studies reporting that the preexistence of dengue virus antibodies is a significant risk factor for severe disease (17, 18), although this is not always the case (19). A cascade of other immune responses initiated by memory T lymphocytes has also been implicated in the immunopathogenesis of dengue virus infection, but sequential infection with different serotypes appears to be the key trigger.

Abstract | Introduction | Discussion | Conclusions | Acknowledgments | Author Contributions | Competing Interests | Funding | References | Figures | Tables | Supplementary Material | Permissions | Reprints | Contact Us | Help | Privacy Policy | Terms of Use | About PLOS

ous feature of epidemiological drivers, both extrinsic, such as host immunity (3), are often web of causal mechanisms (4), (5) strain dynamics | transient case

vol. 103 | no. 31

Serotypes

considerable speculation over the precise mechanisms responsible for generating these dynamics (6, 7, 9).

Alternative Hypotheses

Much of the debate has focused on the immune response to dengue infection and its role in the emergence of DHF. The interaction of dengue serotypes in human hosts is mediated, in part, by the immune system's antibody response to infection. Although the exact nature of this response is not fully understood, results from experiments on human volunteers suggest there is a relatively short period (2–9 months) during which cross-reactive antibody levels are elevated and confer cross-immunity to other serotypes (homologous immunity appears to be lifelong; refs. 10 and 11). This period of temporary cross-immunity is analogous to the convalescent period in models of interaction between sympatric childhood diseases (12). Transient strain-transcending immunity has also been found to be essential to explain key aspects of influenza dynamics (13), whereas short-lived partially cross-reactive immune responses are thought to play a significant role in generating antigenic variation in malaria (14). After the period of transient cross-protection, a second episode of infection with a heterotypic dengue virus may then lead to a process known as antibody-dependent enhancement (ADE; refs. 15–17). ADE occurs when cross-reactive antibodies stimulated by a prior infection wane to levels that no longer neutralize the heterotypic virus. Instead of preventing infection, the binding of antibody to virus at subneutralizing concentrations can result in enhanced viral replication by increased infection of cells bearing the IgG receptor (11). The presence of subneutralizing antibody levels is also thought to be temporary, although how long such levels persist is unknown. Epidemiological evidence in support of ADE is provided by studies reporting that the preexistence of dengue virus antibodies is a significant risk factor for severe disease (17, 18), although this is not always the case (19). A cascade of other immune responses initiated by memory T lymphocytes has also been implicated in the immunopathogenesis of dengue virus infection, but sequential infection with different serotypes appears to be the key trigger.

An alternative view of serotype interaction is based upon variation in virulence among and within dengue serotypes: each serotype exhibits extensive genetic variation, and it is postulated that certain "virulent" virus genotypes are associated with the manifestation of severe disease (20, 21). In particular, Dengue-2 strains originating in southeast Asia appear to be more pathogenic than their American counterparts (22, 23). Evidence as to whether ADE or variation in viral virulence, or both, is consistent with the temporal patterns of dengue incidence remains equivocal (24). One important unresolved issue is whether ADE or virulent strains are phenomena that purely increase the

Conflict of interest statement: No conflicts declared.

This paper was submitted directly to the PLOS office.

Abbreviations: DHF, dengue hemorrhagic fever; ADE, antibody-dependent enhancement.

* To whom correspondence should be addressed. E-mail: hjew@uga.edu.

© 2006 by The National Academy of Sciences of the USA.

www.pnas.org/cgi/doi/10.1073/pnas.0602960103

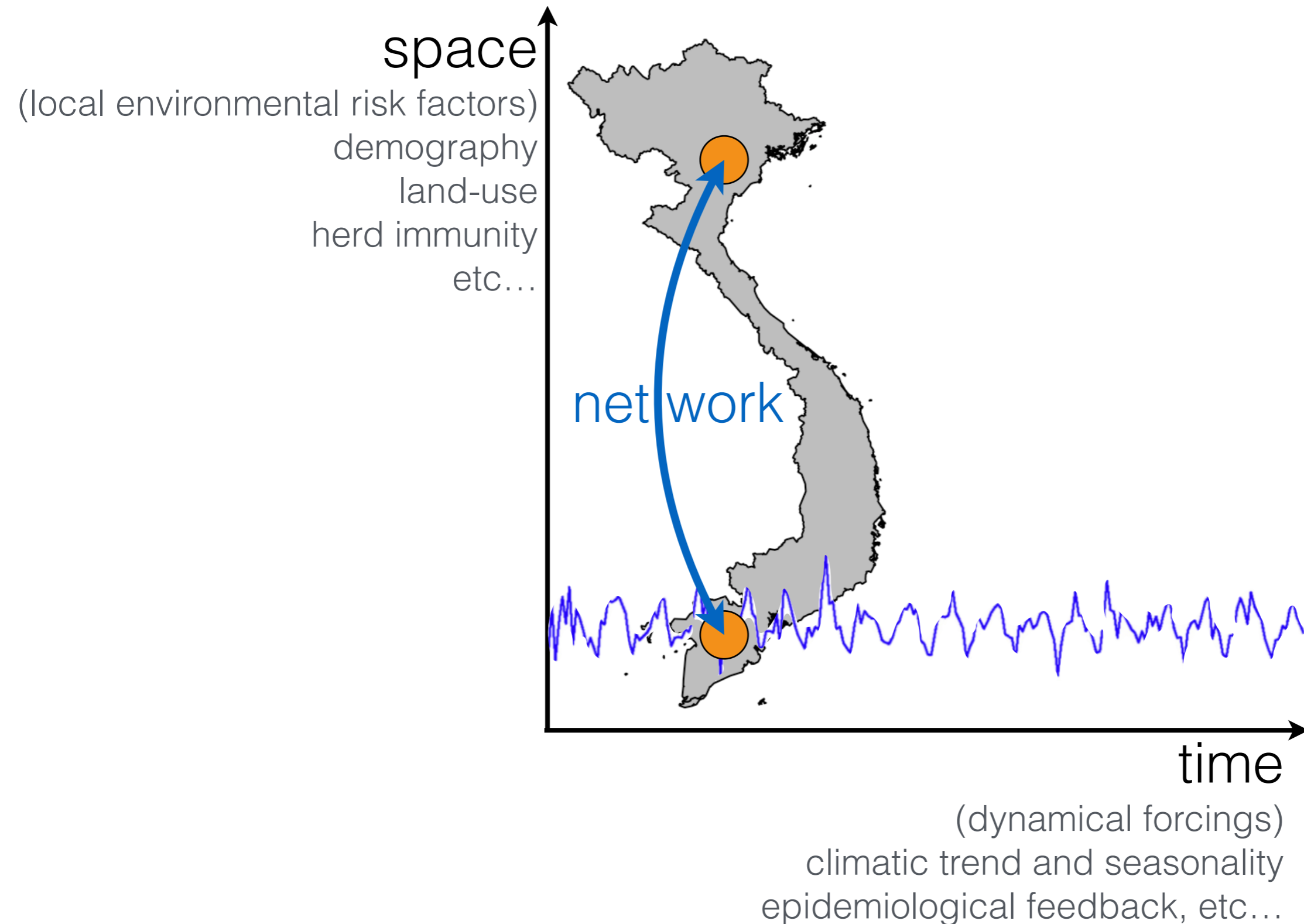
Seasonality

Spatial dynamics

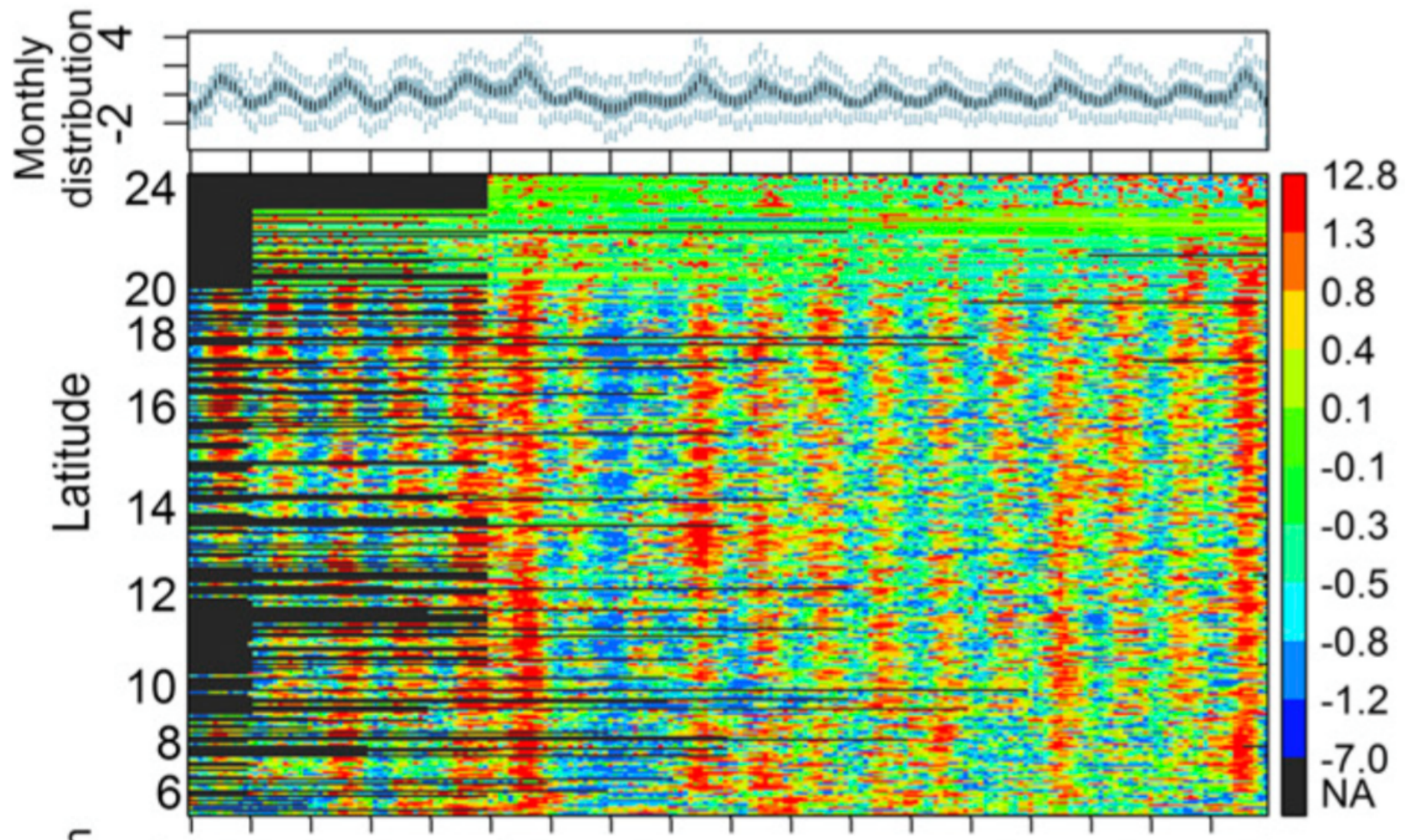
Optimal control

Model & data

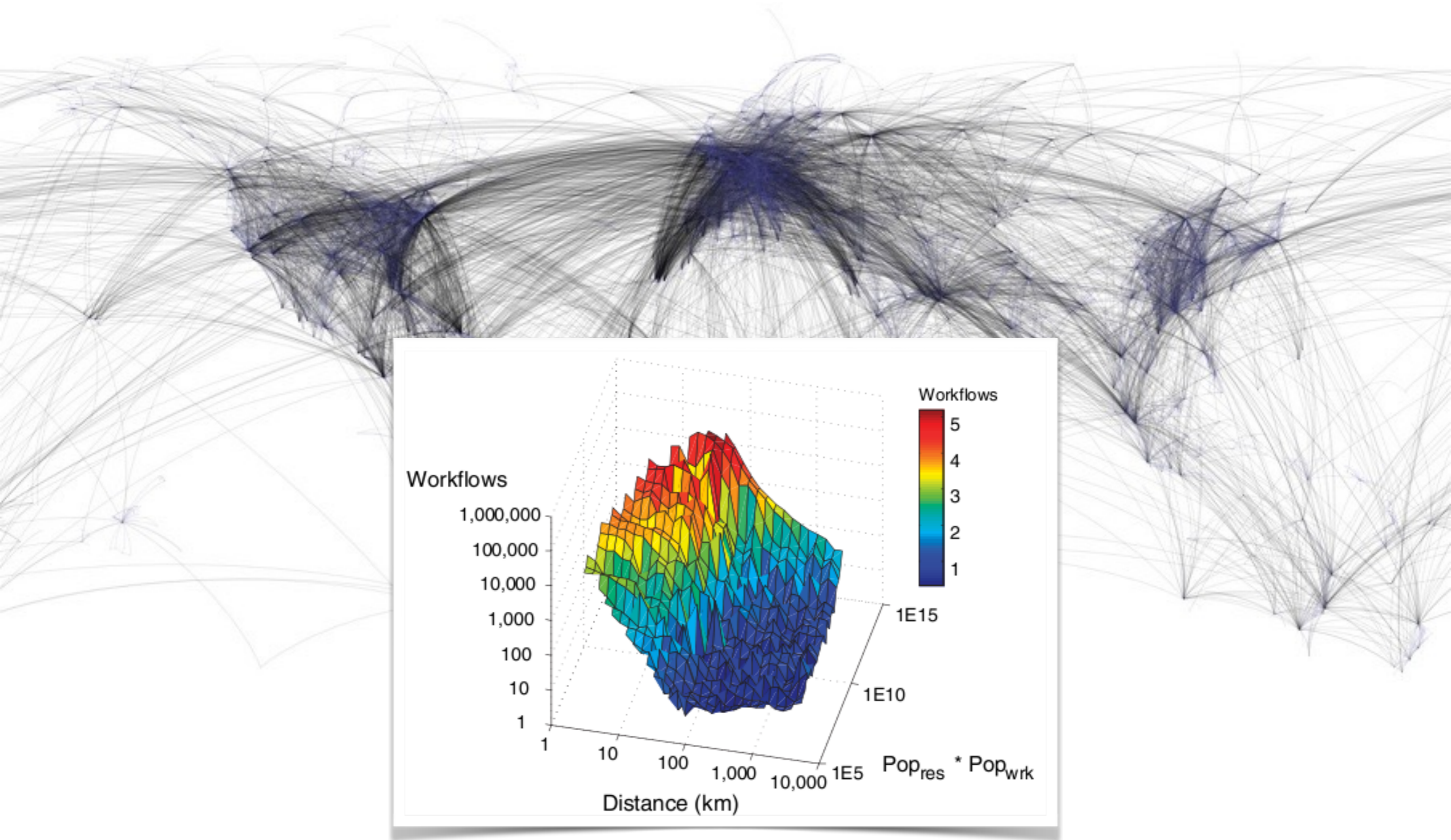
Local risk factors and movements



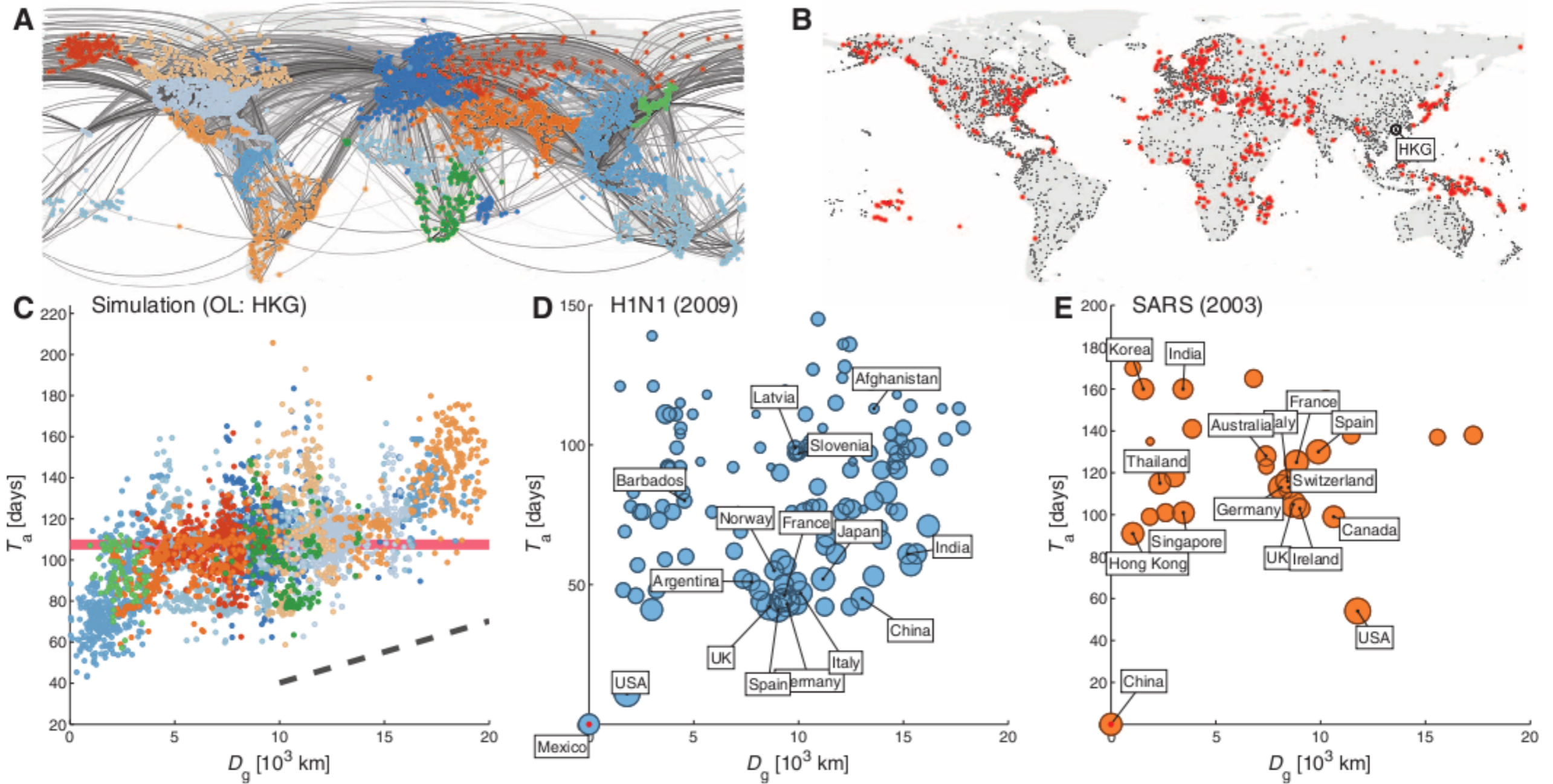
Adding the spatial dimension



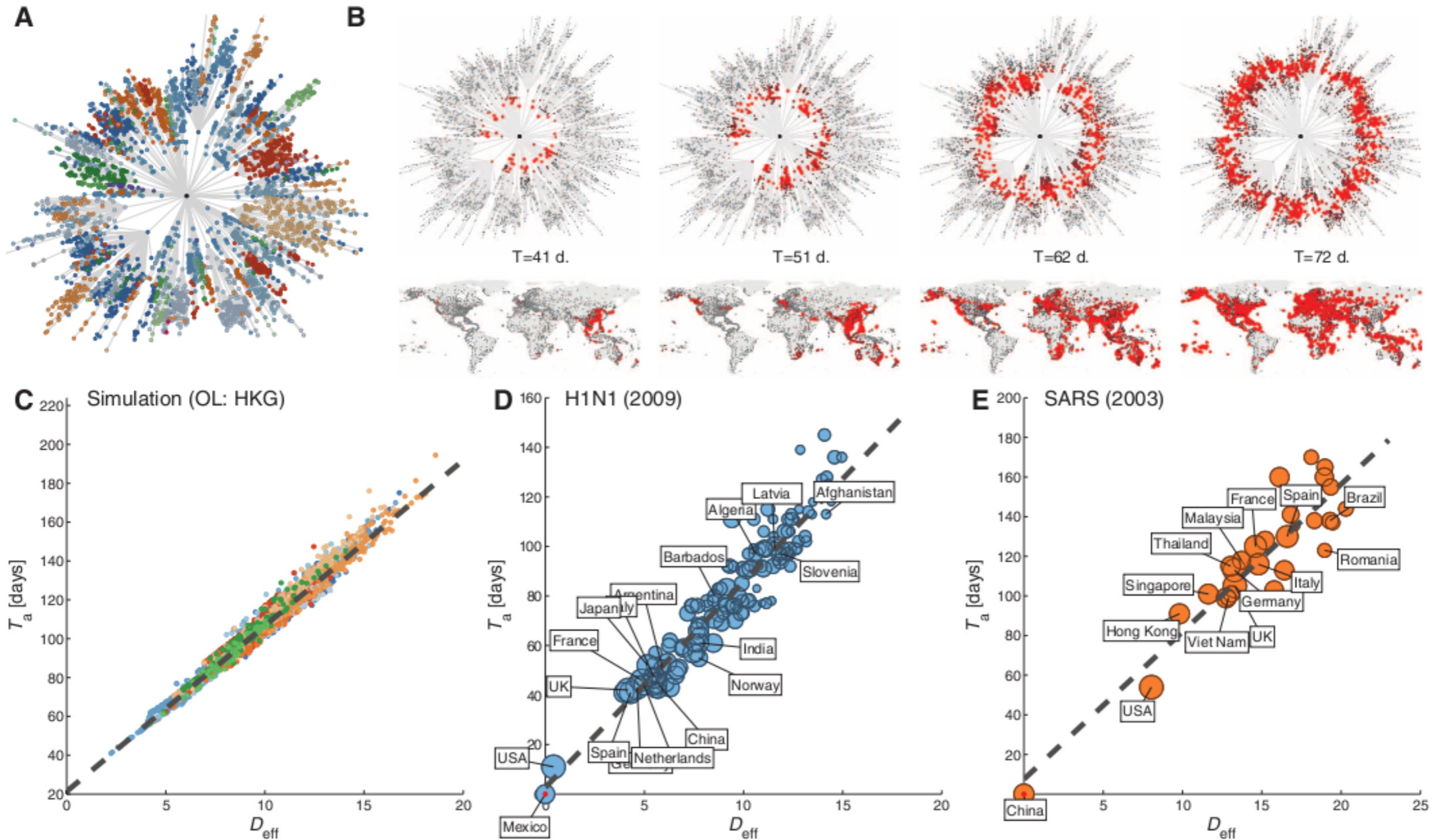
Connections between populations



Redefining distances



Redefining distances



Seasonality

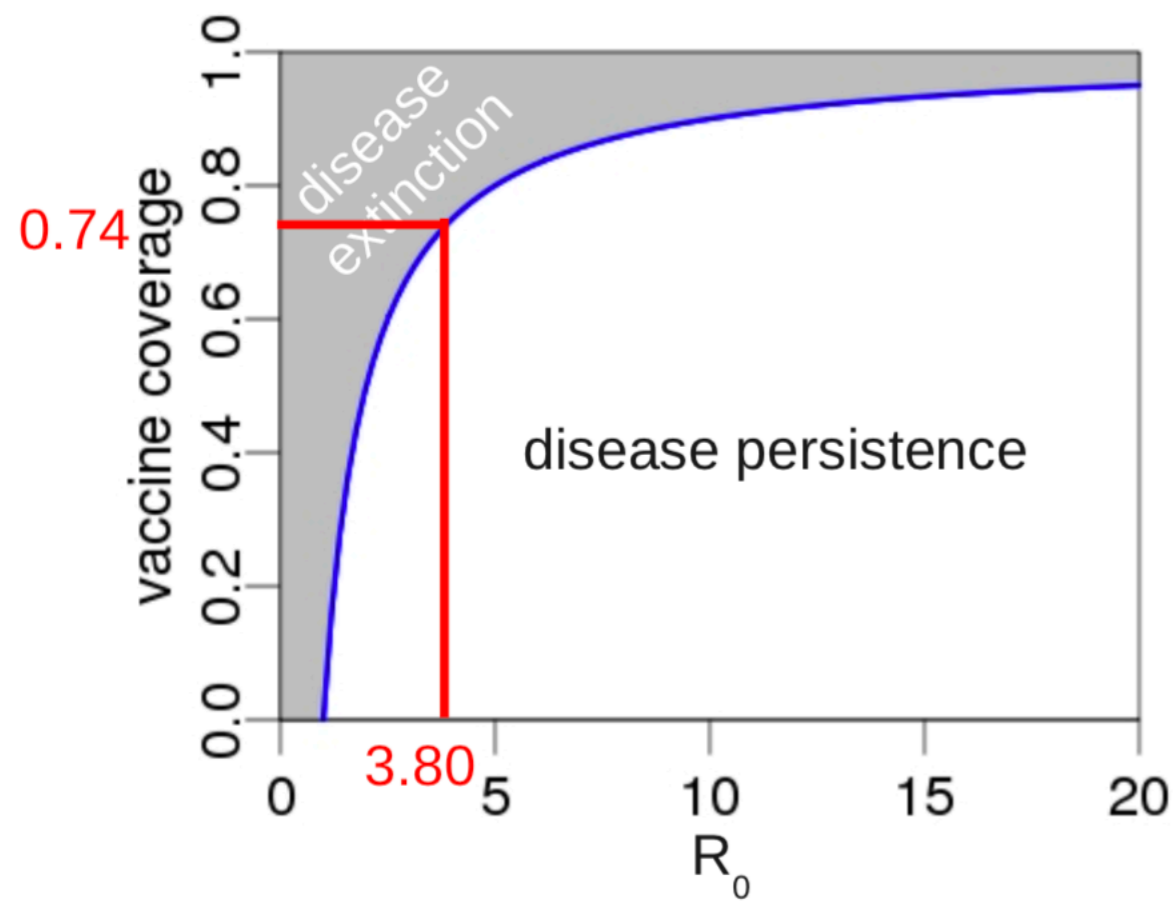
Spatial dynamics

Optimal control

Herd immunity

$$p_c = 1 - \frac{1}{R_0} \approx 0.74$$

herd immunity



$$R_0 = \frac{\beta}{\gamma} = \frac{1.67}{0.44} = 3.80$$

Herd immunity

Disease	Host	R_0	p_c
tuberculosis	cattle	2.6	62%
FIV	domestic cat	1.1-1.5	9-33%
rabies	hyaenas	1.9	47%
phocine distemper	seals	2-3	50-66%
influenza	human	3-4	66-75%
foot and mouth disease	livestock	3.5-4.5	71-78%
smallpox	human	3.5-6	71-83%
rubella	human	6-7	83-86%
chickenpox	human	7-8 / 10-12	86-88% / 90-92%
Measles, whooping cough	human	16-18	94%
mumps	human	7-8 / 11-14	86-88% / 91-93%
rubeola	human	6-7 / 15-16	83-86% / 93-94%
HIV-AIDS	human	4 / 11	75 / 91%

April 19, 1955.

Making History.

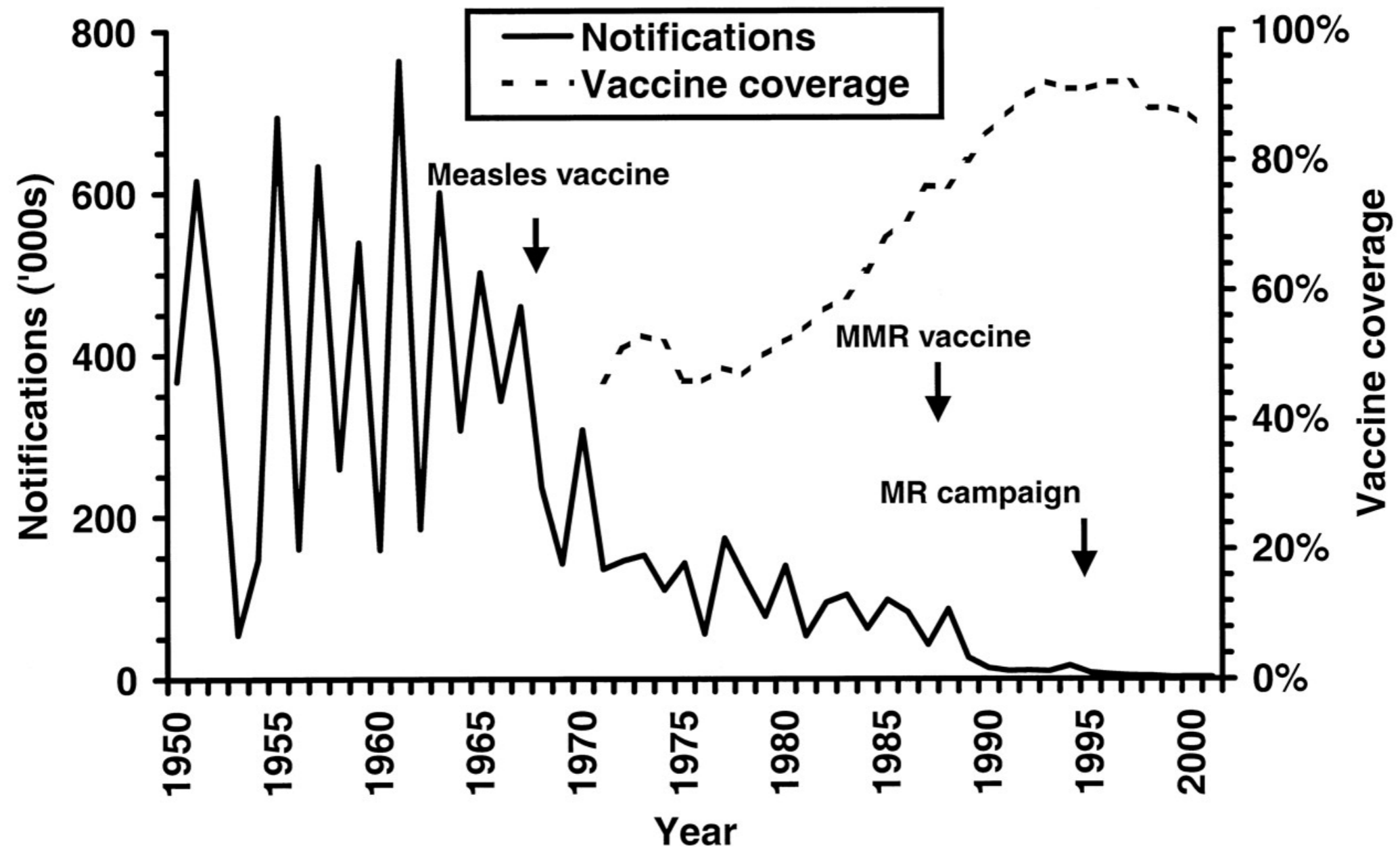
We are among the first children ever
to be given Polio shots. So we are really
making History today.

We are lucky.

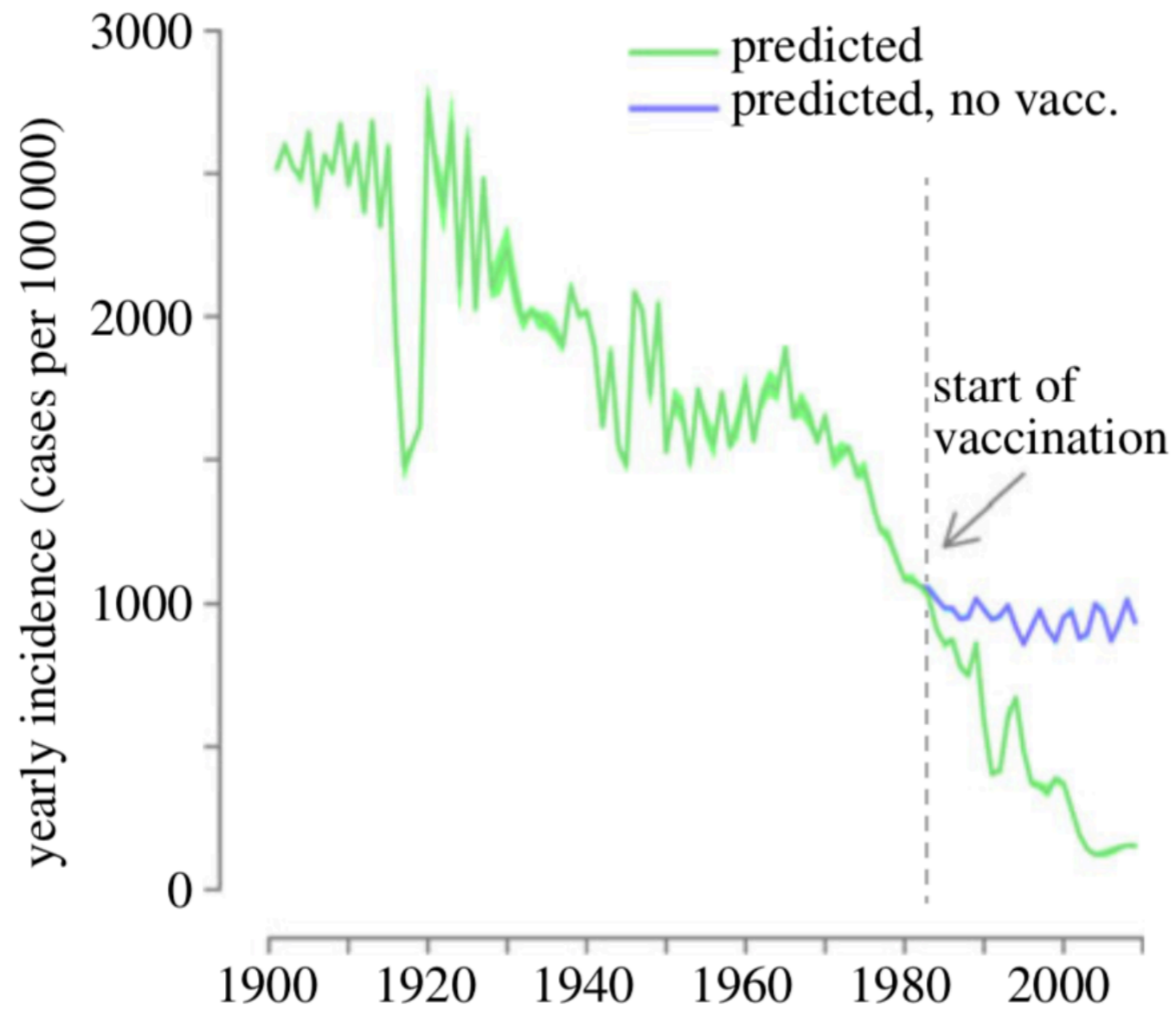
ghed when
happy because
the corn field.



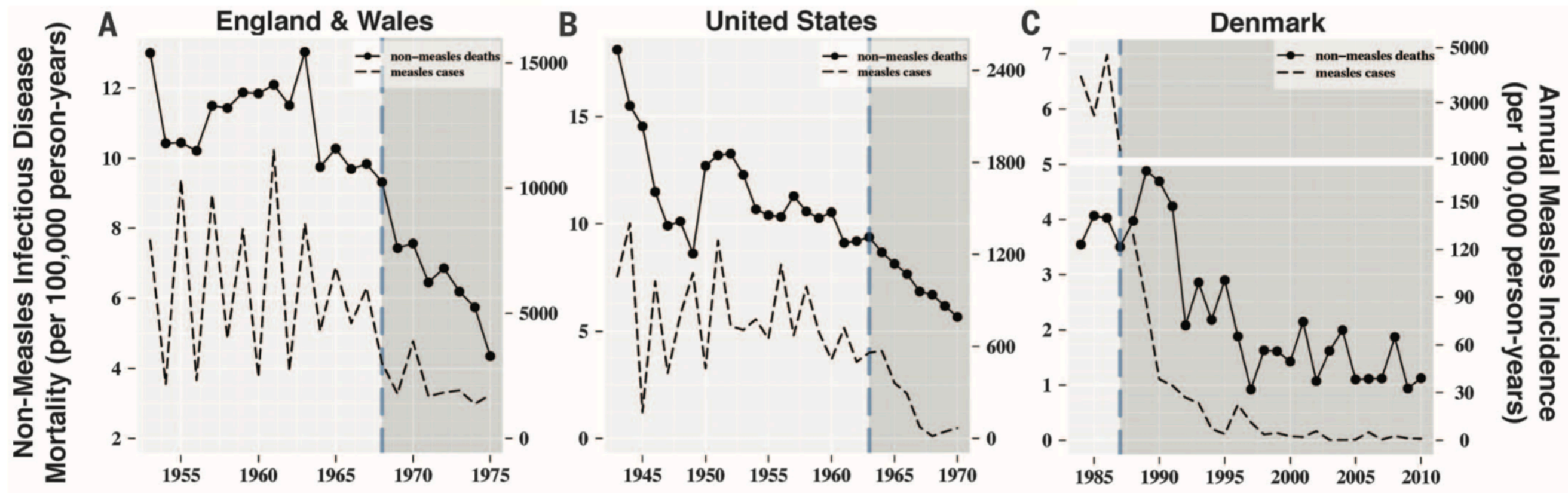
Vaccine policies: a success story



Vaccine policies: a success story



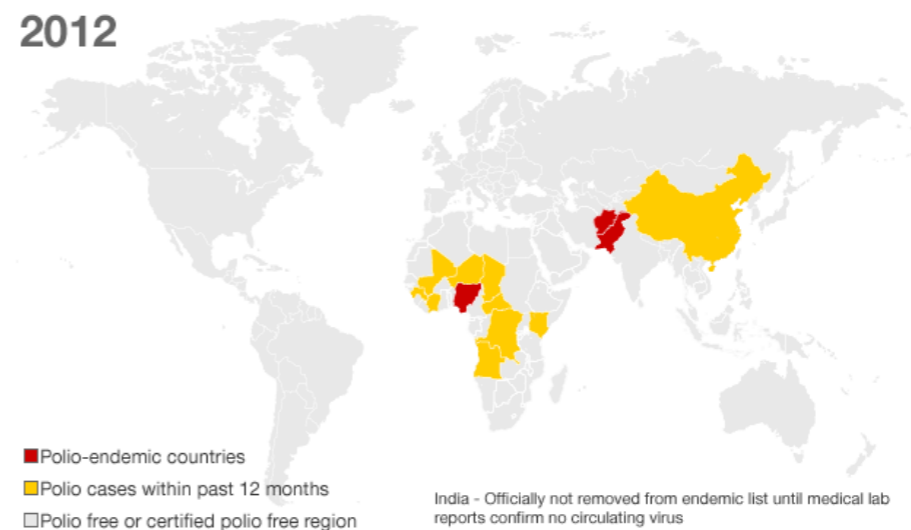
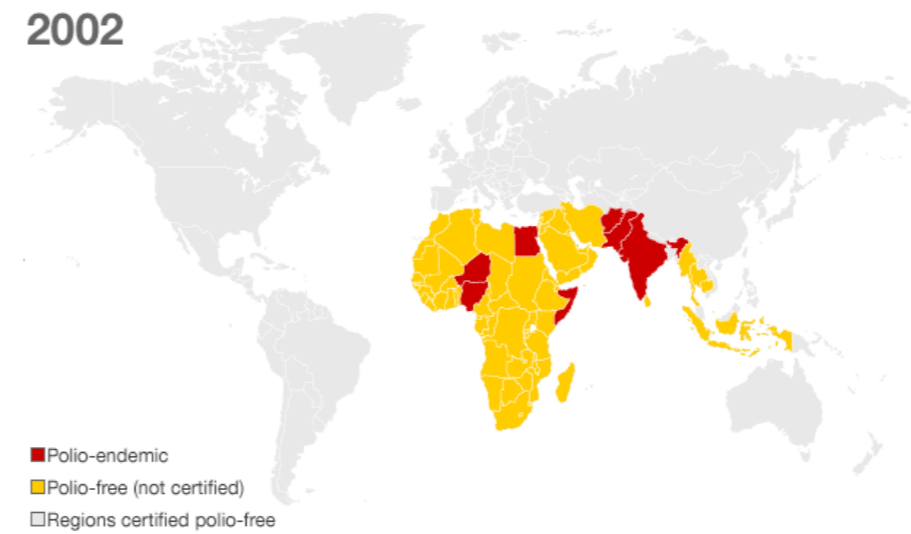
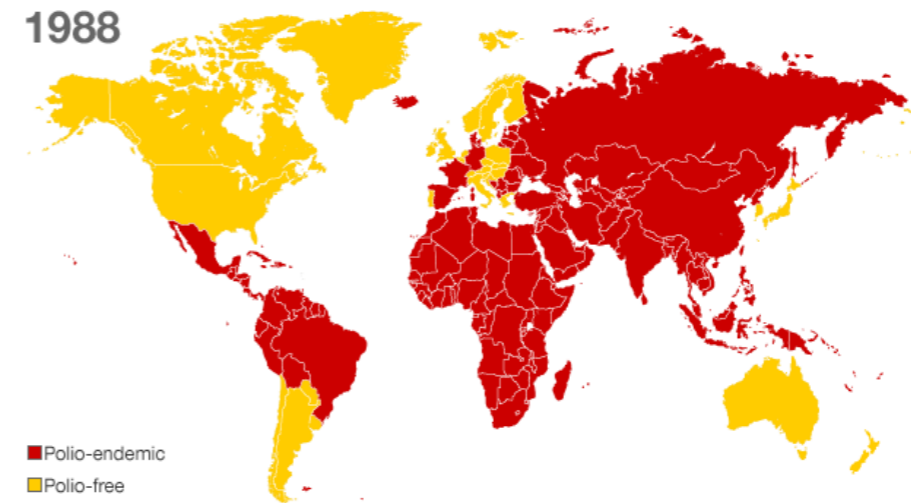
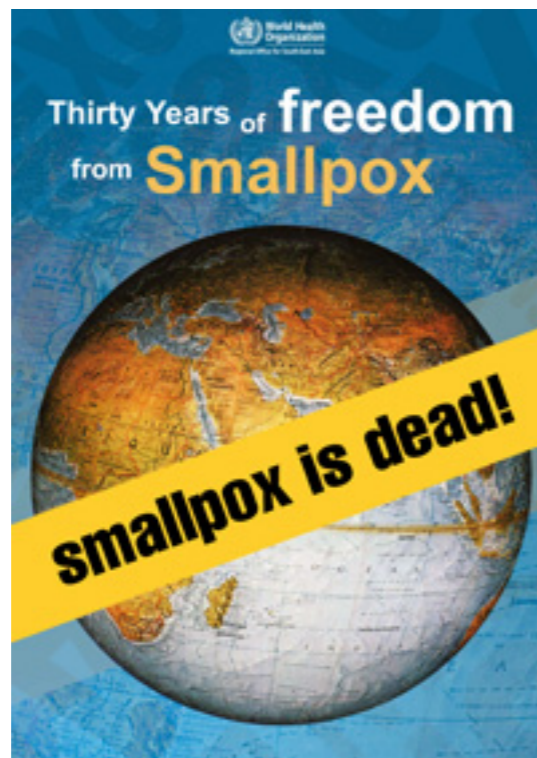
Vaccine policies: a success story



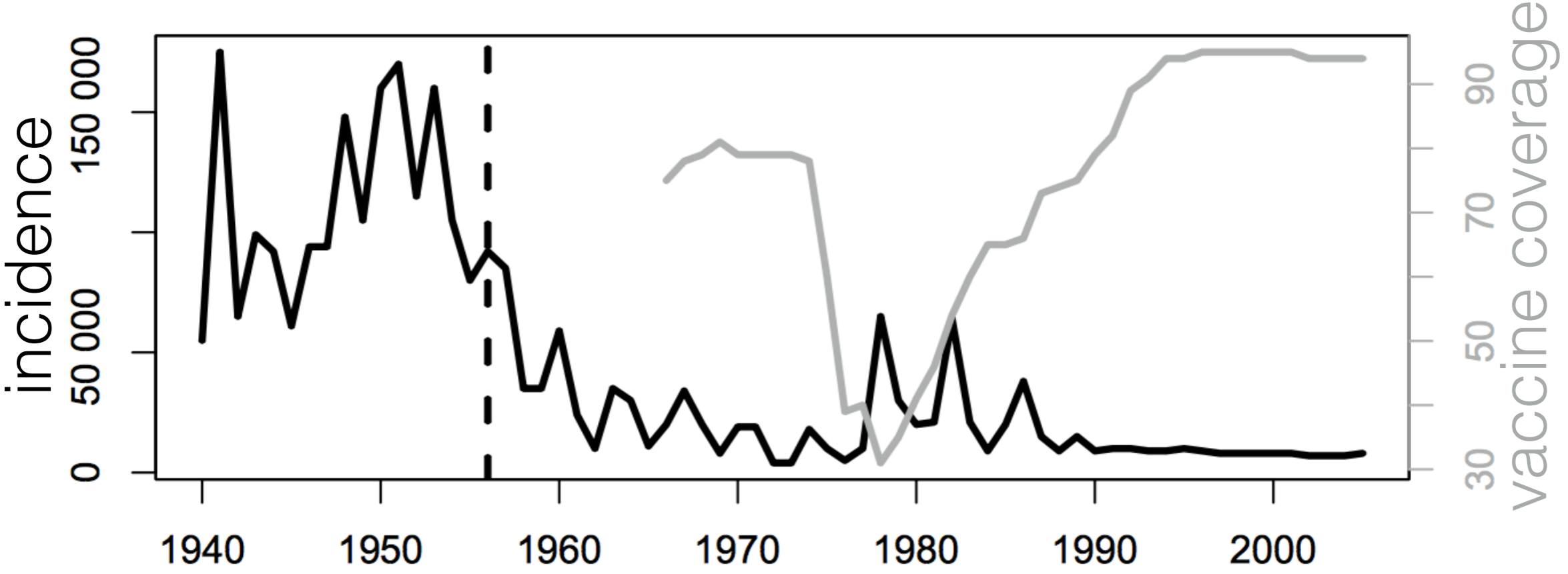
Vaccine policies: a success story



World Health
Organization



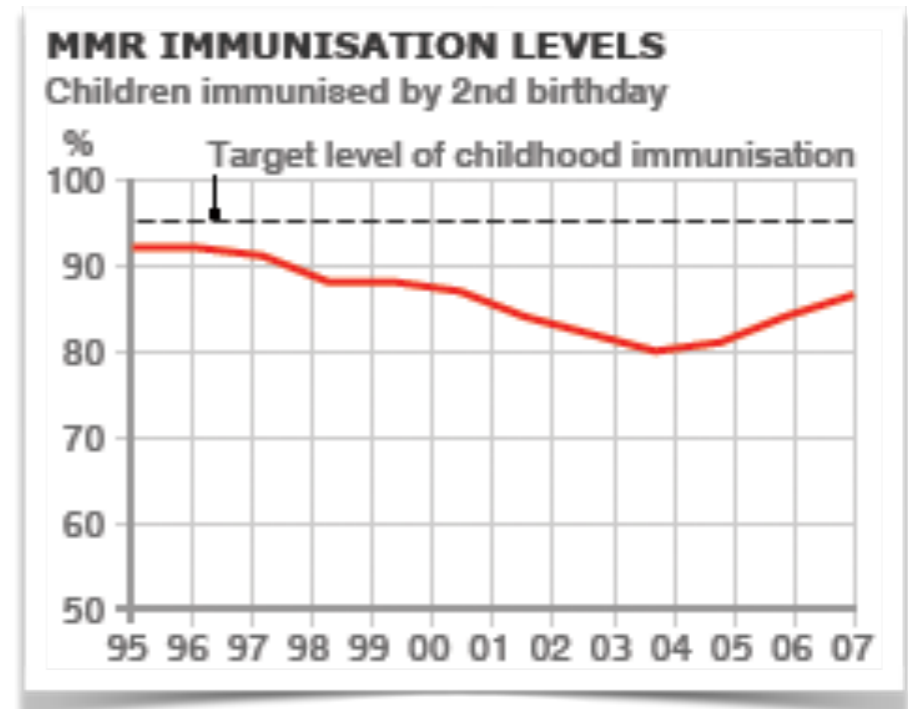
But...



But...

THE LANCET

The Lancet, [Volume 351, Issue 9103](#), Pages 637 - 641, 28 February 1998
doi:10.1016/S0140-6736(97)11096-0



This article was retracted

RETRACTED: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

Dr [AJ Wakefield](#) FRCS ^a, [SH Murch](#) MB ^b, [A Anthony](#) MB ^a, [J Linnell](#) PhD ^a, [DM Casson](#) MRCP ^b, [M Malik](#) MRCP ^b, [M Berelowitz](#) FRCPsych ^c, [AP Dhillon](#) MRCPath ^a, [MA Thomson](#) FRCP ^b, [P Harvey](#) FRCP ^d, [A Valentine](#) FRCP ^e, [SE Davies](#) MRCPath ^a, [JA Walker-Smith](#) FRCP ^a

Summary

Background

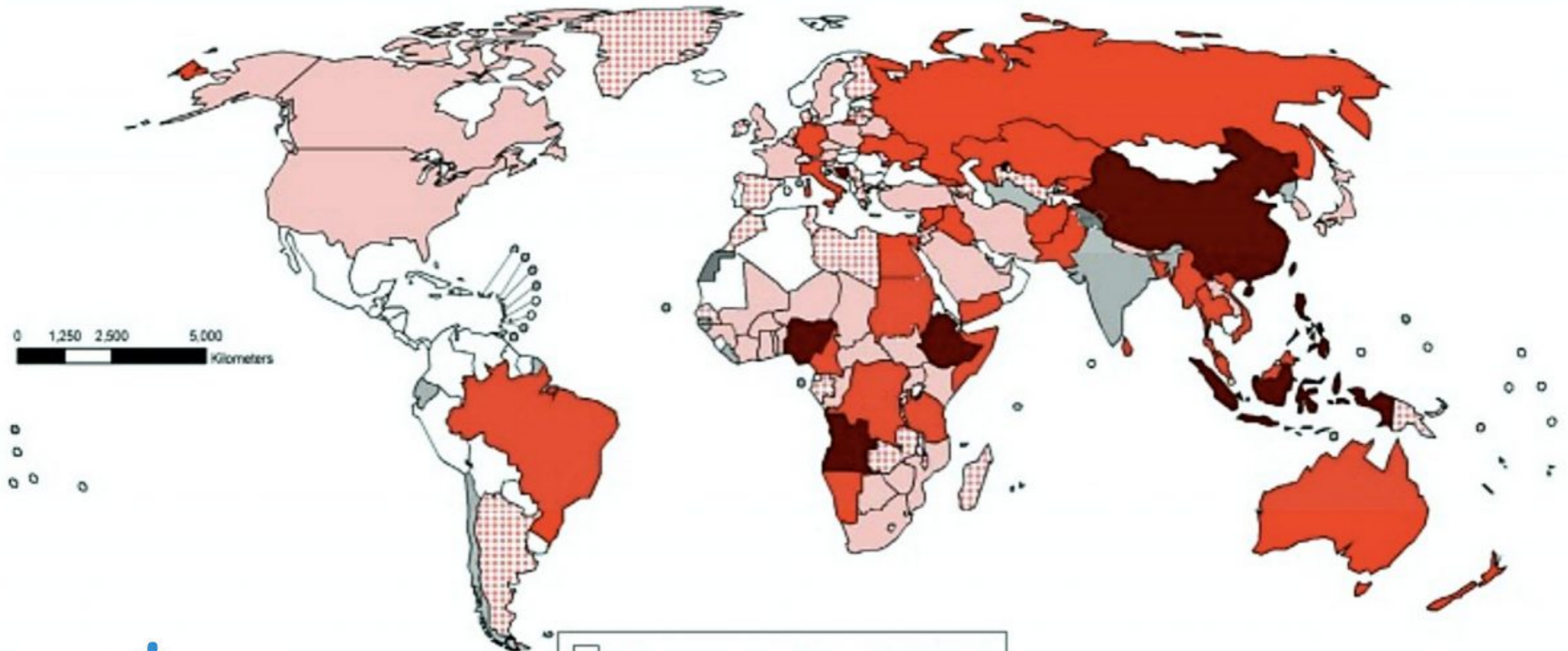
We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

Methods

12 children (mean age 6 years [range 3–10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic-resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined.

RETRACTED

But...



□	0	(64 countries or 33%)
▤	1 - 9	(33 countries or 17%)
■	10 - 99	(42 countries or 22%)
■	100 - 999	(28 countries or 15%)
■	≥1000	(7 countries or 4%)
■	No data reported to WHO HQ	(20 countries or 10%)
■	Not applicable	



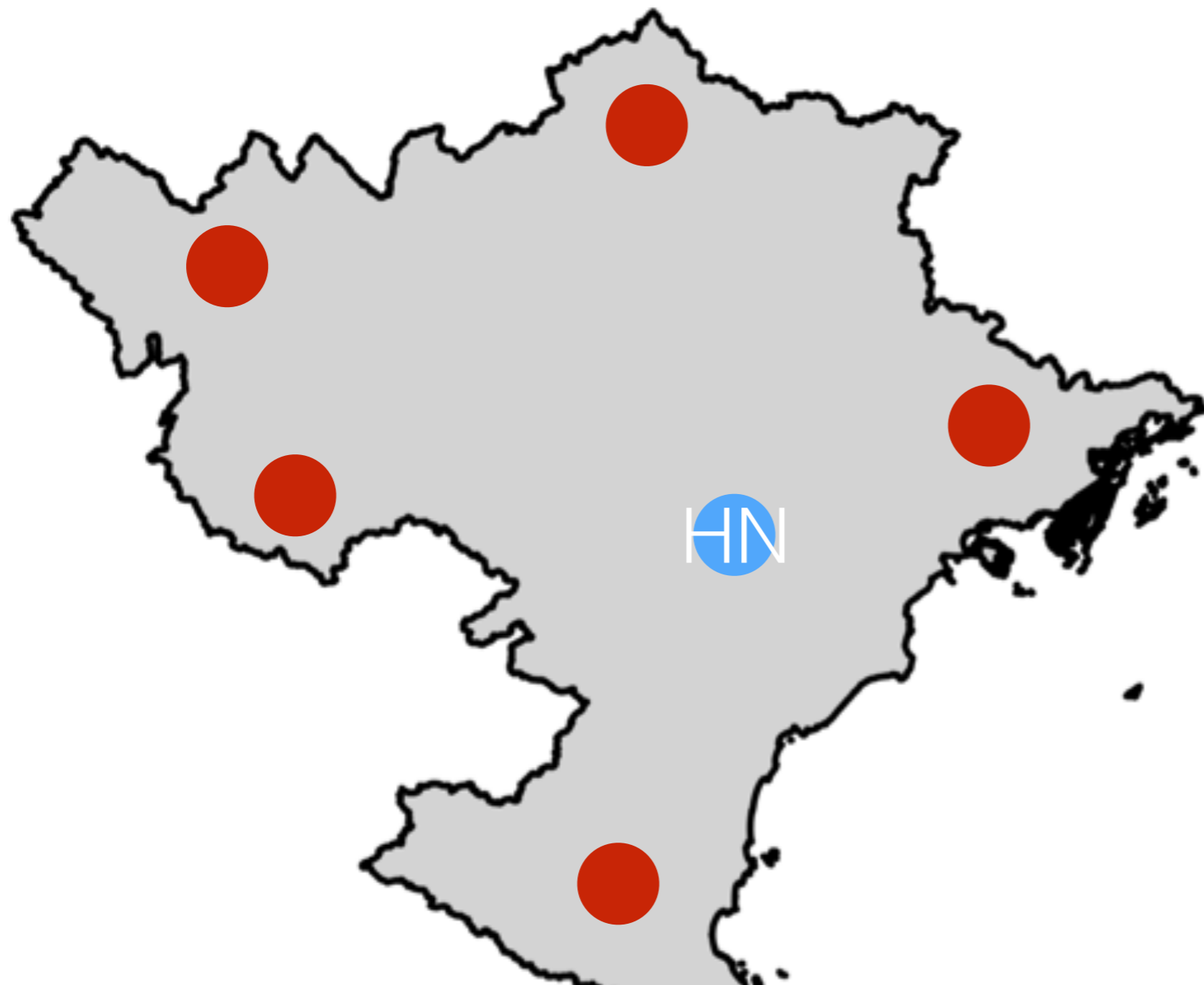
**World Health
Organization**

Consequences of vaccination

Consequences of vaccination

- decreases incidence
- increases age at infection
- may alter severity
- alters periodicity
- decreases spatial synchrony
- decreases maternal protection
- may increase virulence
- etc...

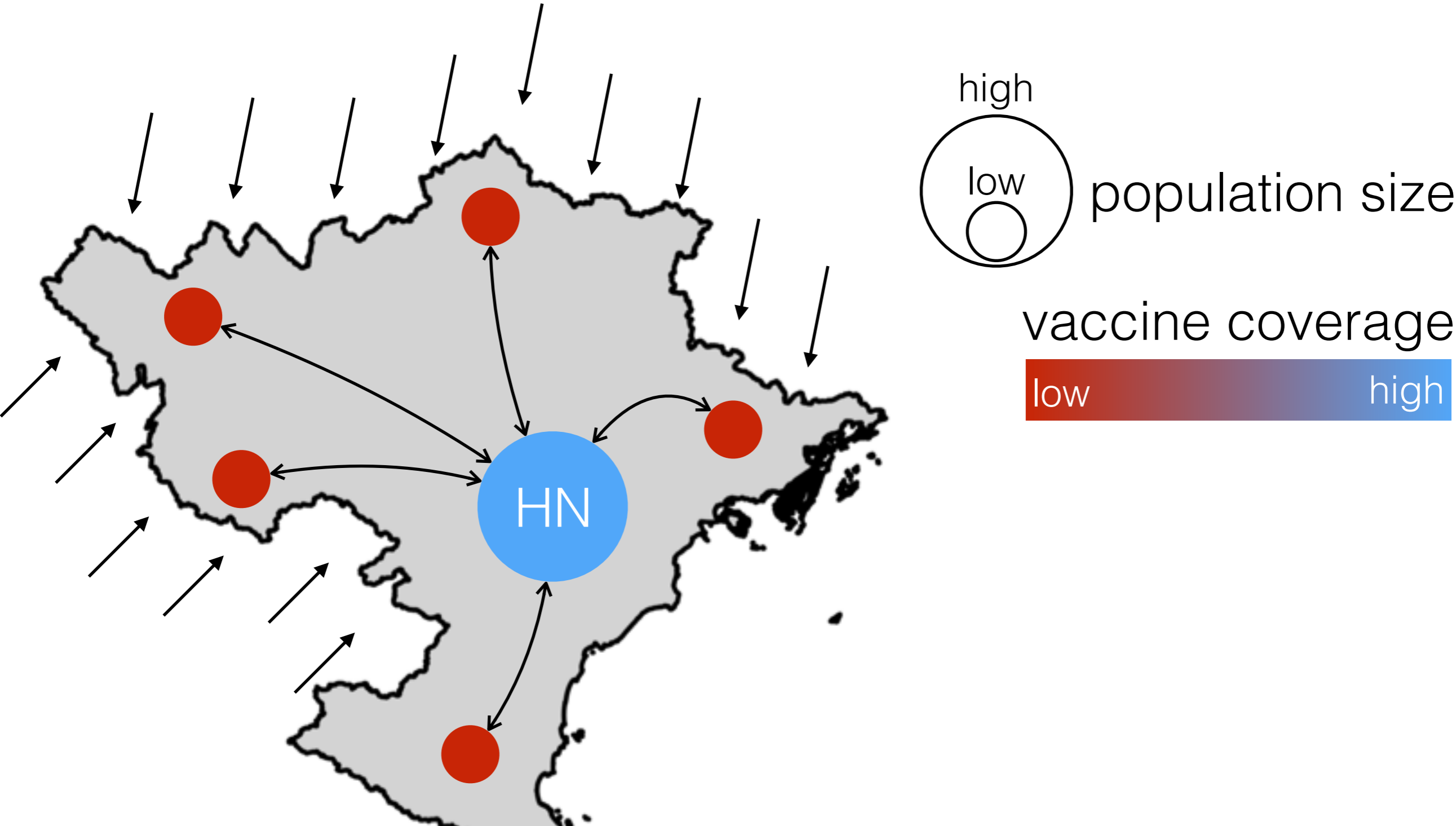
Measles in northern Vietnam



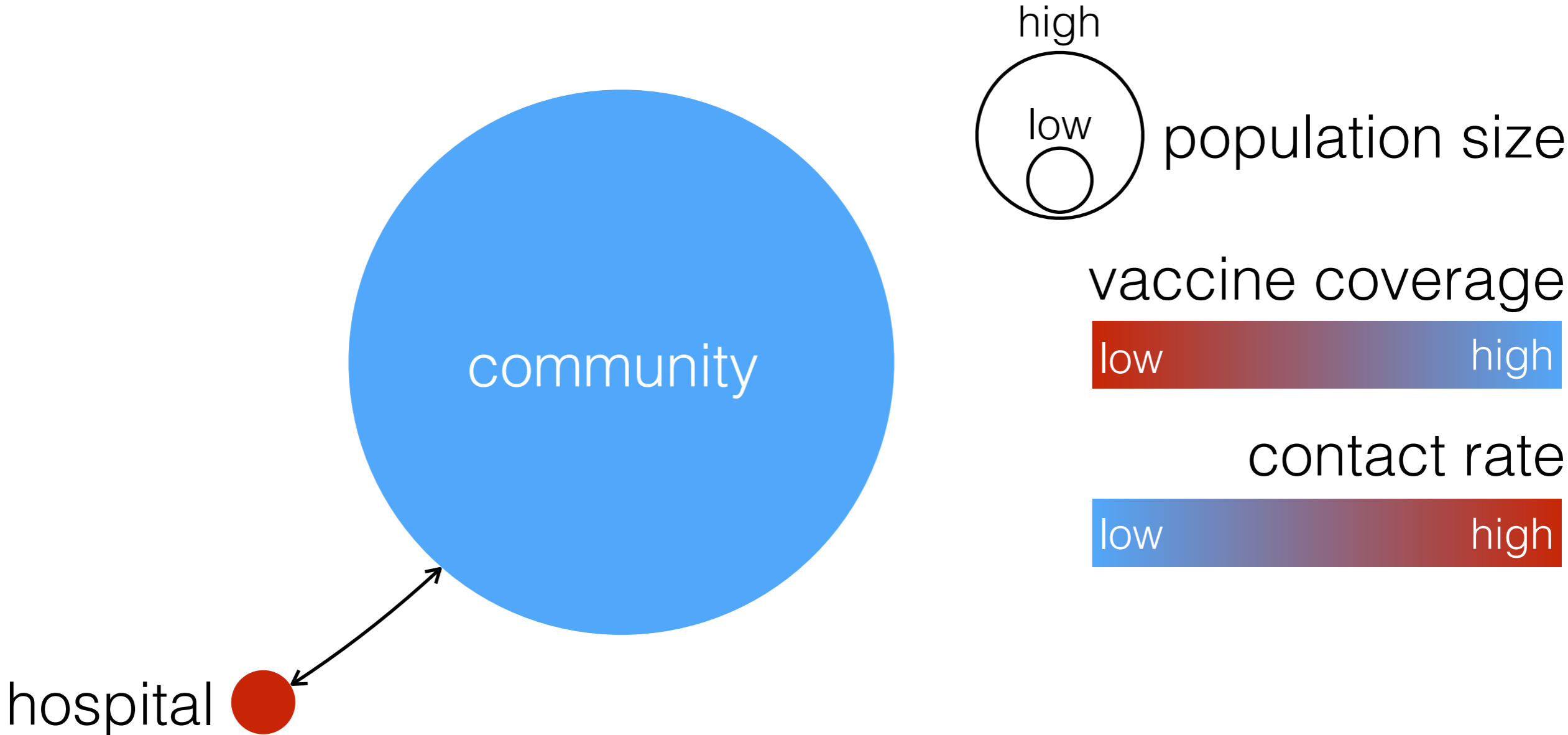
vaccine coverage

low high

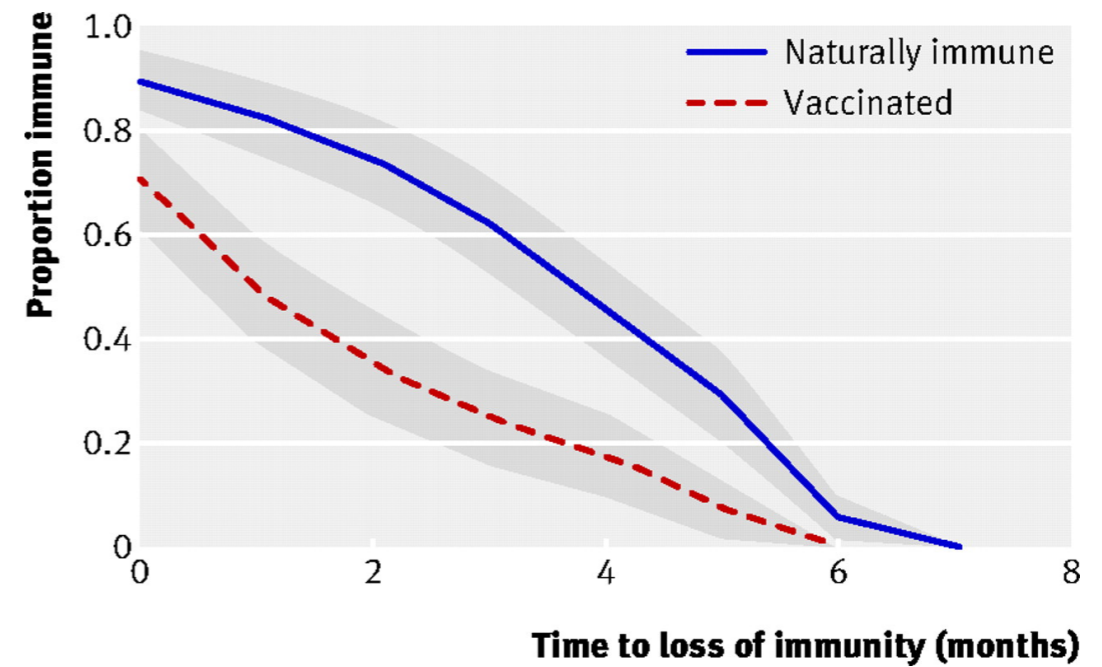
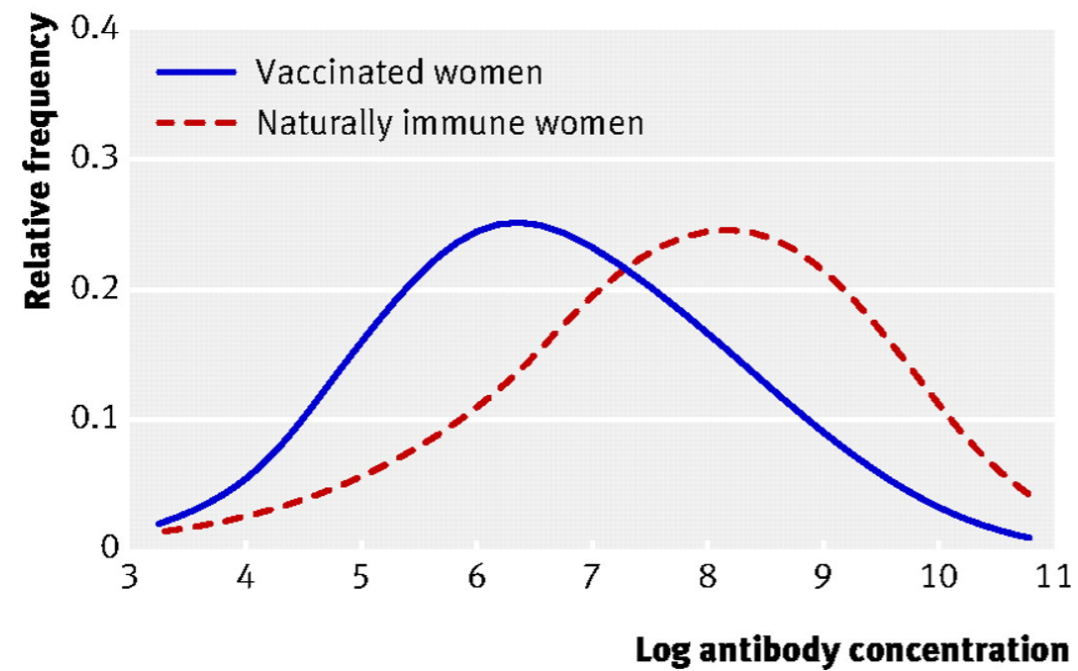
Measles in northern Vietnam

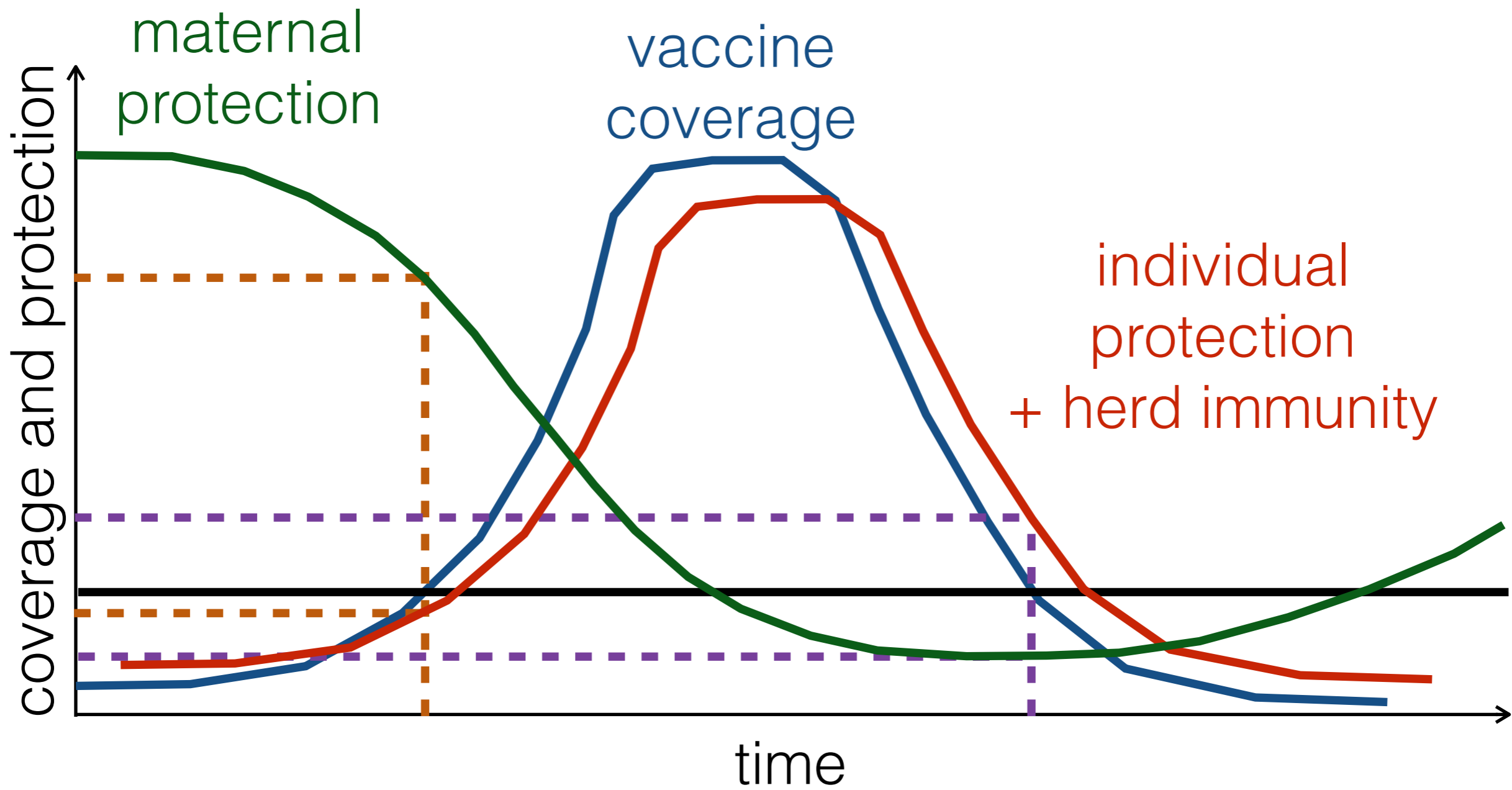


Measles in northern Vietnam



Maternal protection





Conclusions

Conclusions

Disease eradication is difficult

Many constraints to weight

Complex dynamics with emerging properties and interactions

Many consequences of vaccination

Models help understanding and decision making

Models help understanding and decision making

(sero-)surveillance data

Thank you