International Public Workshop
Forum on Microbial Threats
Institute of Medicine
4-5 December 2007

Ecological, environmental, and infectious disease impacts of global climate change and extreme weather events

Donald S. Burke, M.D.

OUTLINE

REPORTS ON WEATHER, CLIMATE AND INFECTIOUS DISEASES

- UNDER THE WEATHER (2001)
- INTERGOVERNMENTAL PANEL ON CLIMATE CHANGE (2007)
  (4TH ASSESSMENT REPORT)
- AN INCONVENIENT TRUTH (2006)

INFECTIOUS DISEASE DYNAMICS AND MODELING

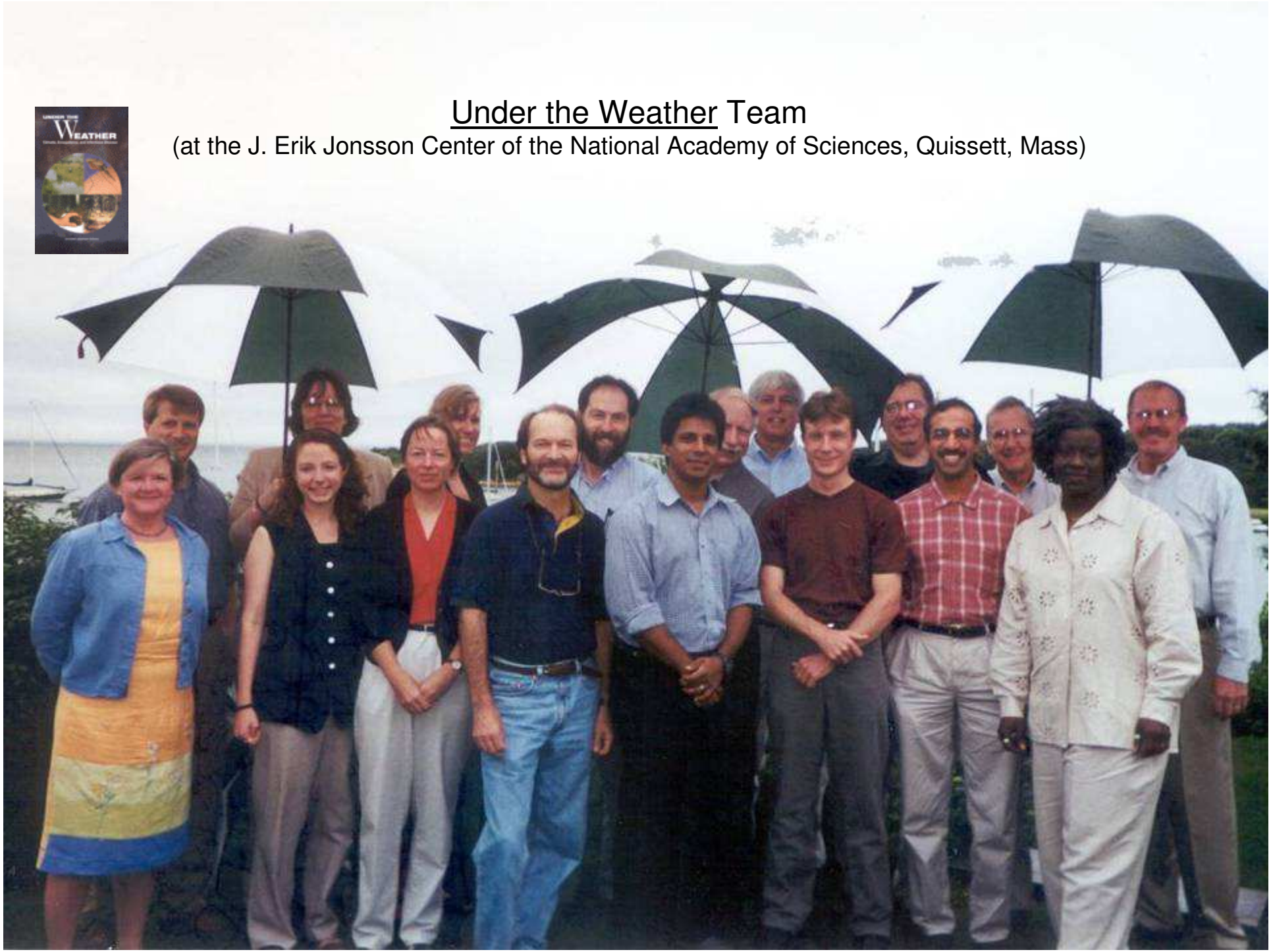
- INFLUENZA
- DENGUE

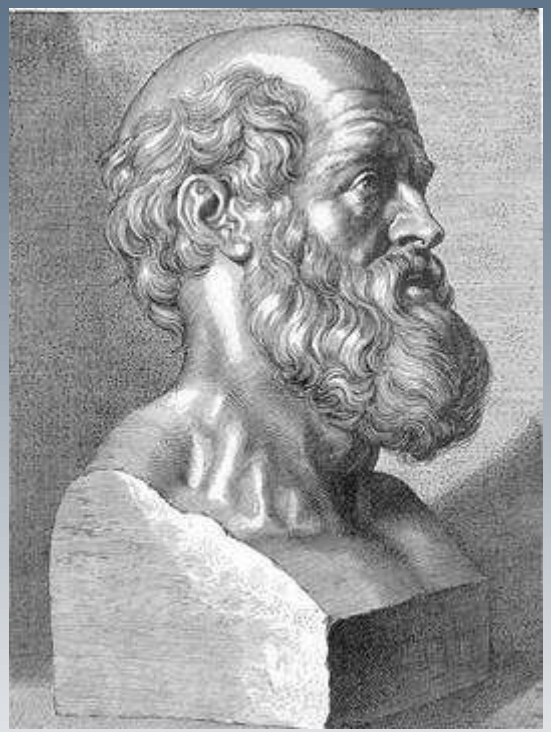
NEW EMERGING INFECTIOUS DISEASES

CONCLUSIONS

Under the Weather Team

(at the J. Erik Jonsson Center of the National Academy of Sciences, Quissett, Mass)





Hippocrates
On Airs, Waters, and Places
(400 B.C.)

"Whoever would study medicine aright must learn of the following subjects.

First he must consider the effect of the seasons of the year and the differences between them.

Secondly he must study the warm and cold winds, both those which are in common to every country and those peculiar to a particular locality.

Lastly, the effect of water on the health must not be forgotten."

Under the Weather
Examples of Diseases Influenced by Environmental Conditions

ENVIRONMENTAL FACTOR	DISEASE FAVORED	EVIDENCE
Warm	Dengue, Malaria	Primarily tropical distribution, seasonal transmission pattern
Cold	Influenza	Seasonal transmission pattern
Dry	Meningococcal meningitis, Coccidioidomycosis	Associated with arid conditions, dust storms
Wet	Cryptosporidiosis Rift Valley Fever	Associated with flooding

UNDER THE WEATHER / KEY FINDINGS: LINKAGES BETWEEN CLIMATE AND INFECTIOUS DISEASES

- Weather fluctuations and seasonal-to-interannual climate variability influence many infectious diseases
- Observational and modeling studies must be interpreted cautiously
- The potential disease impacts of global climate change remain highly uncertain
- Climate change may affect the evolution and emergence of infectious diseases
- There are potential pitfalls in extrapolating climate and disease relationships from one spatial/temporal scale to another
- Recent technological advances will aid efforts to improve modeling of infectious disease epidemiology

INTERGOVERNMENTAL PANEL ON CLIMATE CHANGE

WMO

UNEP

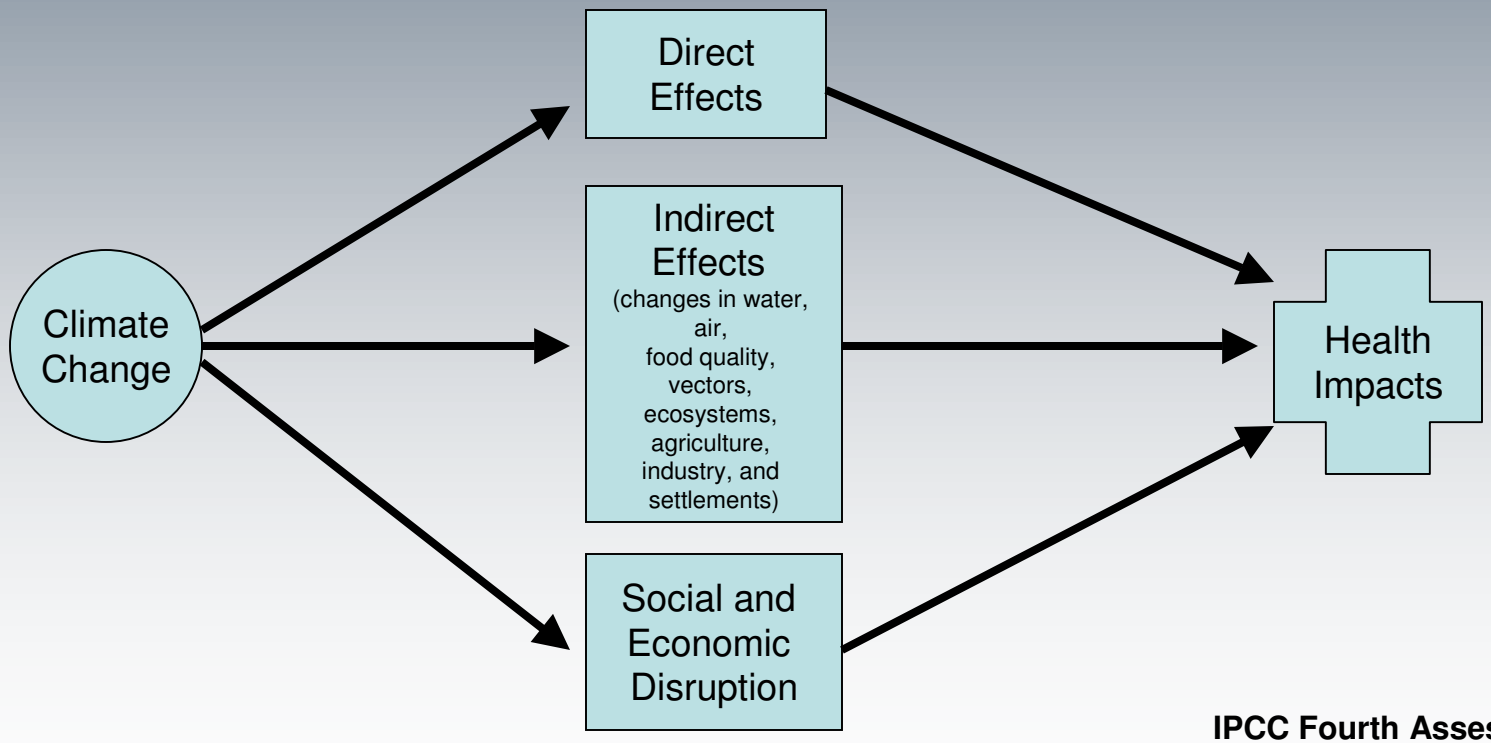
IPCC Fourth Assessment Report

Working Group II Report "Impacts, Adaptation and Vulnerability“

Chapter 8. Human Health

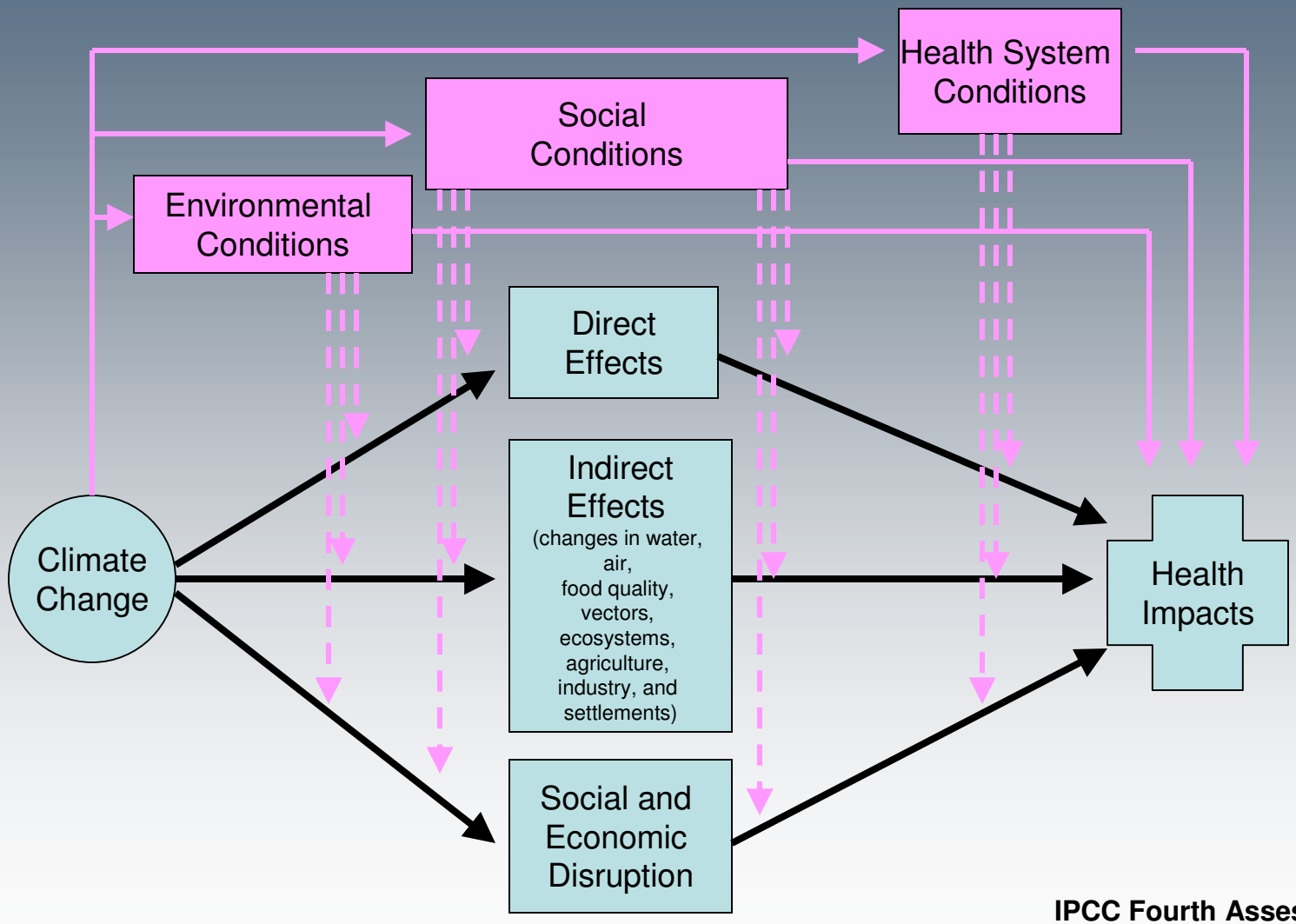
Graduate School of Public Health
University of Pittsburgh

Figure 8.1. ***Schematic diagram of pathways by which climate change affects health, and concurrent direct-acting and modifying (conditioning) influences of environmental, social and health-system factors.***



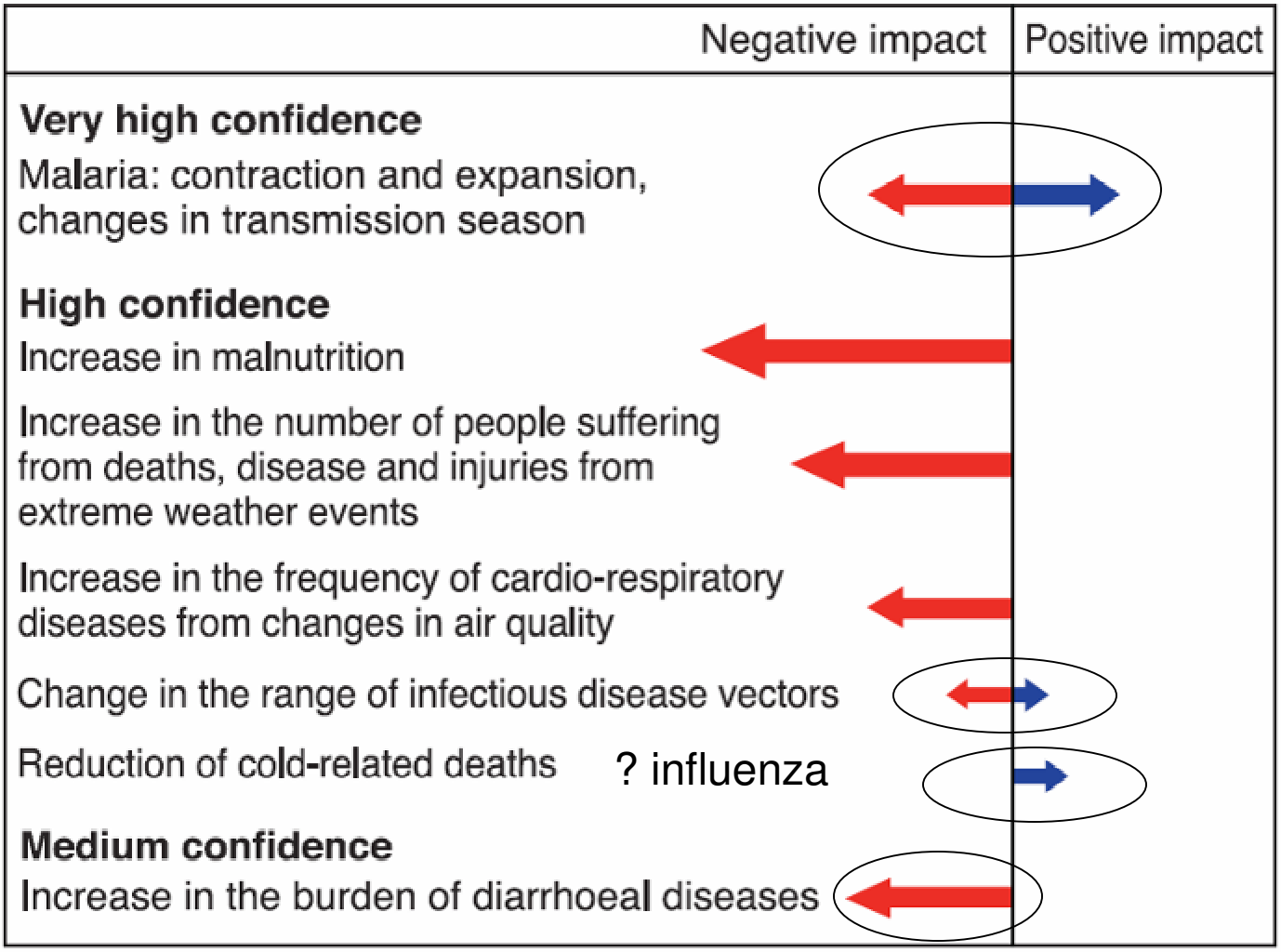
IPCC Fourth Assessment Report

Figure 8.1. ***Schematic diagram of pathways by which climate change affects health, and concurrent direct-acting and modifying (conditioning) influences of environmental, social and health-system factors.***



IPCC Fourth Assessment Report

Figure 8.3 Direction and magnitude of change of selected health impacts of climate change (takes into account numbers of people at risk and potential adaptive capacity).



IPCC Fourth Assessment Report

How does Al Gore deal with infectious diseases in <u>An Inconvenient Truth</u> ?

" There are cities that were founded because they were just above the mosquito line. Nairobi is one. Harare is another. There are plenty of others. Now the mosquitoes with warming are climbing to the higher altitudes. There are a lot of vectors for infectious diseases that are worrisome to us that are also expanding their ranges, not only mosquitoes but all of these others as well.

And we've had 30 so called new diseases that have emerged just in the last quarter century. And a lot of them like SARS have caused tremendous problems. The resistant forms of tuberculosis. There are others.

And there's been a reemergence of some diseases that were once under control. The avian flu, of course, quite a serious matter as you know. West Nile virus. It came to the eastern shore of Maryland in 1999. Two years later it was across the Mississippi. And two years after that it had spread across the continent.

But these are very troubling signs."

Al Gore
An Inconvenient Truth

RECAP

Recent assessments of the probable impact of global climate change on infectious diseases have been cautious and measured. This honestly reflects the scientific uncertainties involved.

No apocalyptic pronouncements.

Q: Why the uncertainty?
A: Epidemic diseases are dynamic, non-linear processes.

Any robust assessment of the impact of climate change on epidemic infectious diseases must be evaluated using dynamical models.

Word arguments and static arrow diagrams ("St. Sebastian diagrams") are not persuasive.

Infectious Disease Dynamics: Dengue and Influenza

Under the Weather
Examples of Diseases Influenced by Environmental Conditions

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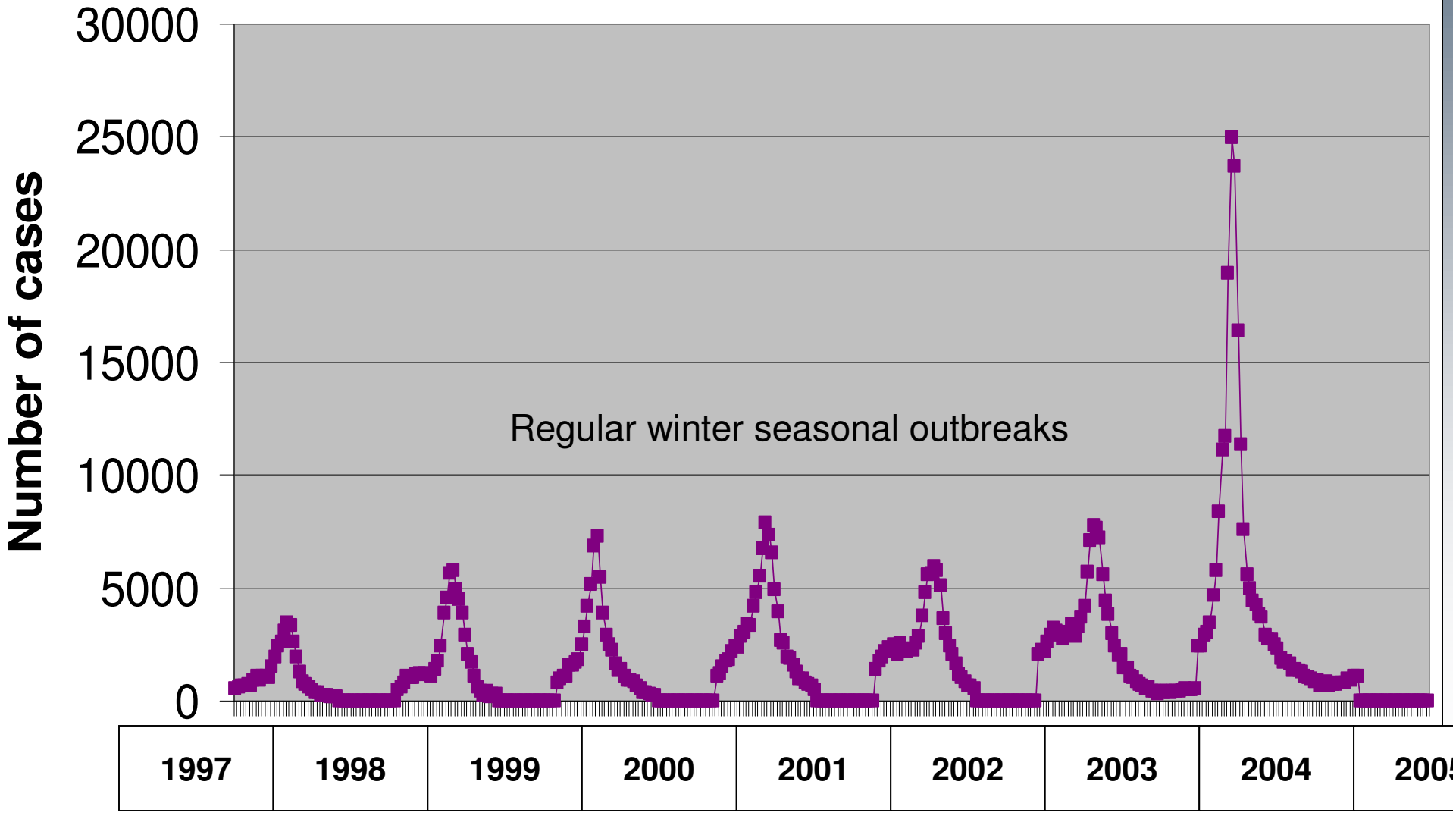
INFLUENZA DYNAMICS

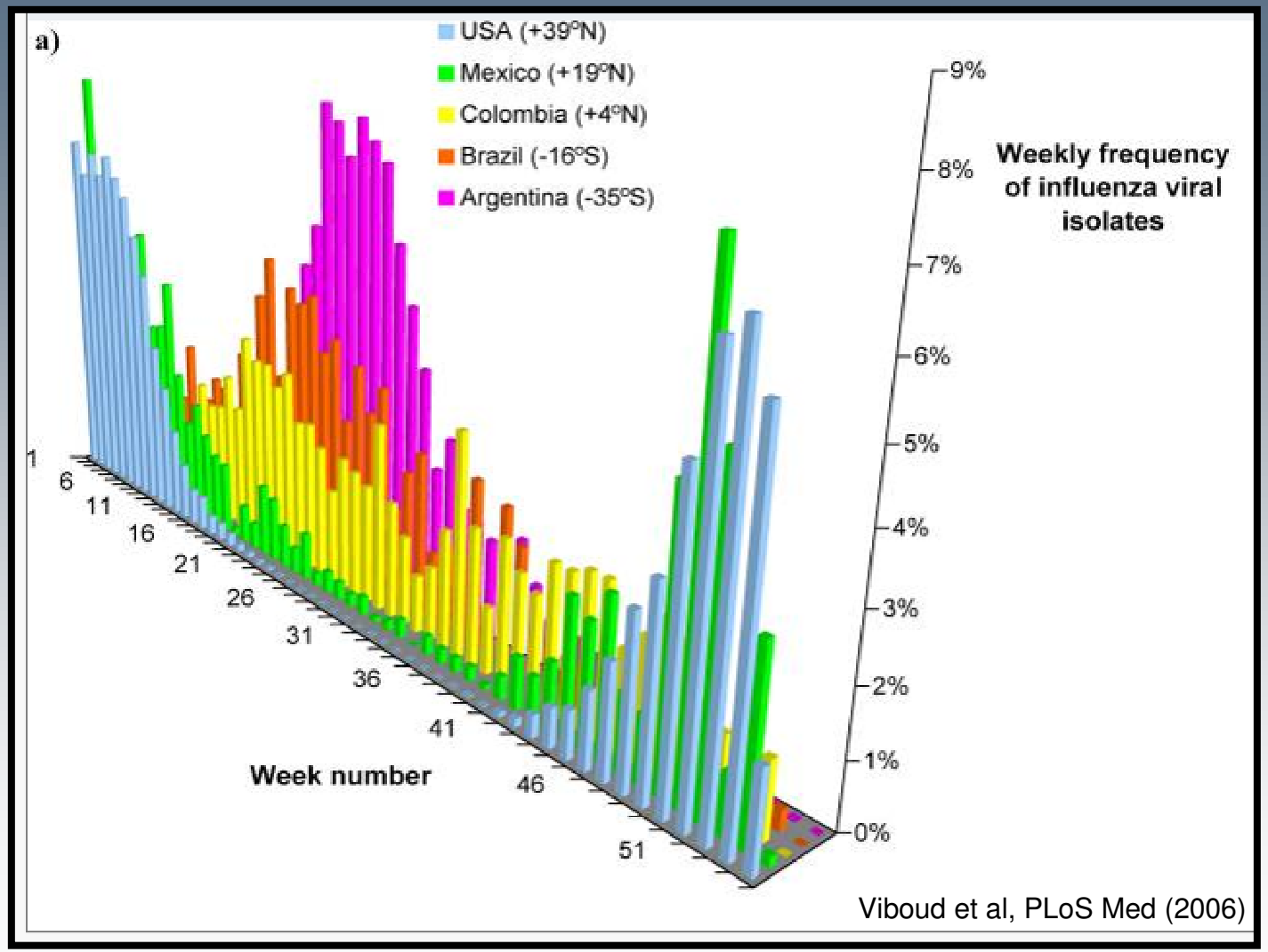
Influenza - Like - Illness

USA Physicans Surveillance Network 1997-2004

US CDC



Seasonality of Influenza Varies with Latitude



Viboud et al, PLoS Med (2006)

WHY IS INFLUENZA A WINTER DISEASE ? SOME PLAUSIBLE MECHANISMS

Environment

Low temperature and low relative humidity

Host immunity

Physiologic change due to photo-period
Low vitamin D due to decreased sunshine

Crowding & Contact

School season crowding
More time indoors

PLoS PATHOGENS
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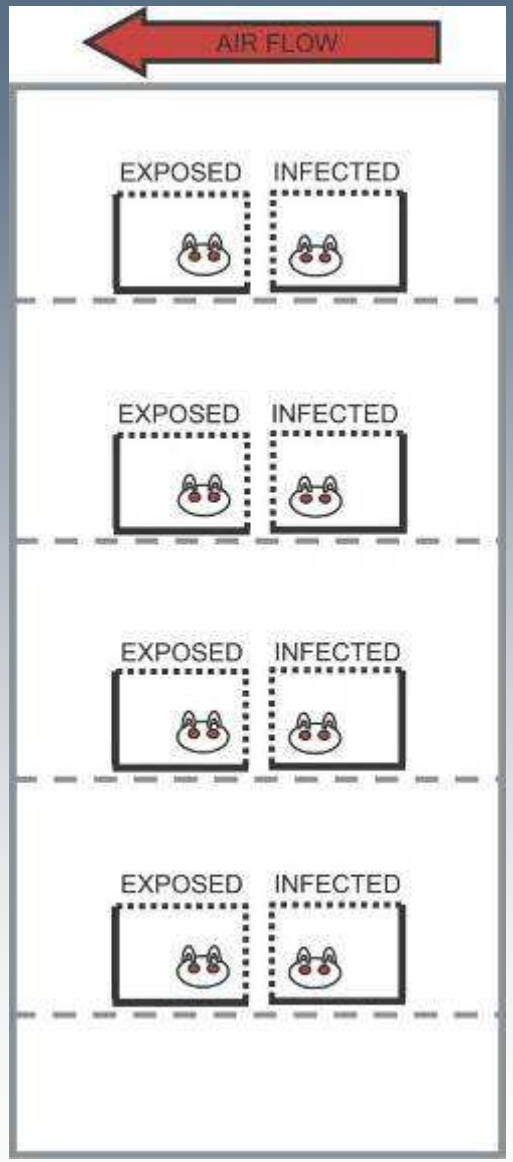
Influenza Virus Transmission Is Dependent on Relative Humidity and Temperature

Anice C Lowen, Samira Mubareka, John Steel, and Peter Palese

Lowen et al, PLoS Pathogen 2007

Arrangement of Infected and Exposed Guinea Pigs in Environmental Chamber



Virus = A/Panama/99; H3N2

Lowen et al, PLoS Pathogen 2007

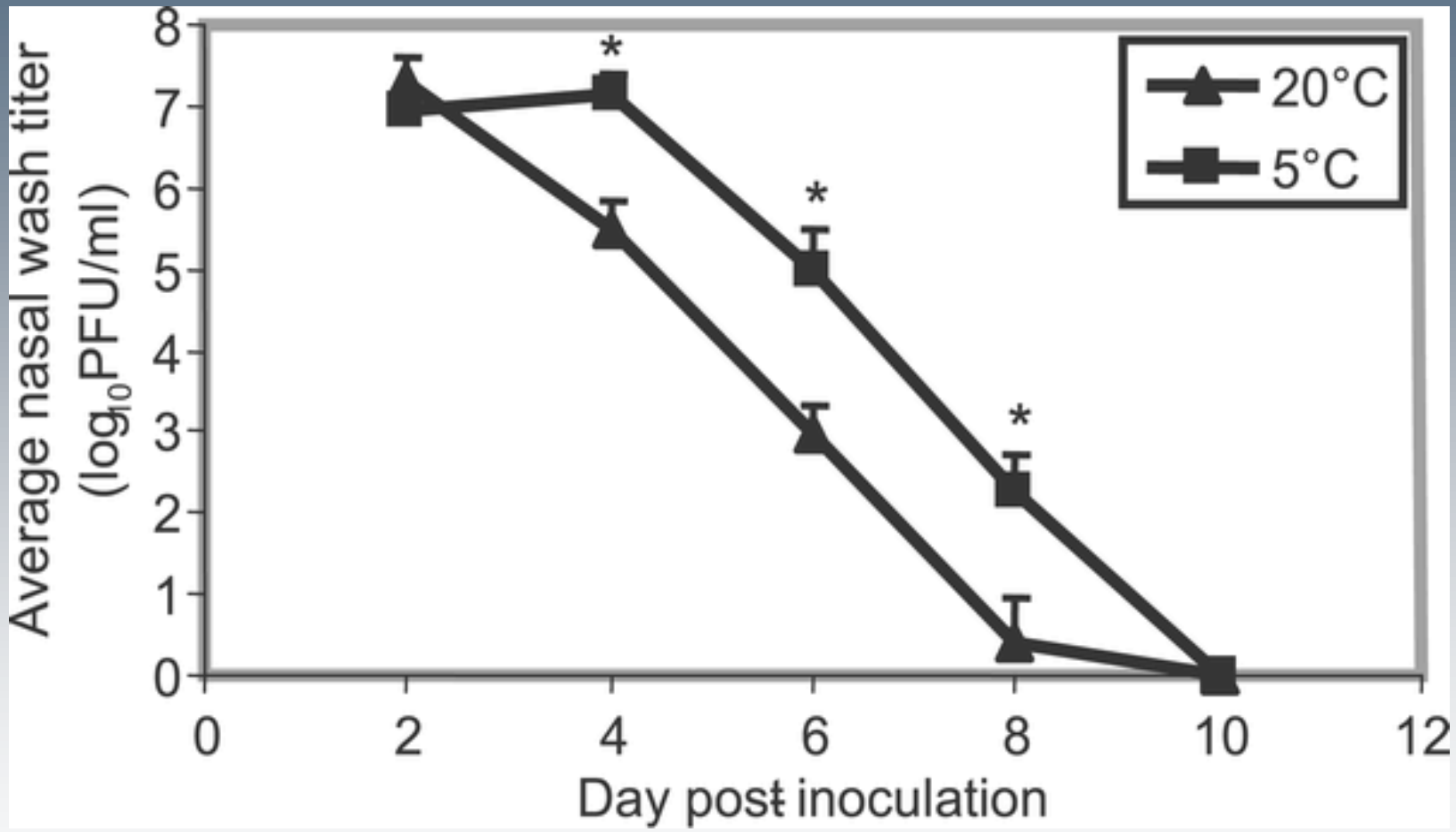
TRANSMISSION OF INFLUENZA FROM INFECTED TO EXPOSED GUINEA PIGS

Results shown as N of 4 exposed animals per group that became infected

	20%RH	35%RH	50%RH	65%RH	80%RH
5 deg		4	4	2	2
5 deg		4	3	2	2
20 deg	4	4	1	3	0
20 deg	3	4	1	3	0
30 deg		0			
30 deg		0			

Lowen et al, PLoS Pathogen 2007

Viral shedding is increased in infected animals held at 5 degrees C.



Lowen et al, PLoS Pathogen 2007

Conclusion from Lown et al:

Aerosol transmission of influenza is increased by low temperature and low relative humidity

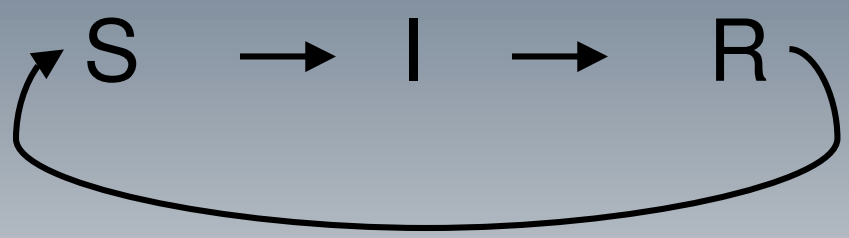
Increased transmission at low temperatures is probably caused by increased viral shedding

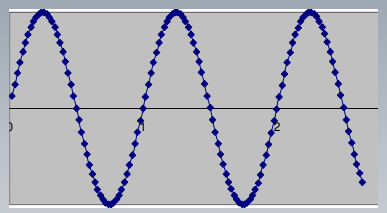
Increased transmission at low relative humidity may be due to formation of bio-aerosol droplet nuclei

Q: HOW MUCH SEASONAL CHANGE IN TRANSMISSIBILITY IS NEEDED TO SEE TYPICAL SEASONAL OSCILLATIONS OF INFECTIOUS DISEASES ?

A: IT DEPENDS ON HOW SEASONAL CHANGES IN TRANSMISSIBILITY INTERACT (RESONATE) WITH OTHER OSCILLATIONS INHERENT IN THE EPIDEMIC PROCESS

Epidemic Systems Can Display Intrinsic Oscillations Without Requiring Any Seasonal Effects on Transmissibility eg S-I-R-S systems





$$dI/dt = \beta I S/N - I/D$$

$$dS/dt = R/L - \beta I S/N$$

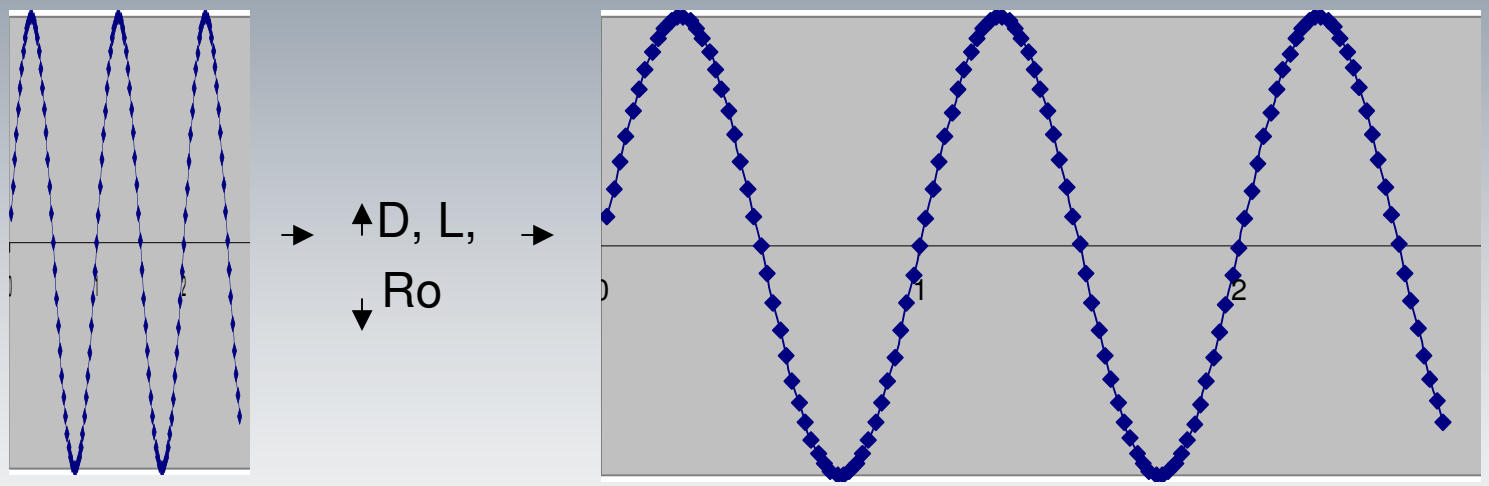
N = Number in Total Population
S = Susceptible
I = Infected
R = Recovered = Immune = N - S - I
D = Duration of Infection
L = Length of Immunity
β = Transmissibility
no births and deaths

Dushoff et al PNAS 2004

S-I-R-S

Intrinsic Period of oscillation approx = $P = 2\pi\sqrt{D\,L / (R_o - 1)}$

D = Duration of Infection
L = Length of Immunity
R_o = # secondary infections caused by a single infected person



Different diseases may have different intrinsic oscillation frequencies. This intrinsic oscillation frequency need not be seasonal (1 year).

β is the transmissiblity parameter

$$dI / dt \approx \beta \times (I \times S)$$

Dushoff et al PNAS 2004

What happens if we impose seasonality? That is, instead of a fixed β we allow β to vary sinusoidally (seasonally) ?

$$\beta(t) = \beta o\ (1 + \beta 1 \cos(2 \pi t))$$

How does this exogenous *"forcing"* oscillation of transmissibility interact with the intrinsic S-I-R-S oscillation?

Dushoff et al PNAS 2004

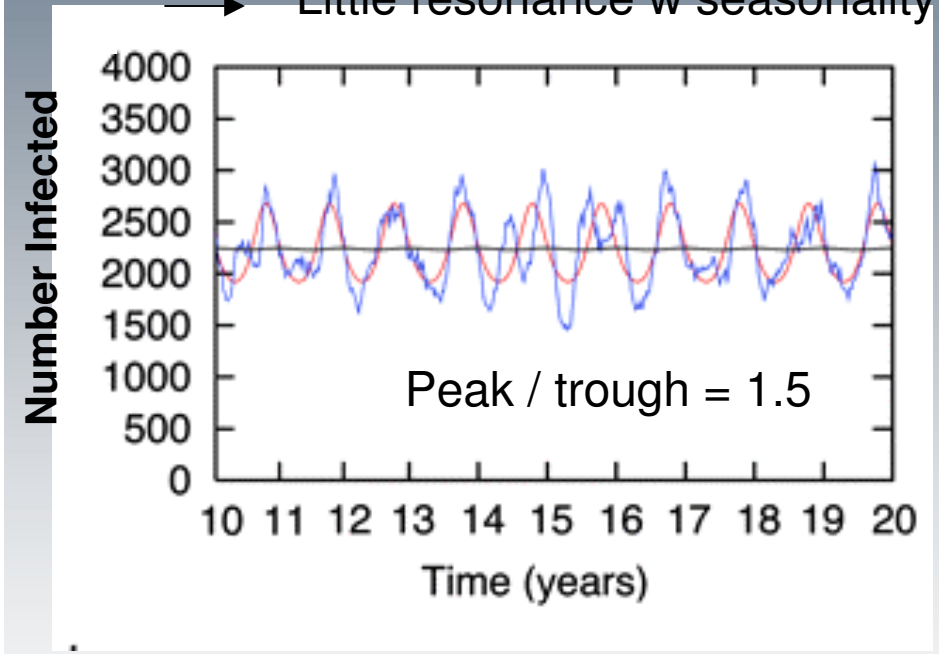
Let β oscillate sinusoidally by only +/- 4 %, and impose this on S-I-R-S systems with different intrinsic periods of oscillation

Dushoff et al PNAS 2004

Let β oscillate sinusoidally by only +/- 4 %, and impose this on S-I-R-S systems with different intrinsic periods of oscillation

Intrinsic SIRS period of oscillation = 0.59 yr

→ Little resonance w seasonality



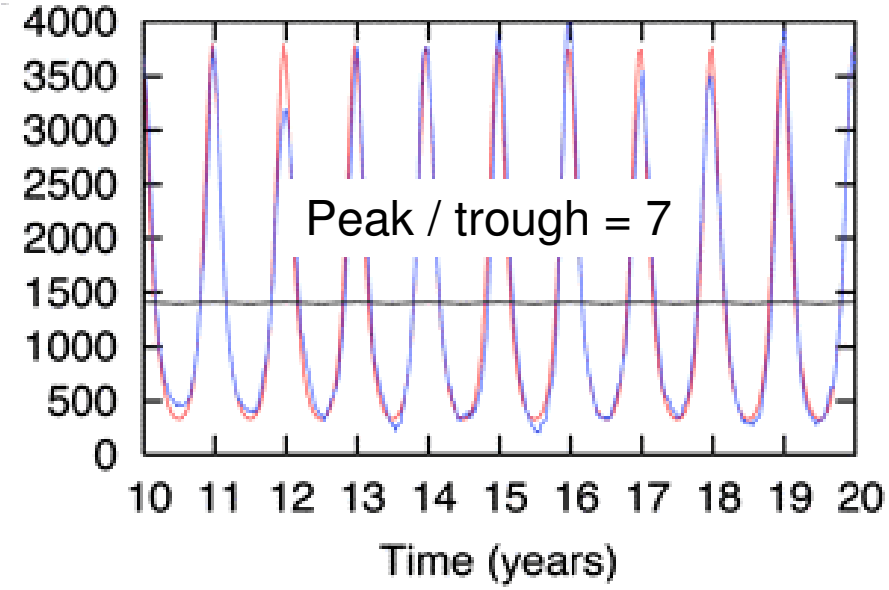
deterministic & stochastic versions

Dushoff et al PNAS 2004

Let β oscillate sinusoidally by only +/- 4 %, and impose this on S-I-R-S systems with different intrinsic periods of oscillation

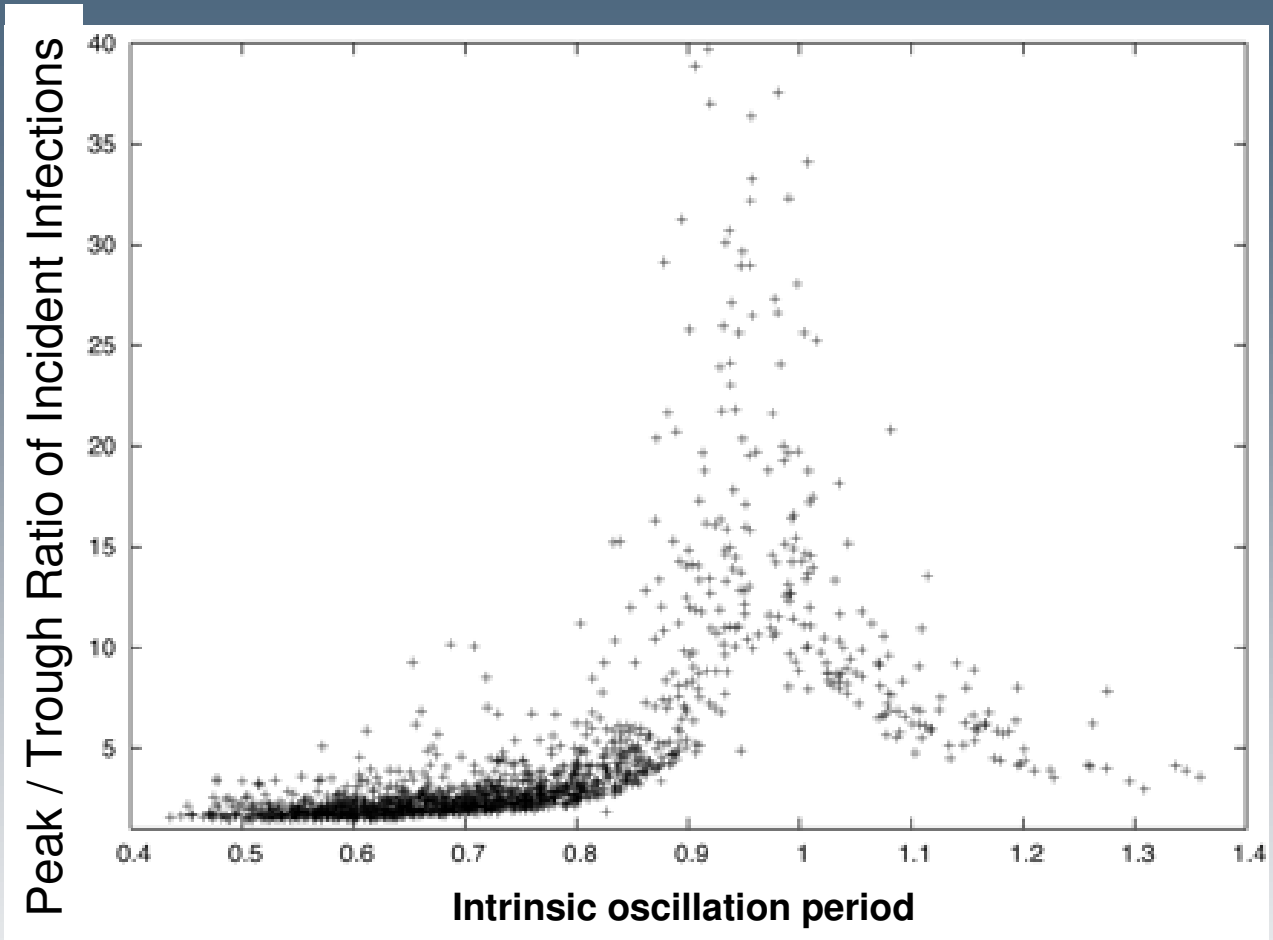
Intrinsic SIRS period of oscillation = 0.94 yr

→ Strong resonance w seasonality



deterministic & stochastic versions

Dushoff et al PNAS 2004



Fixed small seasonal **β** oscillation (4%)
Random combinations of D, L, Ro -> Various intrinsic oscillation values
Strong non-linear resonance of when intrinsic oscillation period = 1 = seasonal

Dushoff et al PNAS 2004

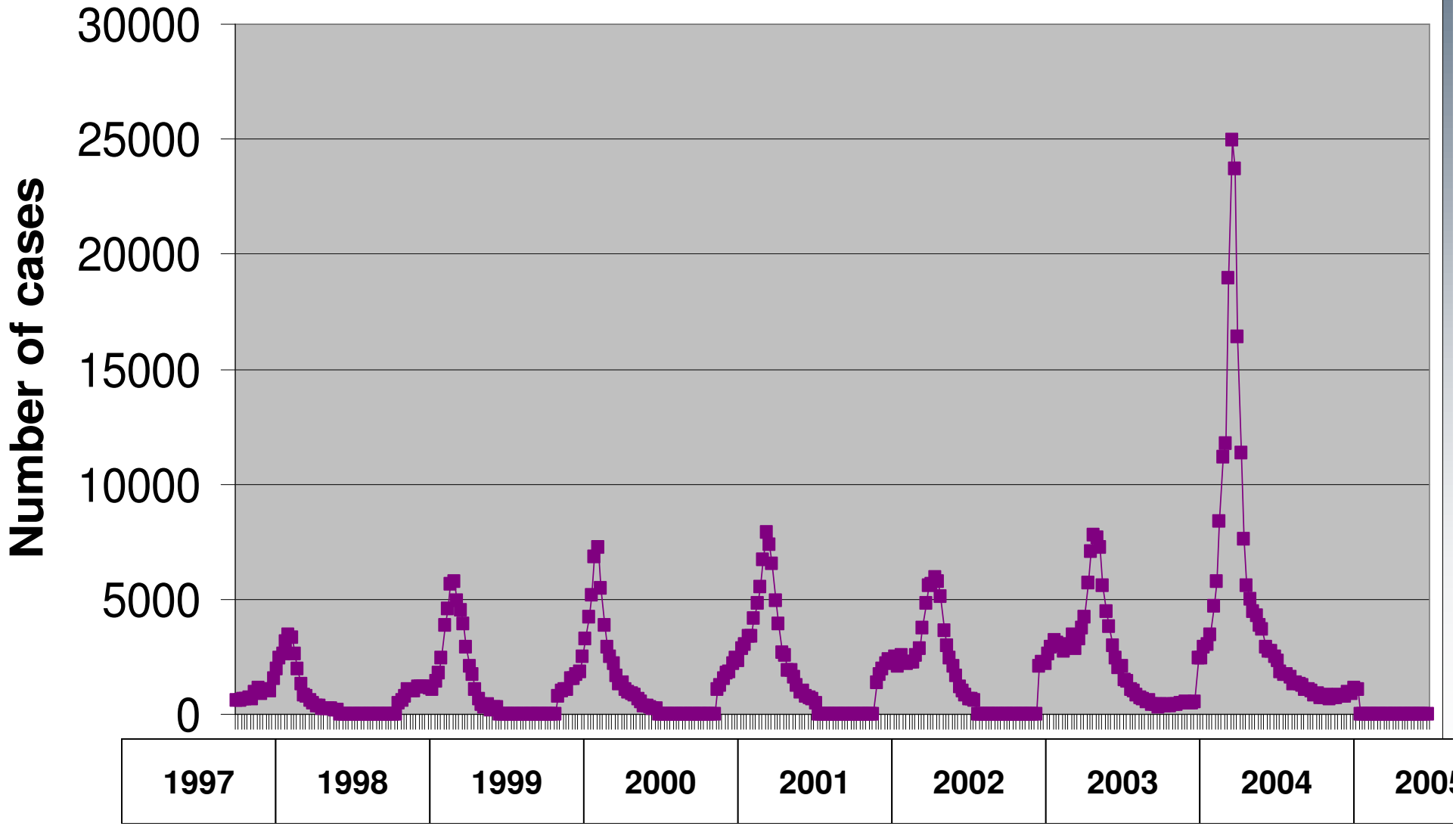
Conclusion from Dushoff et al

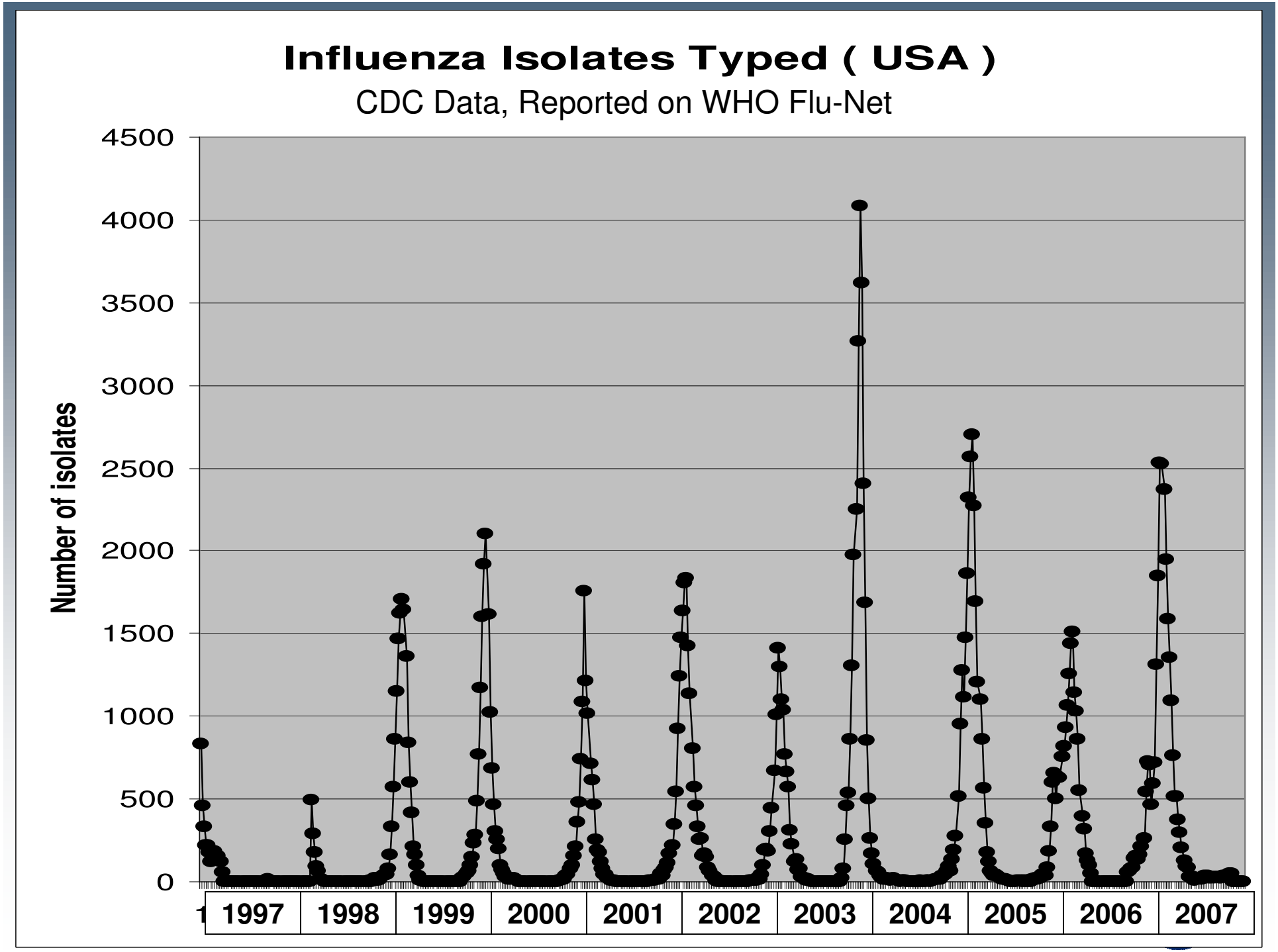
In a theoretical system, large annual oscillations in incidence may be driven by very small seasonal changes in transmissibility

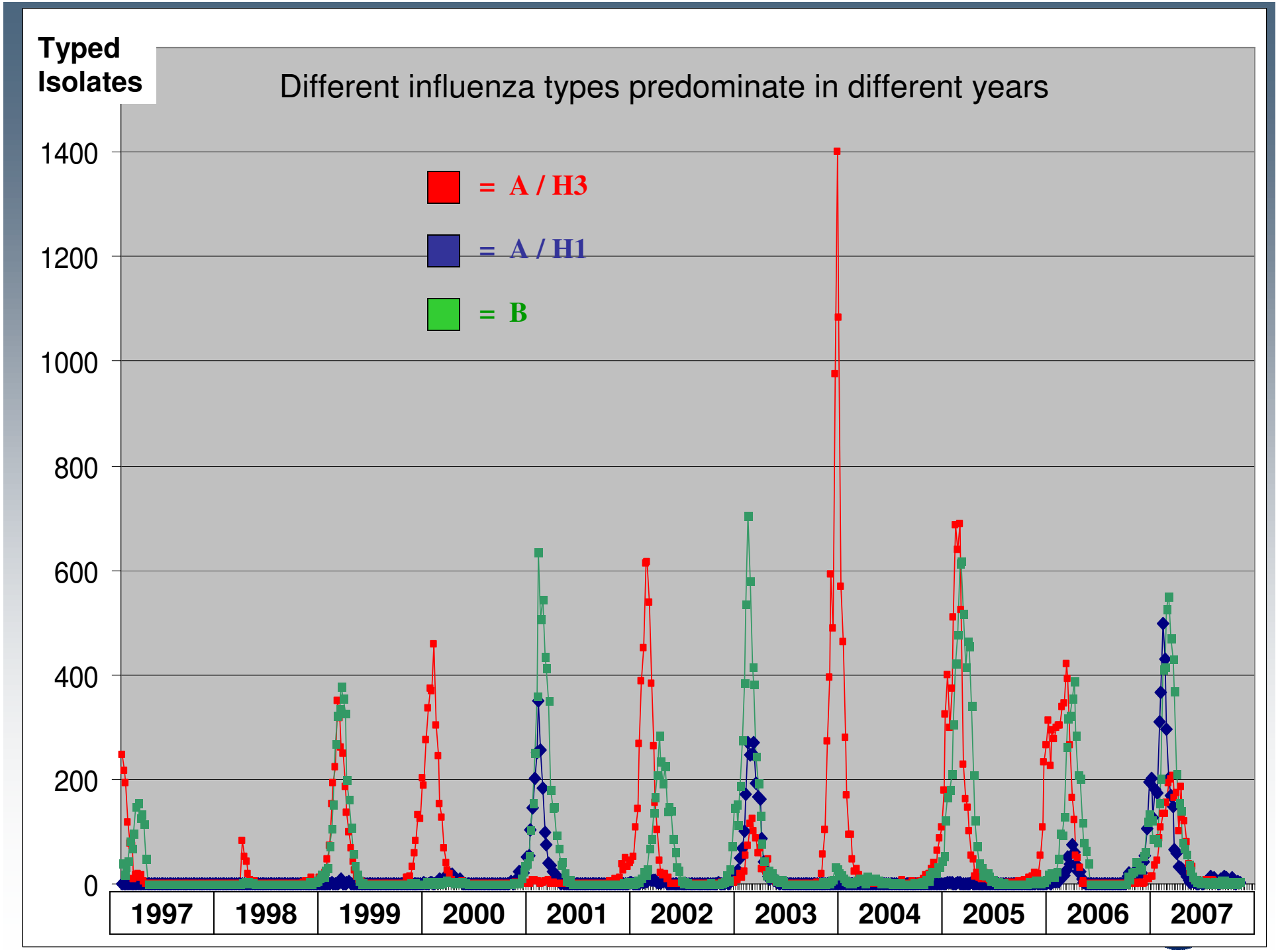
[…. if there is resonance between the intrinsic oscillation period and seasonal oscillation in transmissibility]

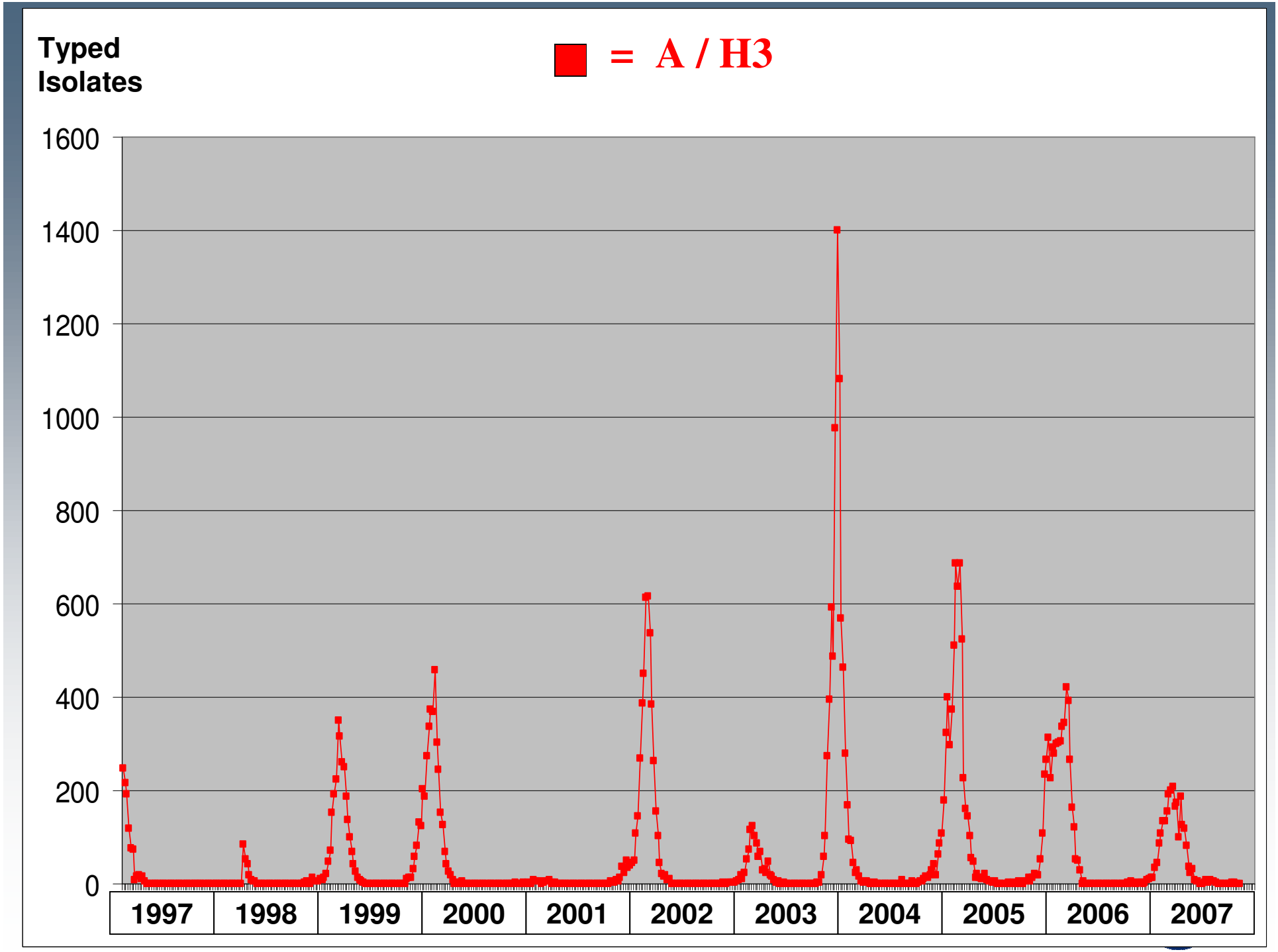
What about real world data on influenza seasonality?

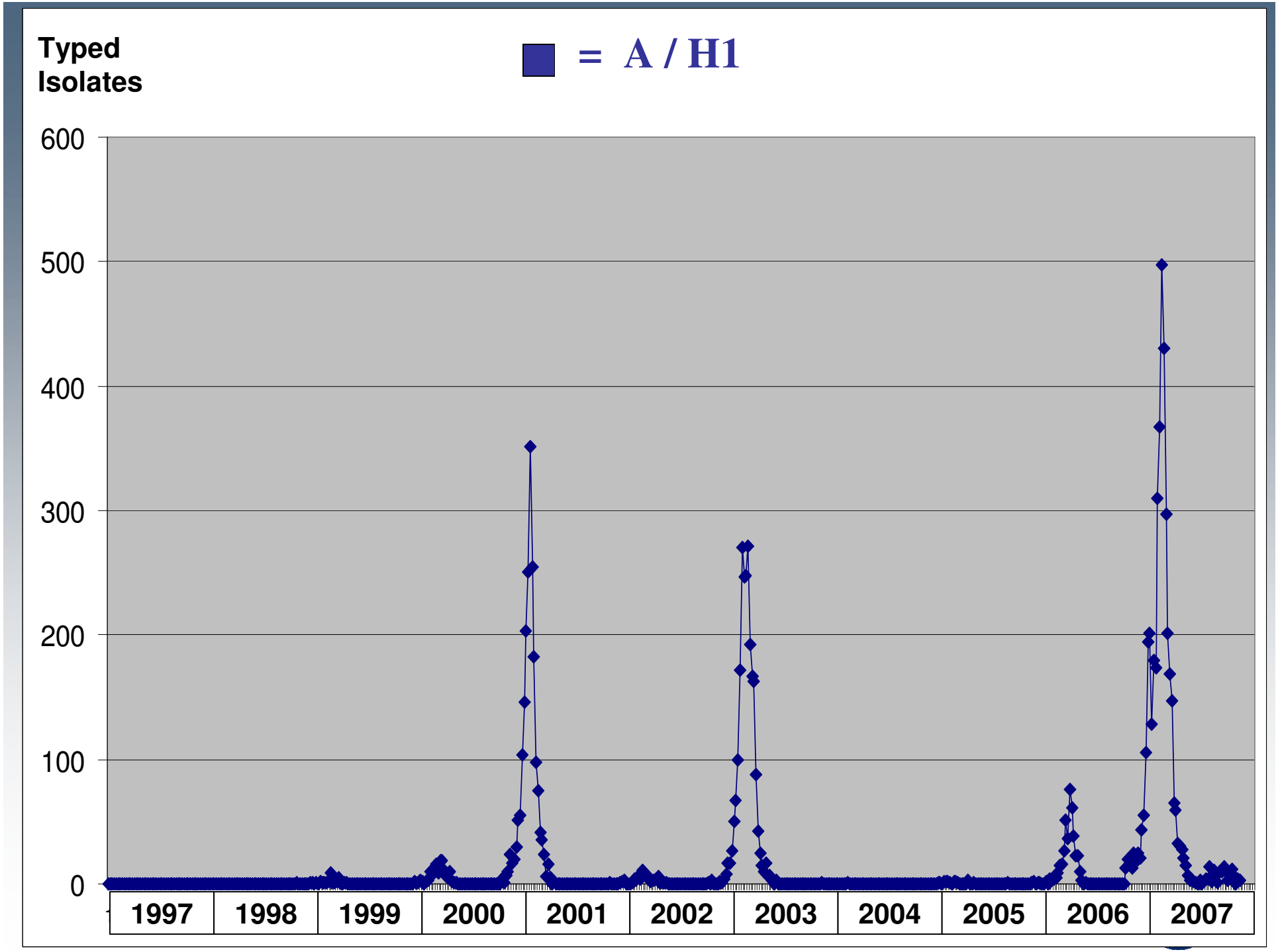
Total ILI USA Physicans Surveillance Network 1997-2004

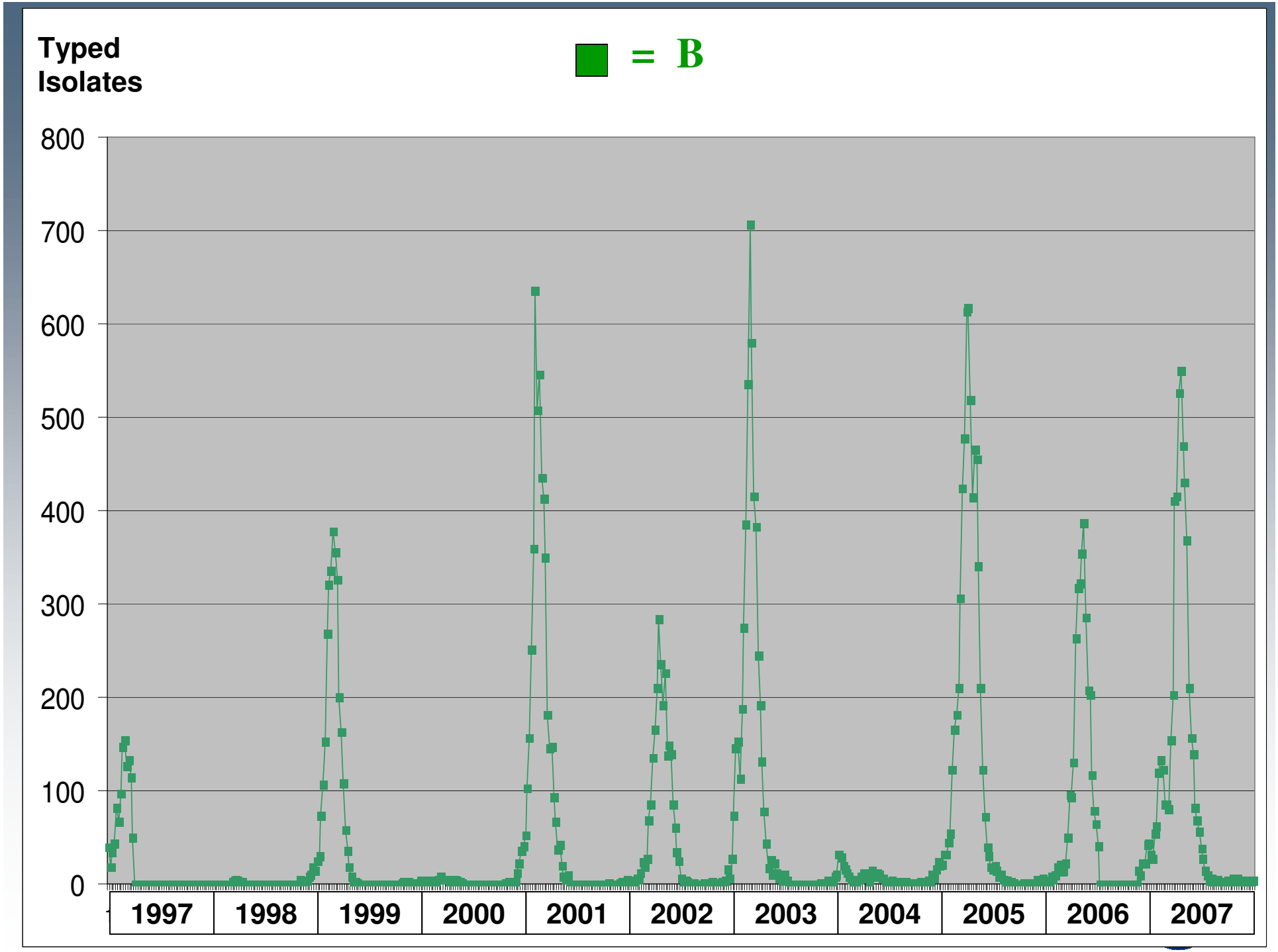


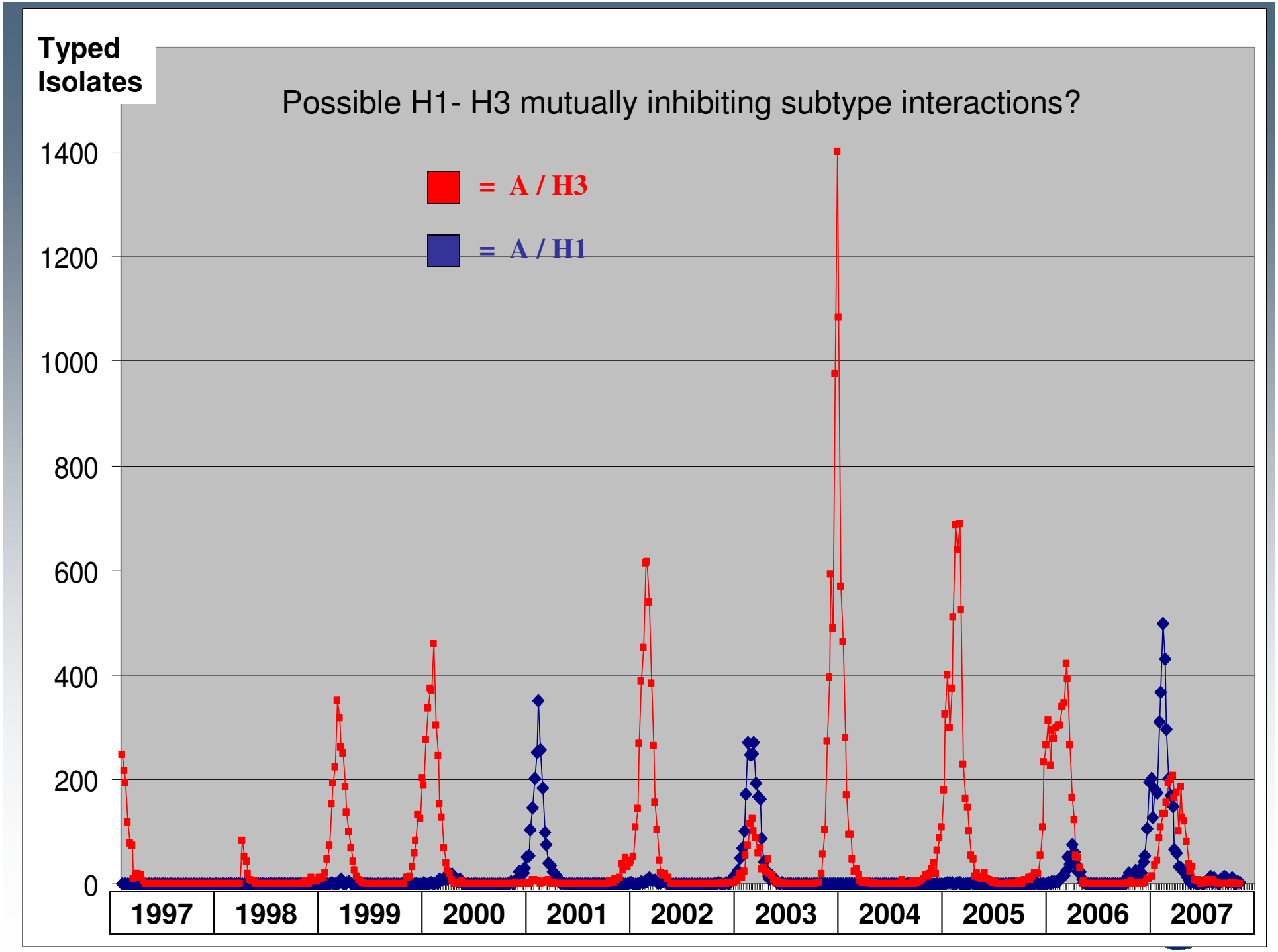

Influenza Isolates Typed (USA)
CDC Data, Reported on WHO Flu-Net
Number of isolates
4500
4000
3500
3000
2500
2000
1500
1000
500
0
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007


Typed Isolates
Different influenza types predominate in different years
= A / H3
= A / H1
= B
1400
1200
1000
800
600
400
200
0
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007


Typed Isolates
= A / H3
1600
1400
1200
1000
800
600
400
200
0
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007


Typed Isolates
= A / H1
600
500
400
300
200
100
0
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007


Typed Isolates
= B
800
700
600
500
400
300
200
100
0
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007


Typed Isolates
Possible H1- H3 mutually inhibiting subtype interactions?
= A / H3
= A / H1
1400
1200
1000
800
600
400
200
0
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007

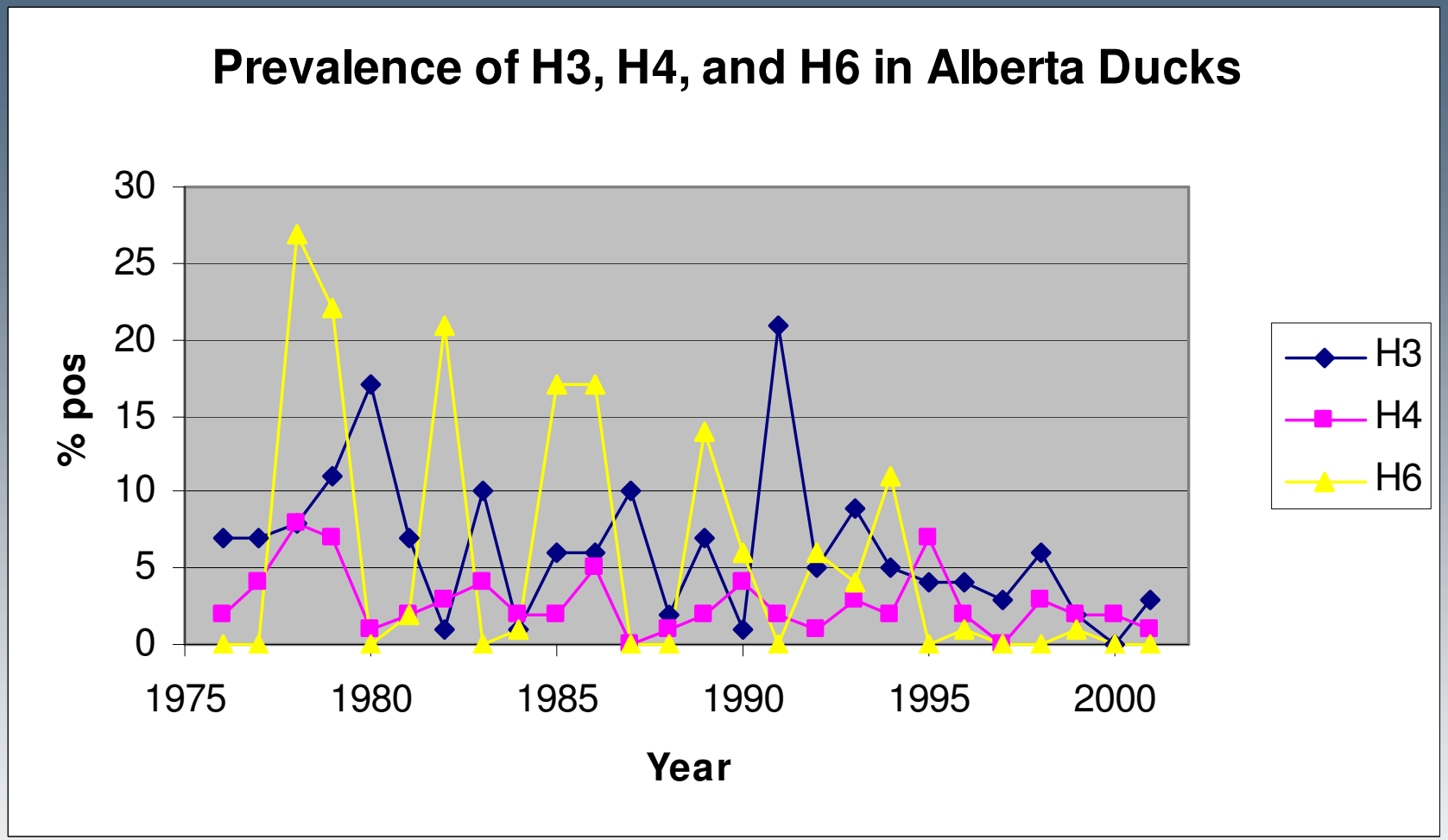
What do we know about the transmissibility of Influenza A/H3 vs A/H1 vs B

Do all three have the same, or different, **endogenous** oscillation periods ?

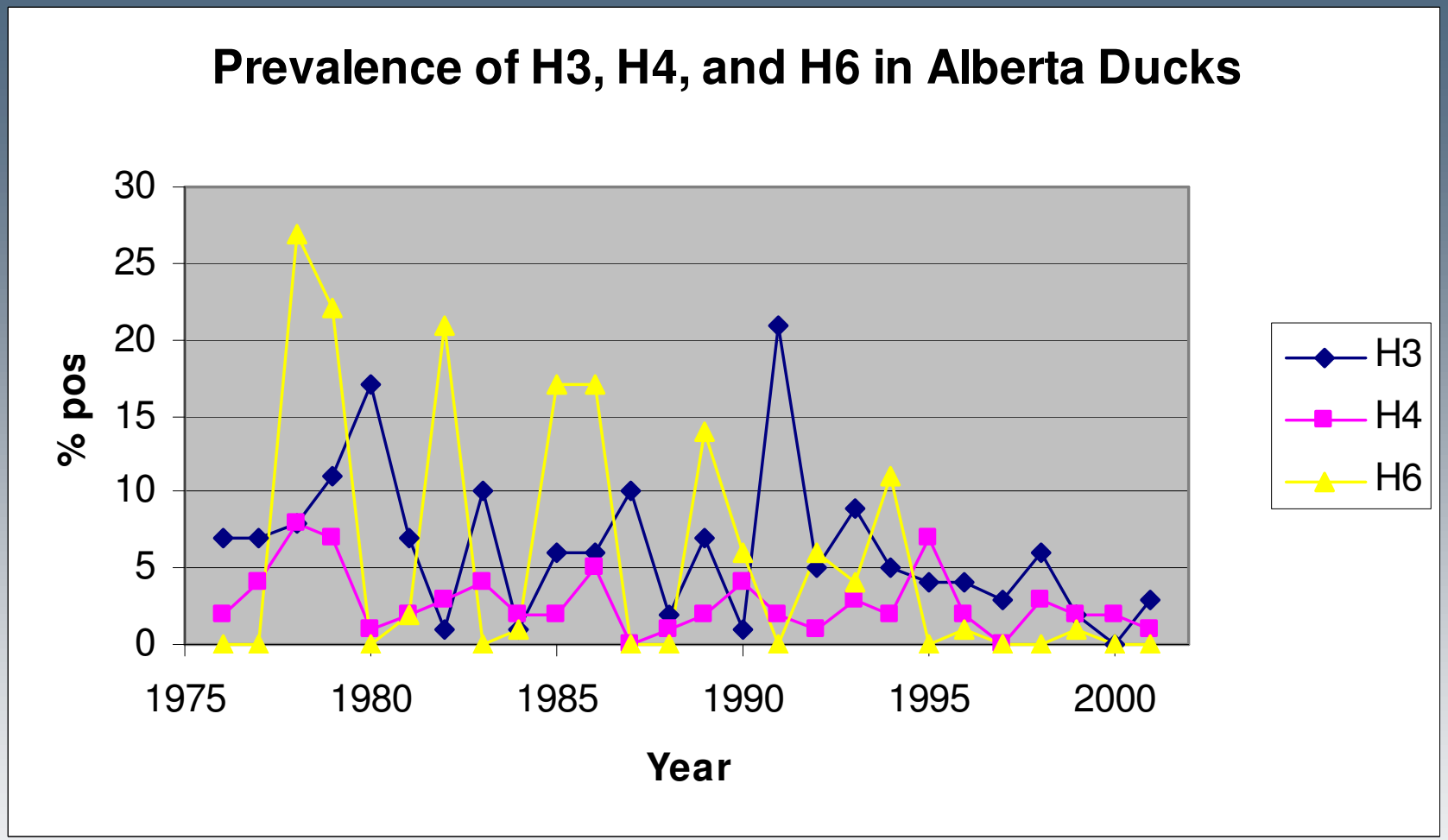
Do all three have the same, or different, seasonal **β** transmissibility oscillation ?

Given that **β** H3 is sensitive to temperature and humidity (see guinea pig experiments). Does this explain H3 seasonality? Are **β** H1 and **β** B similarly sensitive to temperature and humidity ?

What do we know about influenza dynamics in avian populations?



Krauss et al. Vector-borne and Zoonotic Diseases (2004)



? Endogenous oscillations ? Seasonal β transmissibility variations

? β H3 = β H4 = β H6

Krauss et al. Vector-borne and Zoonotic Diseases (2004)

DENGUE DYNAMICS

Analytic “top – down” data-driven model

Synthetic “bottom –up” theoretical model

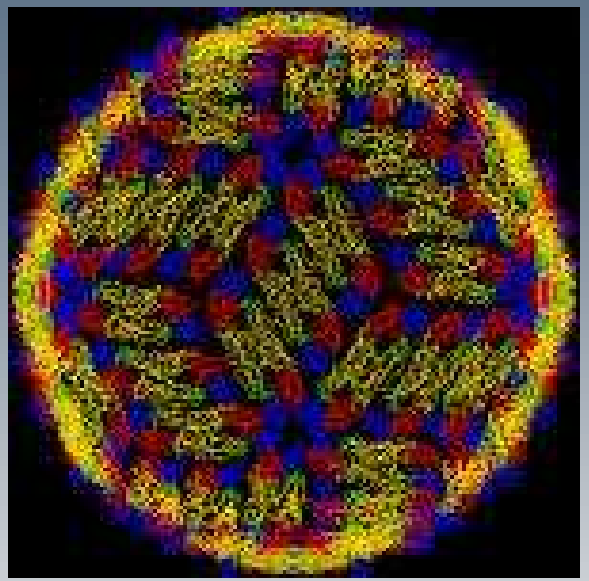
Derek Cummings, Ph.D.
Johns Hopkins Bloomberg School of Public Health

Analytic Model to Detect Patterns in Dengue Hemmorhagic Fever Incidence

Monthly DHF Incidence
Passive Surveillance
72 Provinces
1983-1996
Gathered by Thai Ministry of Public

~850,000 cases

Dengue Virus



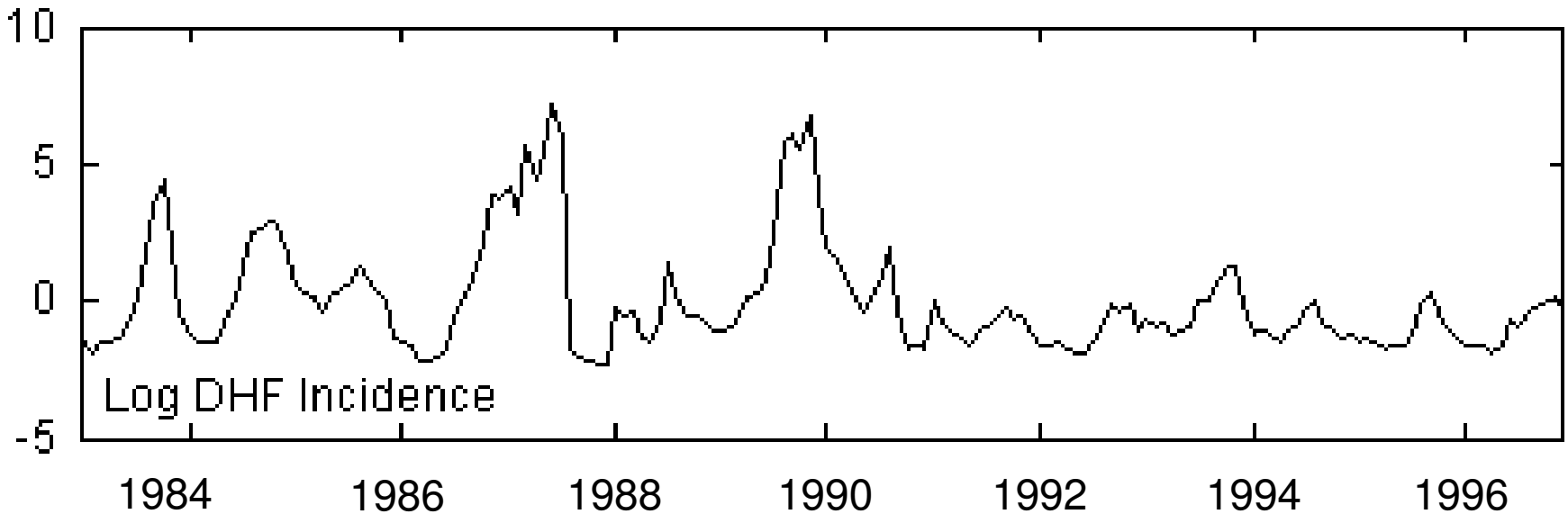
Family Flaviviridae

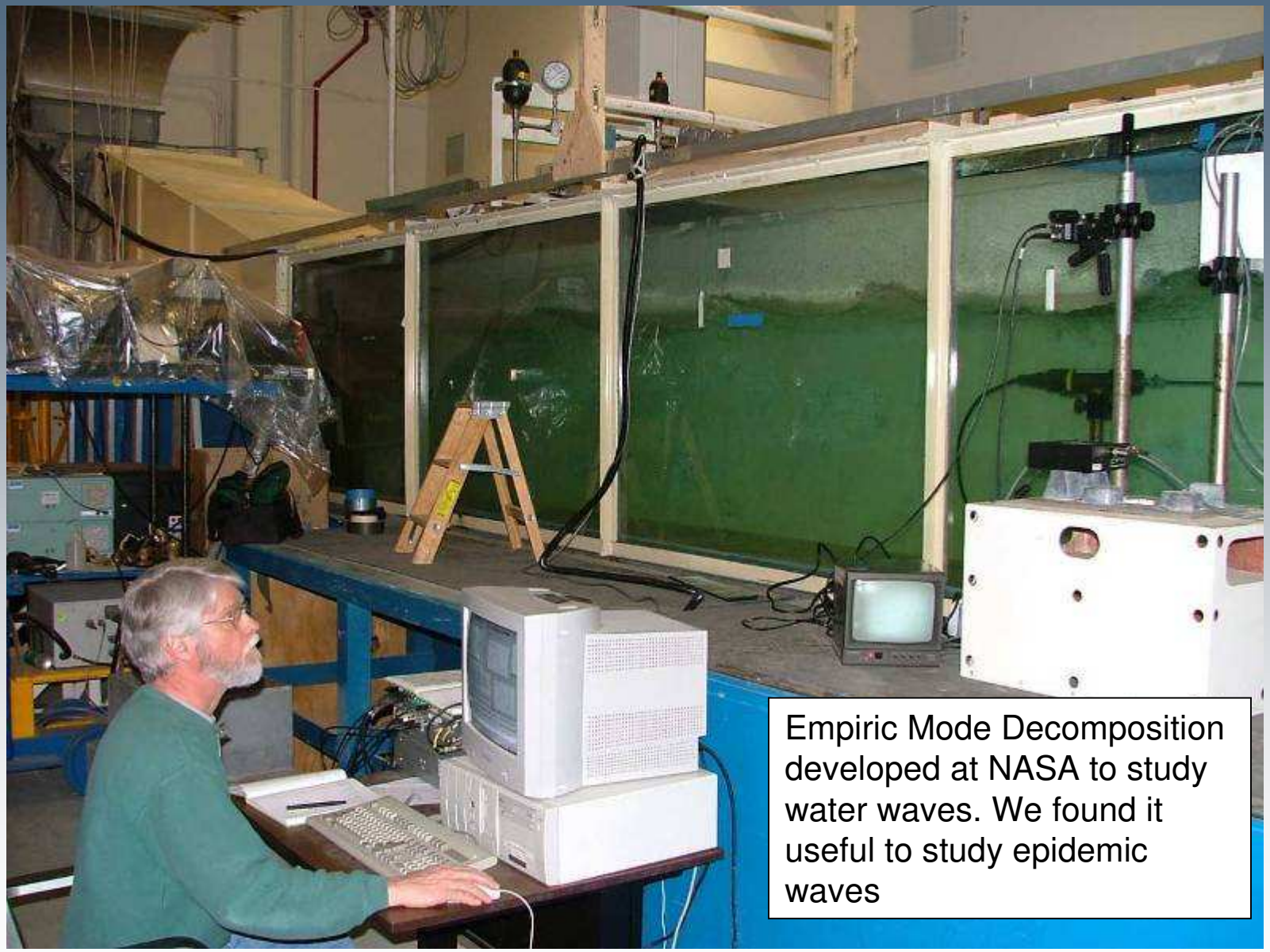
Mosquito-borne

Four antigenically distinct serotypes

Most important mosquito-vector is *Aedes aegypti*

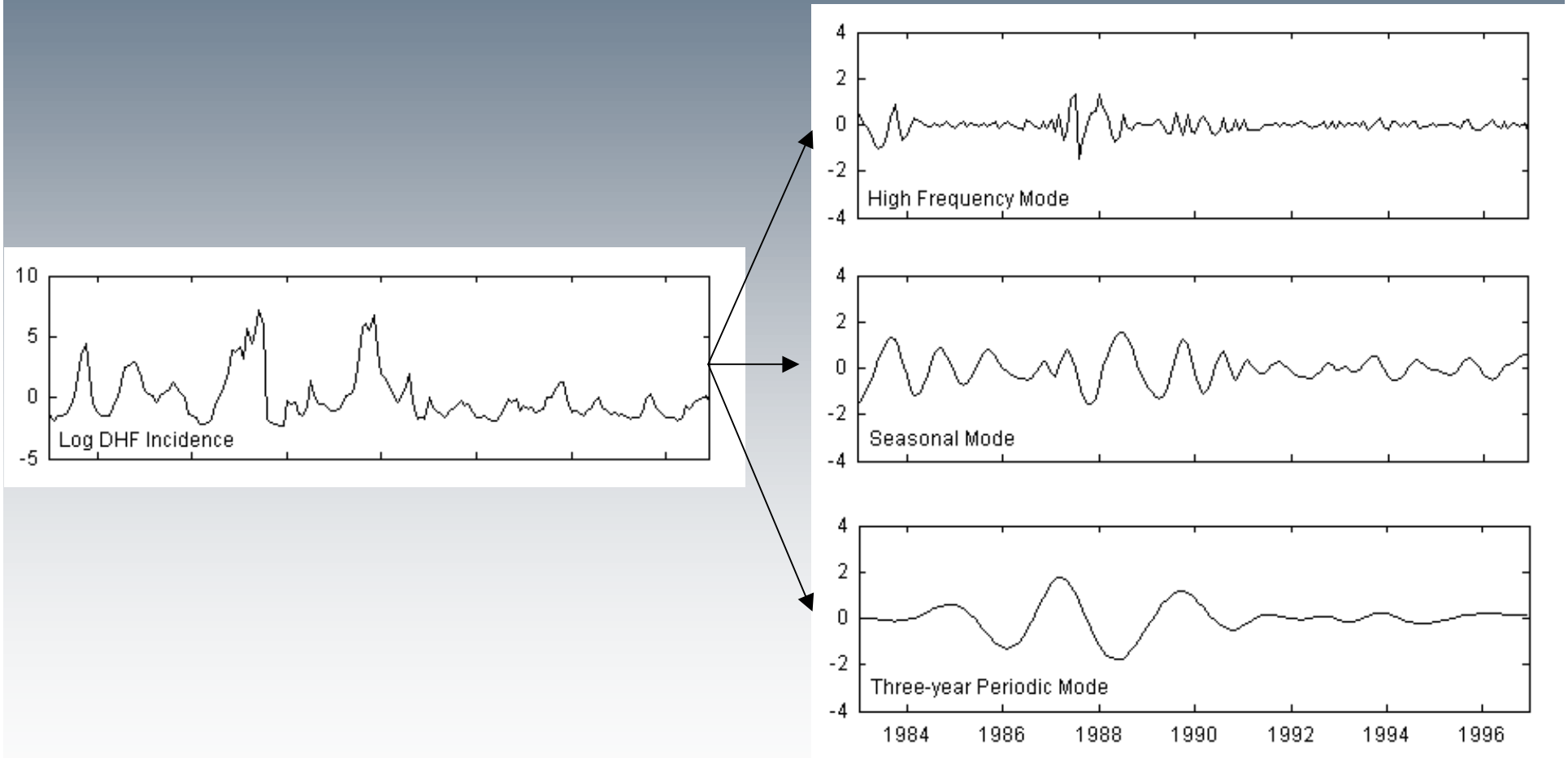
Log of DHF Incidence in Bangkok





Empiric Mode Decomposition developed at NASA to study water waves. We found it useful to study epidemic waves

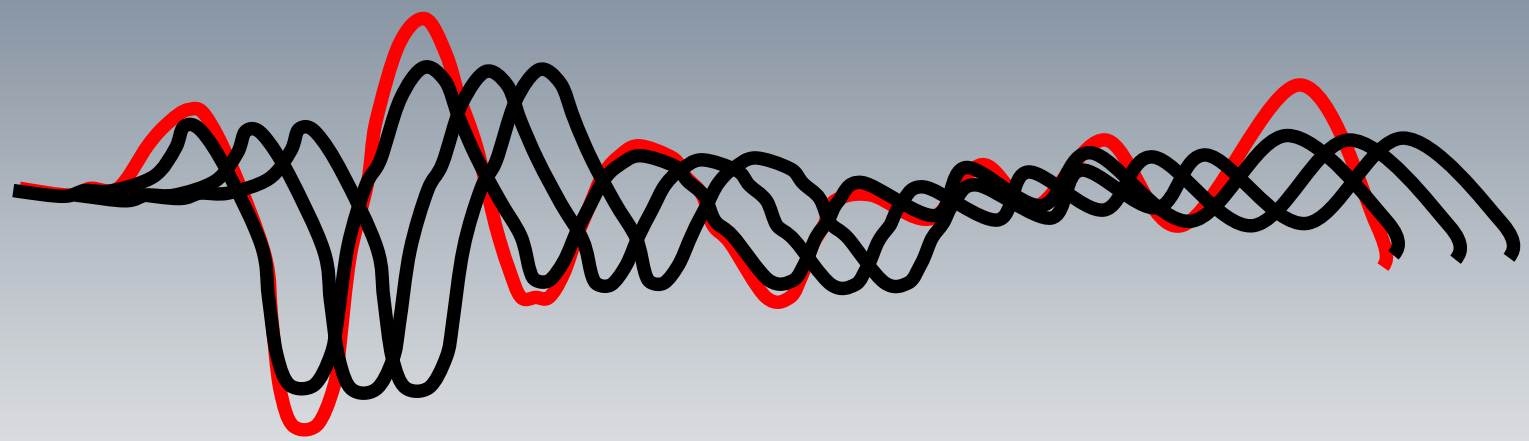
Modal Decomposition of Time Series Using the Empiric Mode Decomposition



Schematic of the three year DHF Intrinsic Mode

= Oscillations in Bangkok

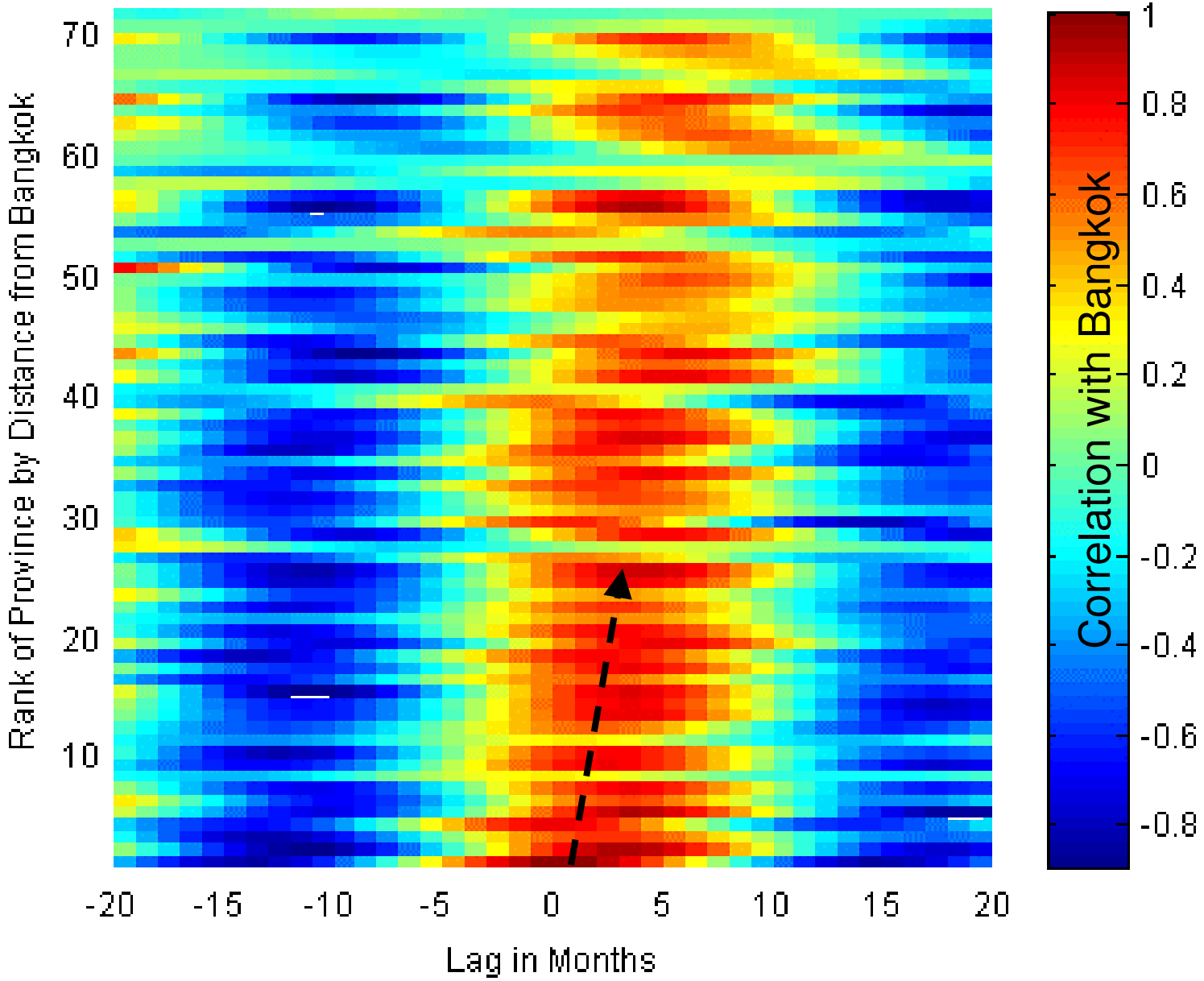
= Oscillations in Provinces



100 km from Bangkok

200 km from Bangkok

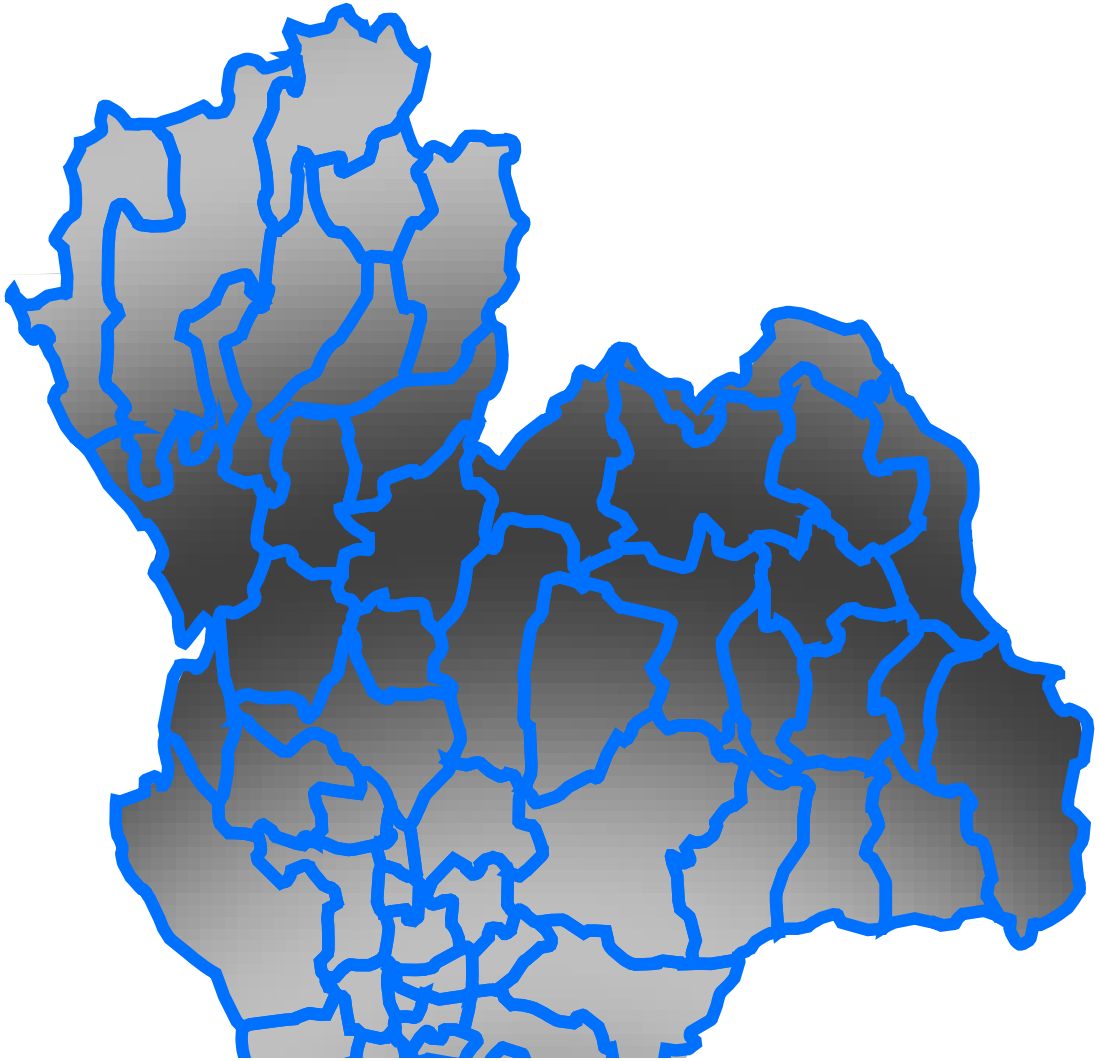
300 km from Bangkok


Rank of Prowince by Distance from Bangkok
70
60
50
40
30
20
10
-20
-15
-10
-5
0
5
10
15
20
Lag in Months
Correlation with Bangkok
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8

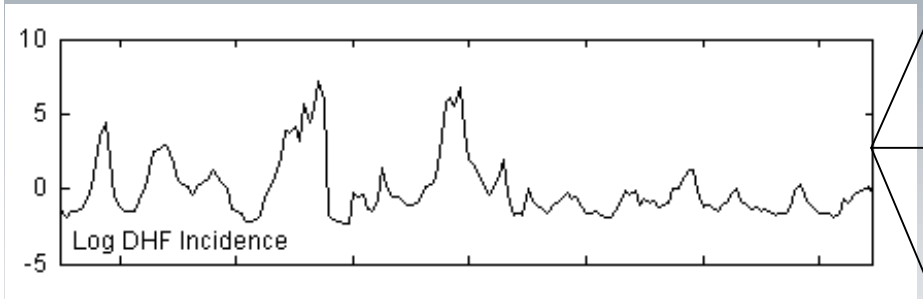
nature 427: 344-7 (2004)

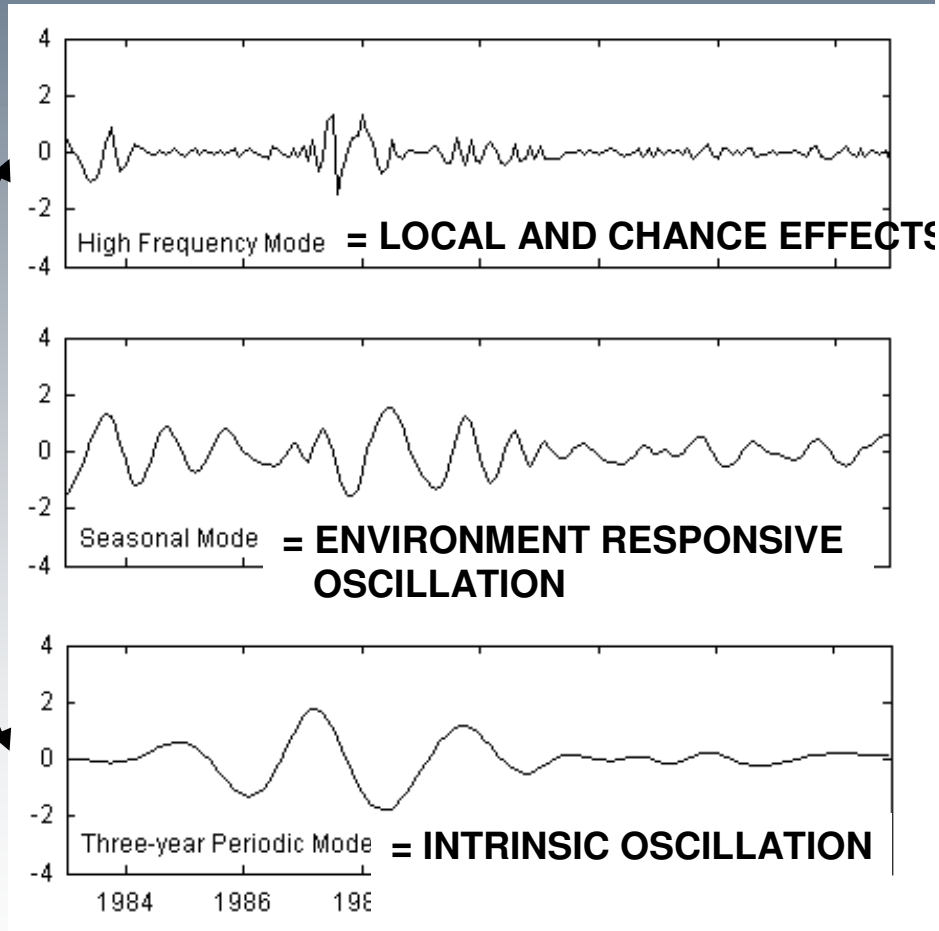
Traveling waves in the occurrence of dengue hemorrhagic fever in Thailand

DEREK A.T. CUMMINGS, RAFAEL A. IRIZARRY, NORDEN E. HUANG, TIMOTHY P. ENDY,
ANANDA NISALAK, KUMNUAN UNGCHUSAK & DONALD S. BURKE

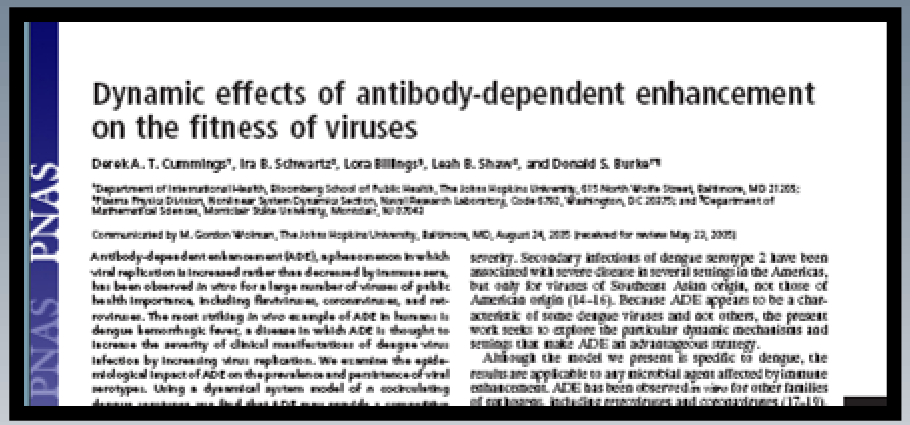


FOR AN ANALYSIS OF THE EFFECTS OF SEASON AND WEATHER ON DHF, THE INTRINSIC TRAVELLING WAVE IS A CONFOUNDER THAT WILL OBSCURE ANY CAUSE AND EFFECT RELATIONSHIPS





Dengue Dynamics
Synthetic, bottom-up theoretical model



PNAS

Dynamic effects of antibody-dependent enhancement on the fitness of viruses

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Antibody-dependent enhancement (ADE), a phenomenon in which viral replication is increased rather than decreased by immune sera, has been observed *in vitro* for a large number of viruses of public health importance, including flaviviruses, coronaviruses, and retroviruses. The most striking *in vivo* example of ADE in humans is dengue hemorrhagic fever, a disease in which ADE is thought to increase the severity of clinical manifestations of dengue virus infection by increasing virus replication. We examine the epidemiological impact of ADE on the prevalence and persistence of viral serotypes. Using a dynamical system model of *n* cocirculating dengue serotypes, we find that ADE may provide a competitive

severity. Secondary infections of dengue serotype 2 have been associated with severe disease in several settings in the Americas, but only for viruses of Southeast Asian origin, not those of Americas origin (14–16). Because ADE appears to be a characteristic of some dengue viruses and not others, the present work seeks to explore the particular dynamic mechanisms and settings that make ADE an advantageous strategy.

Although the model we present is specific to dengue, the results are applicable to any microbial agent affected by immune enhancement. ADE has been observed *in vitro* for other families of pathogens, including arenaviruses and coronaviruses (17–19).

<u>Antibody dependent enhancement of virus replication</u>: Immunity to a cross-reactive dengue type ***increases***, rather than decreases, viral growth, viral burden, and transmissibility upon infection with a second type

Theoretical Transmission Model

SIR model of dengue including four serotypes and enhancement of secondary infections by pre-existing immunity

$$\frac{dX(t)}{dt} = \mu - X(t)\left[\sum_{i=1}^{4}\beta_i\left(Y_i(t) + \phi_i\sum_{i\neq j}Y_{ji}(t)\right)\right] - \mu X(t)$$

$$\frac{dY_i(t)}{dt} = X(t)\left[\beta_i\left(Y_i(t) + \phi_i\sum_{i\neq j}Y_{ji}(t)\right)\right] - \sigma Y_i(t) - \mu Y_i(t)$$

$$\frac{dZ_i(t)}{dt} = \sigma Y_i(t) - Z_i(t)\sum_{j=1,j\neq i}^{4}\left[\beta_j\left(Y_j(t) + \phi_j\sum_{k\neq j,k=1}^{4}Y_{kj}(t)\right)\right] - \mu Z_i(t)$$

$$\frac{dY_{ij}(t)}{dt} = Z_i(t)\left[\beta_j\left(Y_j(t) + \phi_j\sum_{k\neq j,k=1}^{4}Y_{kj}(t)\right)\right] - \sigma Y_{ij}(t) - \mu Y_{ij}(t)$$

$$1 = X(t) + \sum_{i=1}^{4}Y_i(t) + \sum_{i=1}^{4}Z_i(t) + \sum_{i,j=1,i\neq j}^{4}Yij(t) + Z_{**}(t)$$

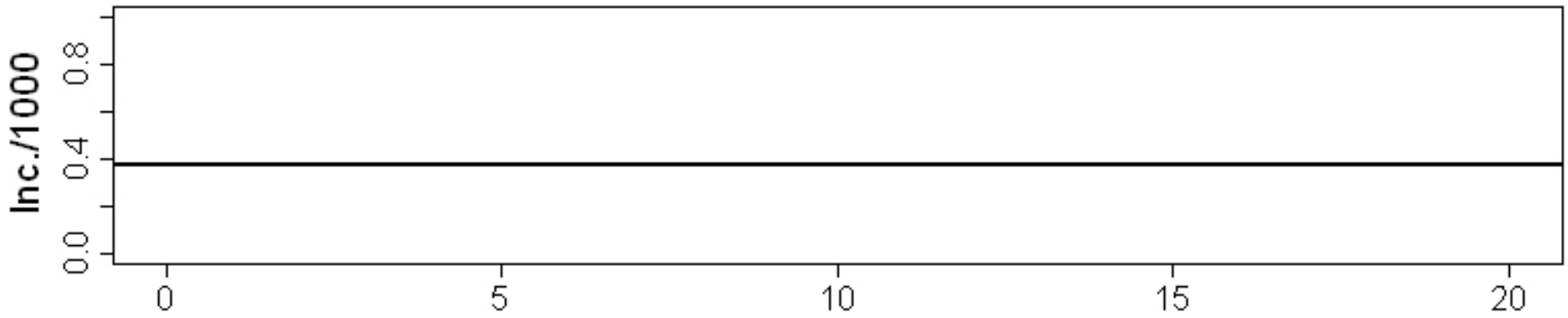
What happens when we impose seasonal forcing?

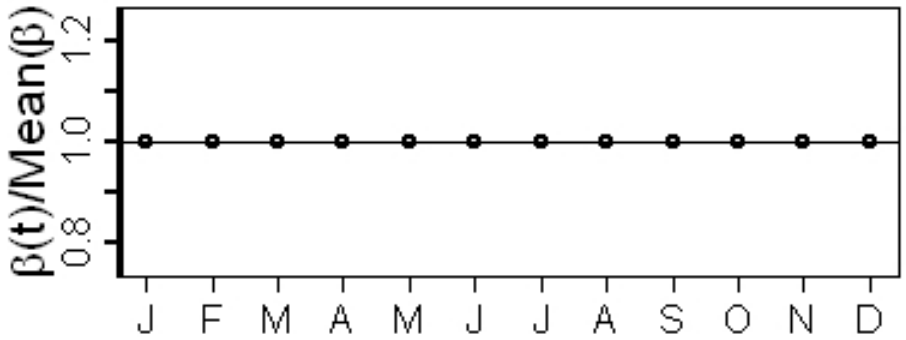
SIR model of dengue including four serotypes and enhancement of secondary infections by pre-existing immunity

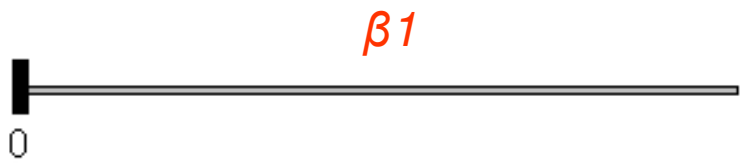
β is the transmissiblity parameter

$$\beta(t) = \beta_0 (1 + \beta_1 \cos(2 \pi t))$$

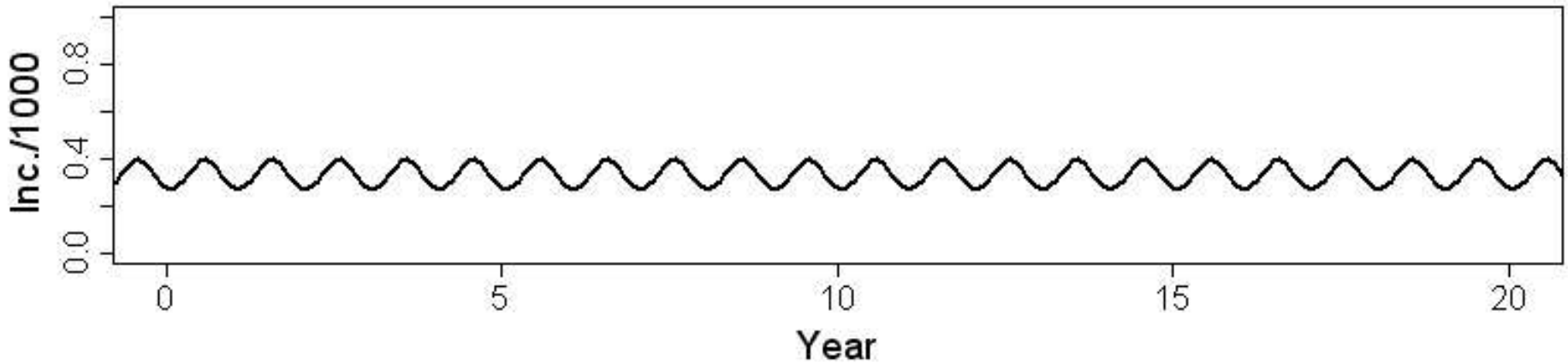
$\beta 1$ is varied from 0.0 to 0.1

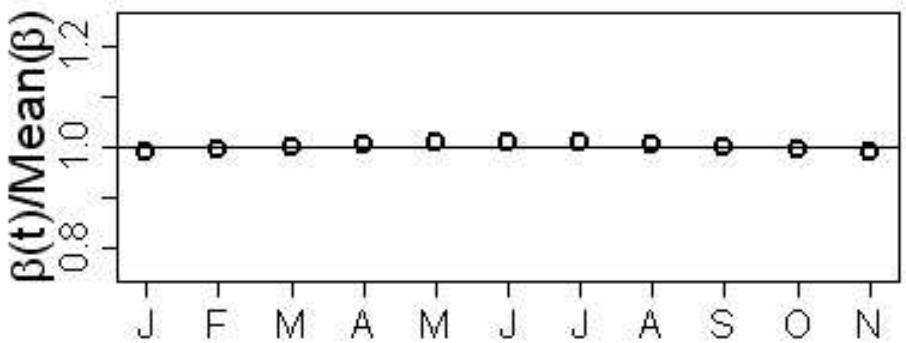






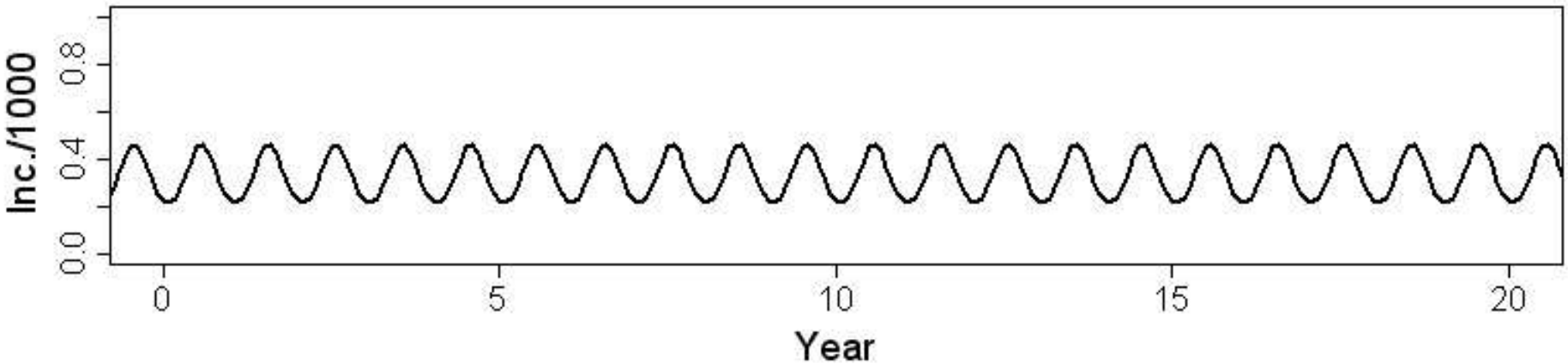
Peak Beta/Trough Beta= 1
Peak Inc./Trough Inc.= 1

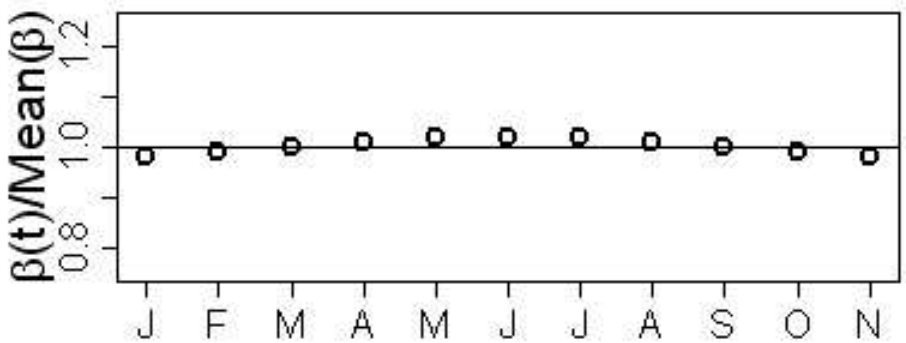




Peak Beta/Trough Beta= 1.02

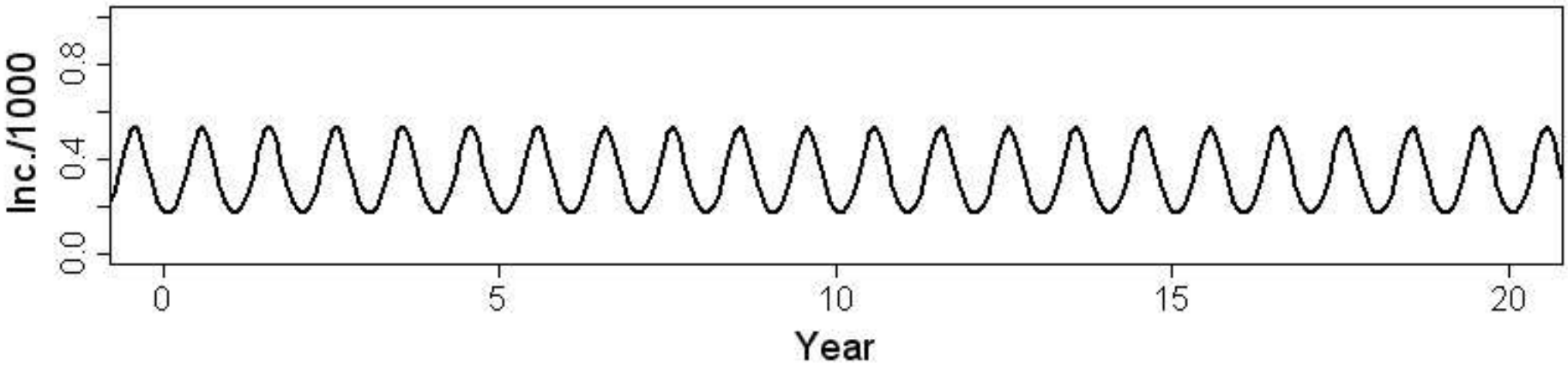
Peak Inc./Trough Inc.= 1.45

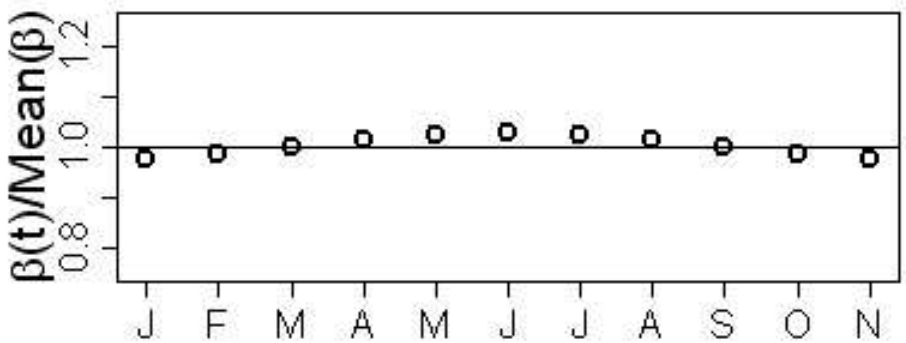




Peak Beta/Trough Beta= 1.04

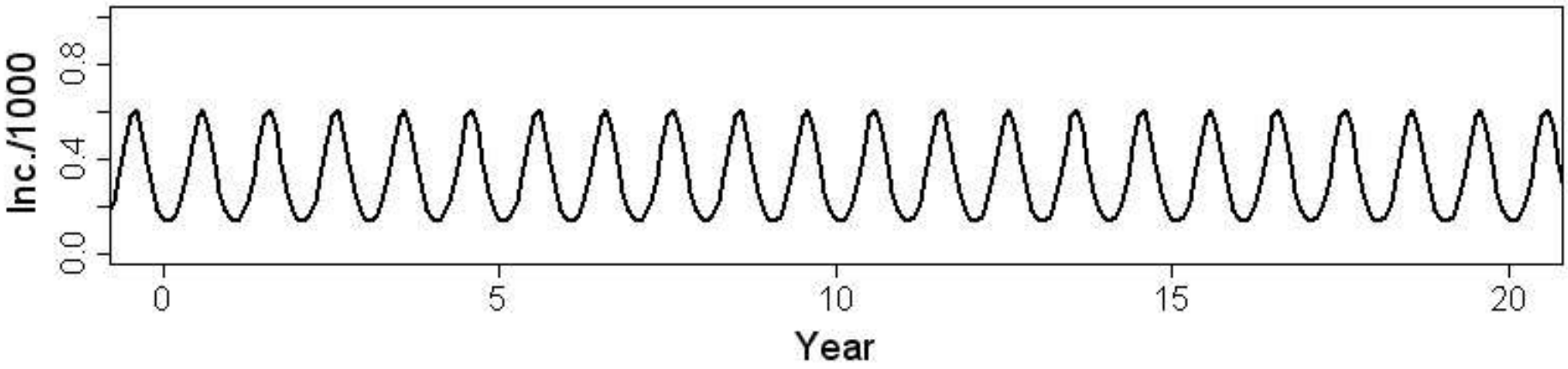
Peak Inc./Trough Inc.= 2.09

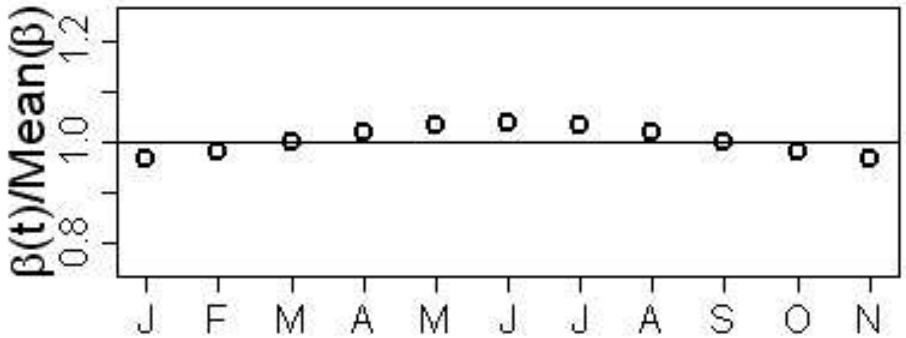


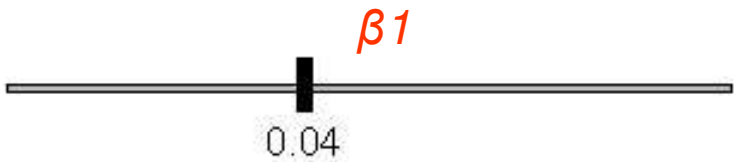


Peak Beta/Trough Beta= 1.06

Peak Inc./Trough Inc.= 3.02

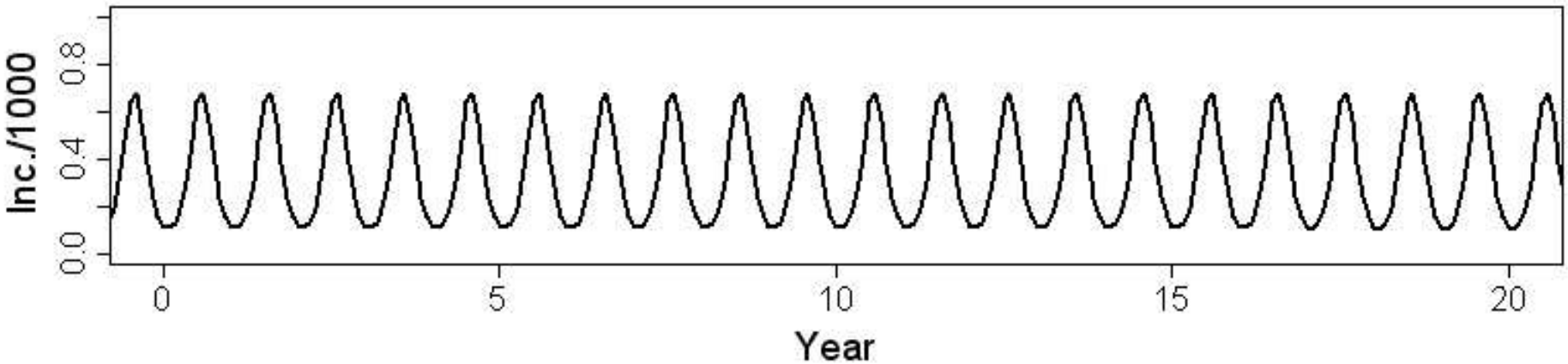


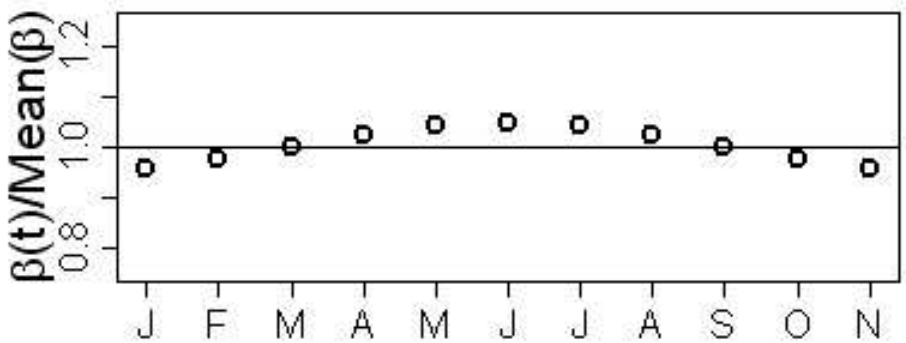




Peak Beta/Trough Beta= 1.08

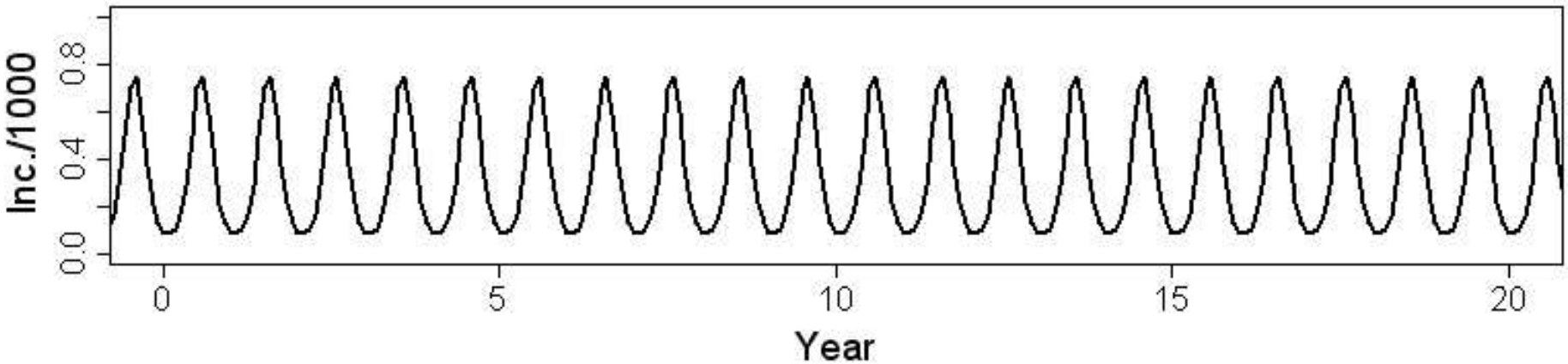
Peak Inc./Trough Inc.= 4.34

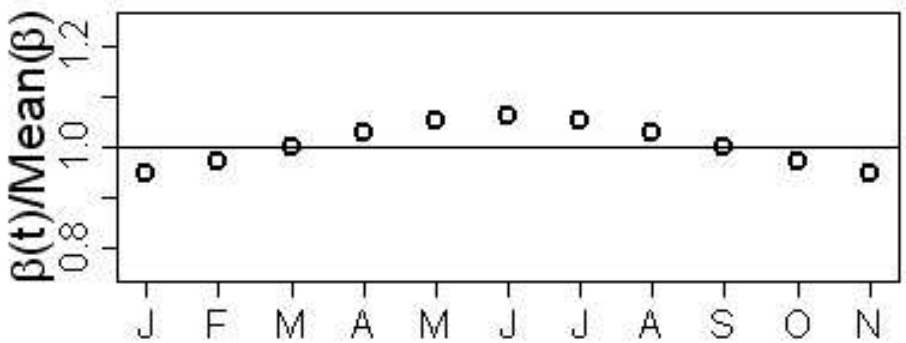


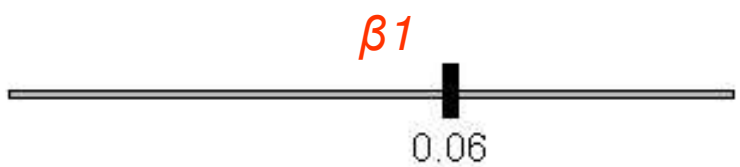


Peak Beta/Trough Beta= 1.1

Peak Inc./Trough Inc.= 6.2

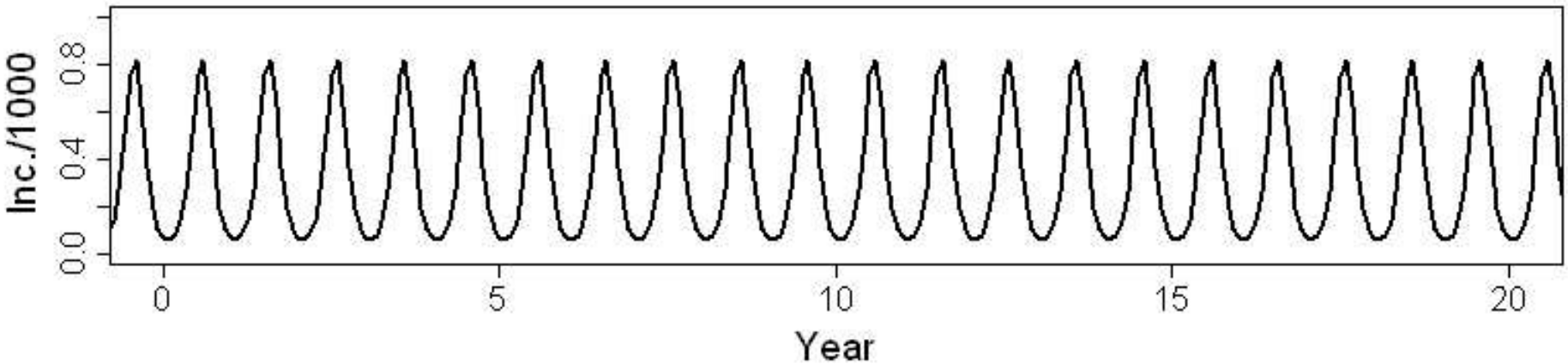


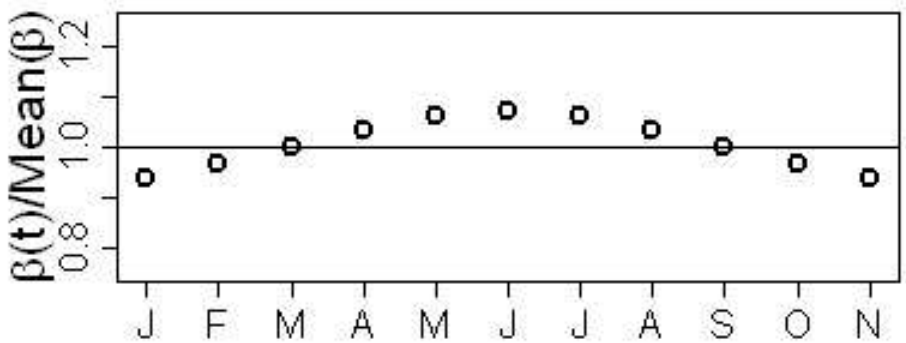


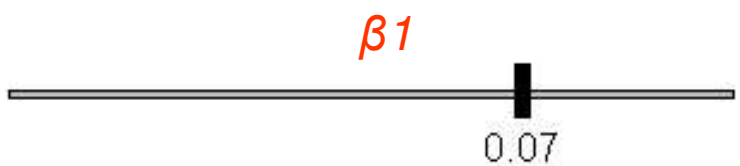


Peak Beta/Trough Beta= 1.12

Peak Inc./Trough Inc.= 8.83

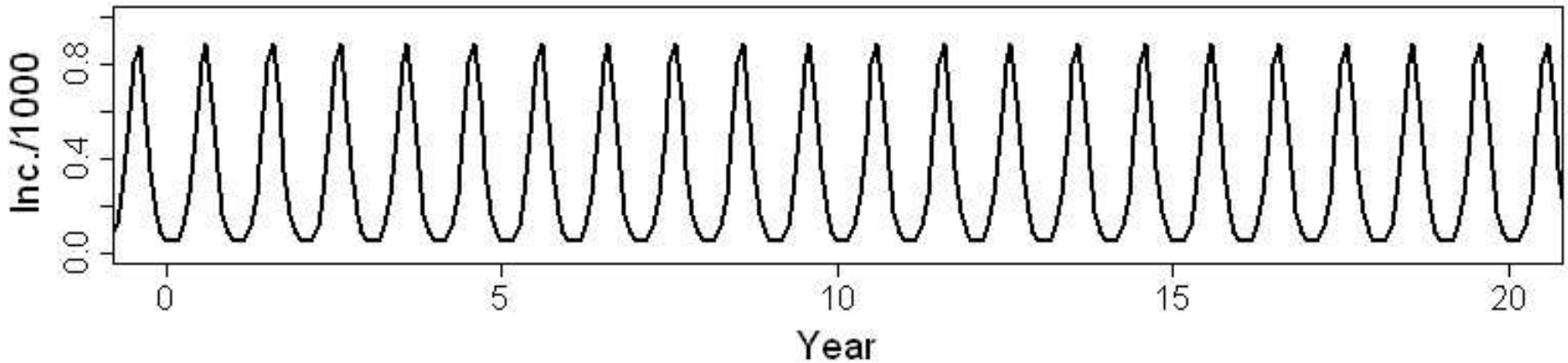


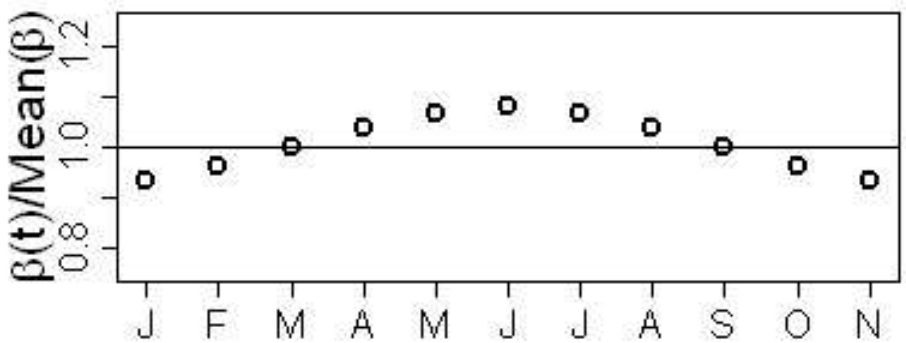




Peak Beta/Trough Beta= 1.14

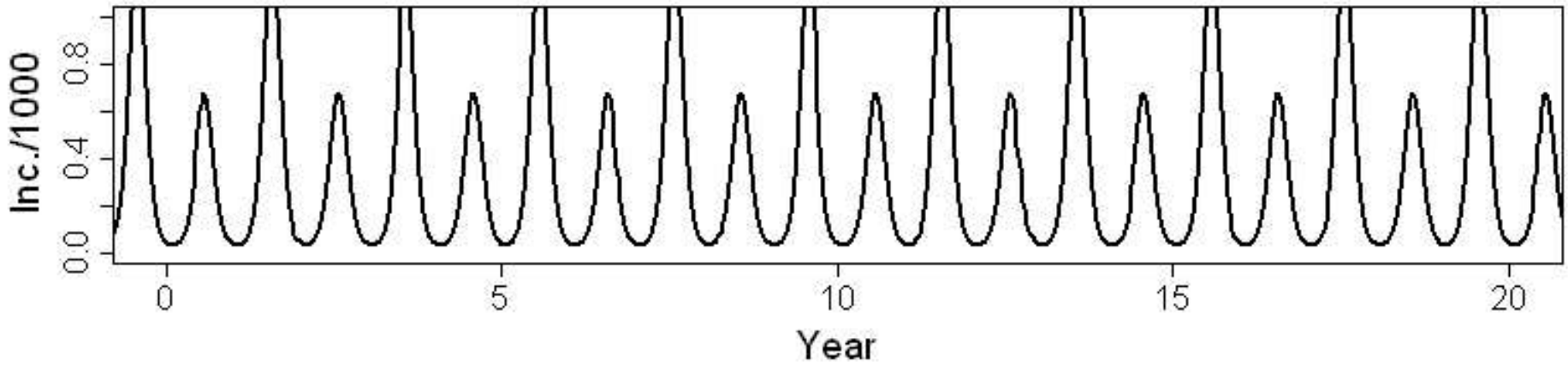
Peak Inc./Trough Inc.= 12.52

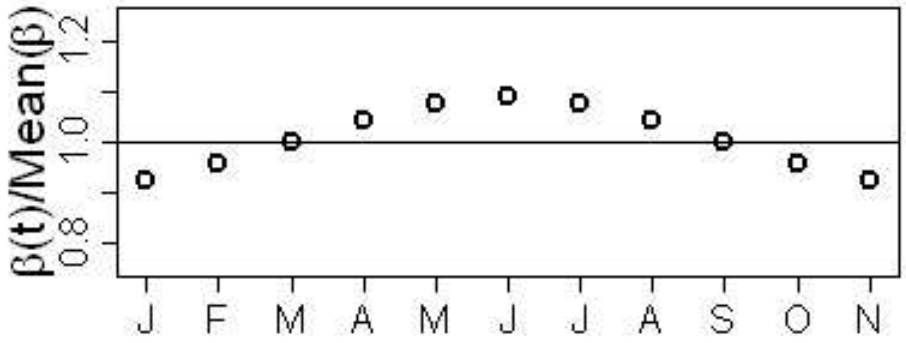




Peak Beta/Trough Beta= 1.16

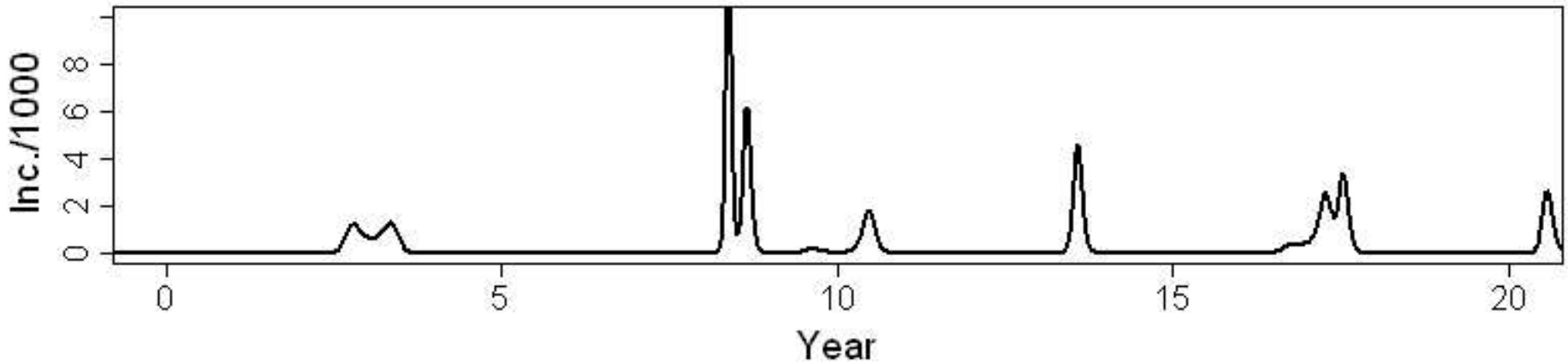
Peak Inc./Trough Inc.= 17.66

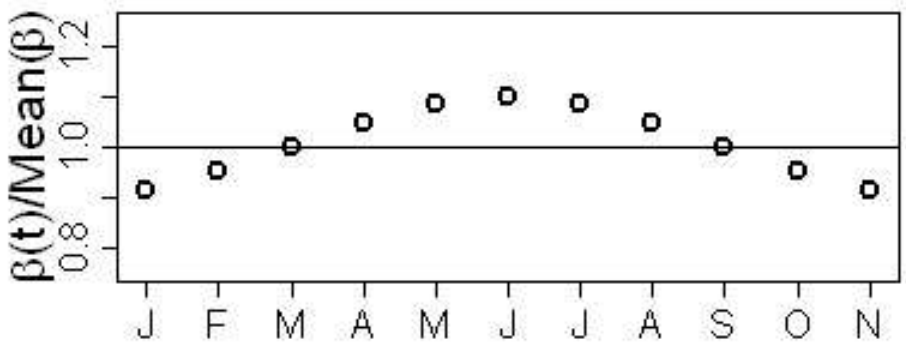


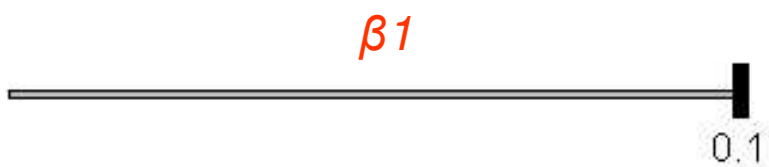


Peak Beta/Trough Beta= 1.18

Peak Inc./Trough Inc.= 3697.66







Peak Beta/Trough Beta= 1.2

Peak Inc./Trough Inc.= **N/A**

In a system with substantial strain-strain interactions, as little as a 20% change in transmissibility (β) can give rise to altered dynamics

SOME GENERAL REFLECTIONS ON EPIDEMIC ANALYES

EPIDEMICS CAN BE APPROACHED AS PARTIALLY DECOMPOSABLE SYSTEMS

EVERY EFFORT SHOULD BE MADE TO ISOLATE AND THEREBY UNDERSTAND THE COMOPONENT SUBSYSTEMS

ANALYSES OF THE FORCING EFFECTS OF ENVIRONMENTAL FACTORS (eg TEMPERATURE, HUMIDITY,RAINFALL) WILL BE MORE ROBUST IF IRRELEVANT OR CONFOUNDING DYNAMIC COMPONENT SUBSYSTEMS ARE ELIMINATED OR CONTROLLED.

CLIMATE CHANGE AND EPIDEMIC EMERGENCE

Global Warming → "Global Weirding"

Science base is lacking to explain KNOWN epidemic emergences

Influenza

- Spatio-temporal dynamics in wild avian populations?
- Interactions with intermediate hosts eg commercial poultry?
- Type-Type interactions? Evolution?

HIV

- SIV dynamics in primate populations?
- Interactions with human bushmeat hunters?

SARS

- Spatio-temporal dynamics in wild bat populations?
- Interactions with intermediate hosts eg civets?
- Evolution?

CONCLUSION

2001 Recommendations are even more urgent today:

- Research on the linkages between climate and infectious diseases must be strengthened
- Further development of disease transmission models is needed to assess the risks posed by climatic and ecological changes
- Epidemiological surveillance programs should be strengthened
- Observational, experimental, and modeling activities are all highly interdependent and must progress in a coordinated fashion
- Research on climate and infectious disease linkages inherently requires interdisciplinary collaborations

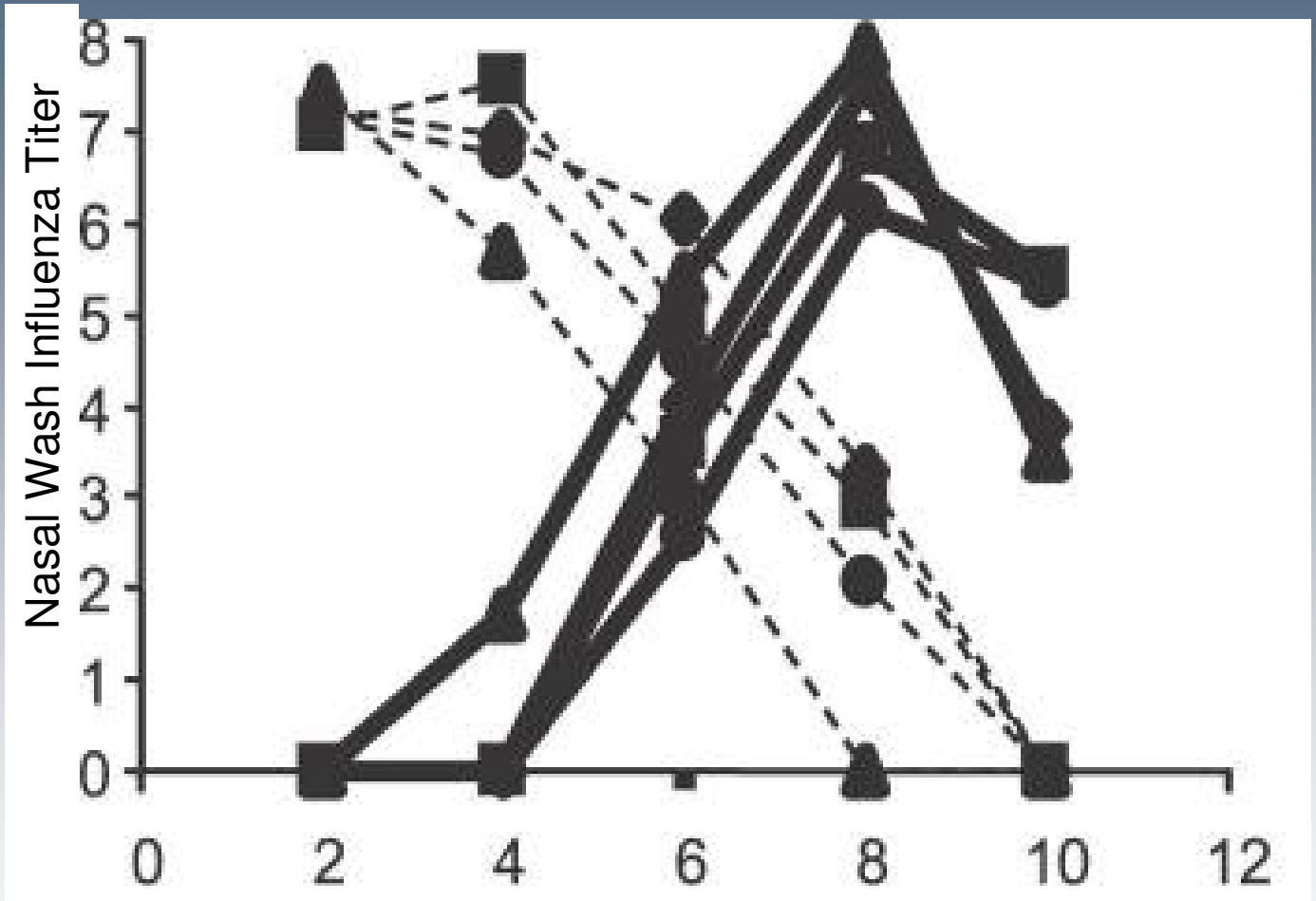
END

UNDER THE WEATHER / KEY FINDINGS: THE POTENTIAL FOR DISEASE EARLY WARNING SYSTEMS

- As our understanding of climate/disease linkages is strengthened, epidemic control strategies should aim towards complementing "surveillance and response" with "prediction and prevention."
- Disease early warning systems can not be based on climate forecasts alone
- Development of early warning systems should involve active participation of the system's end users

4 Infected (transmitting) GPs

4 Exposed (recipient) GPs

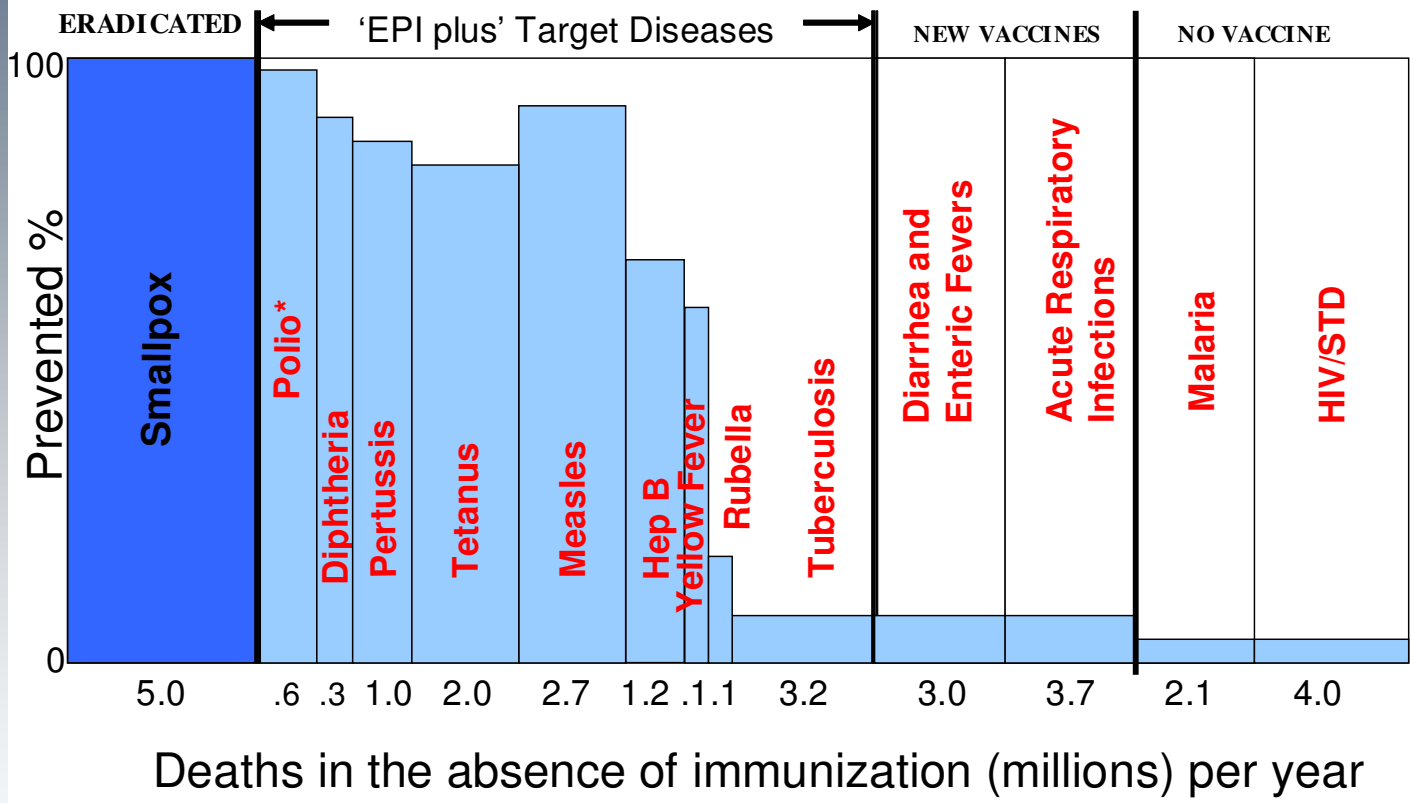


5 degree C.
35% RH

Day Post-inoculation

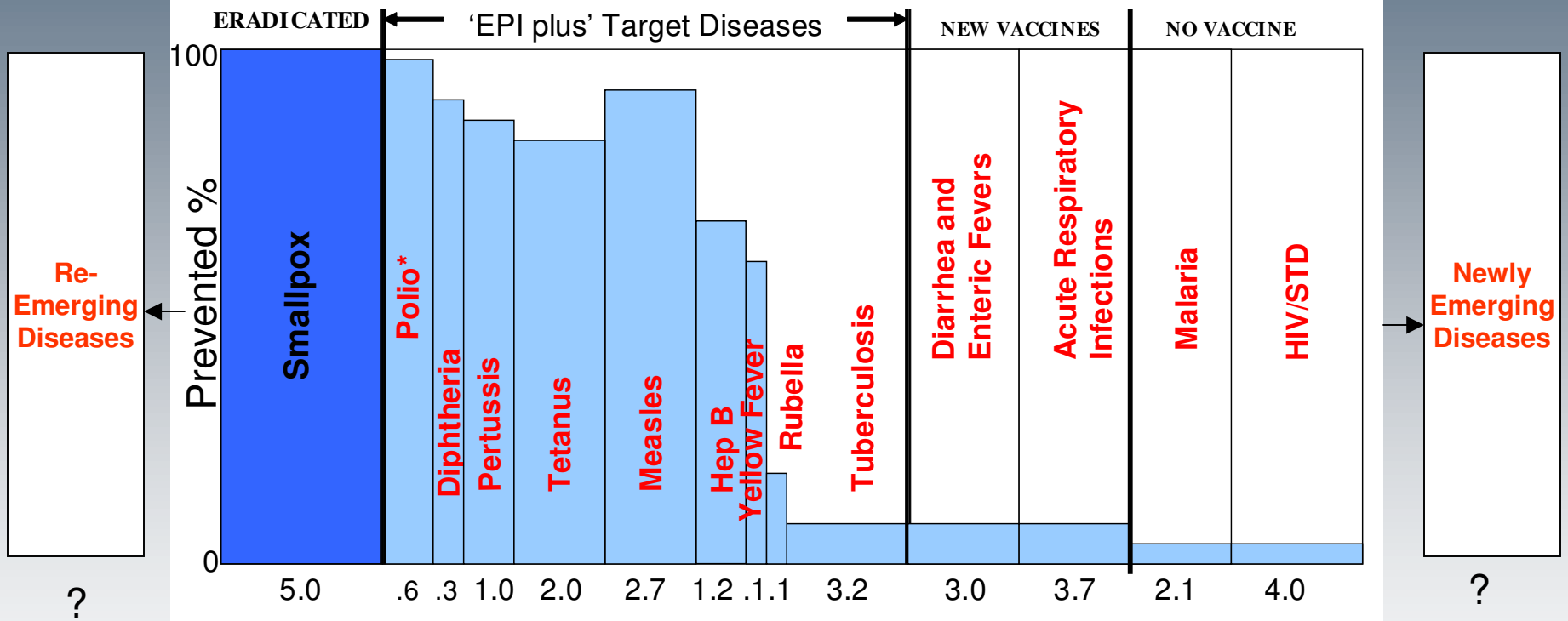
Lowen et al, PLoS Pathogen 2007

Deaths (Global) from Potentially Vaccine Preventable Diseases



*and lifetime disability

Deaths (Global) from Potentially Vaccine Preventable Diseases



*and lifetime disability

WMO

INTERGOVERNMENTAL PANEL ON CLIMATE CHANGE

UNEP

Guidance Notes for Lead Authors of the IPCC Fourth Assessment Report on Addressing Uncertainties

Table 3. Quantitatively calibrated levels of confidence

Terminology	Degree of confidence in being correct
Very High confidence	At least 9 out of 10 chance of being correct
High confidence	About 8 out of 10 chance
Medium confidence	About 5 out of 10 chance
Low confidence	About 2 out of 10 chance
Very Low confidence	Less than 1 out of 10 chance

Under the Weather
Climate, Ecosystems, and Infectious Diseases

Board on Atmospheric Sciences and Climate,
Division of Earth and Life Sciences,
National Research Council, National Academy Press (2001)

Don Burke (Chair)
Ann Carmichael
Dana Focks
Darrell Jay Grimes
John Harte
Subhash Lele
Pim Martens
Jonathan Mayer
Linda Mearns
Roger Pulwarty
Leslie Real
Chester Ropelewski
Joan Rose
Robert Shope
Joanne Simpson
Mark Wilson

Laurie Geller, Susan Roberts, Jonathan Davis, Tenecia Brown

UNDER THE WEATHER / RECOMMENDATIONS FOR FUTURE RESEARCH AND SURVEILLANCE

- Research on the linkages between climate and infectious diseases must be strengthened

  "In most cases, these linkages are poorly understood and research on the causal relationships is in its infancy"

- Further development of disease transmission models is needed to assess the risks posed by climatic and ecological changes

- Epidemiological surveillance programs should be strengthened

  "The lack of high-quality epidemiological data for most diseases is a serious obstacle …"

- Observational, experimental, and modeling activities are all highly interdependent and must progress in a coordinated fashion

- Research on climate and infectious disease linkages inherently requires interdisciplinary collaborations