Challenges in the theory of infectious diseases

Montreal2013Extra

www.noveltp.com

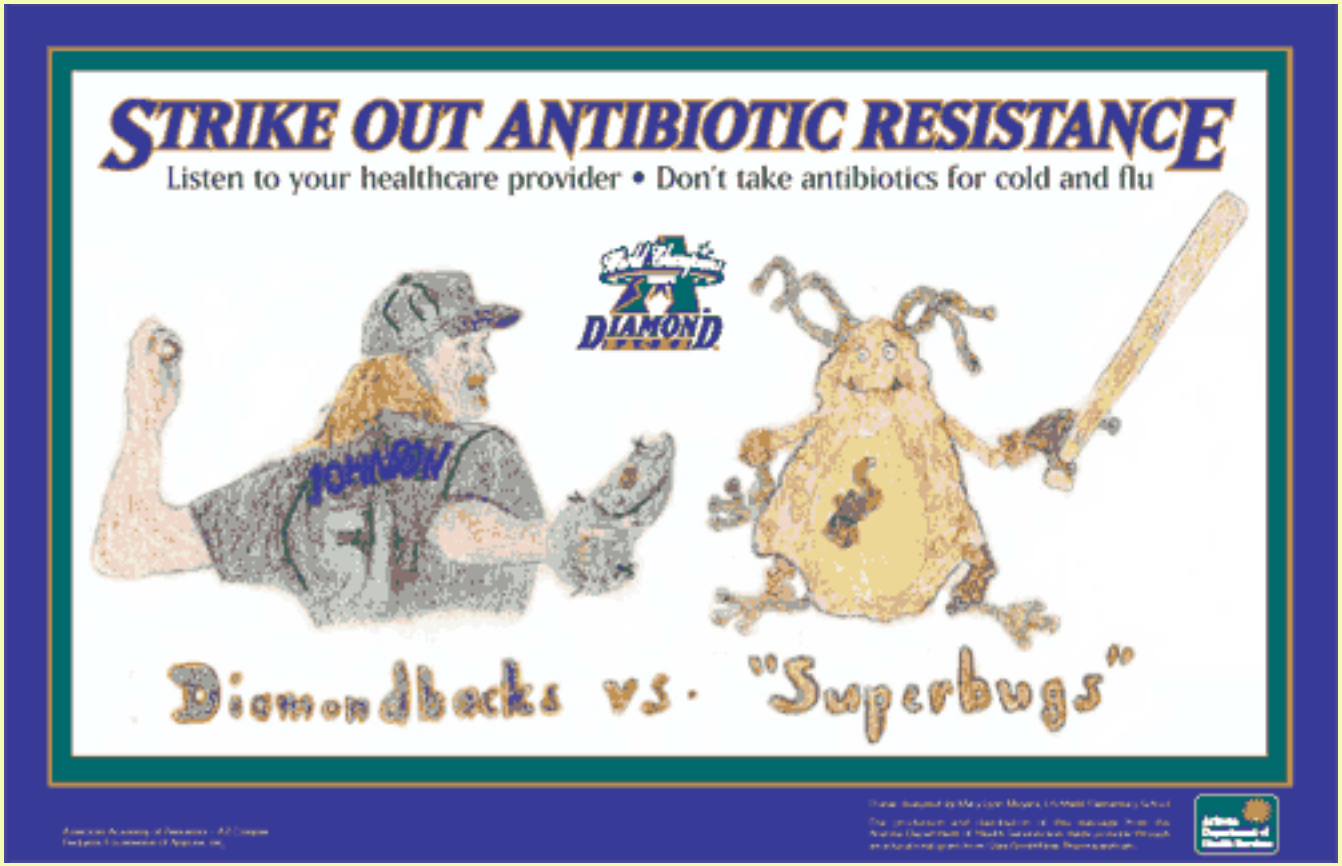
The theory of infectious diseases has a rich history

Sir Ronald Ross
1857-1932

Despite a century of elegant theory, new diseases emerge, old reemerge

http://edie.cprost.sfu.ca/gcnet

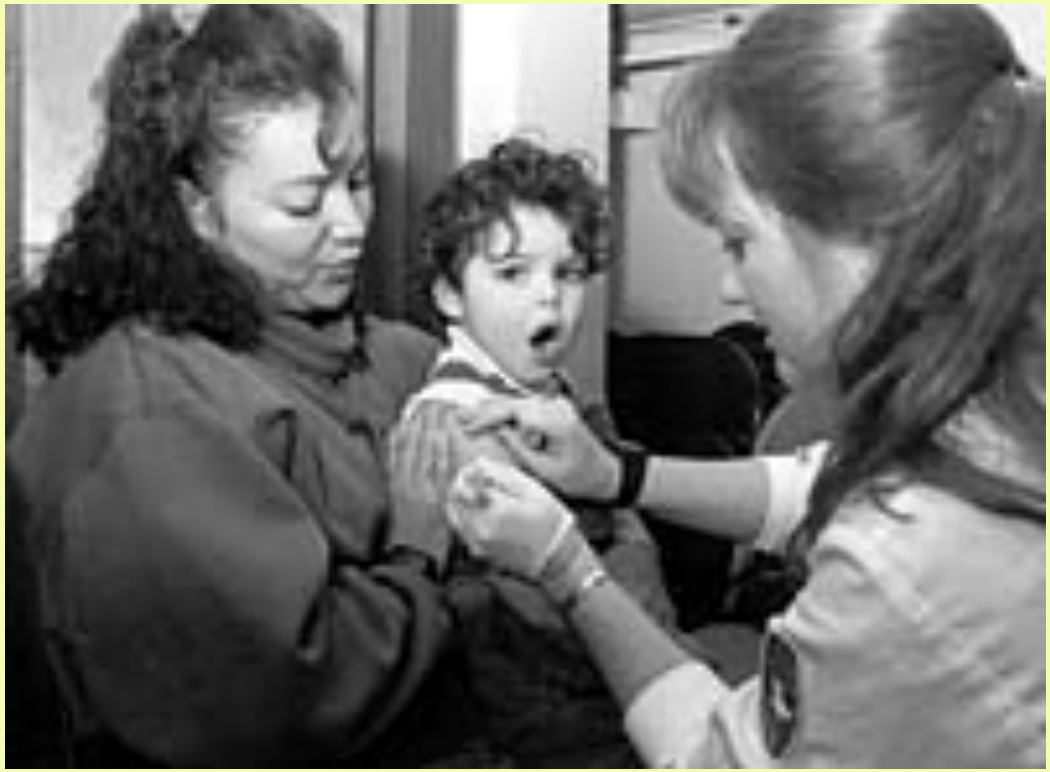
Antibiotic resistance threatens the effectiveness of our most potent weapons against bacterial infections



Significant theoretical challenges remain

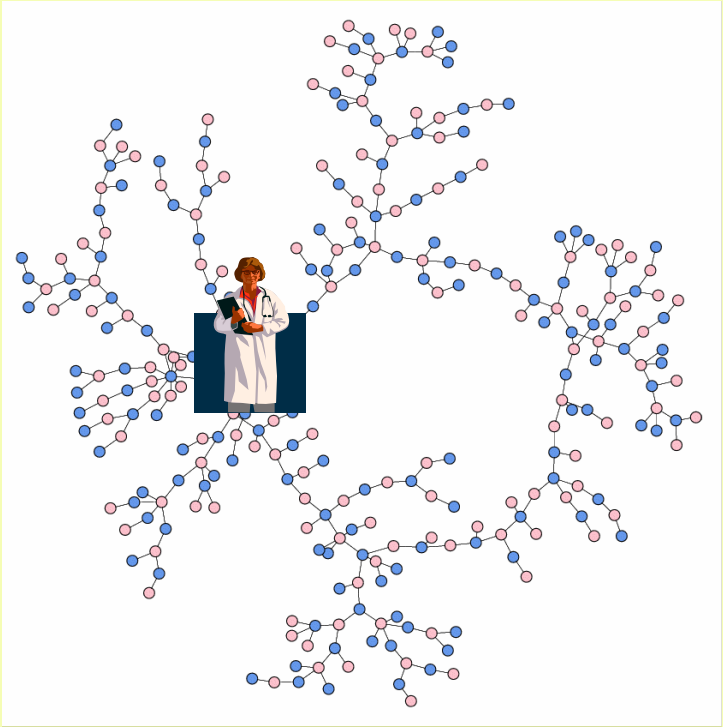
Whom should we vaccinate?

- Those at greatest risk?



Whom should we vaccinate?

- Or those who pose greatest risk to others?

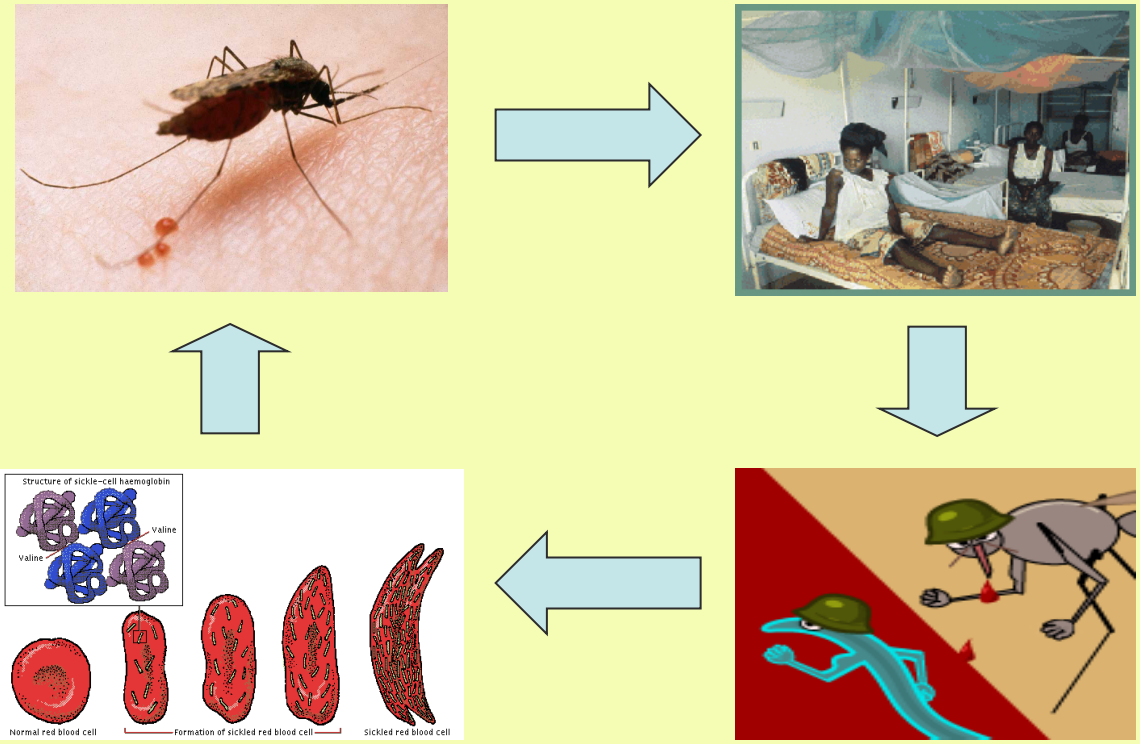


Prediction is difficult

- Disease systems are complex, characterized by nonlinearities and sudden flips

image.guardian.co.uk/

- They also are **complex adaptive systems**, integrating phenomena at multiple scales



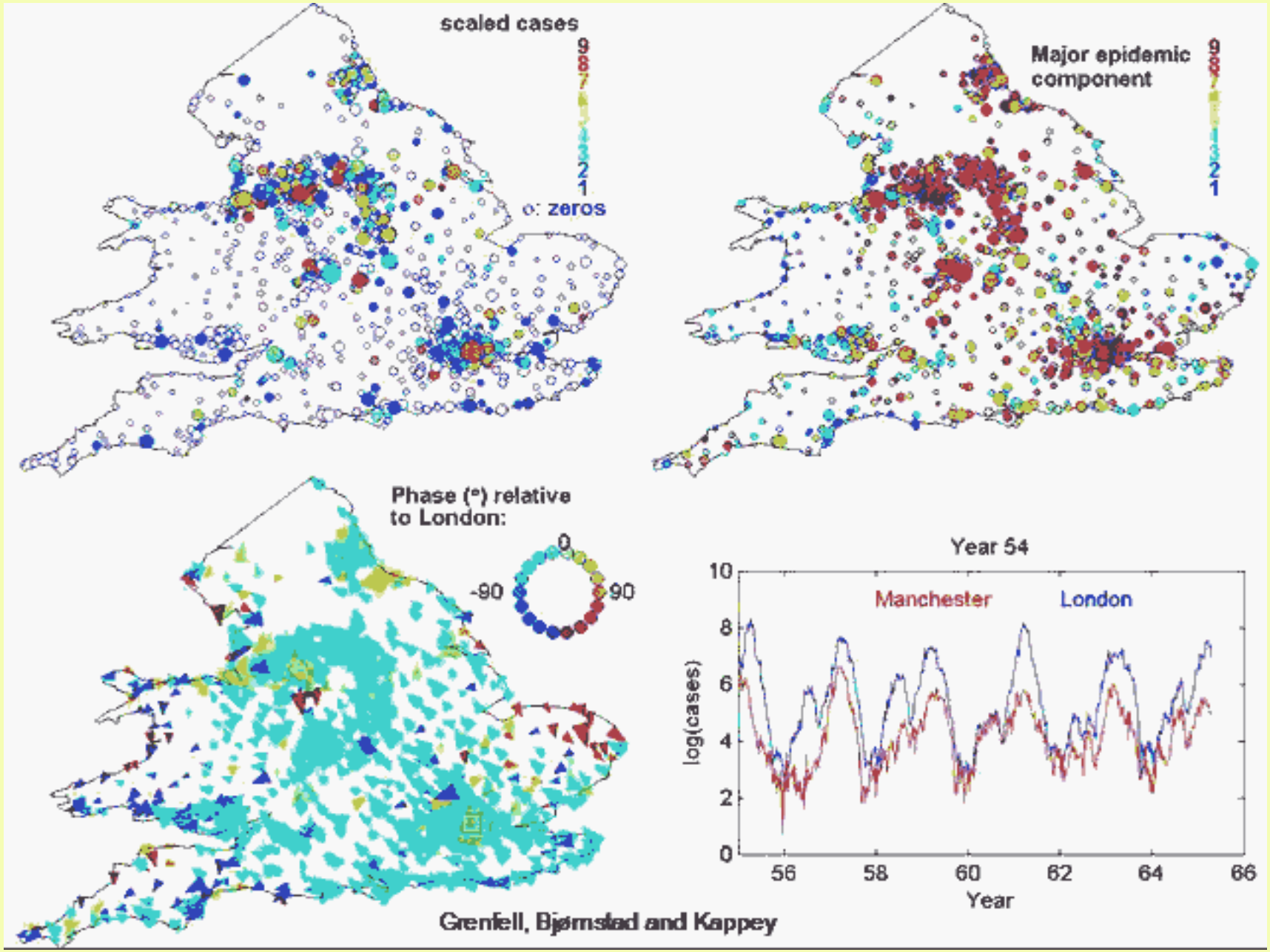
lshtm.ac.uk
encarta.msn.com

www.who.int
www.nobel.org

Recurrent Diseases

are of particular interest

Many important diseases exhibit oscillations on multiple temporal and spatial scales

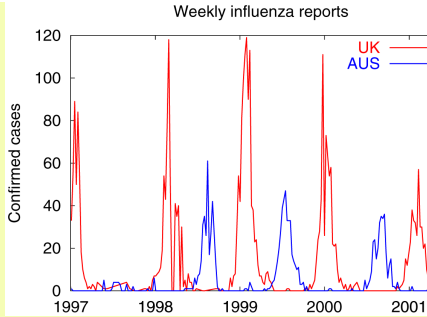

scaled cases
9
8
7
2
1
o: zeros
Major epidemic component
9
8
7
2
1
Phase (°) relative to London:
0
-90
90
Year 54
Manchester
London
log(cases)
10
8
6
4
2
0
56
58
60
62
64
66
Year
Grenfell, Bjørnstad and Kappey

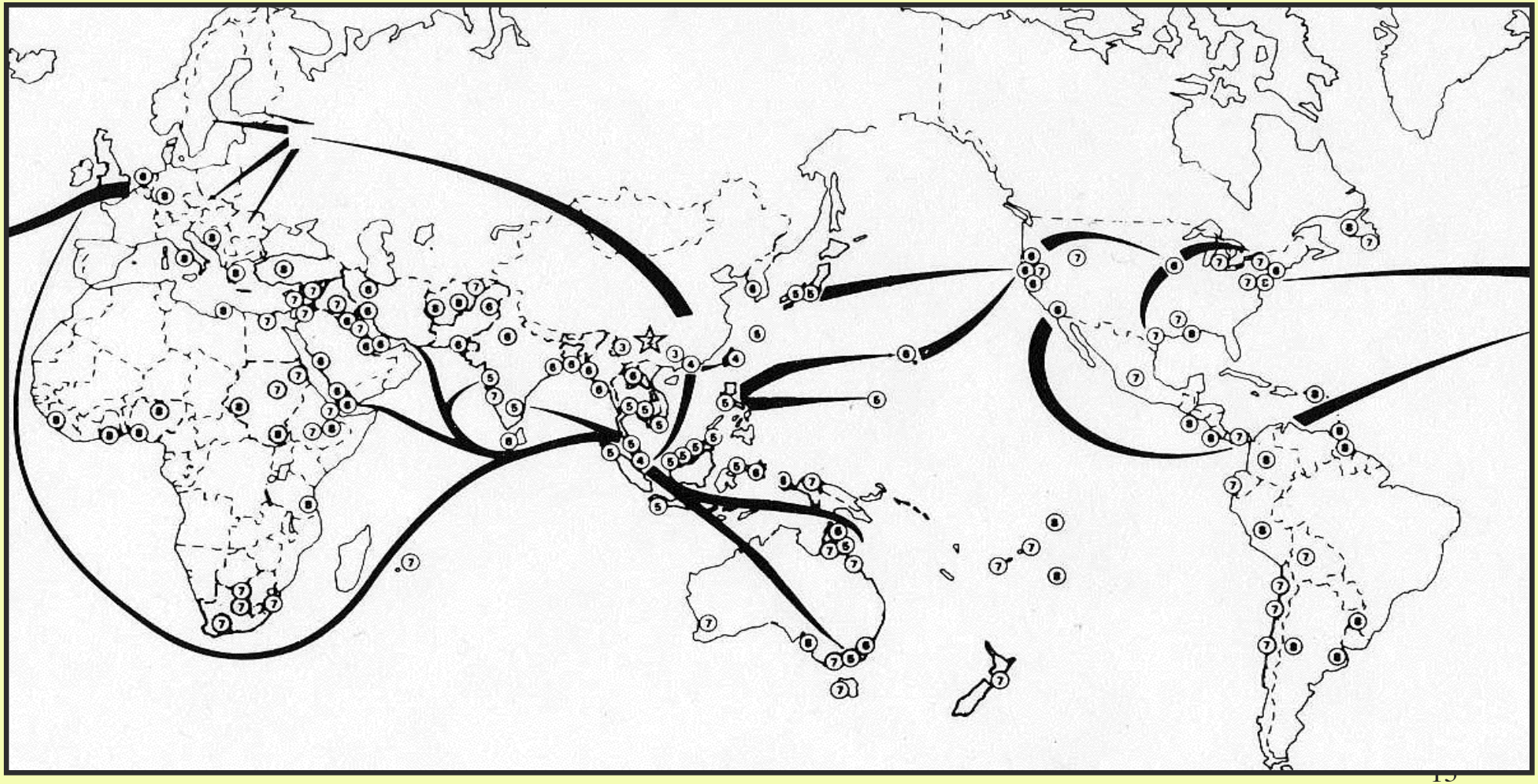
Rabies in Switzerland

Geographic Base Data:
Swiss Federal Office for Statistics GEOSTAT
Swiss Federal Office for Topography L+T

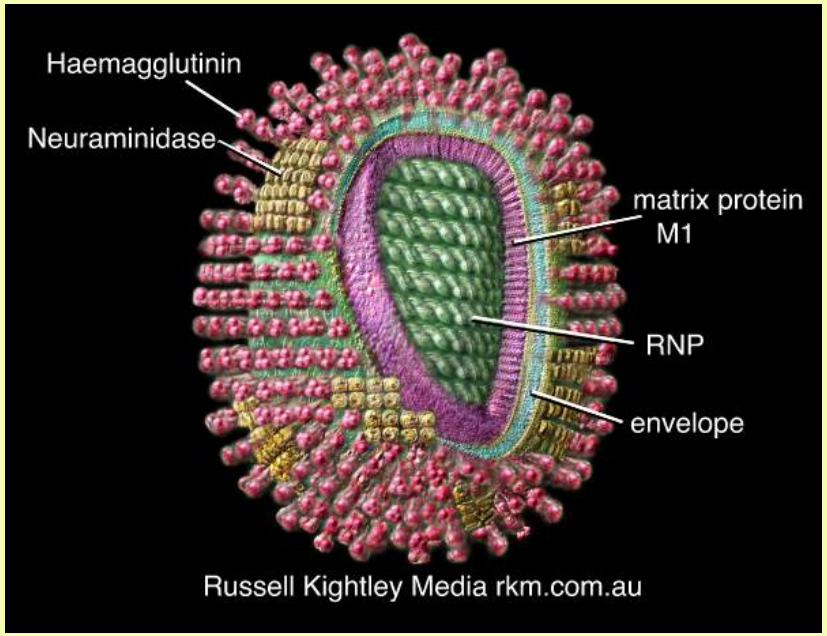
Swiss Rabies Centre
Laenggassstr. 122
CH-3012 Bern

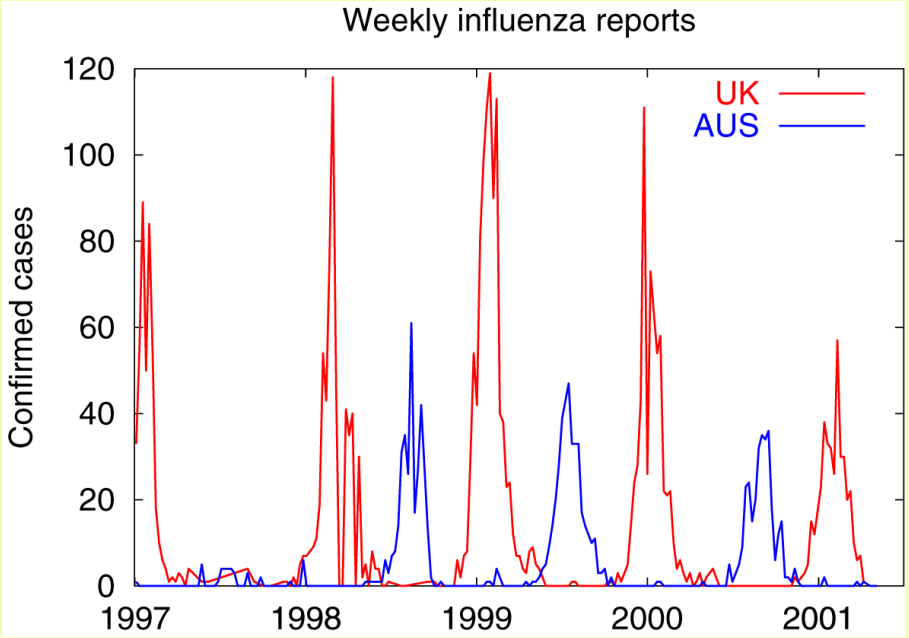
Influenza global spread

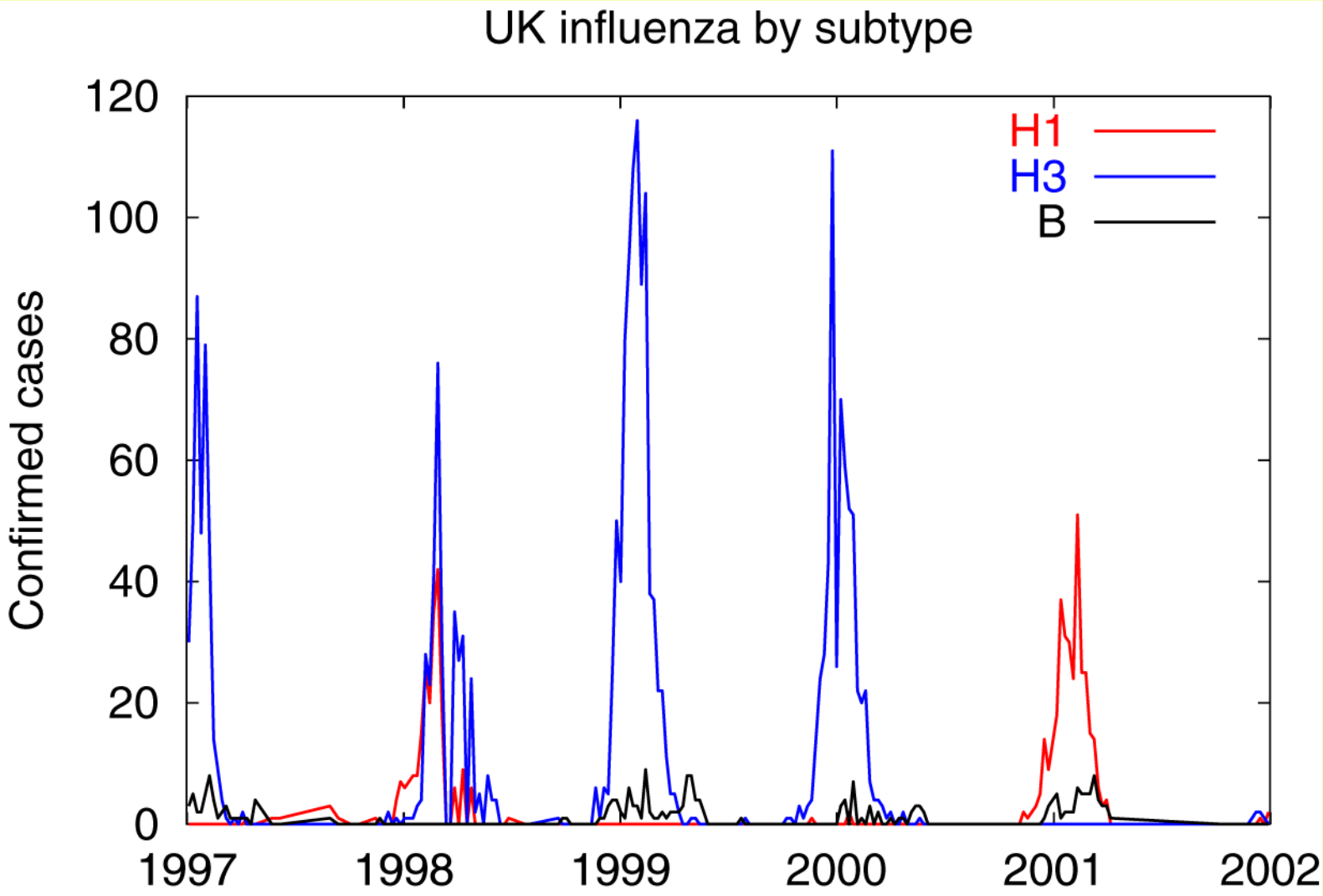




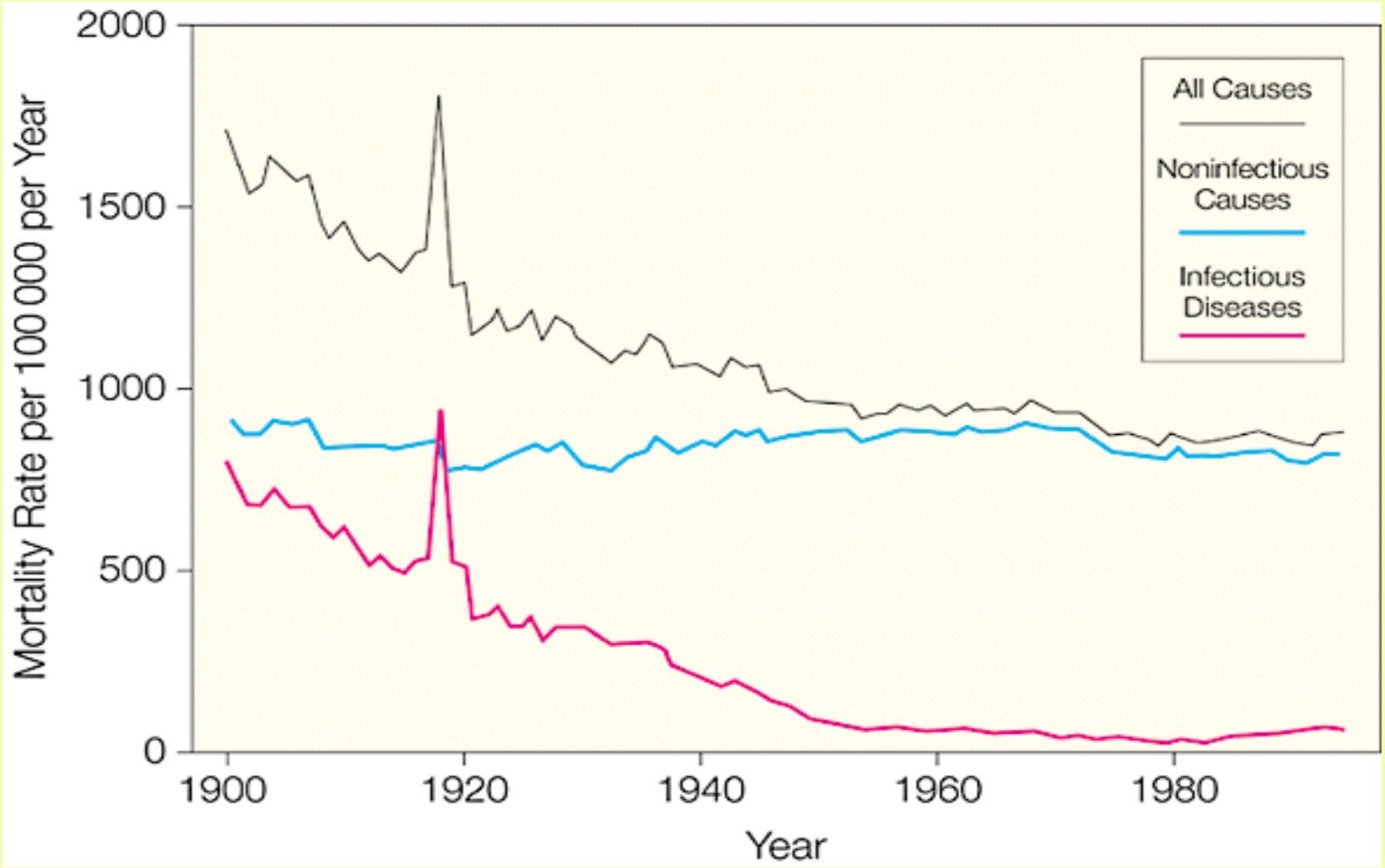
Influenza A reemerges year after year, despite the fact that infection leads to lifetime immunity to a strain





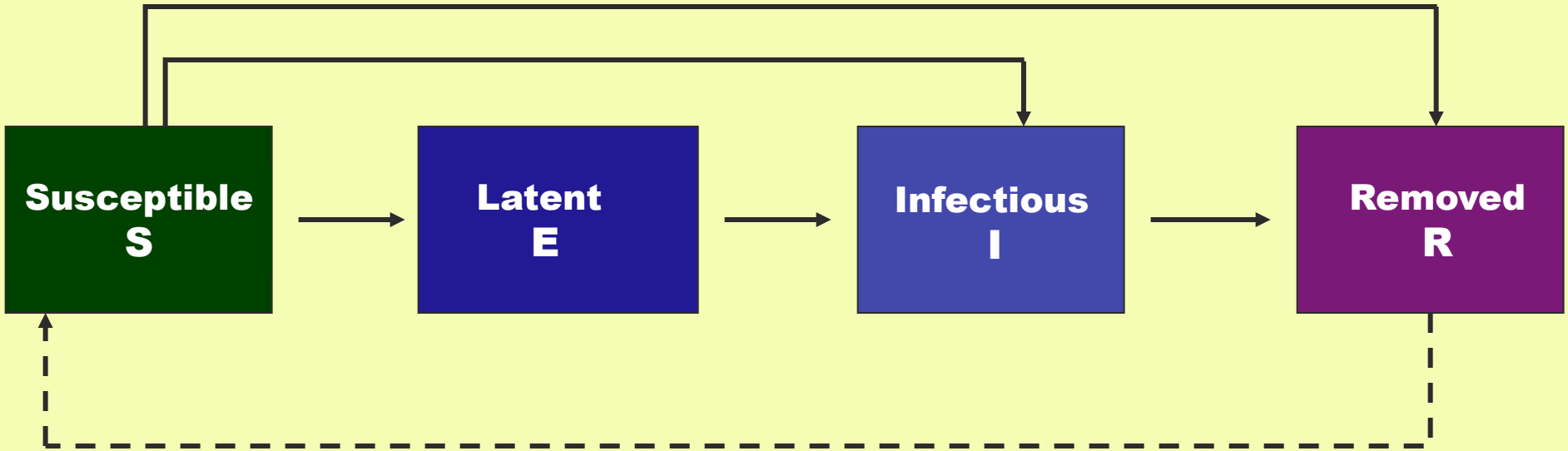

UK influenza by subtype
Confirmed cases
120
100
80
60
40
20
0
1997
1998
1999
2000
2001
2002
H1
H3
B

U.S. mortality in the 20th century

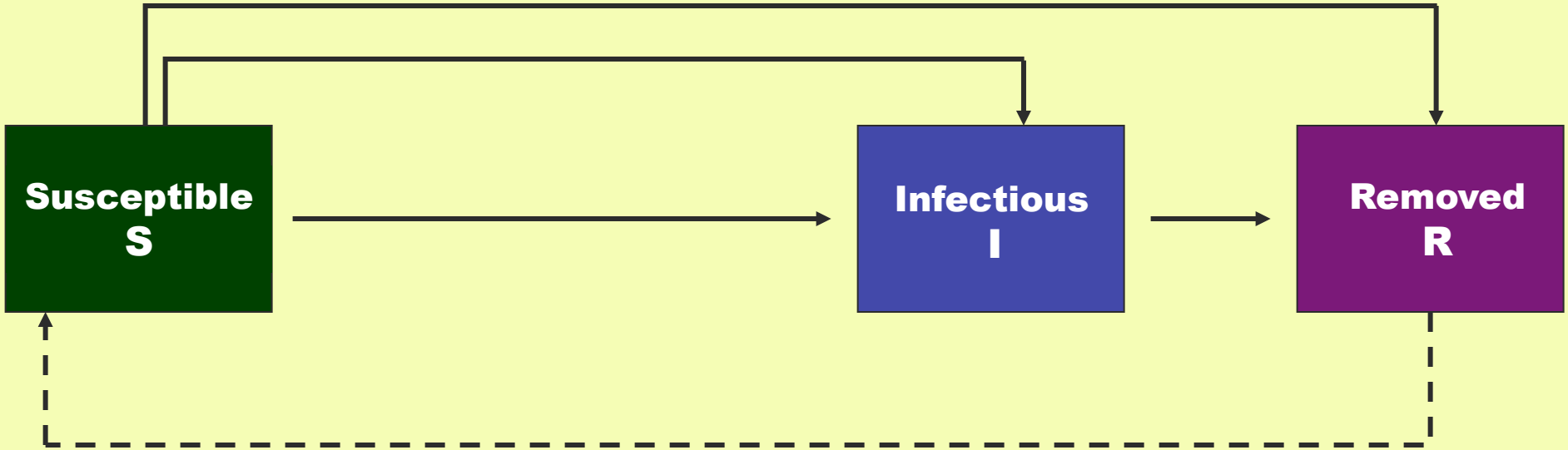


- Classical theory and oscillation

EPIDEMICS—Classical Theory (Kermack - McKendrick)



Simplest SIR Model
(No latency)



Simplest model

No births or deaths

$$\frac{dS}{dt} = -\beta SI$$

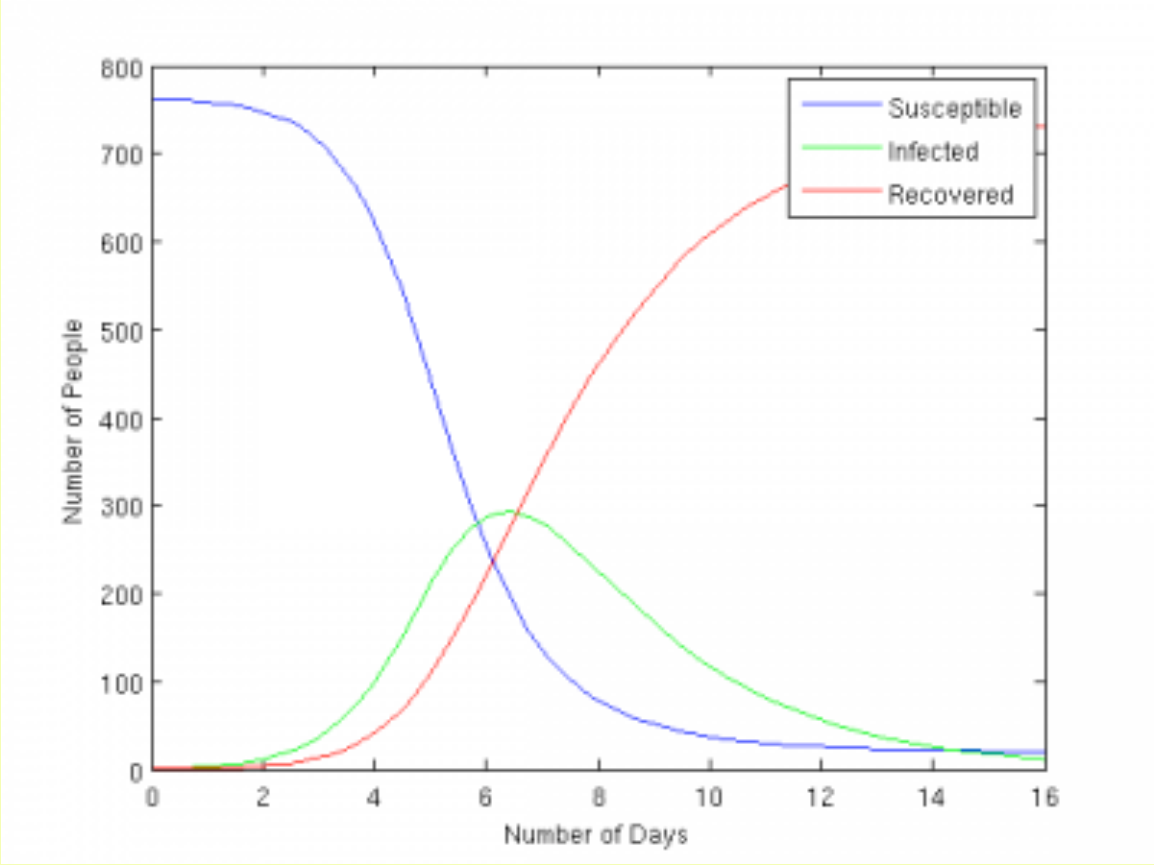
$$\frac{dI}{dt} = \beta SI - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

$$\frac{dS}{dt} = -\beta SI$$

$$\frac{dI}{dt} = \beta SI - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$



http://mathbio.colorado.edu/mediawiki/index.php/Image:Sir.png

$$\frac{dS}{dt} = -\beta SI$$

$$\frac{dI}{dt} = \beta SI - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

Solve for S in terms of I

$$\frac{dI}{dS} = -1 + \gamma / \beta S$$

$$\frac{dI}{dS} = -1 + \gamma / \beta S$$

Solve for I in terms of S

$$I = -S + (\gamma / \beta) \ln S$$

$$\frac{dI}{dS} = -1 + \gamma / \beta S$$

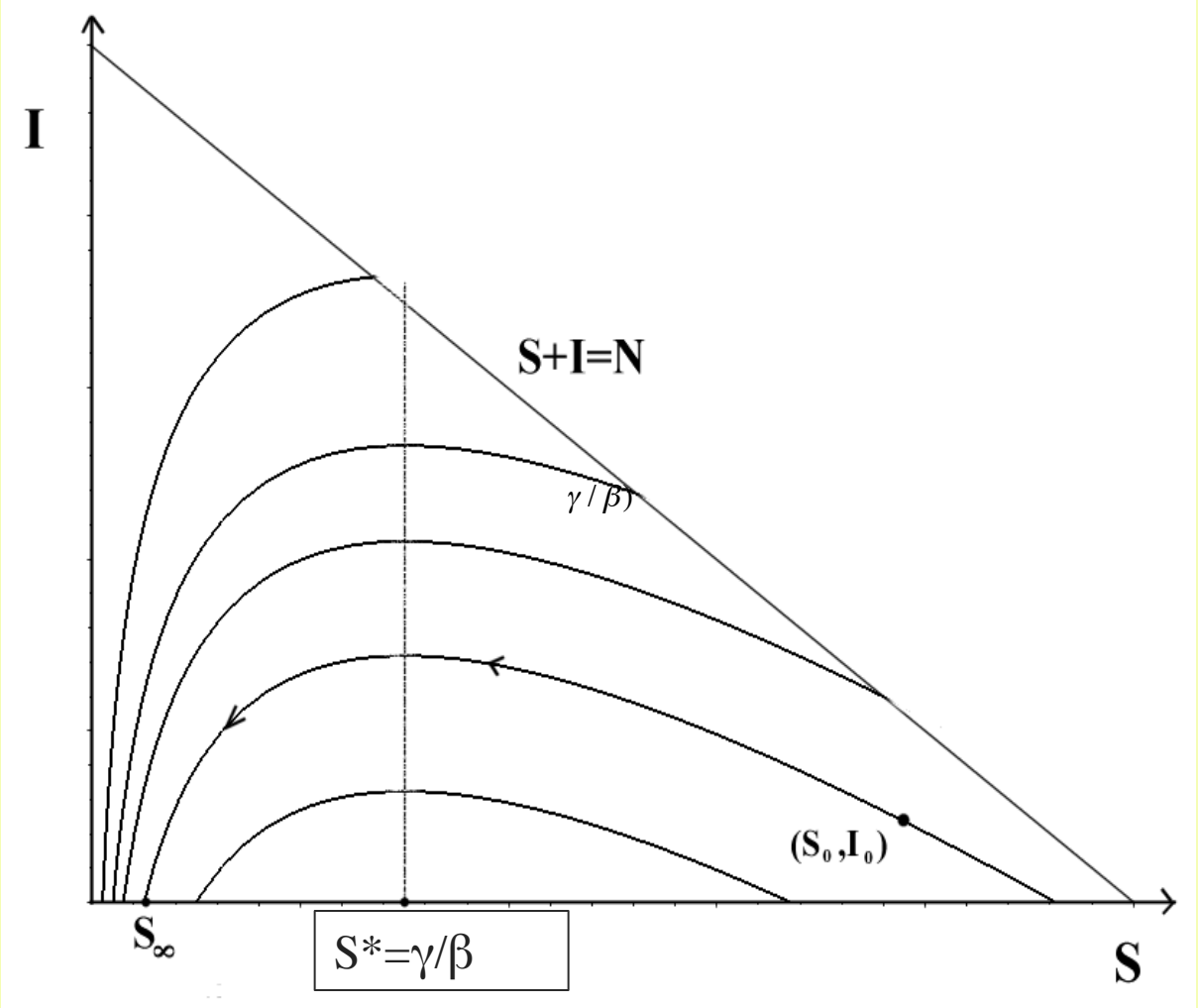
Solve for S in terms of I

$$I = -S + (\gamma / \beta) \ln S$$

or

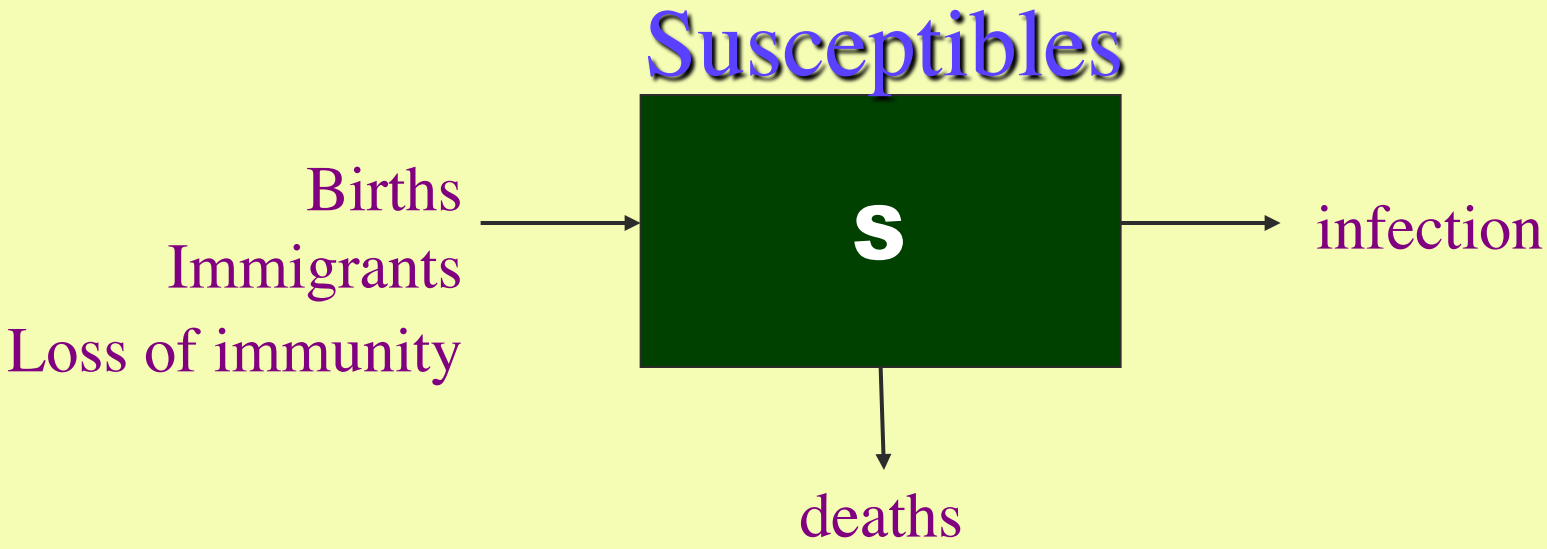
$$S + I - (\gamma / \beta) \ln S = \text{constant}$$

$$S + I - (\gamma / \beta)\ln S = \text{constant}$$



Modified from notes
The Mathematical Modeling of Epidemics by Mimmo Ianneli 2005

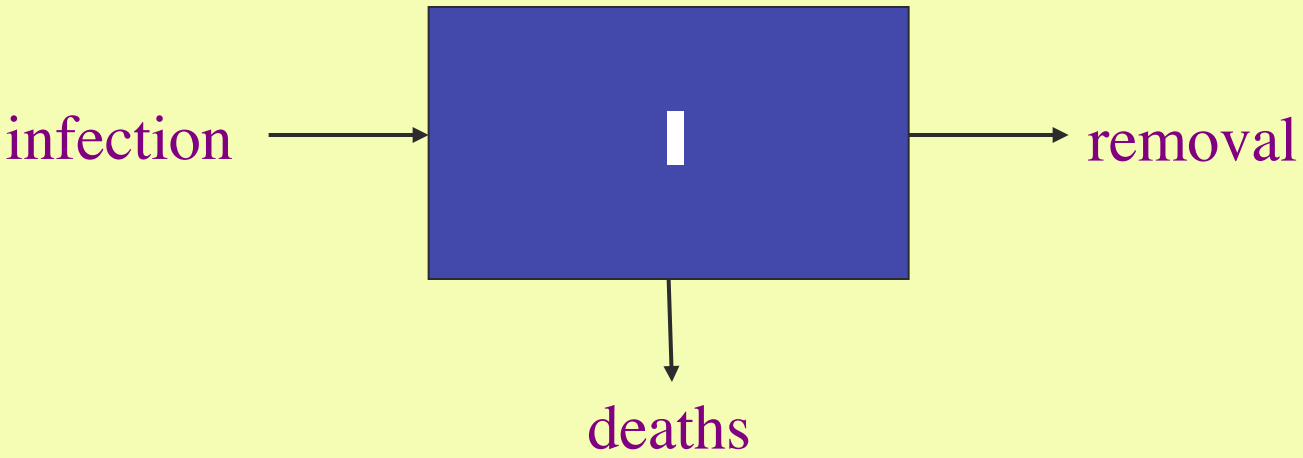
Add demography



e.g. $$\frac{dS}{dt} = (a + bN) - \beta SI - \mu S + \omega R$$

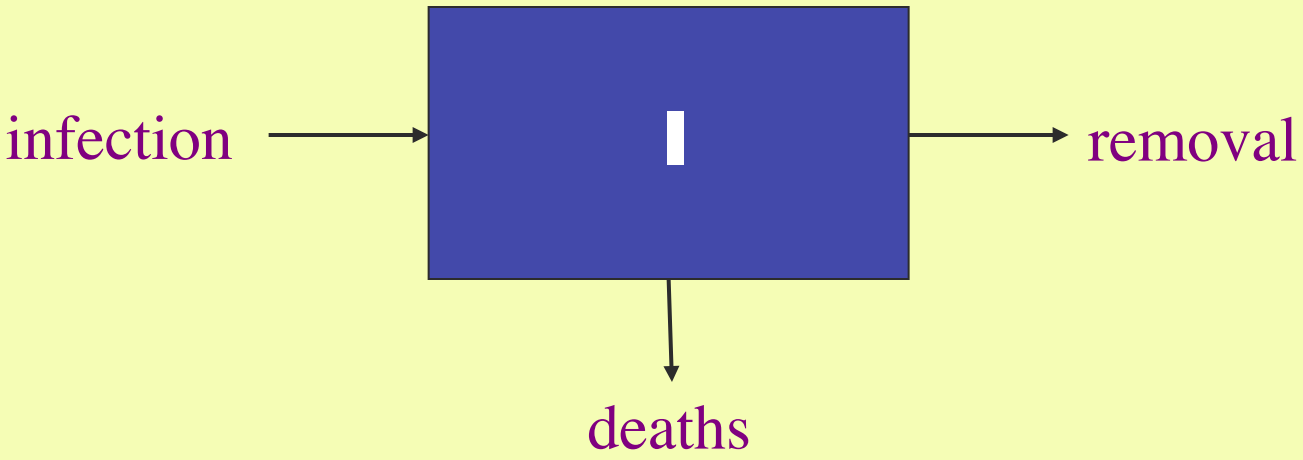
where N is total population size

Infectives



e.g. $$\frac{dI}{dt} = \beta SI - \mu I - \gamma I$$

Infectives



e.g. $$\frac{dI}{dt} = \beta SI - \mu I - \gamma I$$

$$\frac{dI}{dt} = \beta SI - \mu I - \gamma I$$

Threshold for outbreak or endemic

$$\beta SI - \mu I - \gamma I > 0;$$

that is,

$$R_s = \frac{\beta S}{\mu + \gamma} > 1$$

Define

$$R_0 = R_N.$$

$$R_s = \frac{\beta S}{\mu + \gamma} > 1$$

Condition for spread in a naïve population

$$R_0 = \underbrace{\beta N}_{\text{Secondary infections time}} \cdot \underbrace{\frac{1}{\mu + \gamma}}_{\text{Average infectious period}} > 1$$

Thus R_0 is the #secondary/primary infection.

$$R_s = \frac{\beta S}{\mu + \gamma} > 1$$

Control strategies focus on *R*

1. Reduce β (e.g., condoms, isolation)
2. Reduce *S* (e.g., vaccination)
3. Increase γ (e.g., curing, quarantine)
4. Increase μ (culling)

Obviously not ethical for human populations!!

Interpretation if threshold is exceeded

1. With no new recruits, outbreak and collapse
2. With new births, get stable equilibrium
3. So oscillations require a more complicated model

Complications

www.lareau.org

- New immigrants
- Demography
- Heterogeneous mixing patterns
- Genetic changes
- Multiple strains/diseases
- Vectors

Lecture outline

- Classical theory and oscillation
- Recurrent diseases

Oscillations

- Stochastic factors
- Seasonal forcing (e.g., in transmission rates)
- Long periods of temporary immunity
- Other explicit delays (e.g., incubation periods)
- Age structure
- Non-constant population size
- Non-(bilinear) transmission coefficients
- Interactions with other diseases/strains

Oscillations

- Stochastic factors
- Seasonal forcing (e.g., in transmission rates)
- Long periods of temporary immunity
- Other explicit delays (e.g., incubation periods)
- Age structure
- Non-constant population size
- Non-(bilinear) transmission coefficients
- Interactions with other diseases/strains

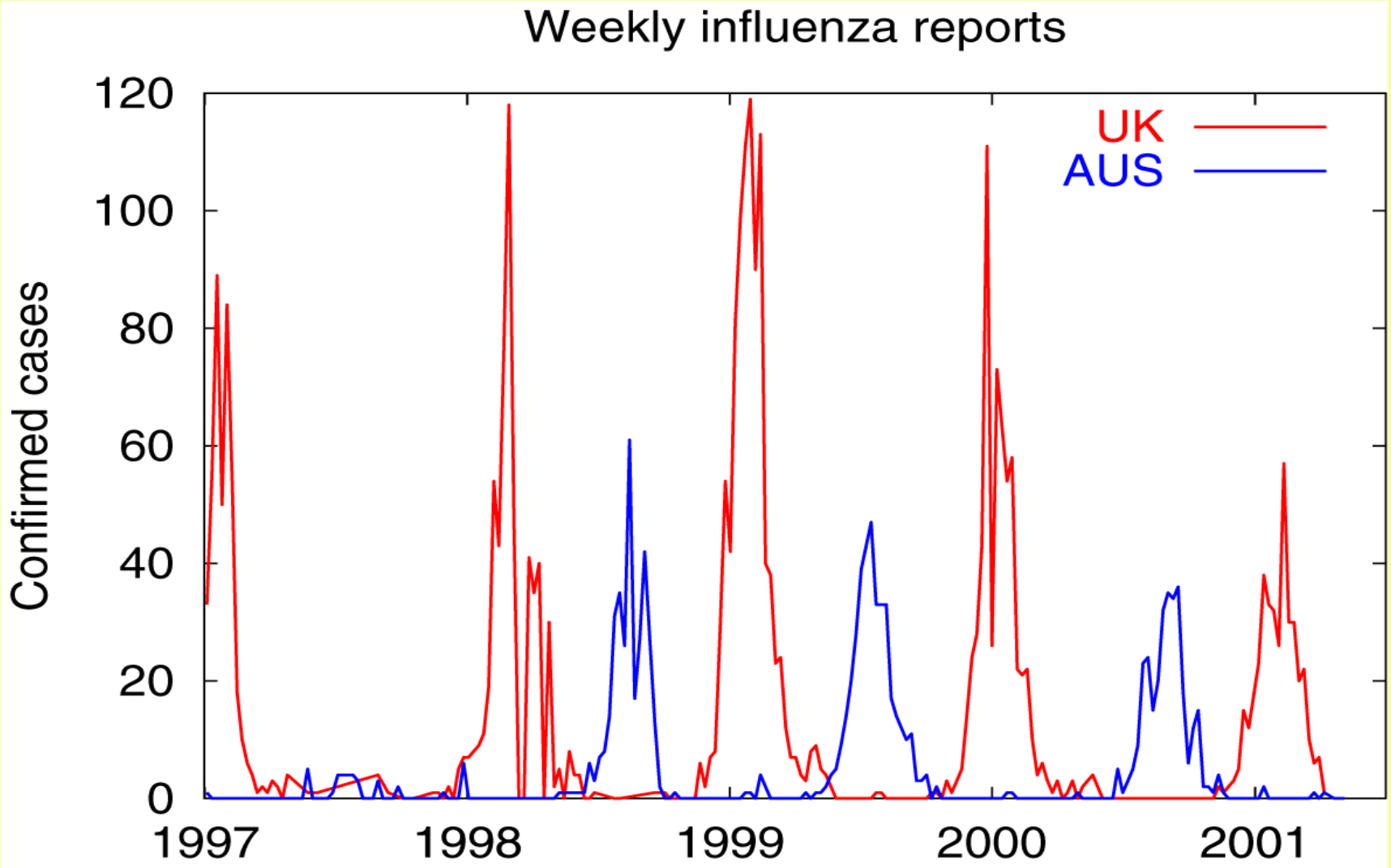
Oscillations

- Stochastic factors
- Seasonal forcing (e.g., in transmission rates)
- Long periods of temporary immunity
- Other explicit delays (e.g., incubation periods)
- Age structure
- Non-constant population size
- Non-(bilinear) transmission coefficients
- Interactions with other diseases/strains

Oscillations

- Stochastic factors
- Seasonal forcing (e.g., in transmission rates)
- Long periods of temporary immunity
- Other explicit delays (e.g., incubation periods)
- Age structure
- Non-constant population size
- Non-(bilinear) transmission coefficients
- Interactions with other diseases/strains

Drift variation



Shift variation (reassortment)

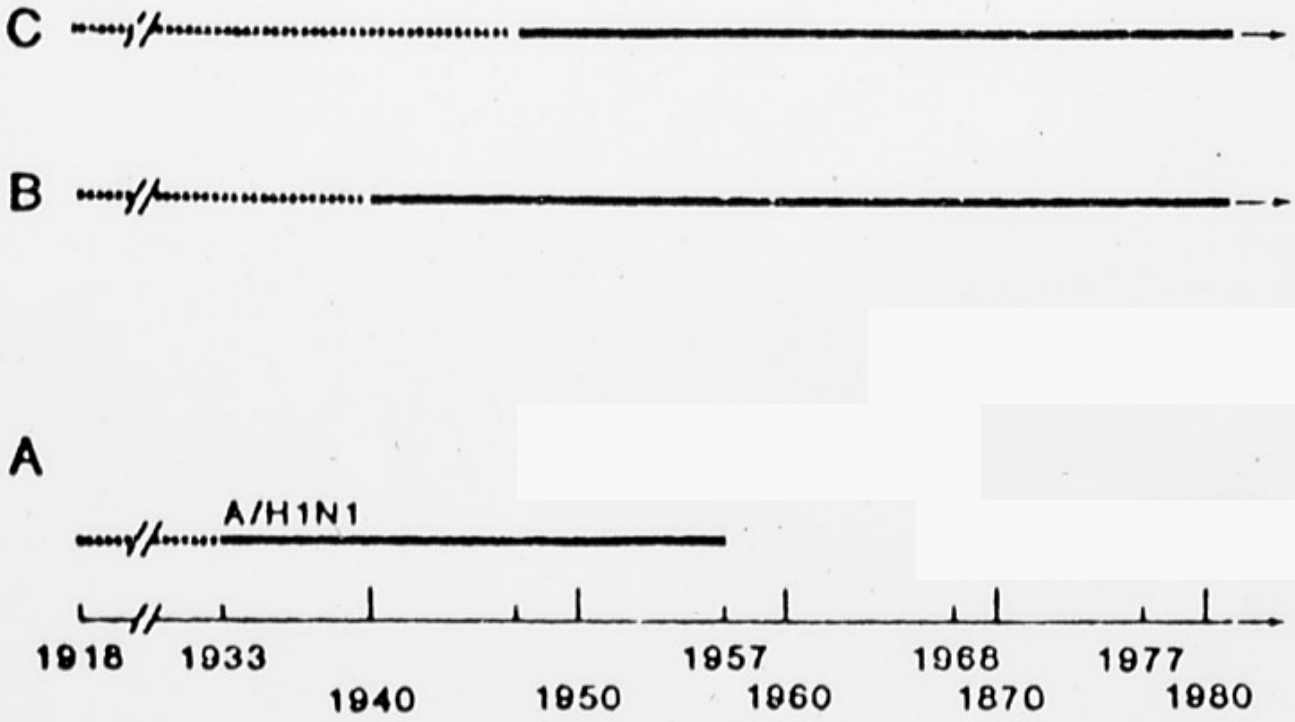


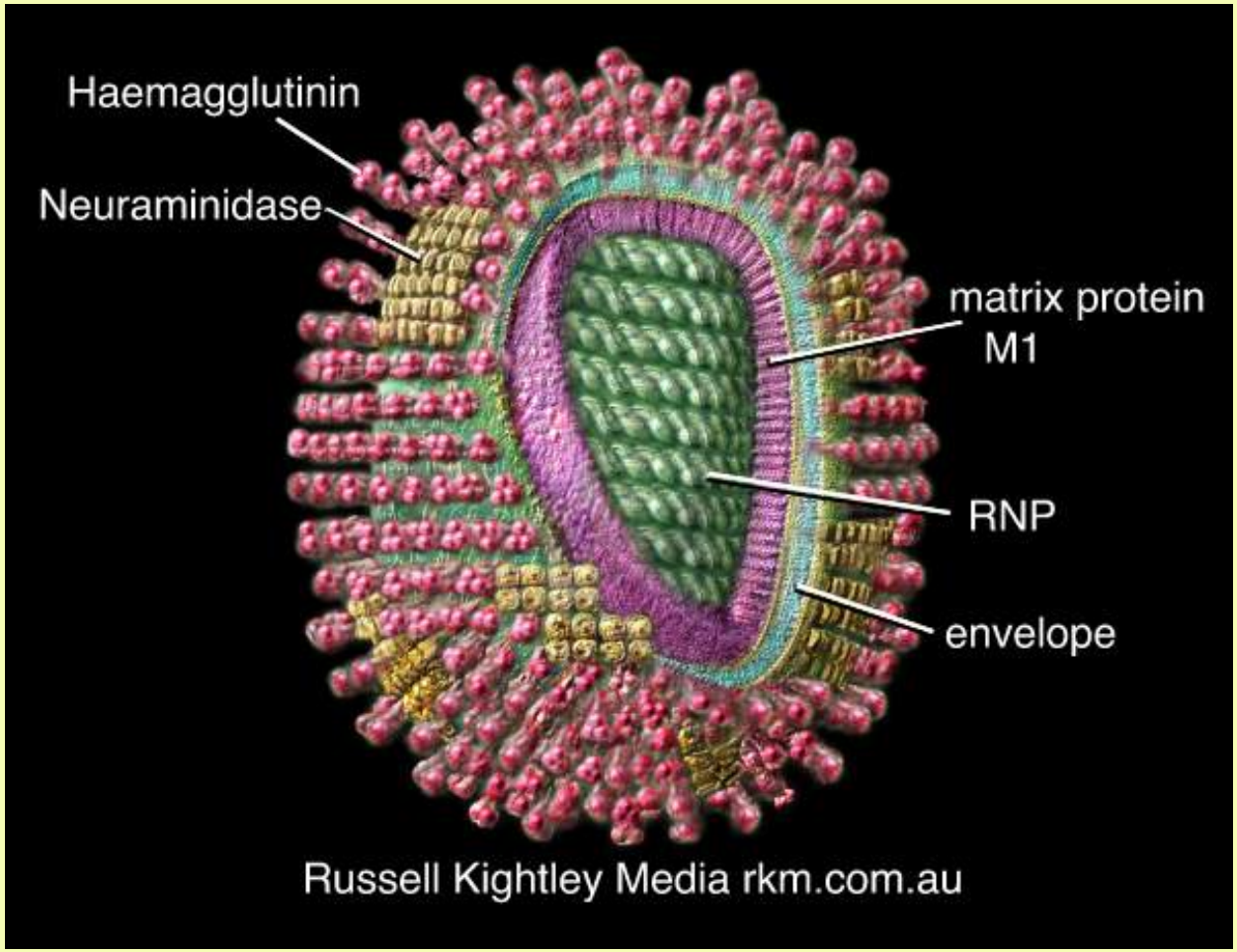
Fig. 2. Prevalence of influenza A, B, and C viruses in man over the last decades. Broken lines indicate that virus isolates are not available from these periods (only indirect evidence is available). Influenza A viruses of the H1N1, H2N2, and H3N2 subtypes were identified during certain time periods as indicated.

From: Palese and Young (1982)

And now a new H1N1

The “Spanish Flu” of 1918

Influenza A capsid



Drift evolution involves change in surface proteins

Table 2 Degree of resistance to challenge with homologous or heterologous type A (H3N2) influenza virus after a documented type A influenza virus infection

Study group		Interval since 1st infection	No. Vol.	Degree of resistance to challenge virus[b]	
1st infection variant	Challenge variant[a]			Infection	Illness
A/Hong Kong/68	A/Hong Kong/68[c]	4	8	++	++
A/Hong Kong/68	A/Hong Kong/68[c]	3	7	+	++
A/Hong Kong/68	A/Hong Kong/68[c]	2	7	++	++
A/Hong Kong/68	A/Hong Kong/68[c]	1	13	++	++
A/England/72	A/England/72[d]	2	7	+	++
A/England/72	A/Port Chalmers/73[d]	2	5	+	++
A/Hong Kong/68	A/Scotland/74[d]	4–7	6	+	++
A/England/72	A/Scotland/74[d]	1	6	+	++
A/Port Chalmers/73	A/Scotland/74[d]	1	3	++	++
A/Hong Kong/68 A/England/72 A/Port Chalmers/73	A/Victoria[d]	5–8	8	0	0
A/Scotland/74	A/Victoria[d]	1	16	+	+

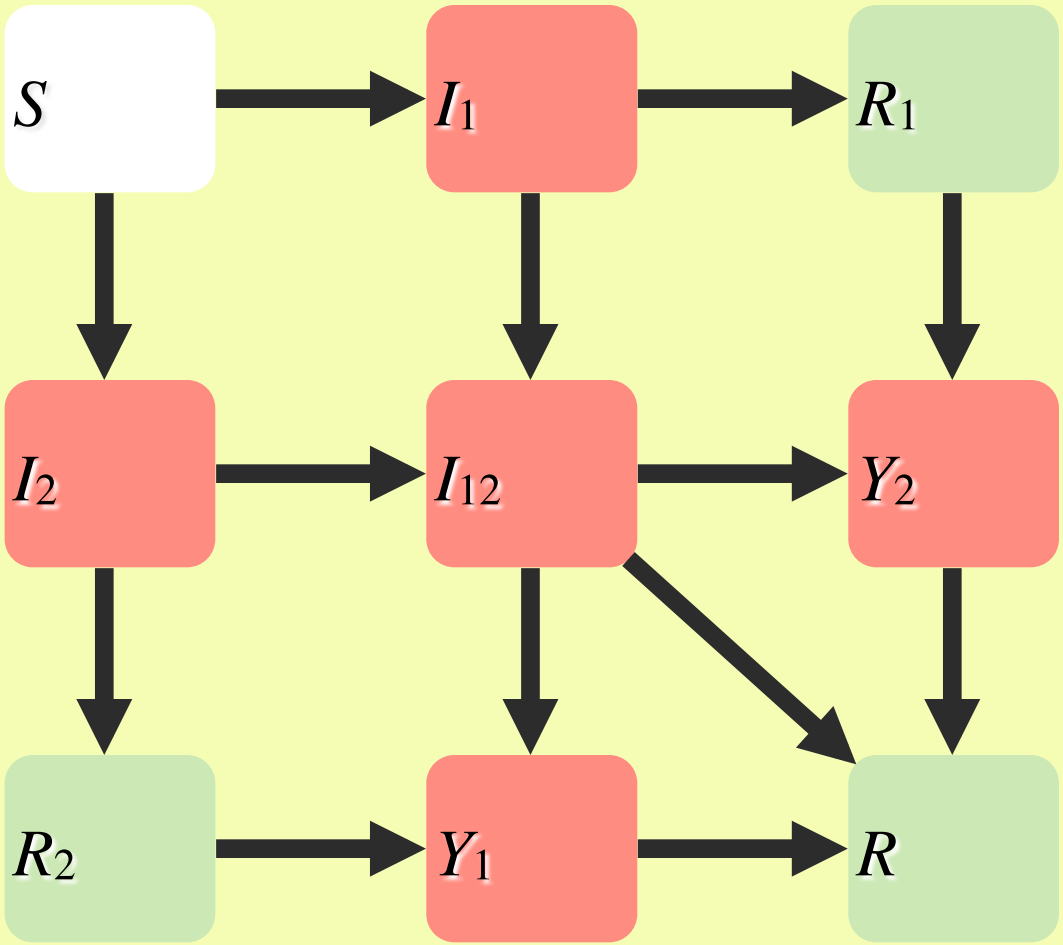
[a] A simultaneously challenged group of neut antibody negative volunteer (not shown) for each variant demonstrated ability of the inoculum to infect and produce illness. Challenge doses were $10^{2.3}$ to $10^{3.3}$ $TCID_{50}$.

[b] ++ = No infections or virus–associated illnesses after challenge.
+ = Reduced infection or illness response compared to controls.

[c] From (12)

[d] R. B. Couch, unpublished data. A/Victoria was a natural challenge, all others were artificial.

two-strain model



n strains

~ 2^n variables

Courtesy Josh Plotkin

n-strain model

$$\dot{S}_J = \sum_{j \in J} \nu I^j_{J \setminus j} - \mu S_J - \sum_{i \notin J} \sigma^i_J \Lambda^i S_J \quad \text{for } J \subseteq K, \ J \neq \emptyset,$$

$$\dot{I}^i_J = \sigma^i_J \Lambda^i S_J - (\mu + \nu) I^i_J \quad \text{for } J \subseteq K \setminus i, \ J \neq \emptyset.$$

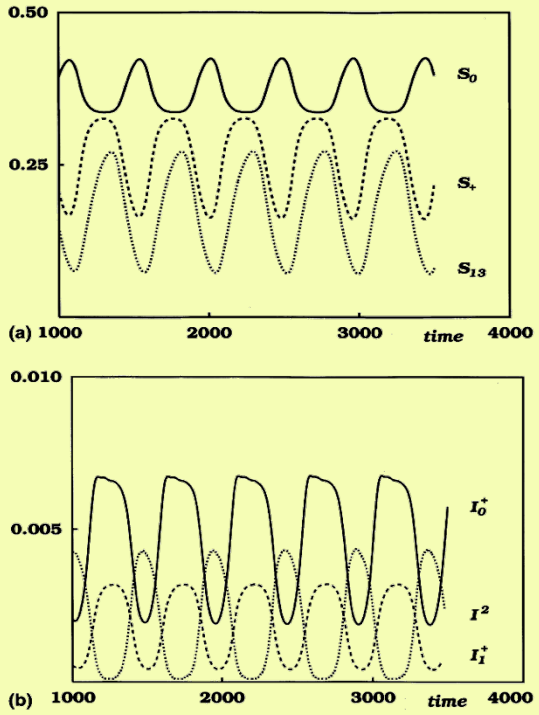
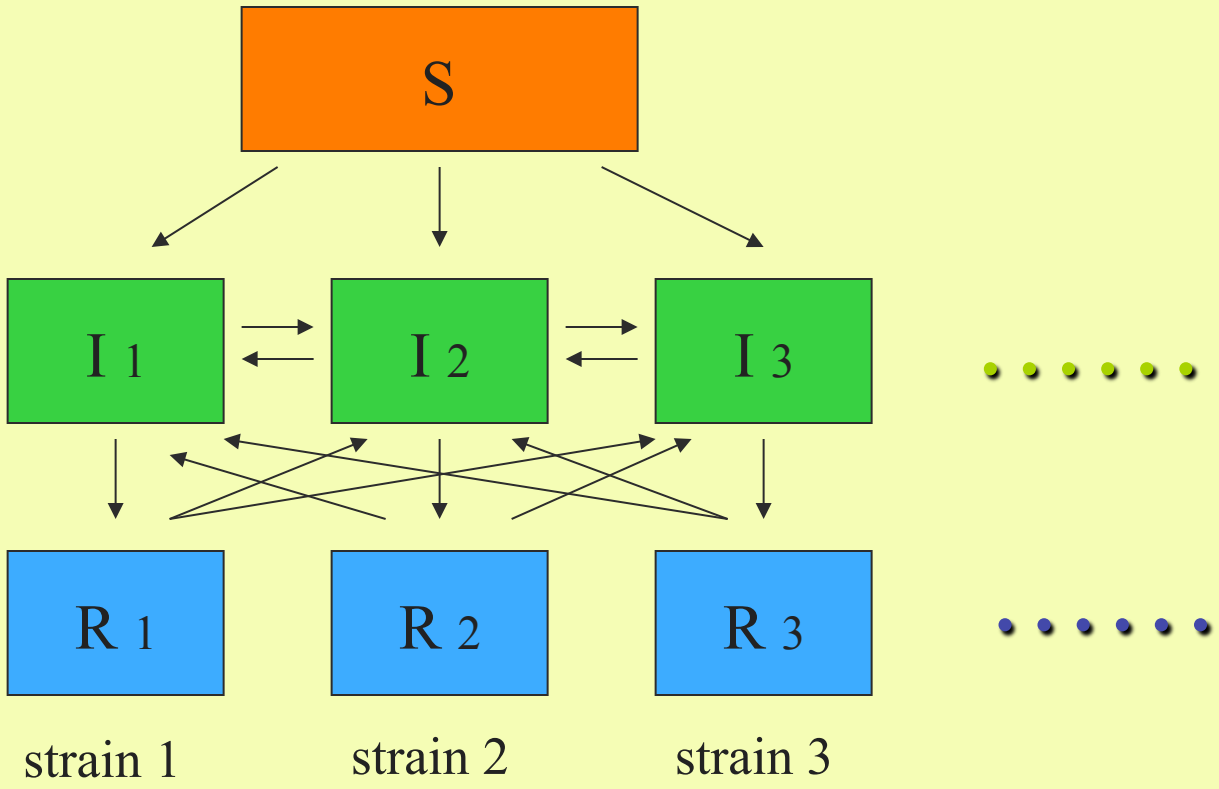


Fig. 4. Oscillations in the six-dimensional kernel consisting of $S_0, S_+, S_{13}, I_0^+, I_1^+$ and $I^2 = \Lambda^2/r_2$. Parameter values used in the simulation are $r_1 = r_2 = 2$ and $\sigma = 0.3$.

Courtesy Josh Plotkin

lin, andreasen, levin 1999

Hundreds of strains may be relevant for influenza



OPEN ACCESS Freely available online

PLoS COMPUTATIONAL BIOLOGY

On State-Space Reduction in Multi-Strain Pathogen Models, with an Application to Antigenic Drift in Influenza A

Sergey Kryazhimskiy[1*], Ulf Dieckmann[2], Simon A. Levin[3], Jonathan Dushoff[3,4]

1 Program in Applied and Computational Mathematics, Princeton University, Princeton, New Jersey, United States of America, **2** Evolution and Ecology Program, International Institute for Applied Systems Analysis, Laxenburg, Austria, **3** Department of Ecology and Evolutionary Biology, Princeton University, Princeton, New Jersey, United States of America, **4** Fogarty International Center, National Institute of Health, Bethesda, Maryland, United States of America

Many pathogens exist in phenotypically distinct strains that interact with each other through competition for hosts. General models that describe such multi-strain systems are extremely difficult to analyze because their state spaces are enormously large. Reduced models have been proposed, but so far all of them necessarily allow for coinfections and require that immunity be mediated solely by reduced infectivity, a potentially problematic assumption. Here, we suggest a new state-space reduction approach that allows immunity to be mediated by either reduced infectivity or reduced susceptibility and that can naturally be used for models with or without coinfections. Our approach utilizes the general framework of status-based models. The cornerstone of our method is the introduction of immunity variables, which describe multi-strain systems more naturally than the traditional tracking of susceptible and infected hosts. Models expressed in this way can be approximated in a natural way by a truncation method that is akin to moment closure, allowing us to sharply reduce the size of the state space, and thus to consider models with many strains in a tractable manner. Applying our method to the phenomenon of antigenic drift in influenza A, we propose a potentially general mechanism that could constrain viral evolution to a one-dimensional manifold in a two-dimensional trait space. Our framework broadens the class of multi-strain systems that can be adequately described by reduced models. It permits computational, and even analytical, investigation and thus serves as a useful tool for understanding the evolution and ecology of multi-strain pathogens.

Citation: Kryazhimskiy S, Dieckmann U, Levin SA, Dushoff J (2007) On state-space reduction in multi-strain pathogen models, with an application to antigenic drift in influenza A. PLoS Comput Biol 3(8): e159. doi:10.1371/journal.pcbi.0030159

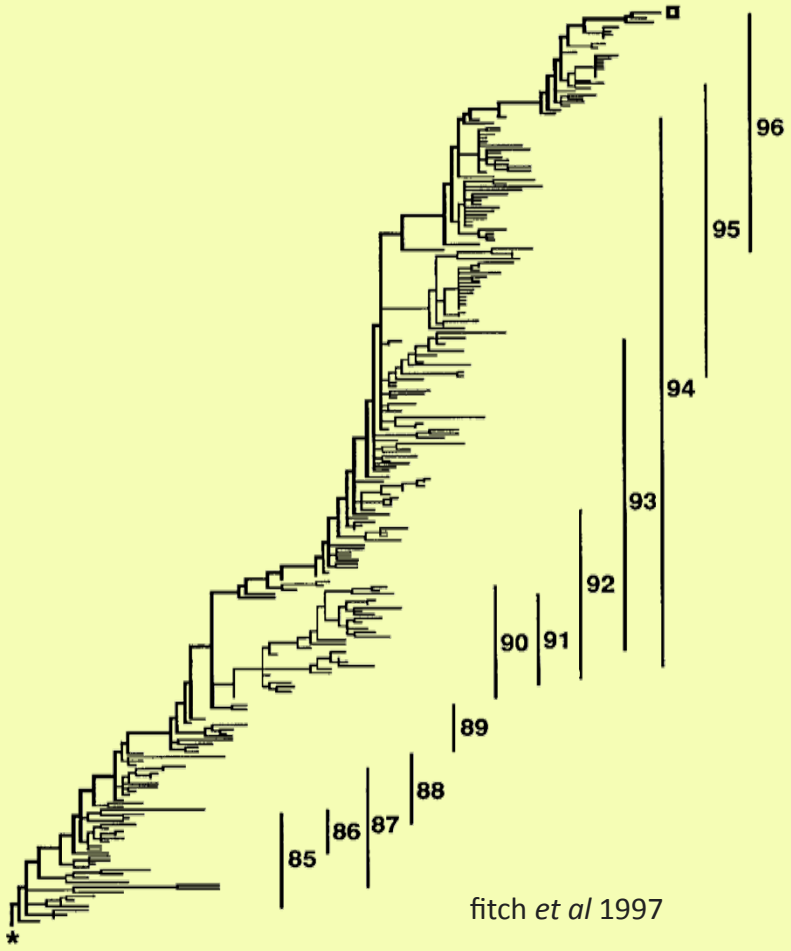
Introduction

Microbial pathogens are tremendously diverse. Pathogens that cause one and the same disease may differ remarkably in pathogen's ecology is thus intrinsically entangled with its evolution.

Understanding the dynamics of multi-strain pathogens at a general, theoretical level, turns out to be extremely

HIV-1 env

influenza HA



fitch *et al* 1997

why this tree?

Thanks to Josh Plotkin

Epidemiological modeling of flu

- What is a "strain"?
- What is the geometry of strain space?
- Do viral isolates form clusters, or "quasispecies"?

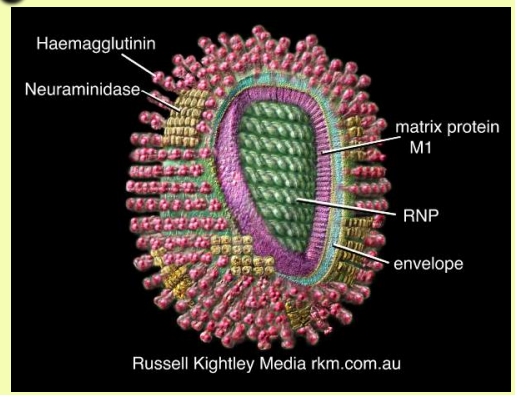
The nature of oscillations in influenza A

- **Subtypes** (shift variants)

  Generational time scale

- **Strains** (drift variants)

  Annual time scale



Is there anything in between?

—Relevance to vaccine choice.

Lecture outline

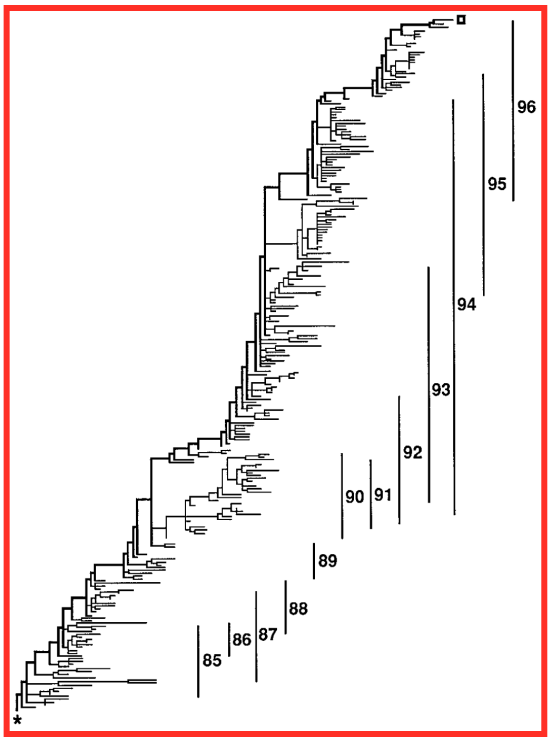
- Classical theory and oscillation
- Recurrent diseases
- Crossing scales: Immunology, epidemiology and evolution

Hemagglutinin sequence clusters and the antigenic evolution of influenza A virus

Joshua B. Plotkin*†‡, Jonathan Dushoff*, and Simon A. Levin*

*Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ 08540; and †Institute for Advanced Study, Princeton, NJ 08540

Contributed by Simon A. Levin, February 22, 2002



Bush, Fitch, Cox

Empirical study of HA evolution

- Database of 560 aligned H3-subtype HA1 sequences, 329 aa long

"Distance" between HA sequences

- Measure distance as sum over each pairwise acid:

$$D(x,y) = \sum_{i=1}^{329} d(x_i, y_i)$$

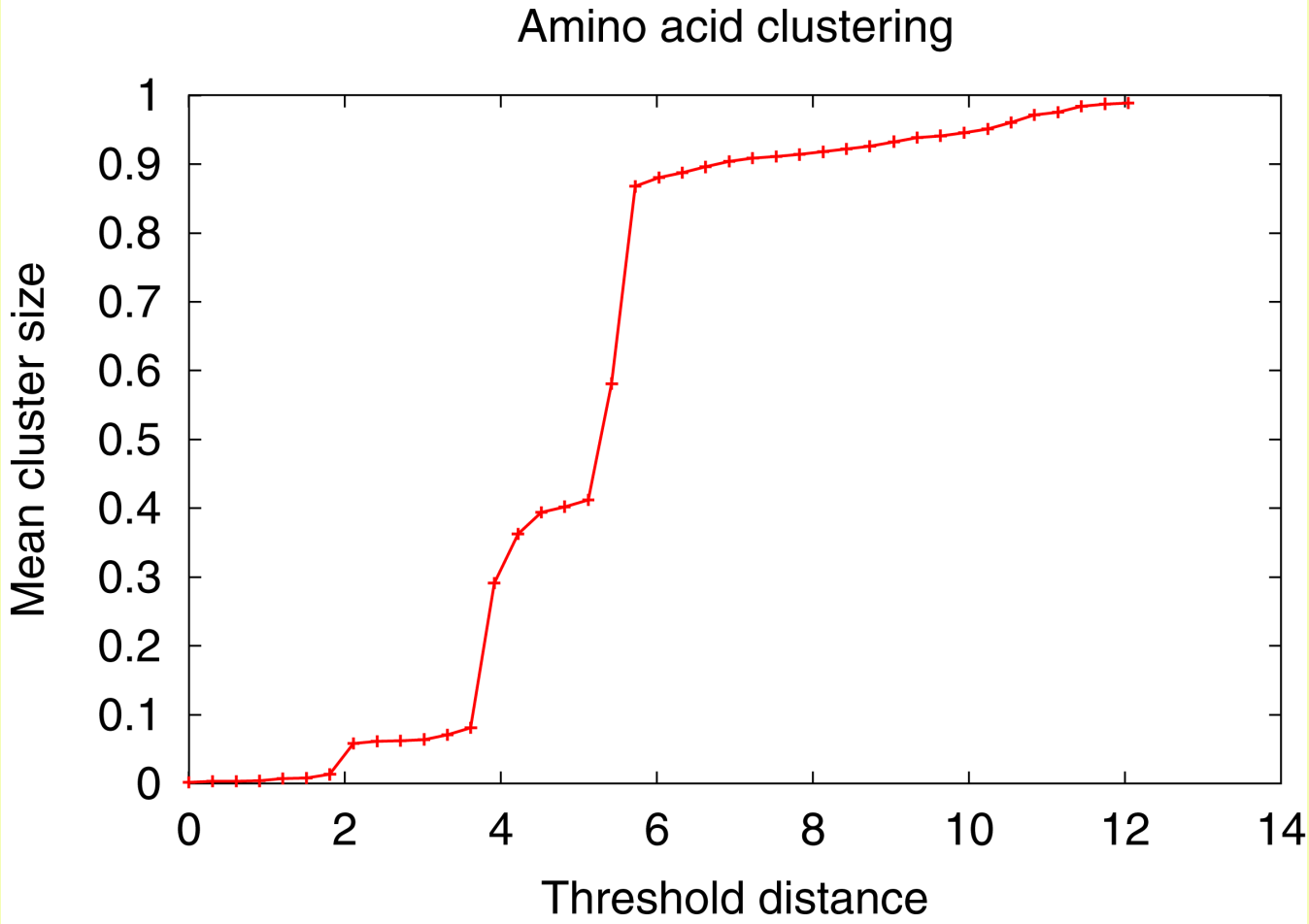
- Amino-acid metrics *d*:
  - Binary (Hamming); ignores synonymous change
  - Stereochemical (Miyata)
  - Replacement frequencies (PAM matrix)

Clustering sequence data

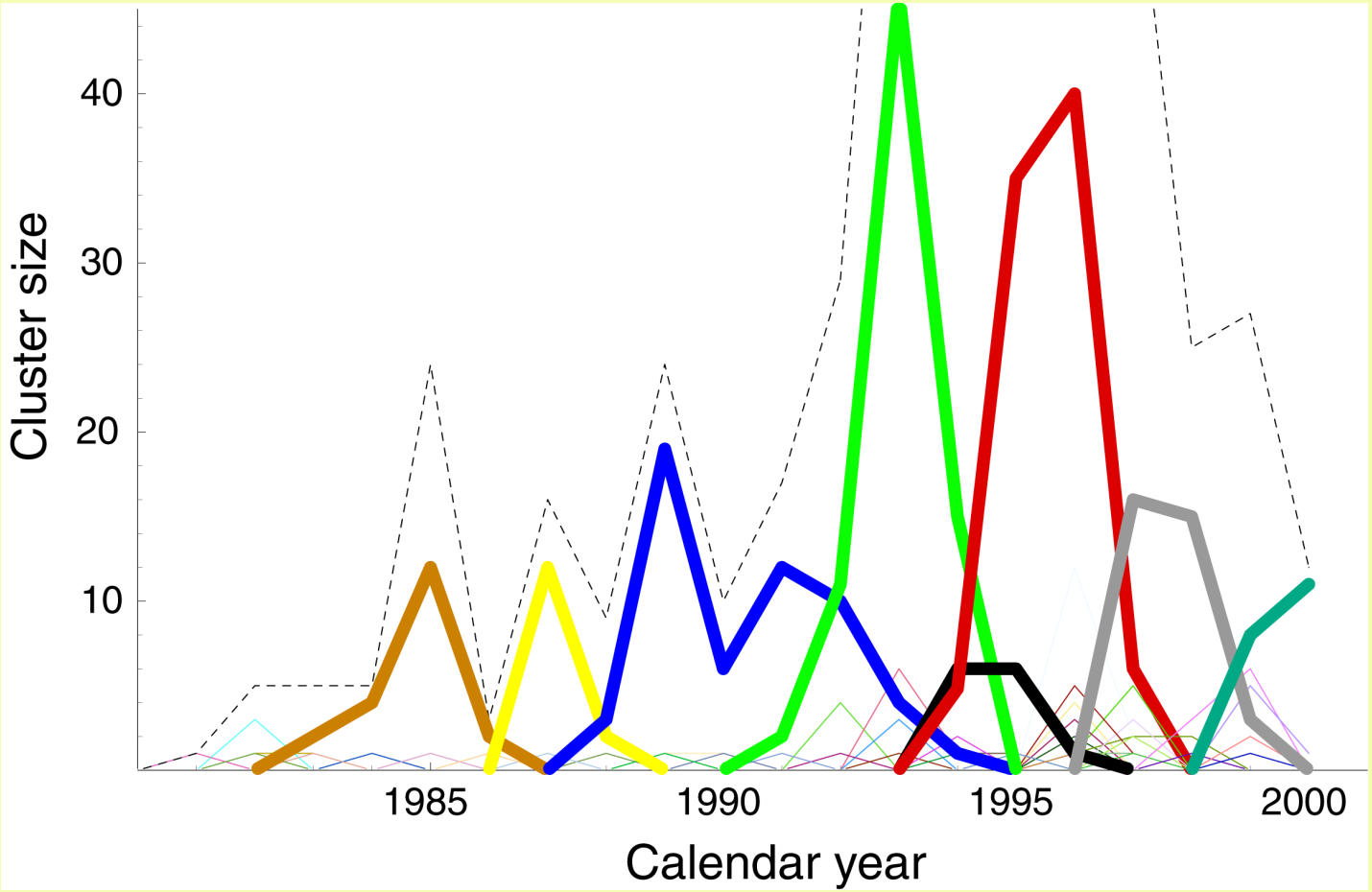
- **Method**
  - Choose threshold distance *d*
  - Join sequences within distance *d*
  - Clusters are connected components

- **Result**
  - Cluster hierarchy, as *d* varies
  - Cluster size curve

HA cluster size curve



Timeseries of viral clusters



The nature of oscillations in influenza A

- **Subtypes** (shift variants such as Spanish flu)

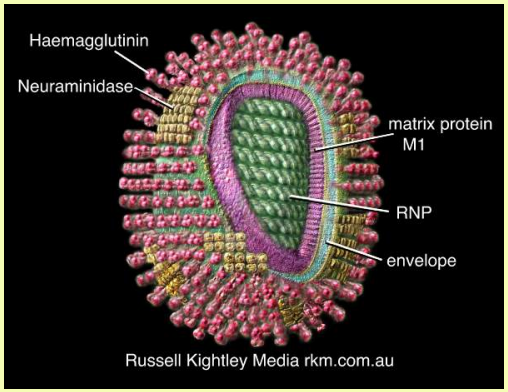
  Generational time scale

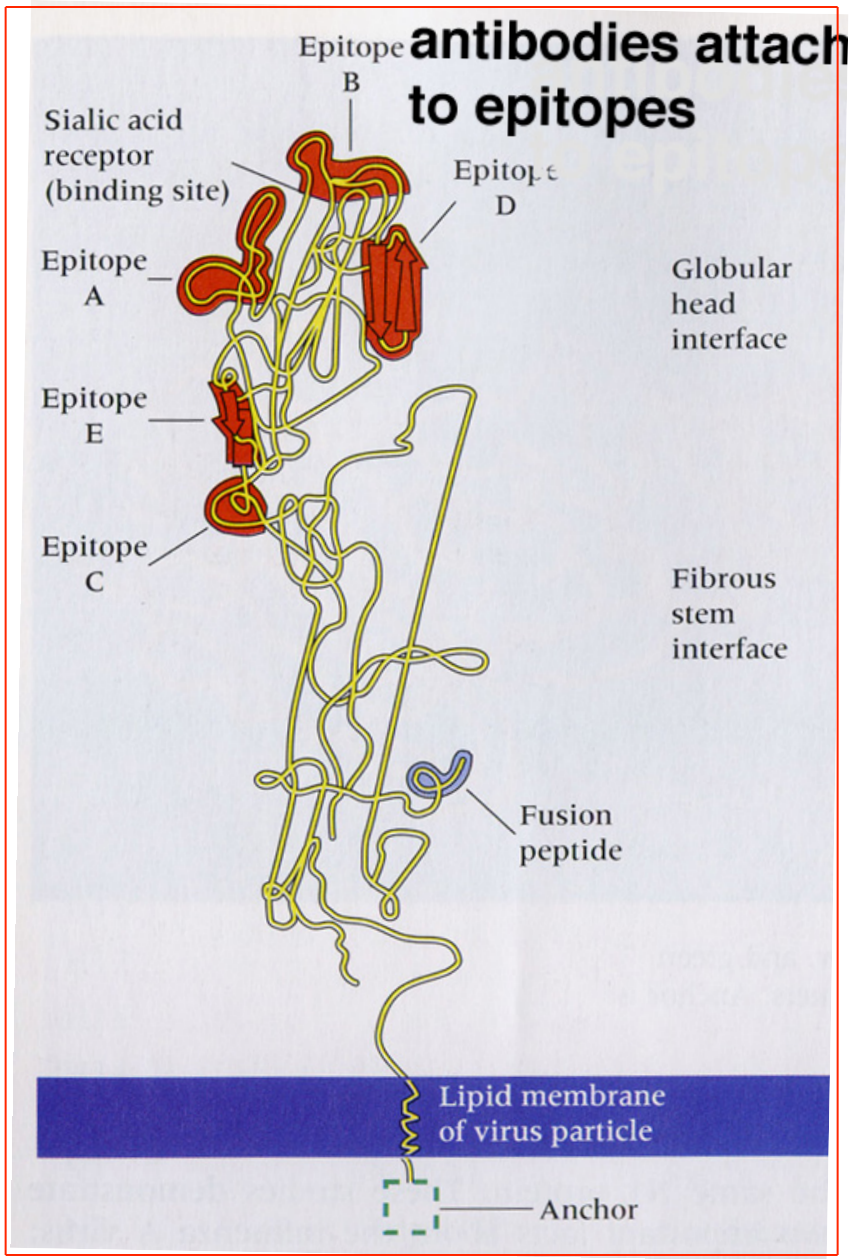
- **Clusters** (drift variants)

  2-5 year time scale

- **Strains** (drift variants)

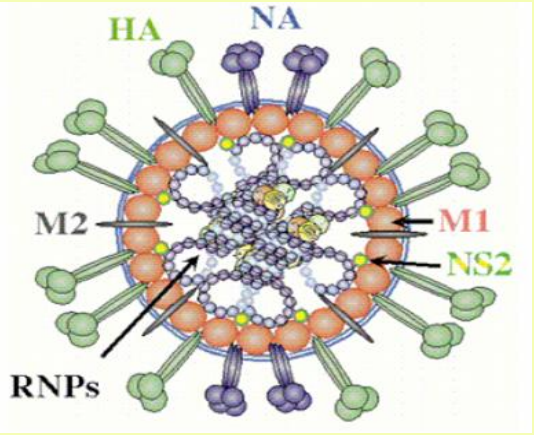
  Annual time scale



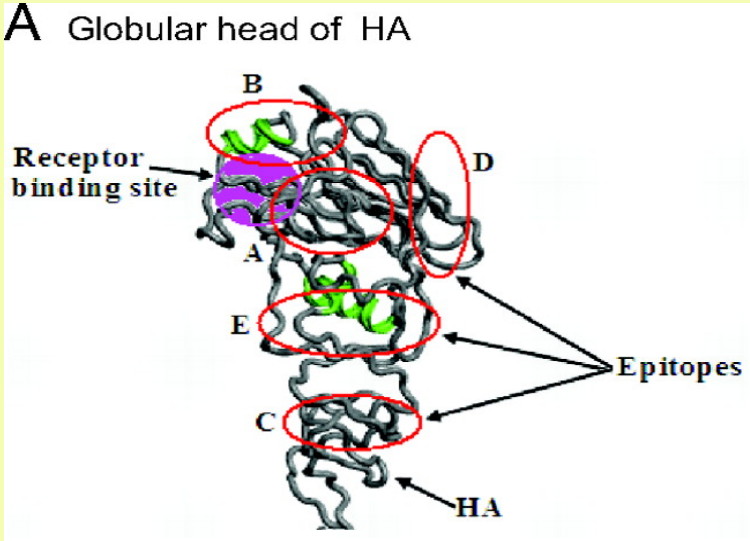

antibodies attach
to epitopes
Epitope B
Sialic acid receptor (binding site)
Epitope D
Epitope A
Globular head interface
Epitope E
Epitope C
Fibrous stem interface
Fusion peptide
Lipid membrane of virus particle
Anchor

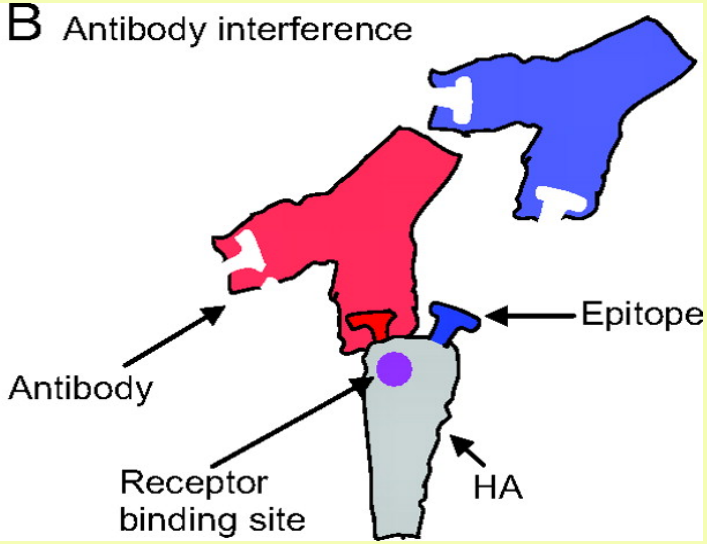
Influenza hemagglutinin (HA) and antibody interference:Ndifon, Wingreen, Levin

Influenza A



(Paul Digard)

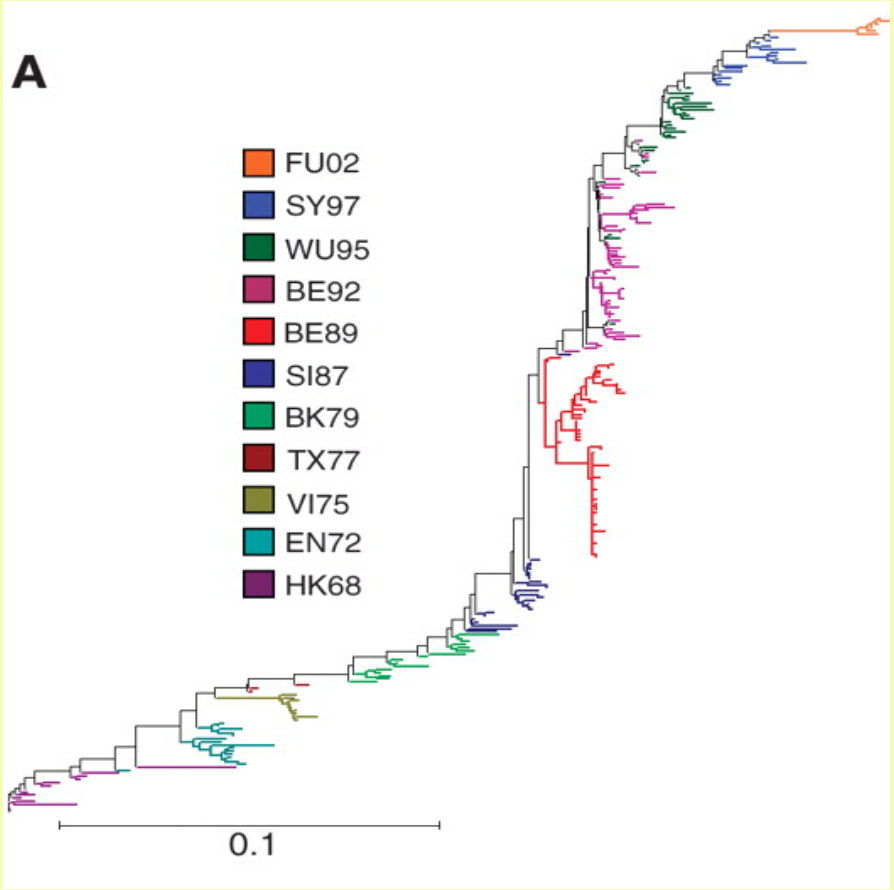




Antibody interference is one facet of Peter Nara's theory of deceptive imprinting.

Wingreen

Current work:
Does antibody interference affect influenza population genetics?



Koelle *et al*., Science 2006

Lecture outline

- Classical theory and oscillation
- Recurrent diseases
- Crossing scales
- Problems of the Commons

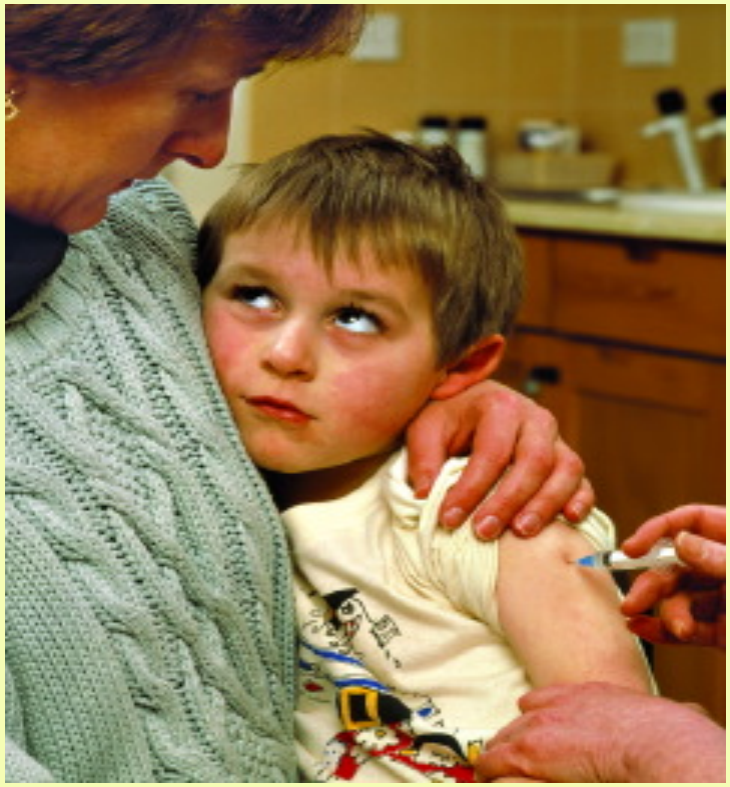
Problems of The Commons

- Fisheries
- Aquifers
- Pollution

Problems of The Commons

- Fisheries
- Aquifers
- Pollution
- Vaccines

images.usatoday.com

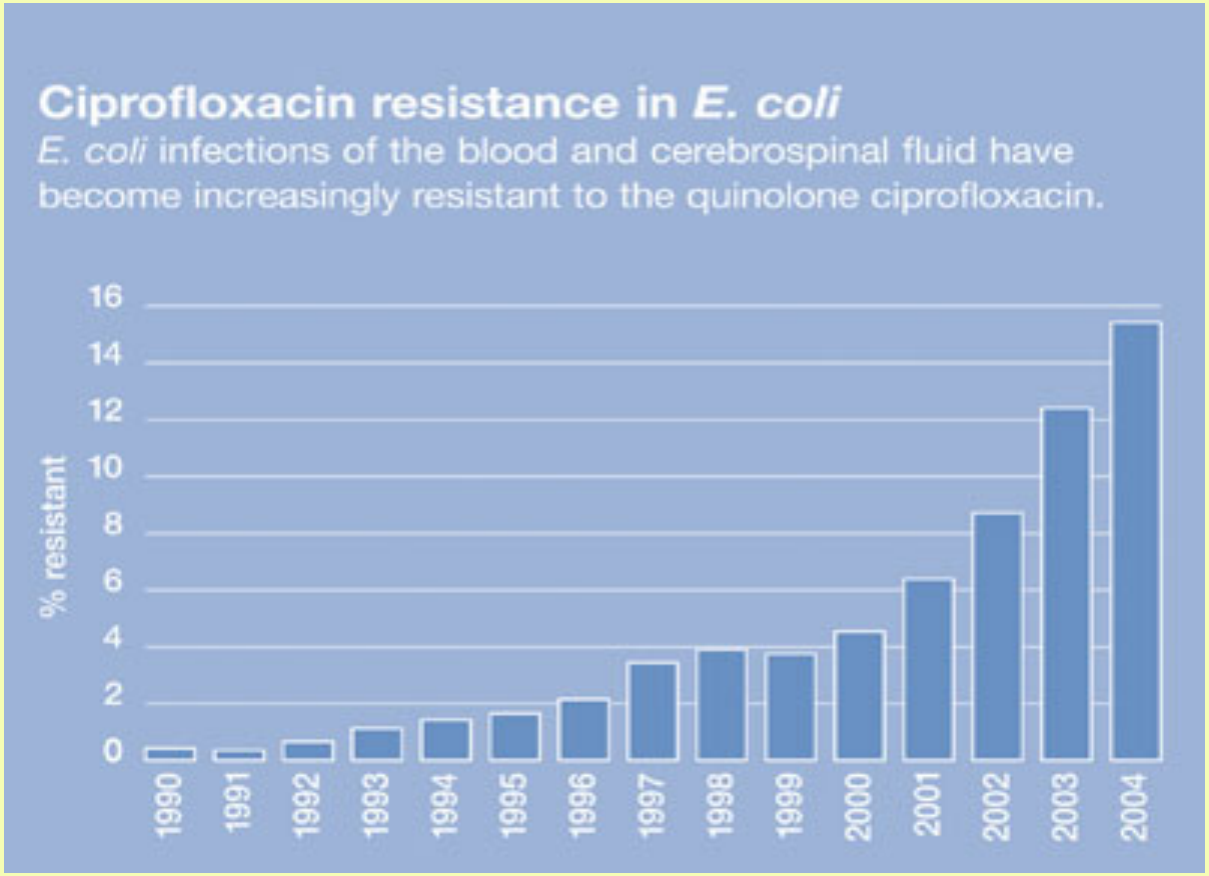


pubs.acs.org

Problems of The Commons

- Fisheries
- Aquifers
- Pollution
- Vaccines
- Antibiotics

Antibiotic resistance is on the rise

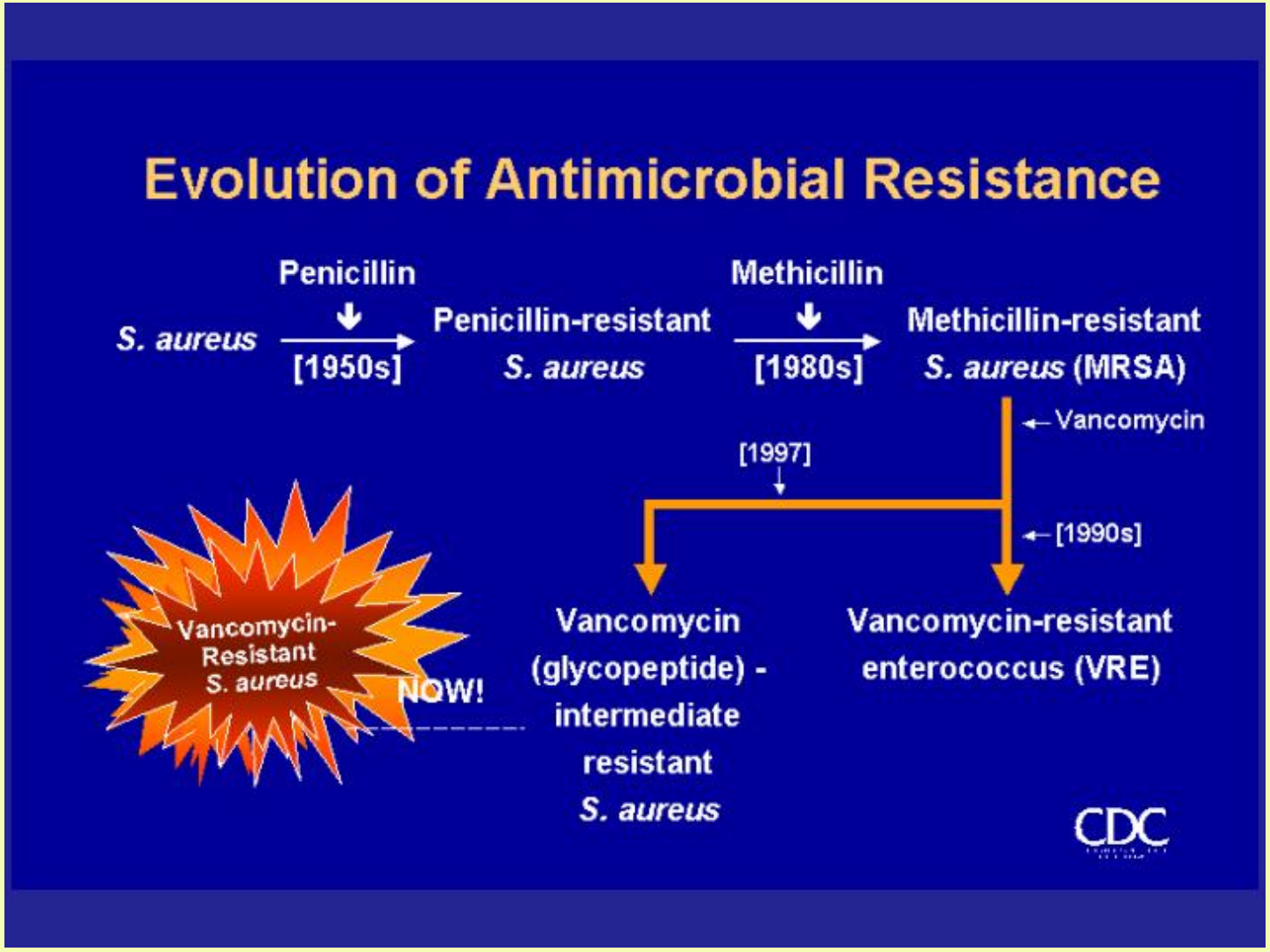



Snort. Sniffle. Sneeze.
No Antibiotics Please.
Treat colds and flu with care.
Talk to your doctor.
As a parent, you want to help your child feel better. But antibiotics aren't always the answer. They don't fight the viruses that cause colds and flu. What will? Fluids and plenty of rest are best. Talk to your doctor. Find out when antibiotics work – and when they don't. The best care is the right care.
For more information, please call 1-888-246-2675
or visit www.cdc.gov/getsmart.
GET SMART
Know When Antibiotics Work
CDC

Would you deny your child antibiotics to maintain global effectiveness?

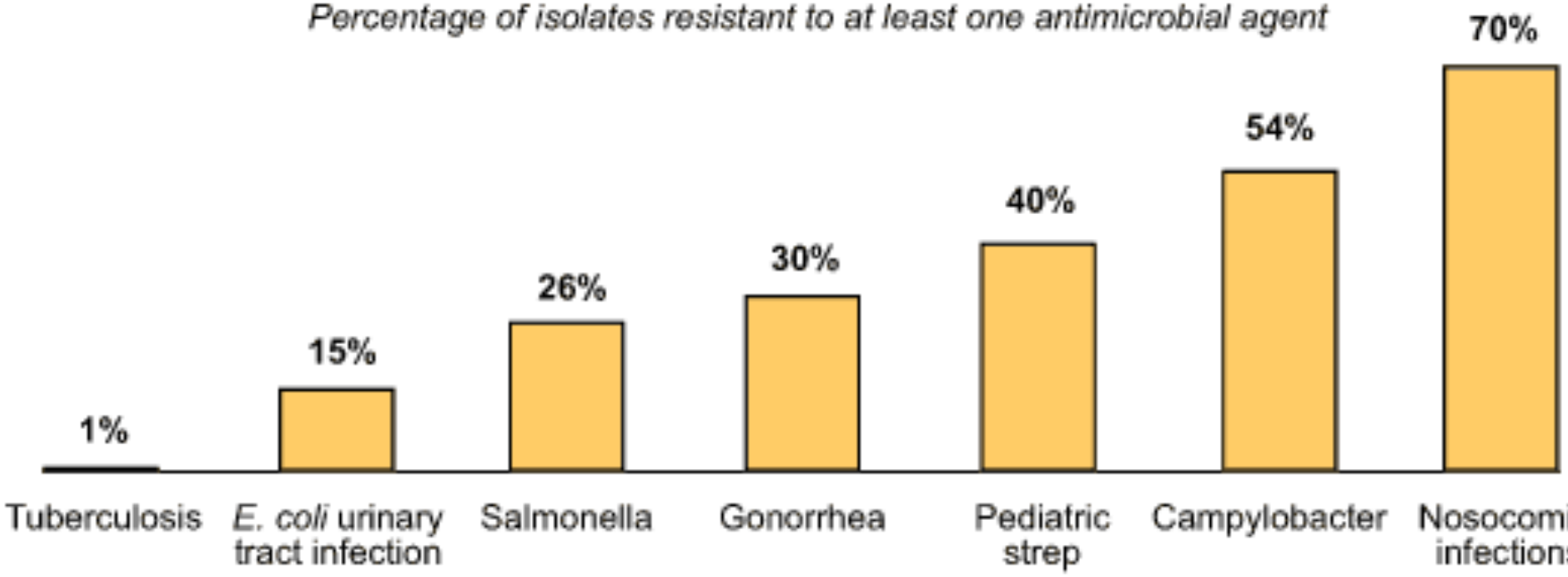
Antibiotic resistance is an increasing problem

We are rapidly losing the benefits antibiotics have given us against a wide spectrum of diseases


Evolution of Antimicrobial Resistance
Penicillin
S. aureus
[1950s]
Penicillin-resistant
S. aureus
Methicillin
[1980s]
Methicillin-resistant
S. aureus (MRSA)
Vancomycin
[1997]
[1990s]
Vancomycin-
Resistant
S. aureus
NOW!
Vancomycin
(glycopeptide) -
intermediate
resistant
S. aureus
Vancomycin-resistant
enterococcus (VRE)
CDC

Rates of antibiotic resistance in common infections, circa 2000

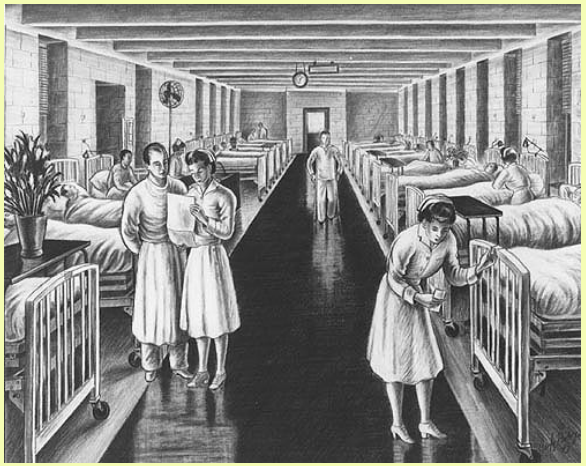
Percentage of isolates resistant to at least one antimicrobial agent



Source: Bulkeley, *Wall Street Journal*, 4/18; American Lung Association; Gorbach, *NEJM*, 10/18/01; Manges et al., *NEJM*, 10/4/01

Reasons for rise of antibiotic resistance

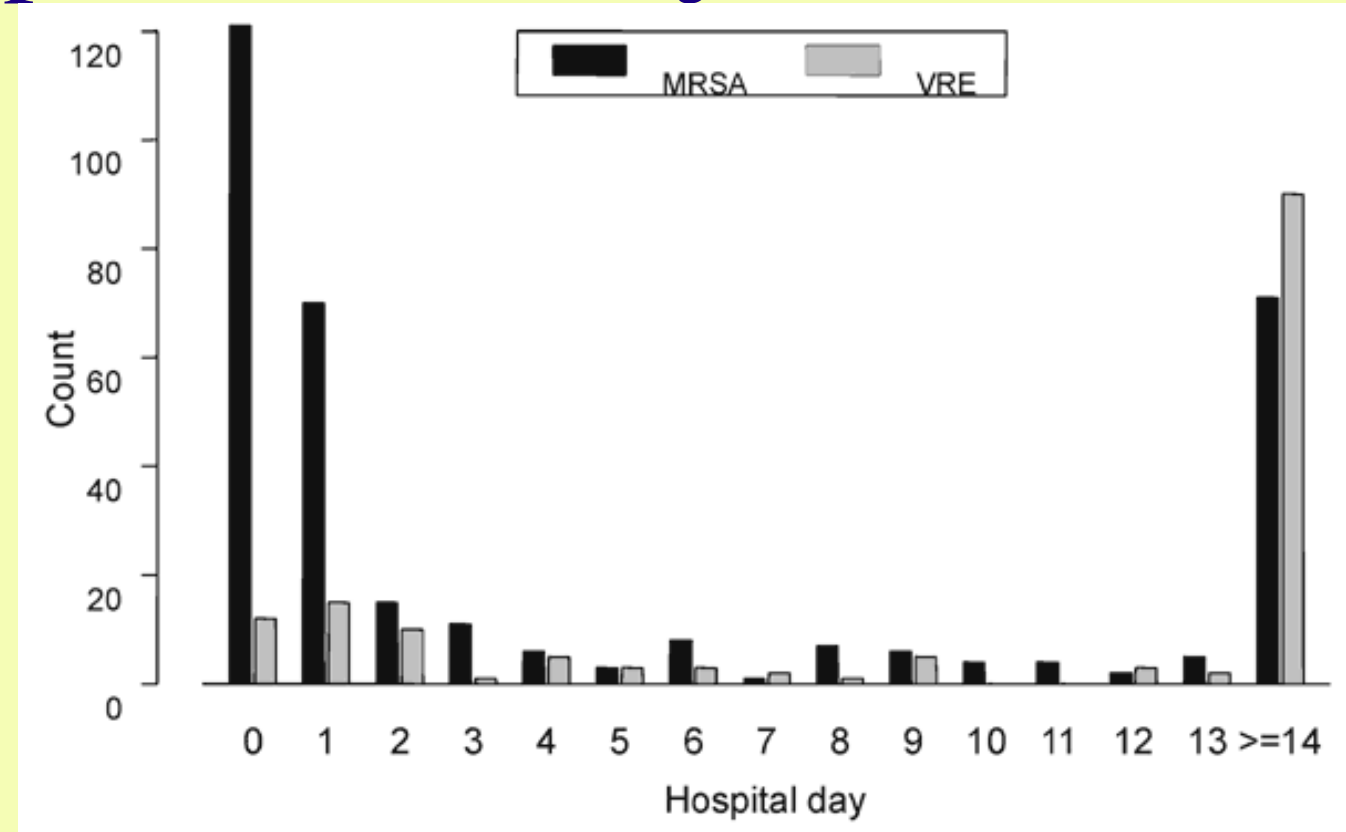
- **Agricultural uses**
- **Overuse by physicians**
- **Hospital spread (nosocomial infections)**



www.history.navy.mil/ac

Huang et al, Emerging Infectious Diseases, 2002

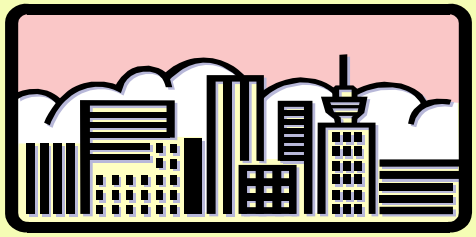
Hospitals are a major source of spread

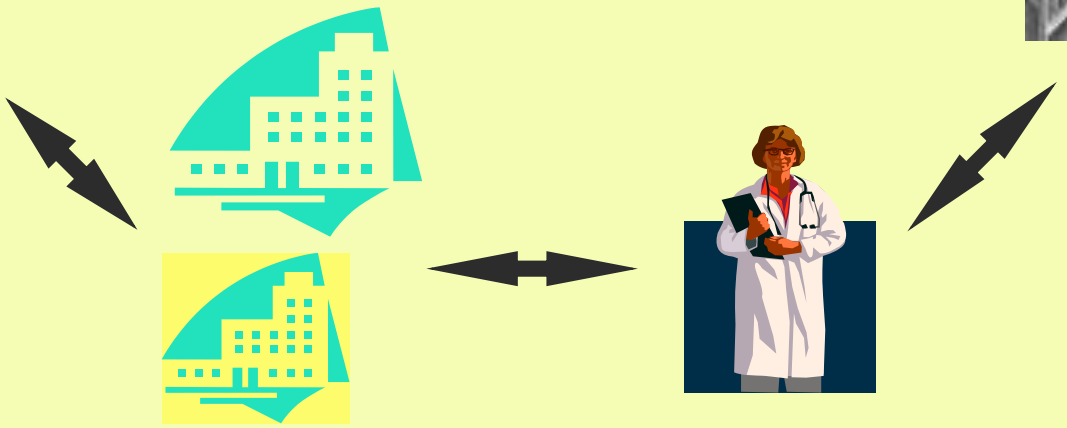


Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) isolates by hospital day of admission. Early peak corresponds to patients entering the hospital with MRSA or VRE bacteremia. Later peak likely represents nosocomial acquisition. (San Francisco County)

Antibiotic use

- Hospitals and communities create a metapopulation framework (*Lipsitch et al; Smith et al*)
- Spatially- explicit strategies could help
- Economics dominates control

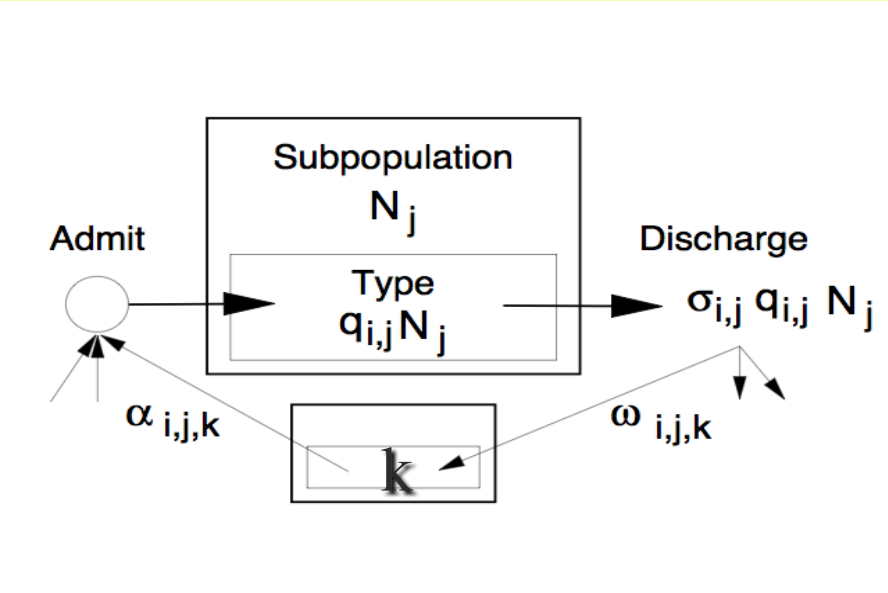




Individuals may harbor ARB on admission…carriers

- How do increases in the general population contribute to infections by ARB in the hospital, and what can be done about it?
- Develop metapopulation models exploring colonization of hosts by antibiotic resistant strains

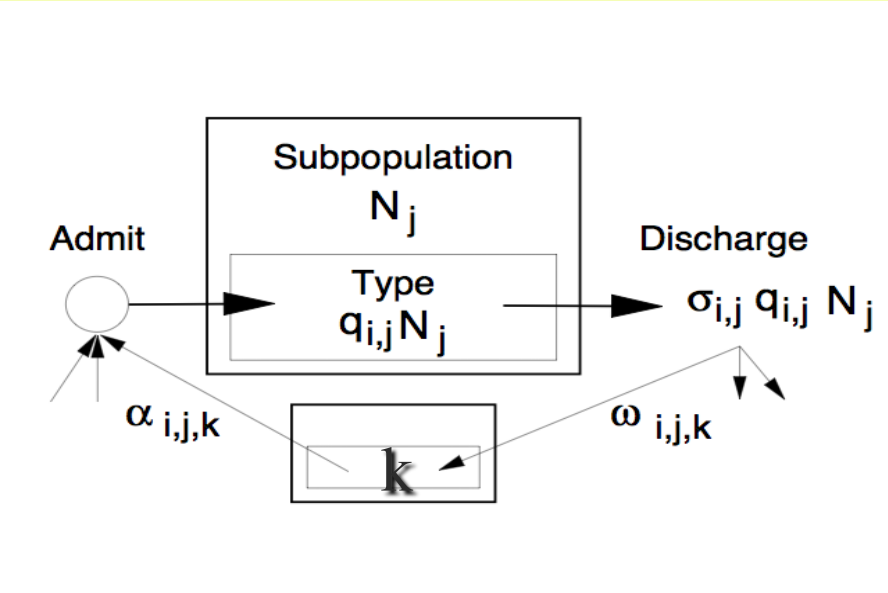
Individual movement
Basic model structure



i indicates group, such as elderly

Smith et al, PNAS 2004

Individual movement
Basic model structure



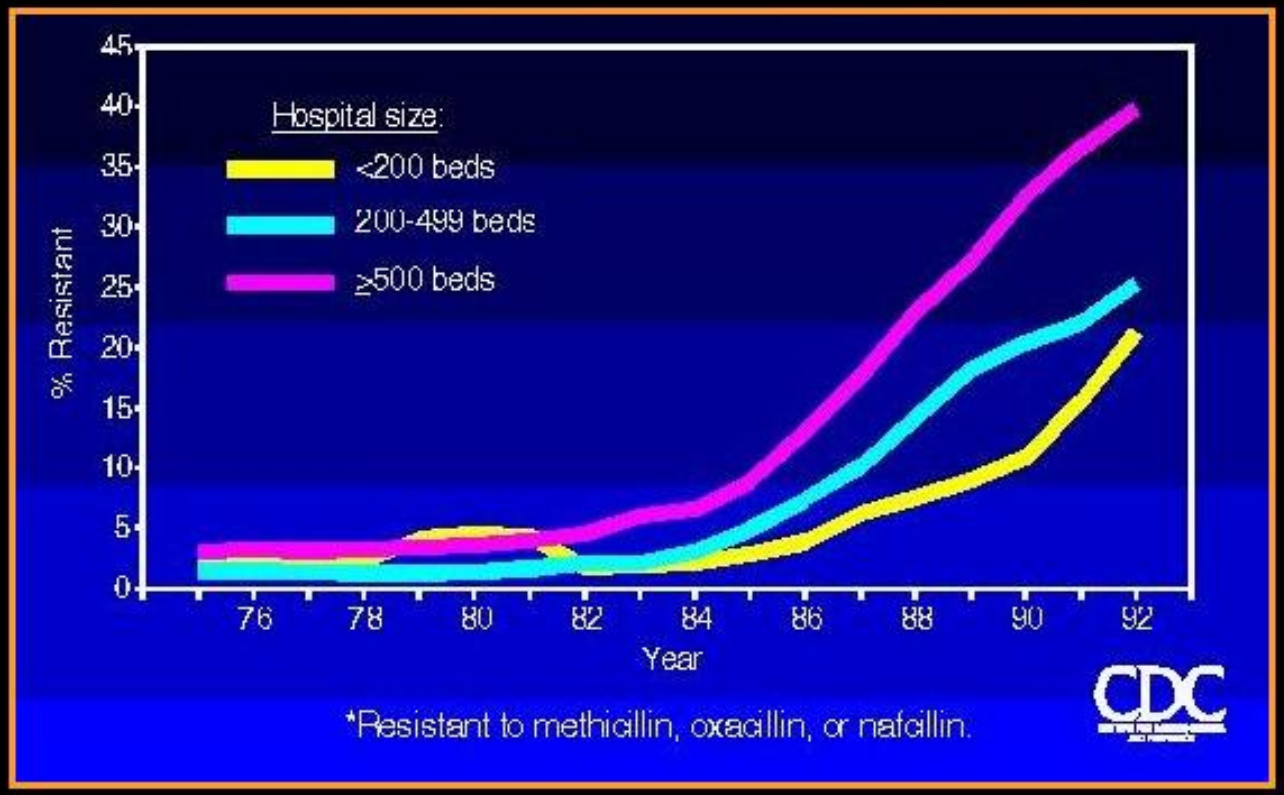
i indicates group, such as elderly

j,k indicate subpopulations, such as hospital, community

Smith et al, PNAS 2004

Bigger hospitals have bigger problems

Drug-Resistant *Staphylococcus aureus* Infections in ICU Wards Early in the Crisis

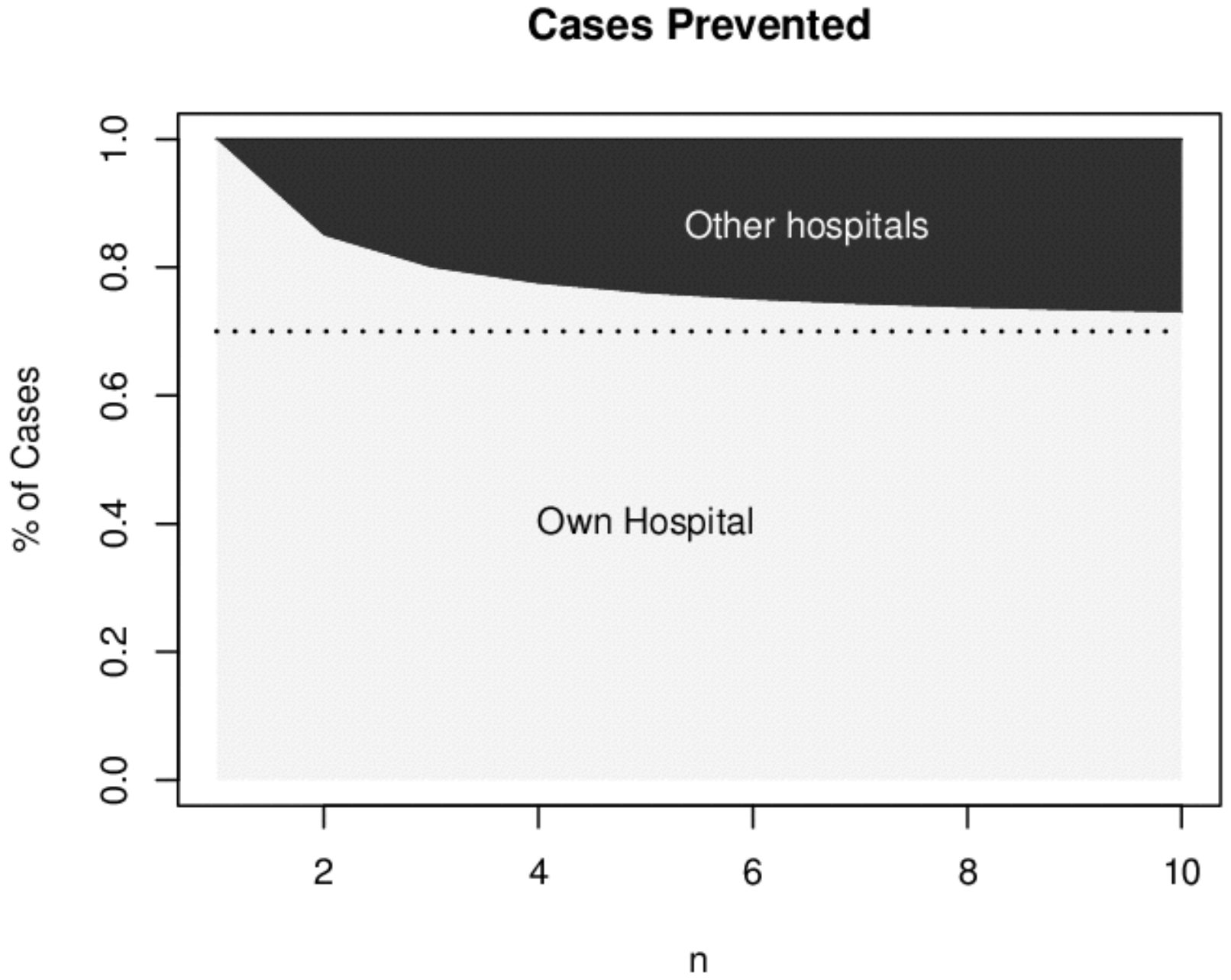


Increase in methicillin-resistant *S. aureus* (MRSA) from 1975-1992, plotted as a function of hospital size.

Hospitals in larger cities have larger problems

Smith, Levin, Laxminarayan

- Consider a game among hospitals
- Compute optimal investment for a single hospital in controlling antibiotic resistance
- Compute game-theoretic optimal strategy in a mixed population, with discounting
- Investment decreases with city size


Cases Prevented
% of Cases
0.0
0.2
0.4
0.6
0.8
1.0
Other hospitals
Own Hospital
2
4
6
8
10
n

Lecture outline

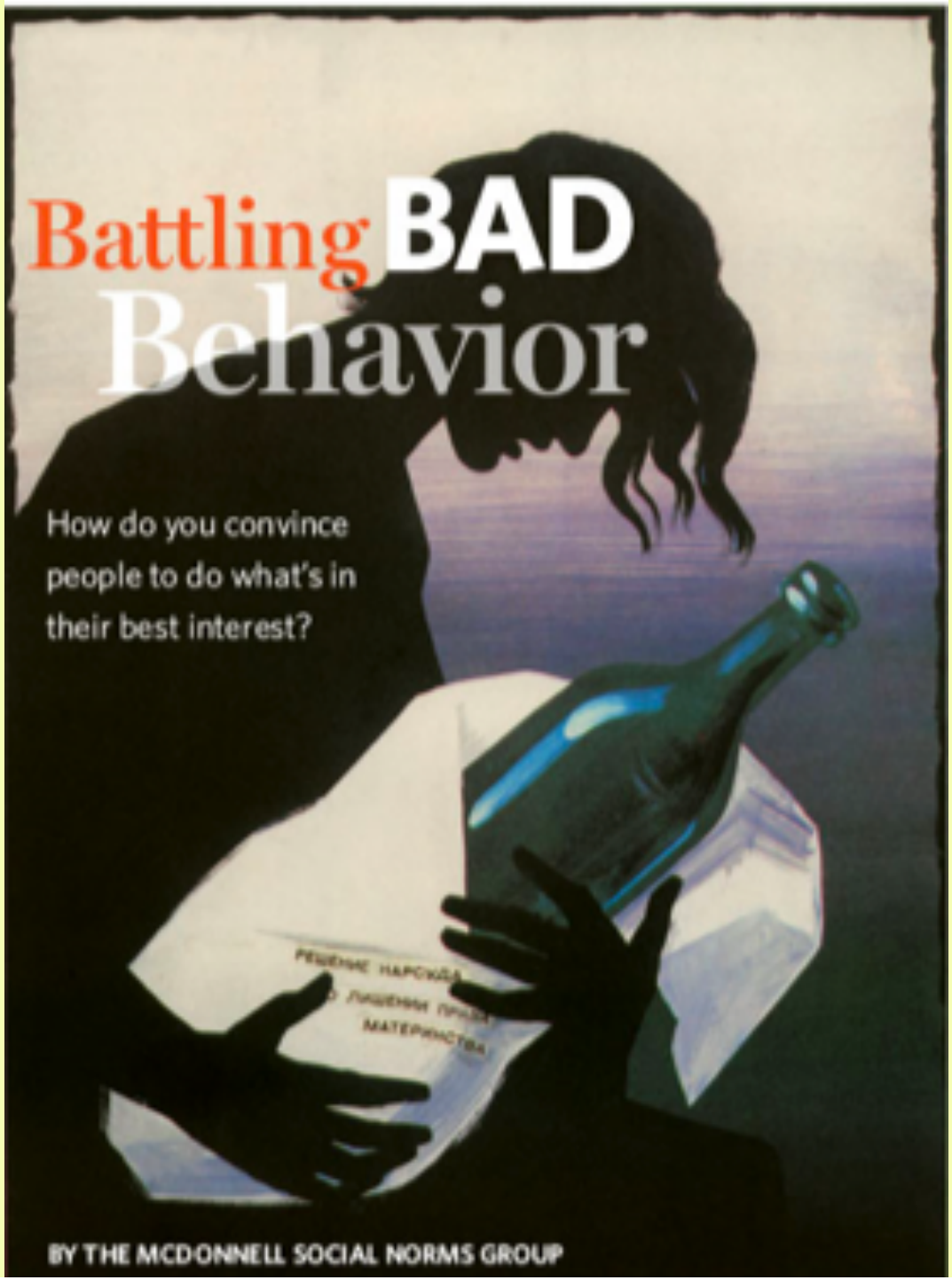
- Classical theory and oscillation
- Recurrent diseases
- Crossing scales
- Problems of the Commons
- Social norms

Social norms and medical practice

- Patient expectations
- Physician practice
- Social norms and litigation
- Public goods and common pool resources

Social norms and medical practice
Games among

- Patients
- Physicians
- Hospitals and nursing homes
- Health-care organizations
- Public
- Governments



Dushoff et al. McDonnell Social Norms Group

McDonnell #2(*Buchman et al.*)
J. Am. College of Surgeons

Enhancing the Use of Clinical Guidelines: A Social Norms Perspective

The McDonnell Norms Group

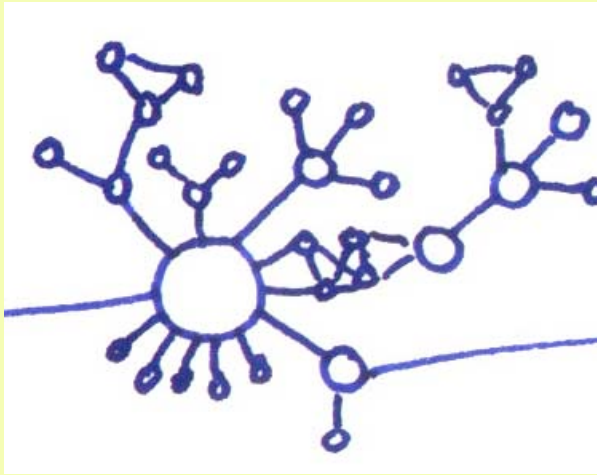
Advances in clinical investigation, data analysis, rapid dissemination, and rigorous evaluation of the findings led to the accumulation of medical "evidence." This evidence now forms the basis of thousands of guidelines developed and promulgated by professional societies, safety and outcomes organizations, provider institutions, and regulators. With rare exception, these guidelines are inconsistently implemented or used.

This article reviews the history of guideline development and use, assesses the current state of implementation, identifies obstacles to adoption, and suggests strategies to overcome these obstacles. The major finding is that the current approach to development, dissemination, and encouraged use of guidelines is inconsistent with knowledge of psychology.

and collegial opinion, forming the basis for "eminence-based medicine."

After the US Great Society legislation, which guaranteed health care to the elderly (Medicare), the Congressional Office of Technology Assessment and the Institute of Medicine increasingly voiced the need for studies that would evaluate proliferating technologies in a meaningful and unbiased framework. The first efforts included creation of "clinical algorithms," which were intended to guide both physicians and their "extenders" (nurse practitioners and physician assistants) in the proper triage and treatment of individuals with common medical disorders.[1] Such algorithms typically were expressed as paper flowcharts to which clinicians could refer when seeking guidance, but they were never well accepted by

Modeling



blog-msb.embo.org

- How are behaviors sustained?
- When do they shift?
- How can we intervene (where on the network)?
- How can the public goods challenges be addressed (Dixit?

Conclusions

- Infectious diseases have a rich modeling history
- Remain an important area for application of theory
- Relevant methods will span a broad range