Centennial Reflections on the 1918 Spanish Influenza Pandemic: Insights and Remaining Puzzles

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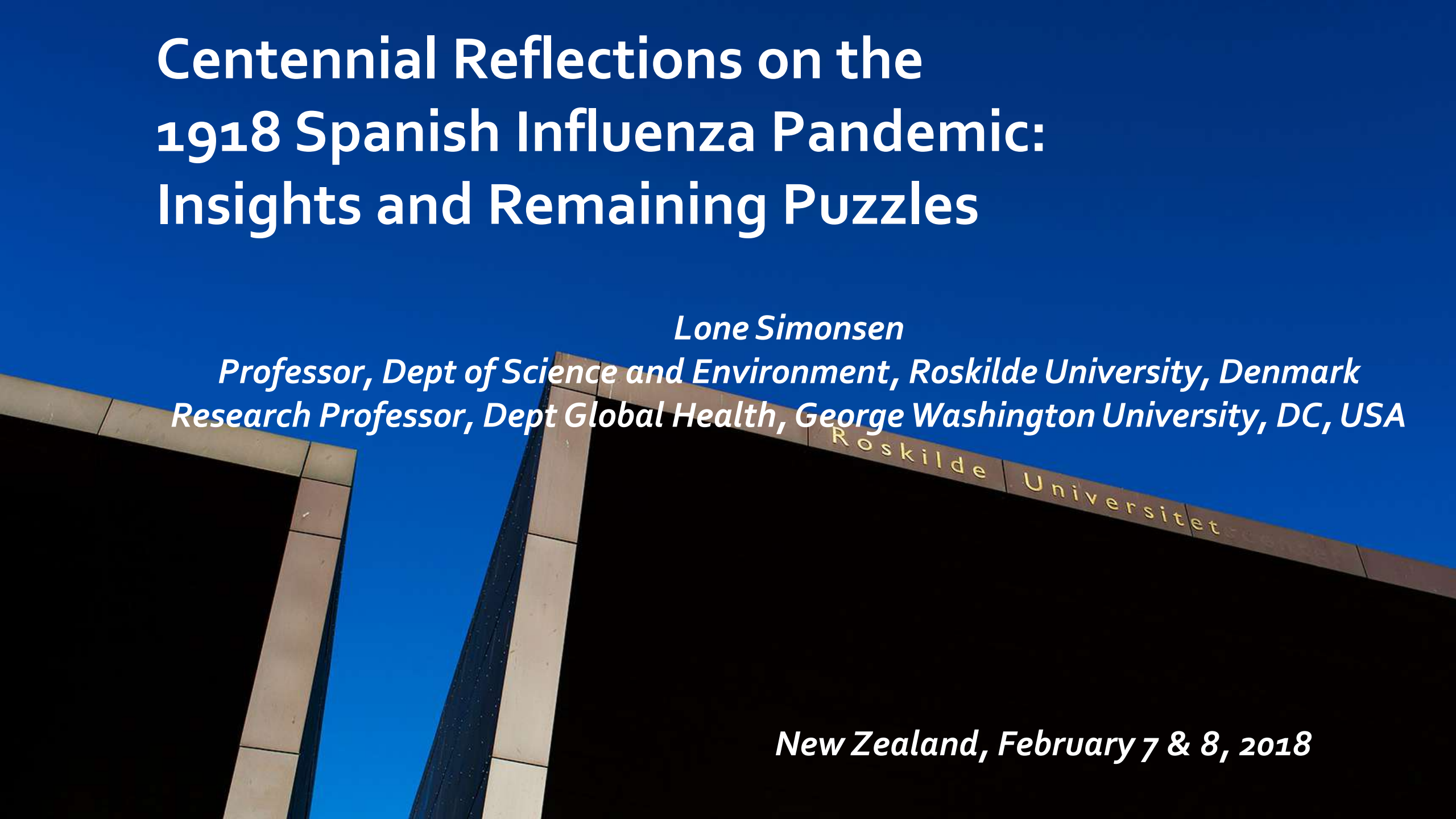


New Zealand, February 7 & 8, 2018

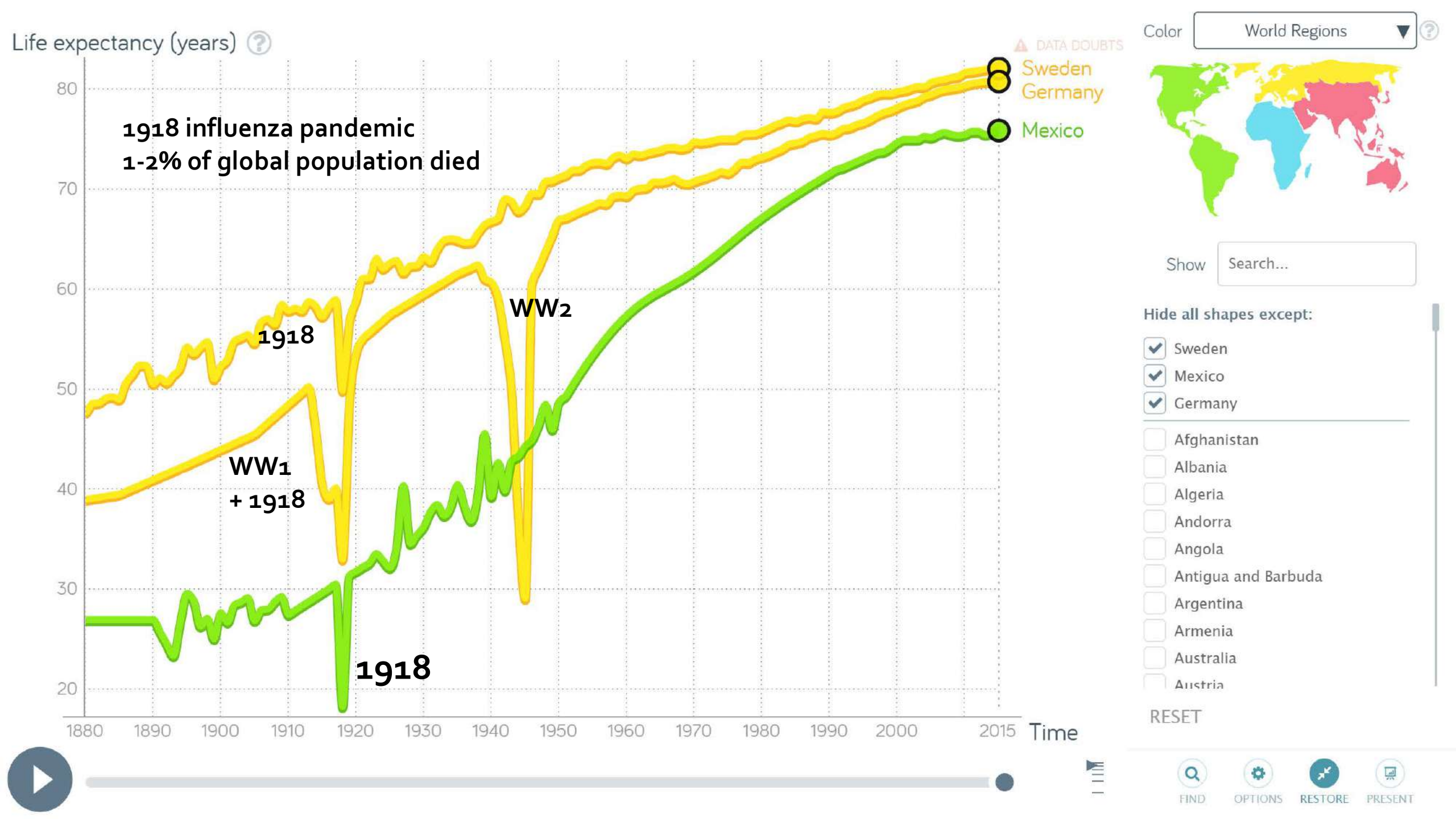
BUSINESS INSIDER

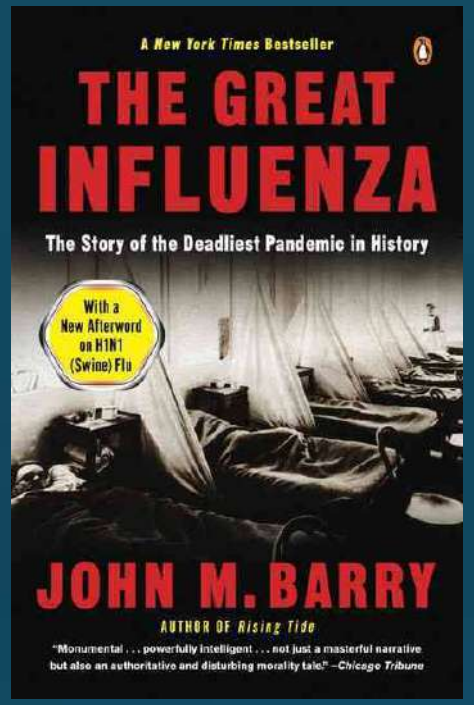
A fast-moving airborne pathogen could kill more than 30 million people in less than a year."

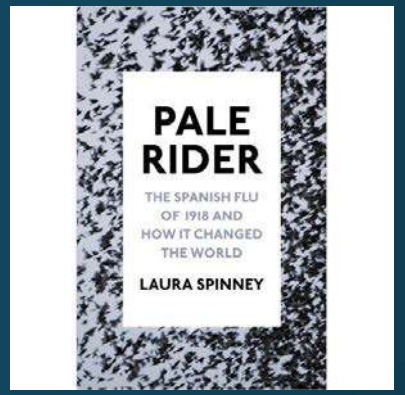
BILL GATES

Pandemic preparedness
Learns from historical
Pandemics

1918 is "poster child"
So important to get it right


Life expectancy (years)
DATA DOUBTS
Color
World Regions
Sweden
Germany
Mexico
1918 influenza pandemic
1-2% of global population died
WW2
1918
WW1
+ 1918
1918
80
70
60
50
40
30
20
1880
1890
1900
1910
1920
1930
1940
1950
1960
1970
1980
1990
2000
2015
Time
Show
Search...
Hide all shapes except:
Sweden
Mexico
Germany
Afghanistan
Albania
Algeria
Andorra
Angola
Antigua and Barbuda
Argentina
Armenia
Australia
Austria
RESET
FIND
OPTIONS
RESTORE
PRESENT





What the historians, demographers
And geographers knew

Origins of deadly pandemic debated

The "Spanish flu" outbreak of 1918-20 killed perhaps 50 million people worldwide. Here are three possible origins:

heliotrope cyanosis

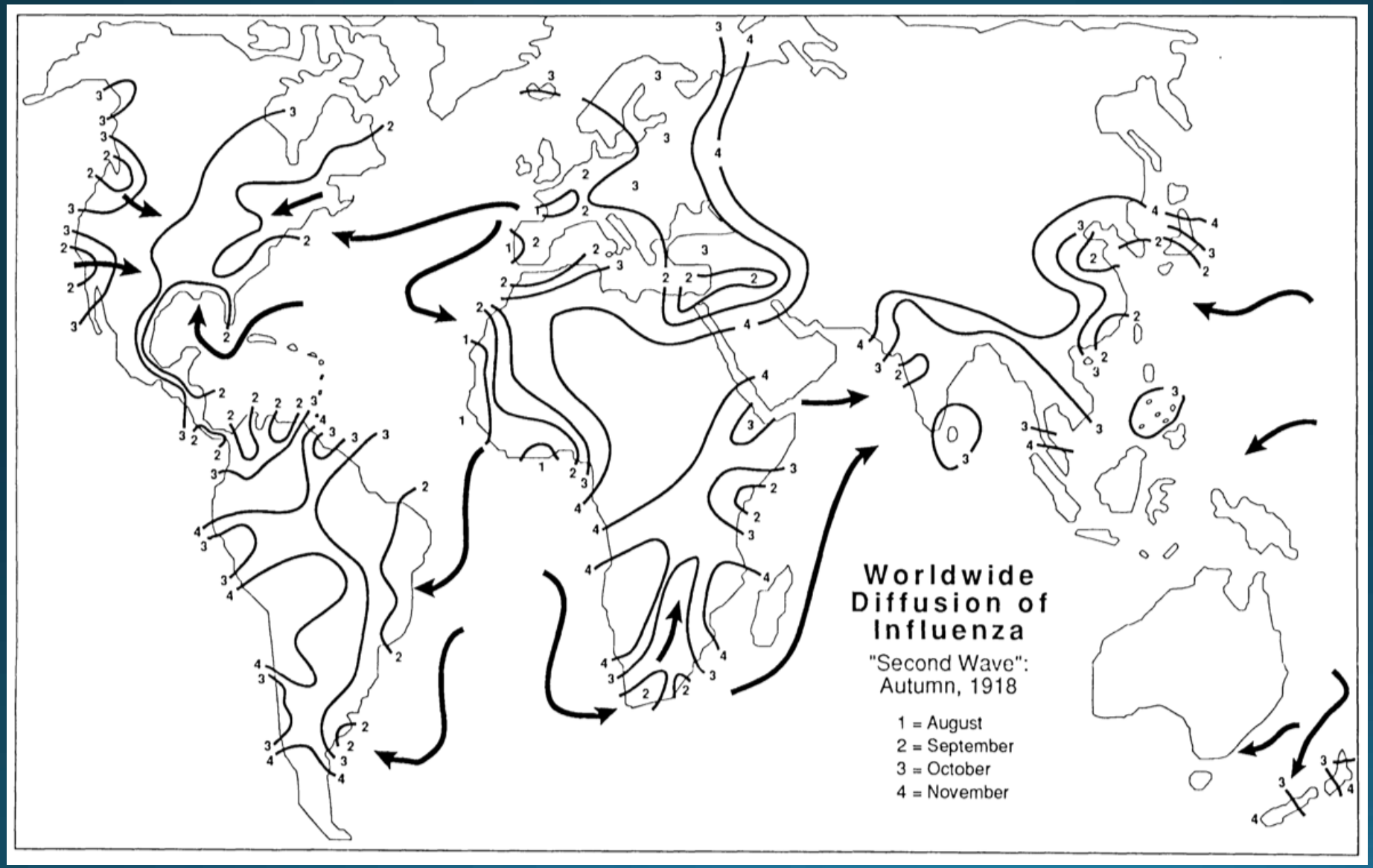
ALDERSHOT, U.K. ÉTAPLES, FRANCE
World War I's trenches were first seen as the source of the disease.

SHANXI PROVINCE, CHINA
A respiratory disease outbreak in 1917 may have been the first stirrings of the flu.

KANSAS, U.S.
At Camp Funston, 48 soldiers died in March 1918, just ahead of the outbreak.

JOHN TOMANIO, RYAN MORRIS, KELSEY NOWAKOWSKI, NG STAFF
SOURCES: *WAR IN HISTORY; JOURNAL OF PUBLIC HEALTH POLICY*

Rapid worldwide diffusion of 1918 pandemic (4 months)



All kinds of data
Used to compile
Evidence of
Pandemic activity
(newspapers,
Rapports, more)

Patterson & Pyle

Devastation in remote areas

-- only children survived in remote setting, like Alaska, 1918

"The flu? Why yes, my son, I remember the flu. That's why everybody here is related the way they are. When my grandmother died from it, my grandfather had to marry XX because her husband died of it. …"

See Lisa Sattenspiel papers

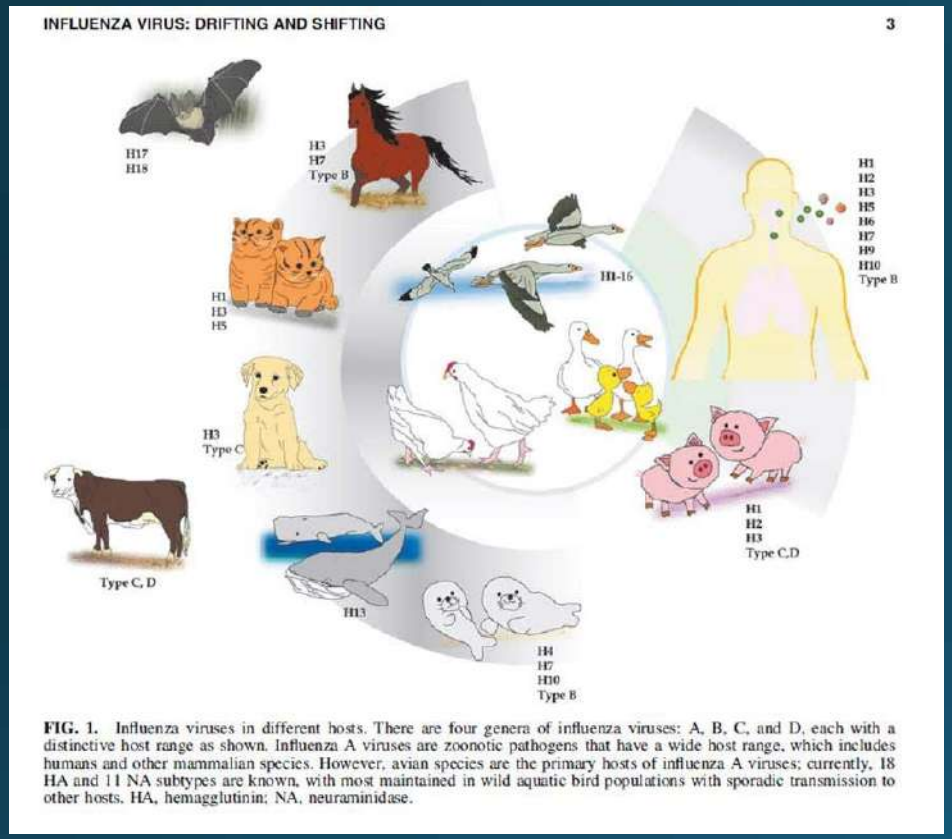
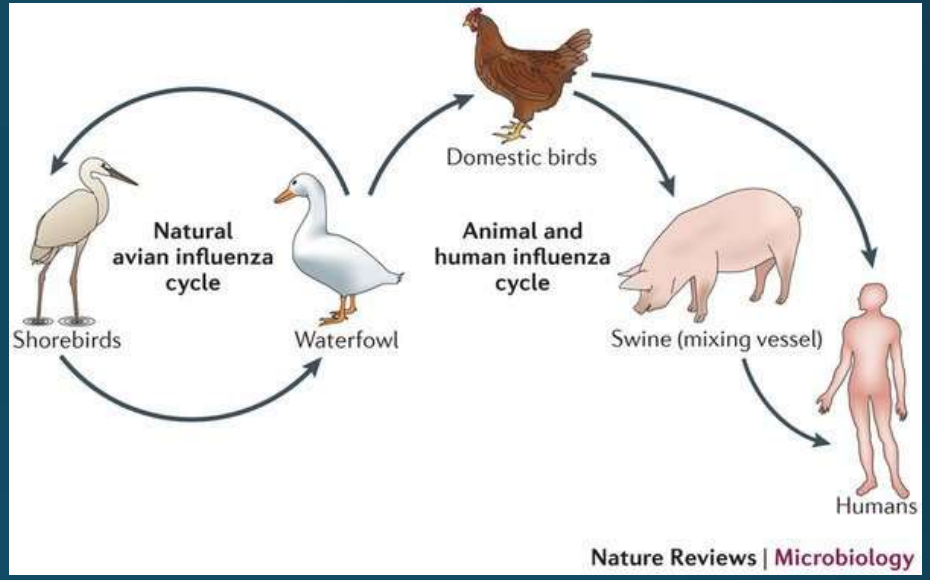


FIG. 1. Influenza viruses in different hosts. There are four genera of influenza viruses: A, B, C, and D, each with a distinctive host range as shown. Influenza A viruses are zoonotic pathogens that have a wide host range, which includes humans and other mammalian species. However, avian species are the primary hosts of influenza A viruses; currently, 18 HA and 11 NA subtypes are known, with most maintained in wild aquatic bird populations with sporadic transmission to other hosts. HA, hemagglutinin; NA, neuraminidase.



What the virologists and phylogeneticists knew

1918 autopsy case 3

Johan Hultin as a young man
in 1951 at the Brevig gravesite

46 years later

Johan Hultin
in 1997 at the same gravesite

Attempt to grow live 1918 virus in 1951

X
FAILED

Frozen cadaver lung tissue
Jeffery Taubenberger and Ann Reid

By 2005: complete genome sequenced

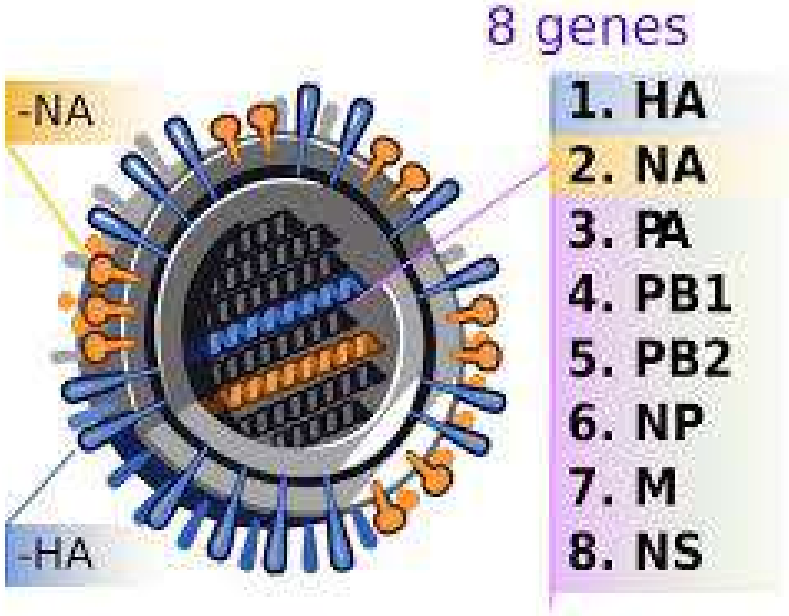
1918 viral gene
sequencing

CDC

Characterization of the 1918 influenza virus polymerase genes

2005 **Nature**

Jeffery K. Taubenberger[1], Ann H. Reid[1]†, Raina M. Lourens[1]†, Ruixue Wang[1], Guozhong Jin[1] & Thomas G. Fanning[1]



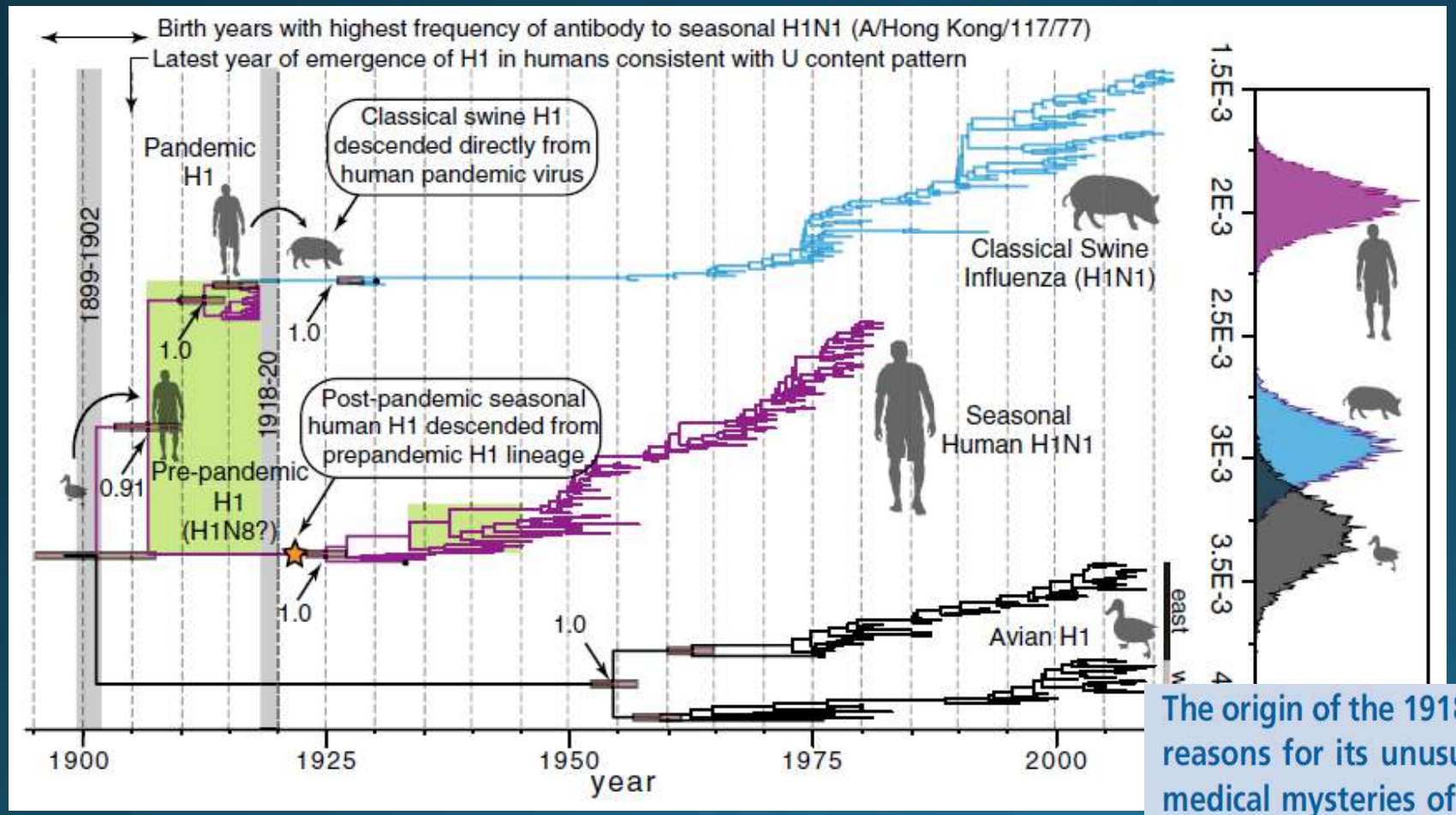
evolutionary distance from known avian strains. Here we present sequence and phylogenetic analyses of the complete genome of the 1918 influenza virus[4–8], and propose that the 1918 virus was not a reassortant virus (like those of the 1957 and 1968 pandemics[9,10]), but more likely an entirely avian-like virus that adapted to humans. These data support prior phylogenetic studies suggesting that the 1918 virus was derived from an avian source[11]. A total of

Genesis and pathogenesis of the 1918 pandemic H1N1 influenza A virus

Michael Worobey[a,1], Guan-Zhu Han[a], and Andrew Rambaut[b,c,d]

[a]Department of Ecology and Evolutionary Biology, University of Arizona, Tucson, AZ 85721; [b]Institute of Evolutionary Biology and [c]Centre for Infection, Immunity, and Evolution, University of Edinburgh, Edinburgh EH9 3JT, United Kingdom; and [d]Fogarty International Center, National Institutes of Health, Bethesda, MD 20892

Edited by Neil M. Ferguson, Imperial College London, London, United Kingdom, and accepted by the Editorial Board April 8, 2014 (received for review December 30, 2013)

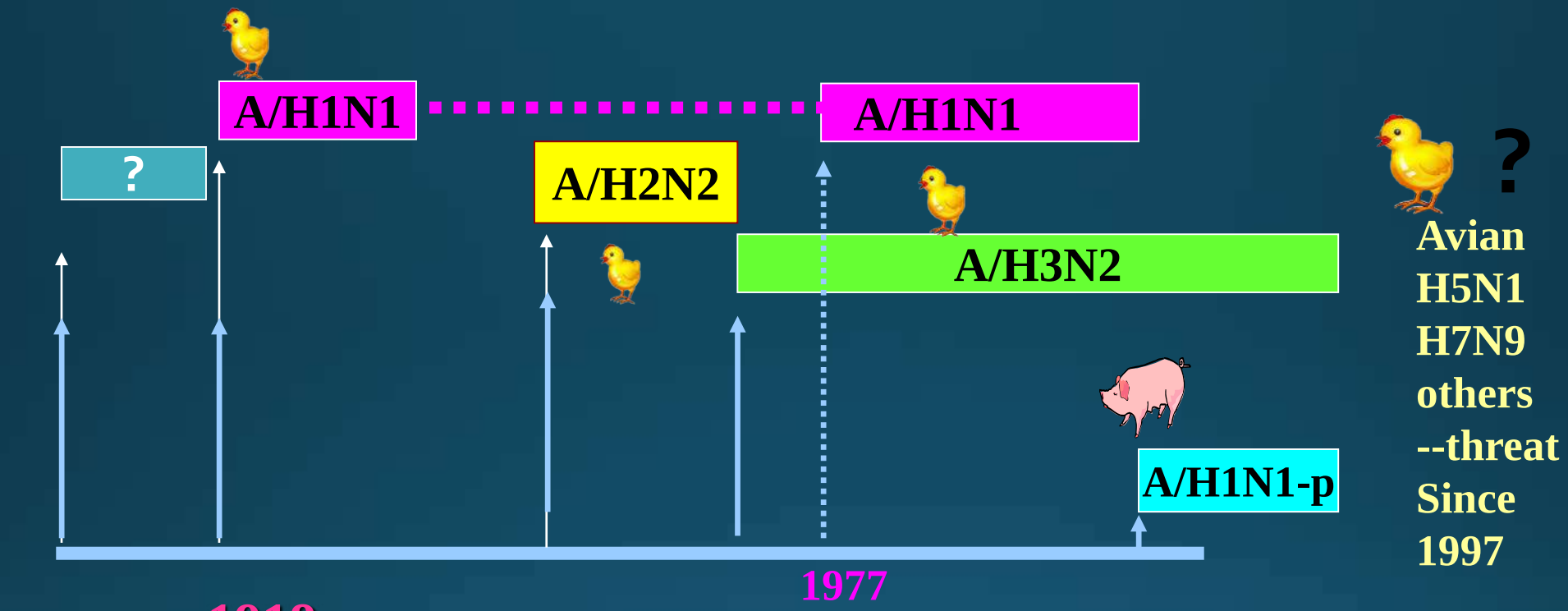


But Worobey et al disagree….

The origin of the 1918 pandemic influenza A virus (IAV) and the reasons for its unusual severity are two of the foremost biomedical mysteries of the past century. We infer that the virus arose via reassortment between a preexisting human H1 IAV lineage and an avian virus. Phylogenetic, seroarcheological,

H3N8? → 1907 H1N8? → 1918 H1N1

Influenza A Virus Pandemics and Circulation for a Century



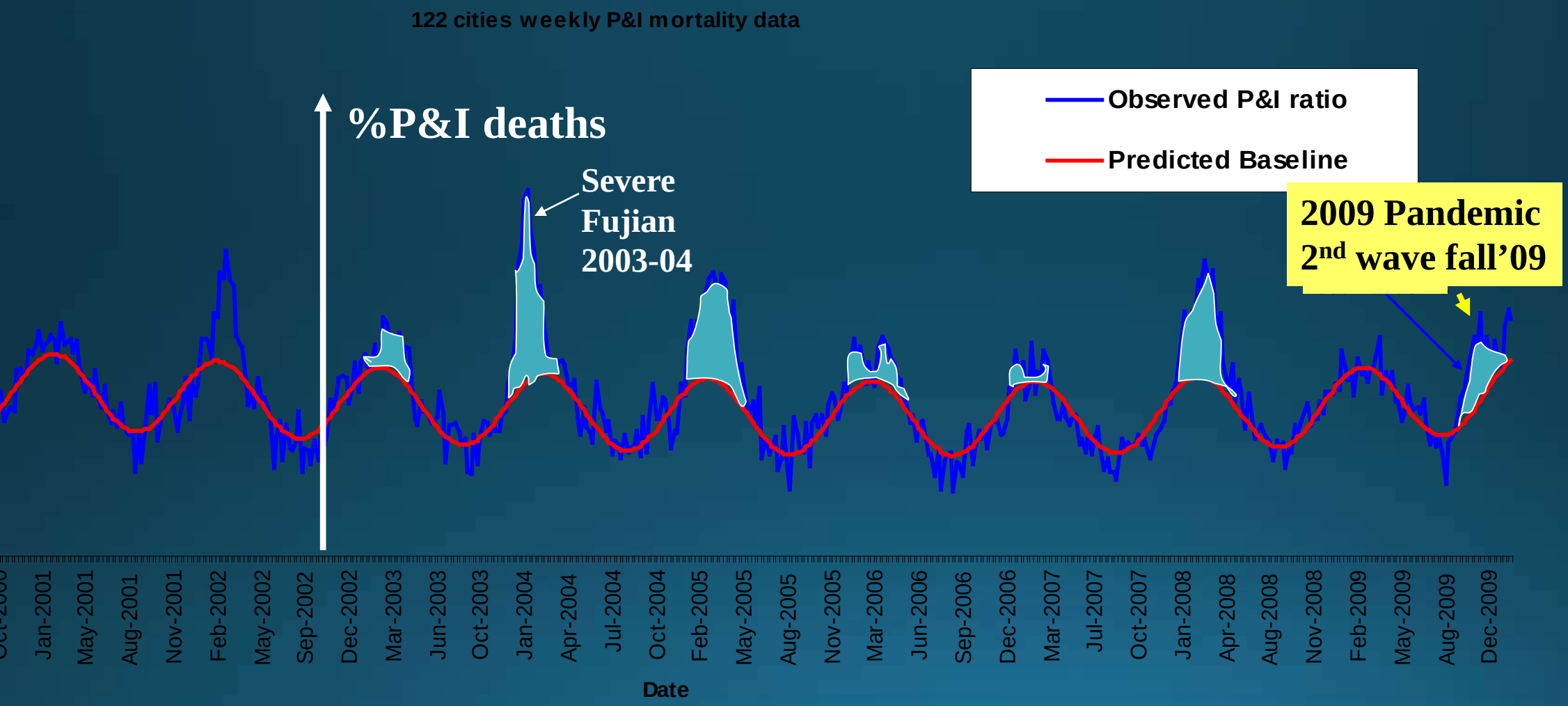
Origin: Zoonotic viruses (1918?, 2009) or genetic re-assortment
Involving zoonotic viruses and human viruses (1957, 1968)

Pandemic mortality age patterns:

Elderly sparing, multiple waves, extreme mortality in young adults

What the epidemiologists knew

How to Measure Influenza-Related Mortality Burden
Modeling National Time Series Mortality Data



Modeling Global 1918 Burden:

62M deaths in today's population; 95% of these in low income countries

	Excess mortality
Argentina	0·54% (0·53–0·56)
Australia*	0·29% (0·28–0·31)
Austria	1·61% (1·59–1·64)
Belgium	0·83% (0·81–0·84)
Canada	0·63% (0·61–0·65)
Chile	0·52% (0·49–0·55)
Denmark*	0·20% (0·18–0·23)
England*†	0·34% (0·33–0·35)
Finland*†	0·85% (0·81–0·89)
France*†	0·75% (0·74–0·76)
Germany	0·76% (0·75–0·76)
India	4·39% (4·39–4·39)
Bengal/Sikkim	2·33% (2·32–2·34)
Bihar/Orissa	3·60% (3·59–3·61)
Bombay	6·18% (6·17–6·20)
Burma	2·12% (2·10–2·14)
Central/Berar	7·82% (7·79–7·84)

Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918–20 pandemic: a quantitative analysis

Christopher J L Murray, Alan D Lopez, Brian Chin, Dennis Feehan, Kenneth H Hill

Murray et al, Lancet 2006

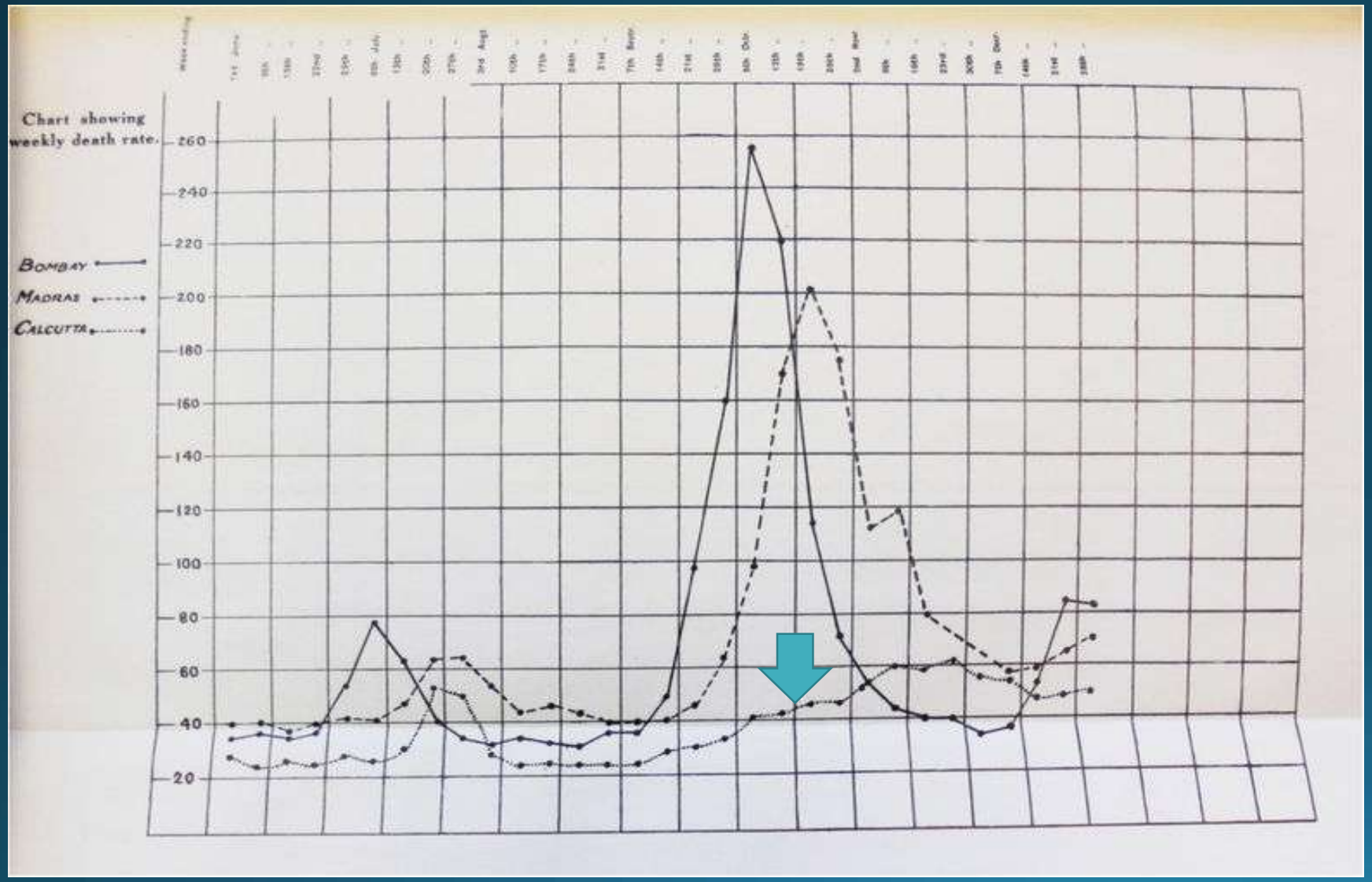
Estimate based on 13 countries data

Notice ~40-fold difference !

Caveat: Low income areas represented by 5 Indian sub-national estimates

1918 Pandemic influenza in India

-- heterogeneity suggests uncertainties in global burden estimates



Chandra & Kassens-Noor BMC ID 2014

Calcutta completely escaped 1918 autumn wave – how?

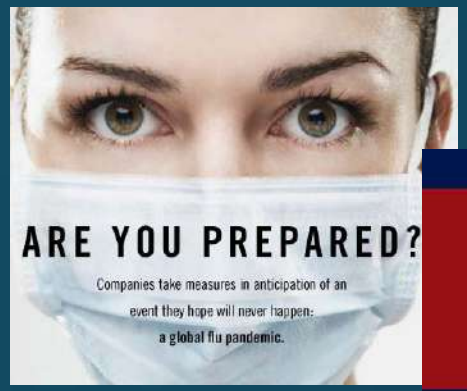
Across India, 5% population died

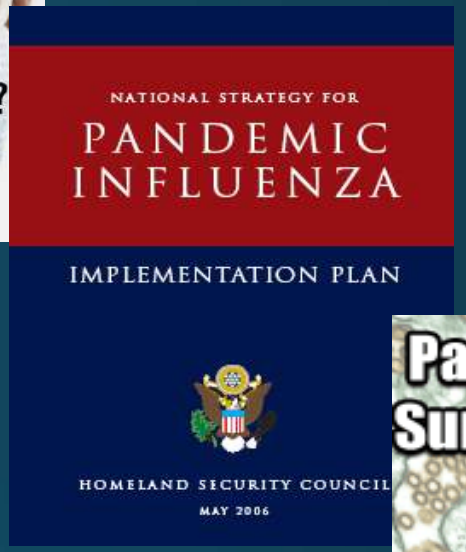
United States: Pandemic Mortality and Mean Age for all 5 pandemics adjusted to 2000 population – great for between-pandemic comparison

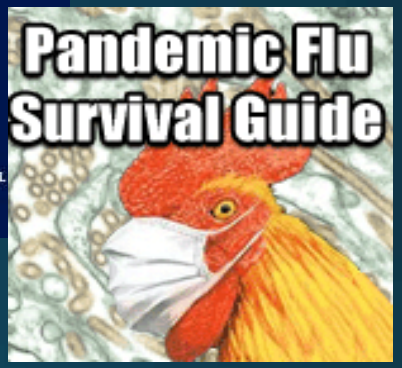
Pandemic Season	Number deaths*	% of population died	Mean age at deaths (years)
1889	?		?
1918	1,300,000	0.5%	27
1957	150,600	0.1%	65
1968	86,000	0.03%	62
2009	7,500-44,100	0.003-0.2%	37
Seasonal influenza (avg)	~30,000	0.01%	76

Viboud et al, Plos Currents 2009

2009 Pandemic -- A Perplexing Situation







- Risk scenario: disaster
  - 1918-like risk scenario: ~1% may die
  - Expected: Avian H5N1 virus: ~50% of cases died

- But… 2009 pandemic was far "milder"
  - Unexpectedly originated in Mexico, from pigs

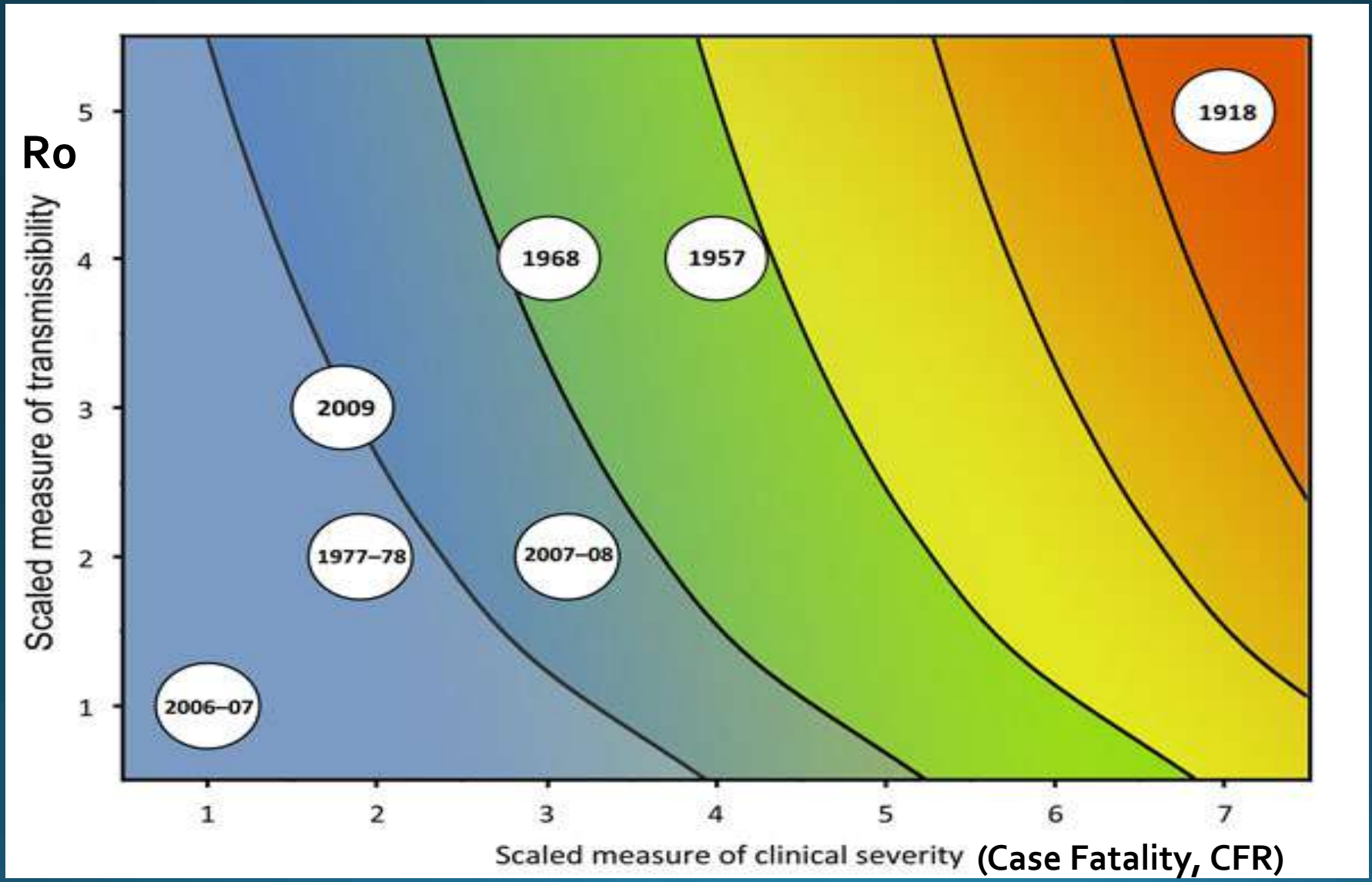
- First test of global, national, regional pandemic response plans

100 years of Human Experience with influenza A Pandemics

-- A Rainbow Scale for Pandemic "Seriousness"

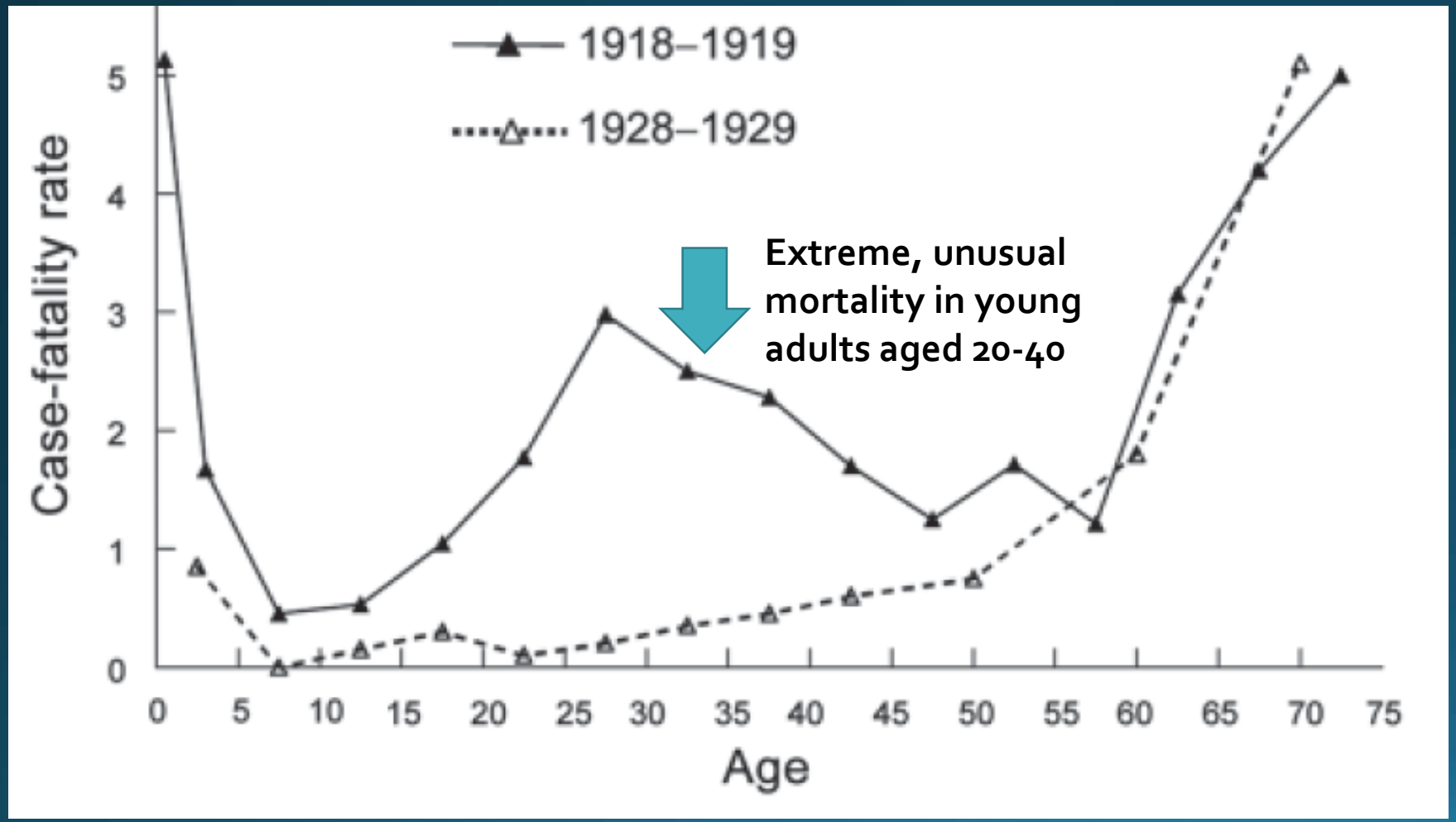
Reed et al, EID 2013

-- *Since 2011 WHO includes clinical severity in pandemic definition*



Strange and Unusual Pandemic Age Patterns

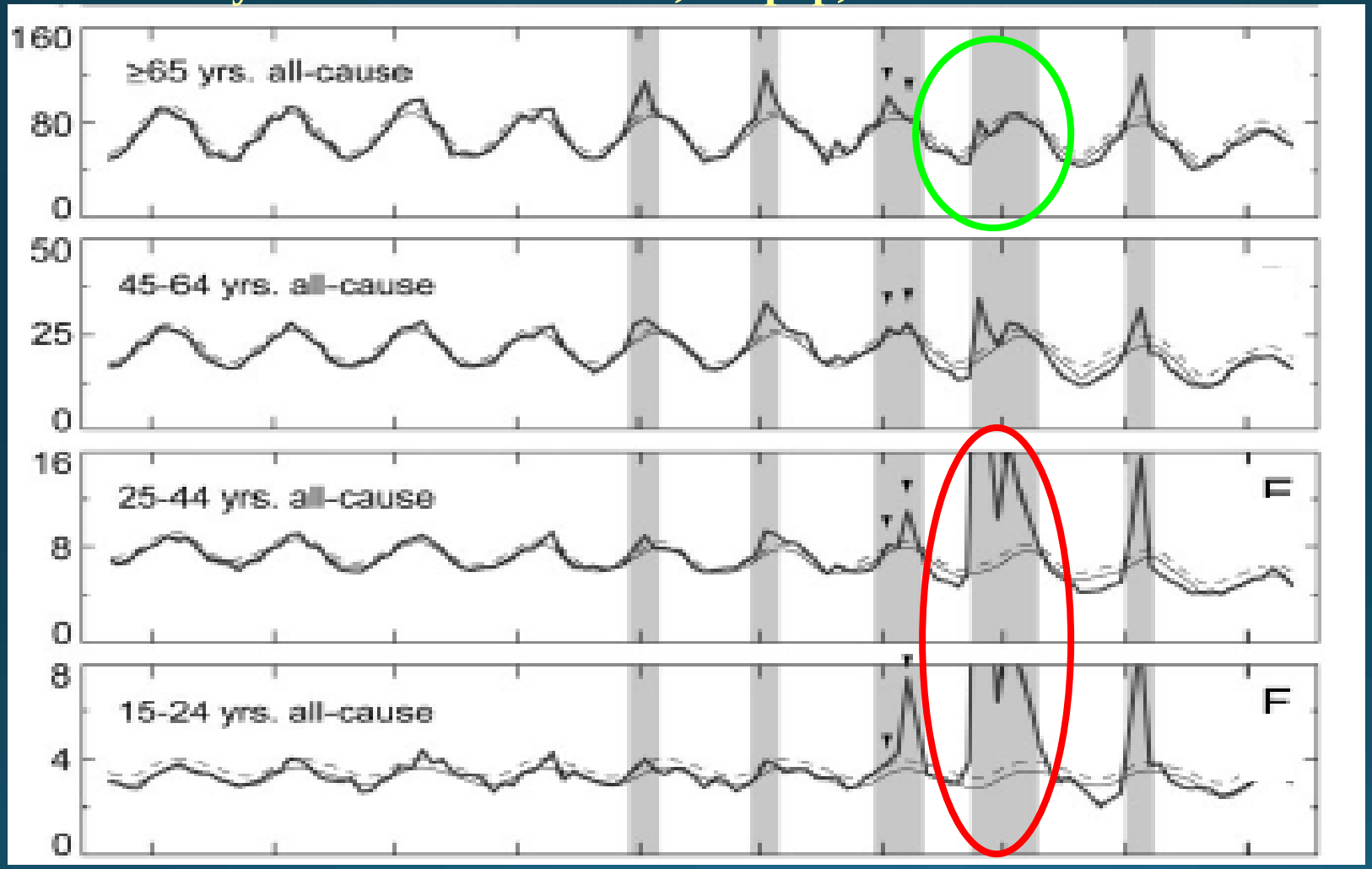
The Classical W-shaped 1918 mortality was…. a mistake !



What is shown is ANNUAL deaths – Not influenza-related deaths

1918 Pandemic: Elderly were completely spared

Monthly All Cause Deaths / 10,000 pop, for 1910-1919



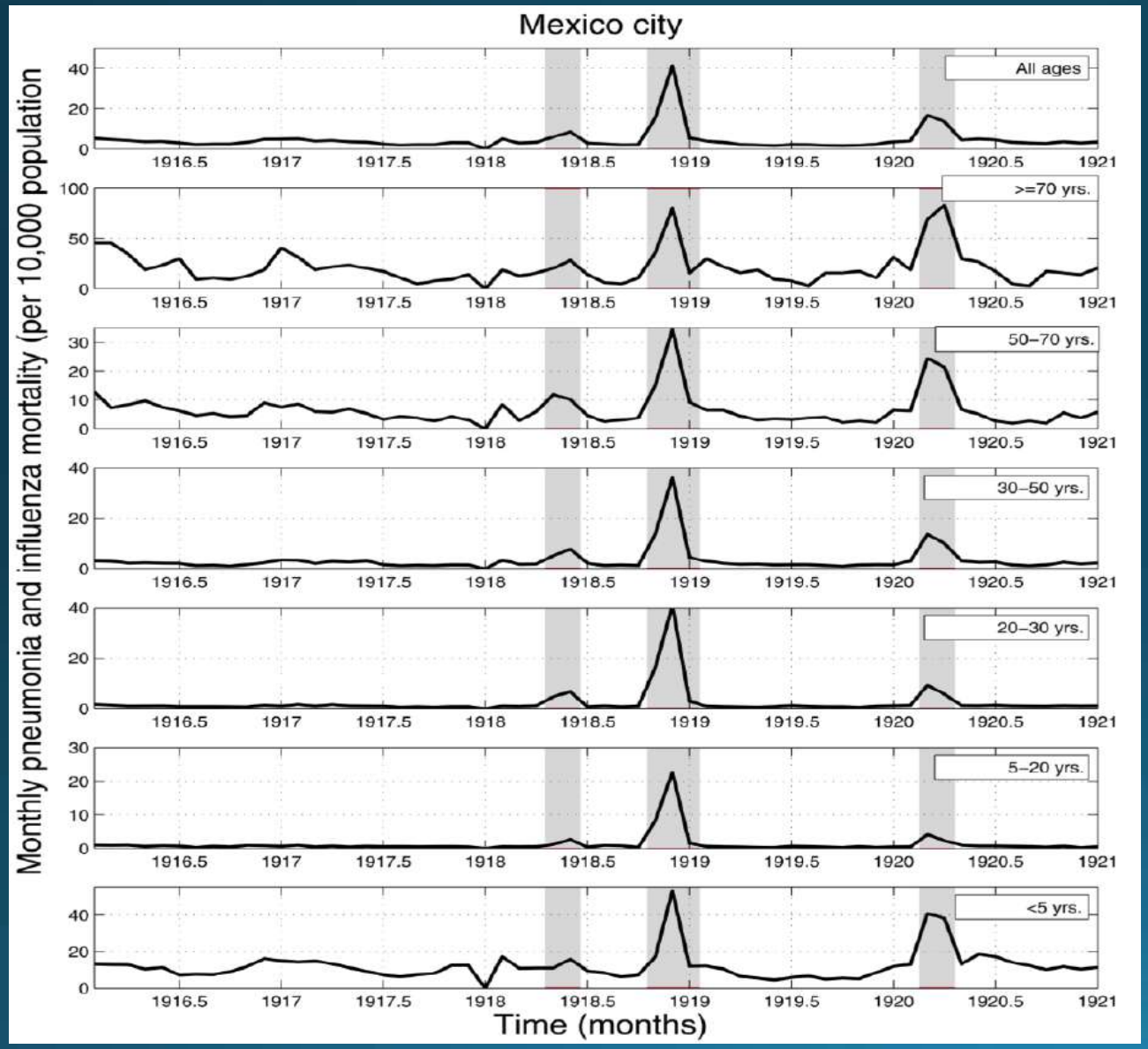
1910 **1918** 1920

Seniors ≥65 years

Young Adults 15-44 years

Olsen et al PNAS 2005, Andreasen et al, JID 2008

BUT…elderly sparing not everywhere



All ages were affected
In S America

Interpretation under the "recycling" Hypothesis:

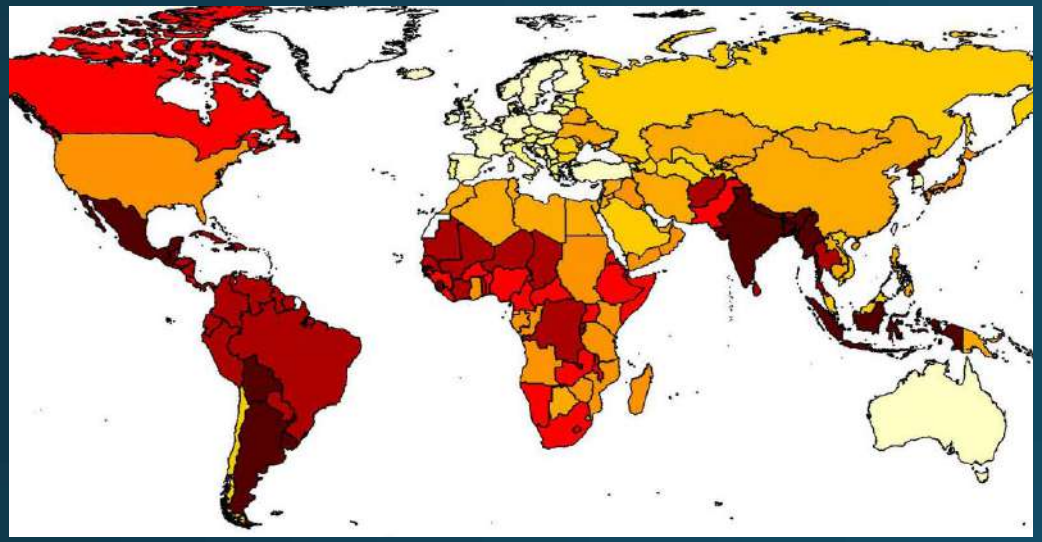
Remote locales had not encountered H1-like influenza in their childhood

Chowell et al, multiple publications of data from Colombia, Peru, Mexico…

2009 Pandemic Confirmed Recycling hypothesis

Elderly sparing – due to documented protective antibodies from childhood exposure

Mildish – M. Baker et al, Eurosurveillance 2009



Geographic heterogeneity

~200,000 deaths globally

~20-fold higher in S.America than Europe

WHO GLaMOR project

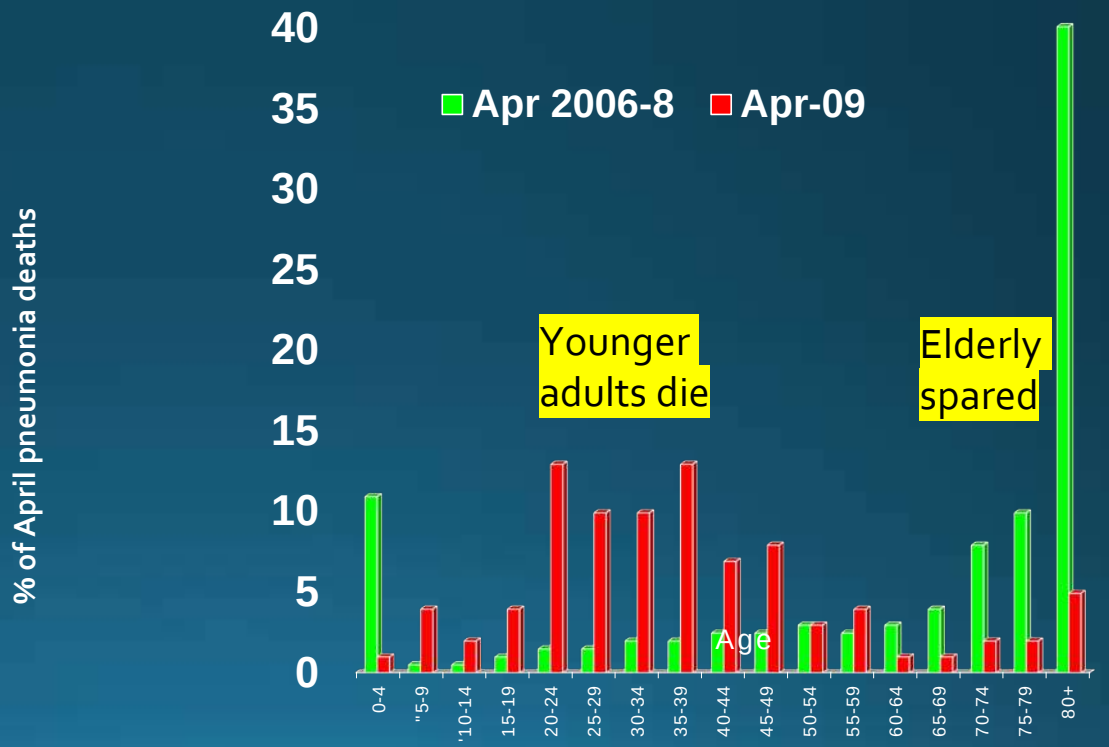
Global Mortality Estimates for the 2009 Influenza Pandemic from the GLaMOR Project: A Modeling Study

Lone Simonsen[1,2*], Peter Spreeuwenberg[3], Roger Lustig[2], Robert J. Taylor[2], Douglas M. Fleming[4], Madelon Kroneman[3], Maria D. Van Kerkhove[5,6], Anthony W. Mounts[6], W. John Paget[3], the GLaMOR Collaborating Teams[¶]

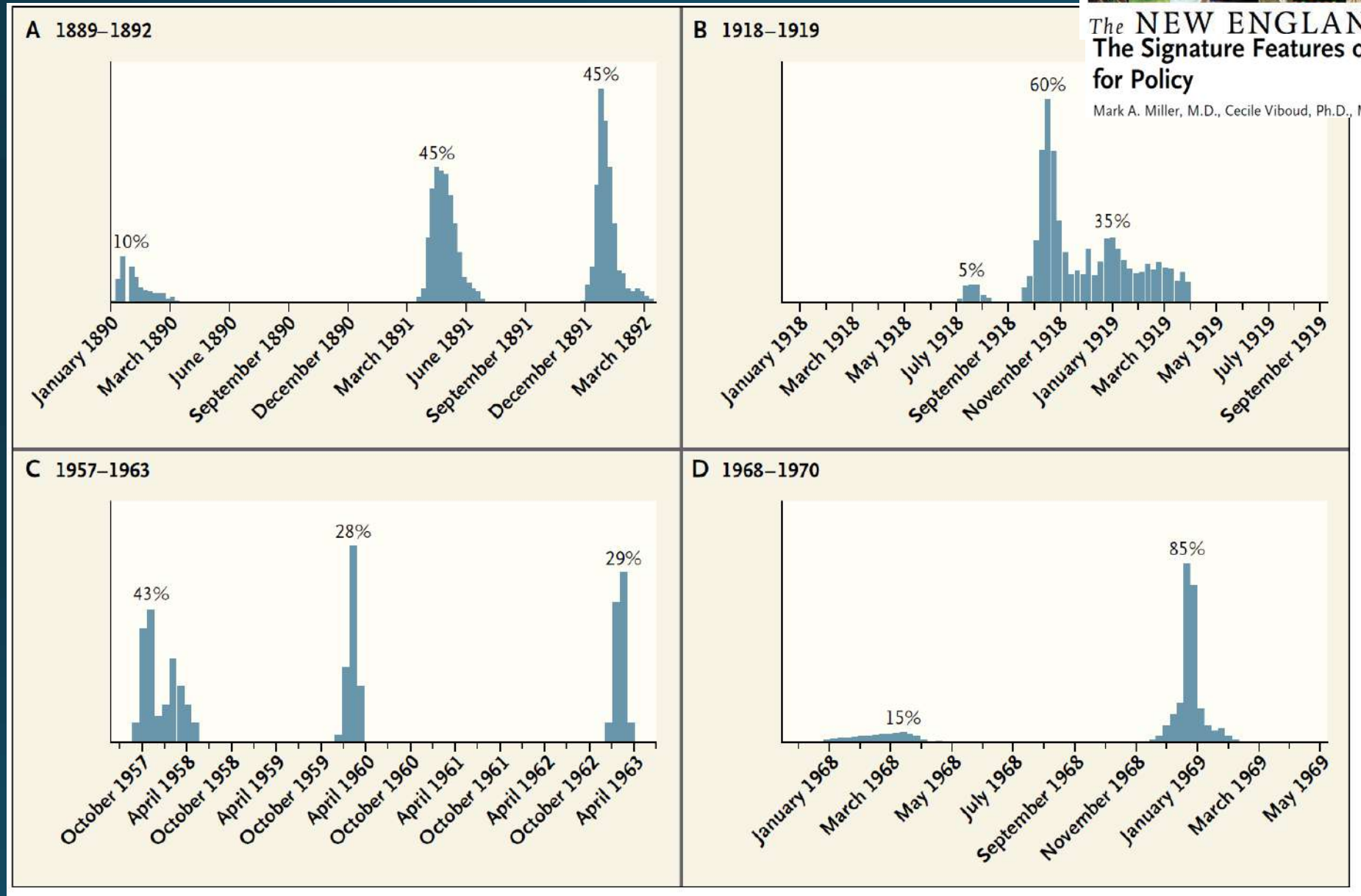
2009 Pandemic age shift

Pneumonia mortality in Mexico

Chowell et al, NEJM, August 2009



Pandemic have multiple waves

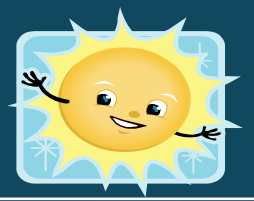


Pandemic deaths may be delayed to 2nd or 3rd wave

Good news: There is time to vaccinate!

A mild 1st 1918 Pandemic "Herald" Summer Wave identified by "signature" age patterns and speed of spread

Pandemic A/H1N1 virus eventually identified in US soldiers who died in summer 1918 (Sheng et al, PNAS 2011)

Copenhagen Population: 540,000	1918 summer wave 	1918 fall wave 
Excess Illness	25,000	61,000
Excess Deaths	85	1,300
Case Fatality	0.3%	2.1%
% occurred in young <65	95%	95%
Transmissibility Ro	>2	1.3

Pandemic A/H1 virus later identified in May-Aug 1918 in specimens From dead US soldiers (Sheng….Taubenberger, PNAS 2011)

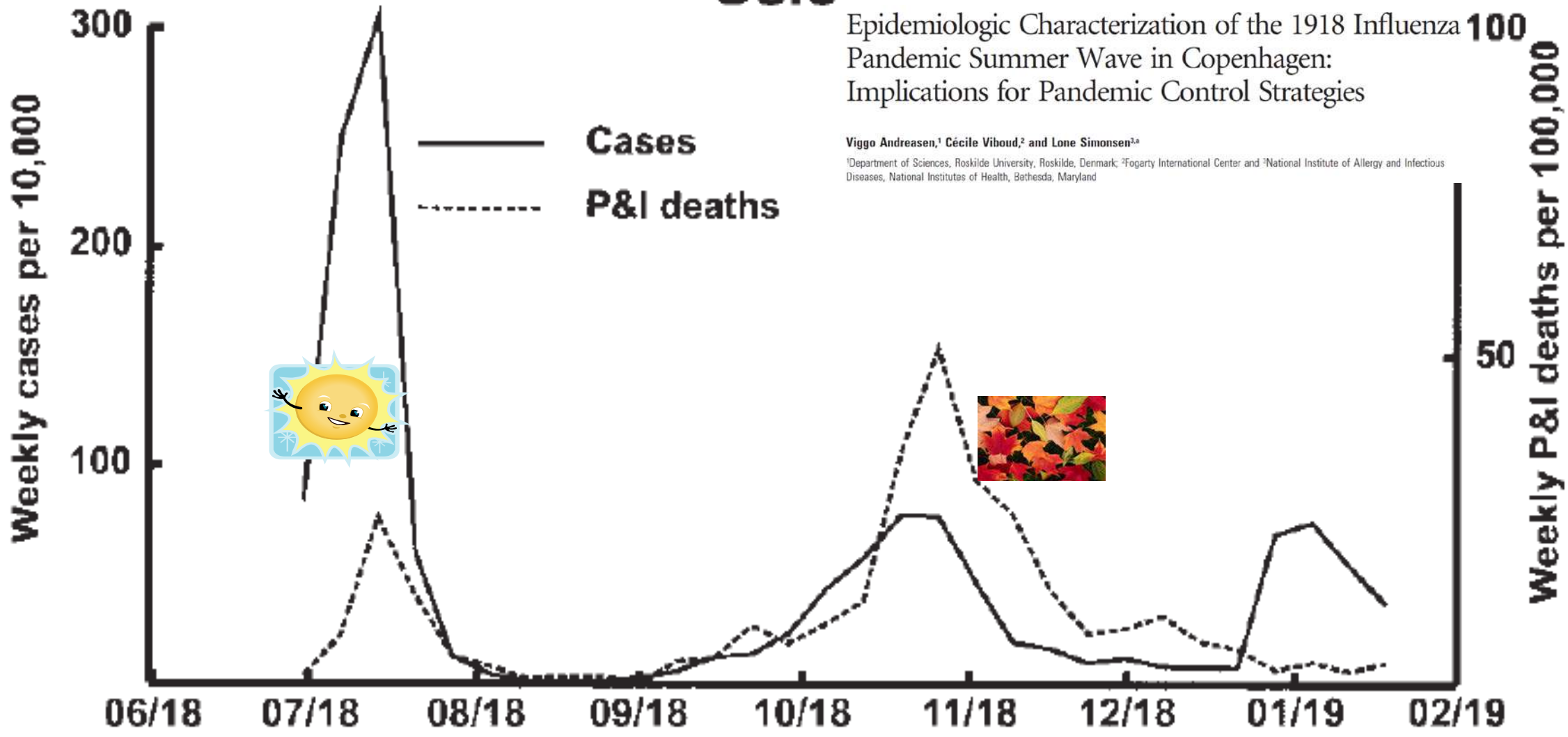
Epidemiologic Characterization of the 1918 Influenza Pandemic Summer Wave in Copenhagen: Implications for Pandemic Control Strategies

Viggo Andreasen,[1] Cécile Viboud,[2] and Lone Simonsen[3,a]

[1]Department of Sciences, Roskilde University, Roskilde, Denmark; [2]Fogarty International Center and [3]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

Did summer 1st wave protect against severe 2nd wave?

-- YES! by 56%-94% according to Barry et al, JID 2008



What if a population escaped the pandemic virus in 1918?

- A mixed picture of severity of later waves

Epidemiol. Infect. (2013), **141**, 353–356. © Cambridge University Press 2012
doi:10.1017/S0950268812000866

SHORT REPORT

Pacific islands which escaped the 1918–1919 influenza pandemic and their subsequent mortality experiences

SUMMARY

Very few Pacific islands escaped the 1918–1919 influenza pandemic. Subsequent influenza epidemics in the established colonial outposts of American Samoa and New Caledonia infected many but killed very few persons whereas the extraordinarily isolated Niue, Rotuma, Jaliut and Yule islands experienced high mortality influenza epidemics (>3% of population) following 1918. These dichotomous outcomes indicate that previous influenza exposure and degree of epidemiological isolation were important mortality risk factors during influenza epidemics on Pacific islands.

Shanks & Brundage, Epidemiol & Infect 2013

PNAS 2017

Risk Factors for Severe Pandemic Influenza Outcomes….

Age /childhood exposure to similar virus, 1st wave exposure, Ethnicity, human genetics, poverty, bacterial coinfection, co-morbidity (TB)

Autopsy series of 68 cases dying before and during the 1918 influenza pandemic peak

Zong-Mei Sheng[a], Daniel S. Chertow[a], Xavier Ambroggio[b], Sherman McCall[c], Ronald M. Przygodzki[d], Robert E. Cunningham[e], Olga A. Maximova[f], John C. Kash[a], David M. Morens[g], and Jeffery K. Taubenberger[a,1]

[a]Viral Pathogenesis and Evolution Section, Laboratory of Infectious Diseases, [b]Bioinformatics and Computational Biosciences Branch, [f]Office of the Chief, Laboratory of Infectious Diseases, and [g]Office of the Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892; [c]Clinical Pathology Laboratory, US Army Medical Research Institute of Infectious Diseases, Fort Detrick, MD 21702; [d]Department of Veterans Affairs, Washington, DC 20420; and [e]Department of Biophysics, Armed Forces Institute of Pathology, Rockville, MD 20850

Is bacterial coinfection the explanation for variability in 1918 mortality risk ?

Variable mortality during the 1918 influenza pandemic in Chicago

G. Dennis Shanks[a,1] and John F. Brundage[b]

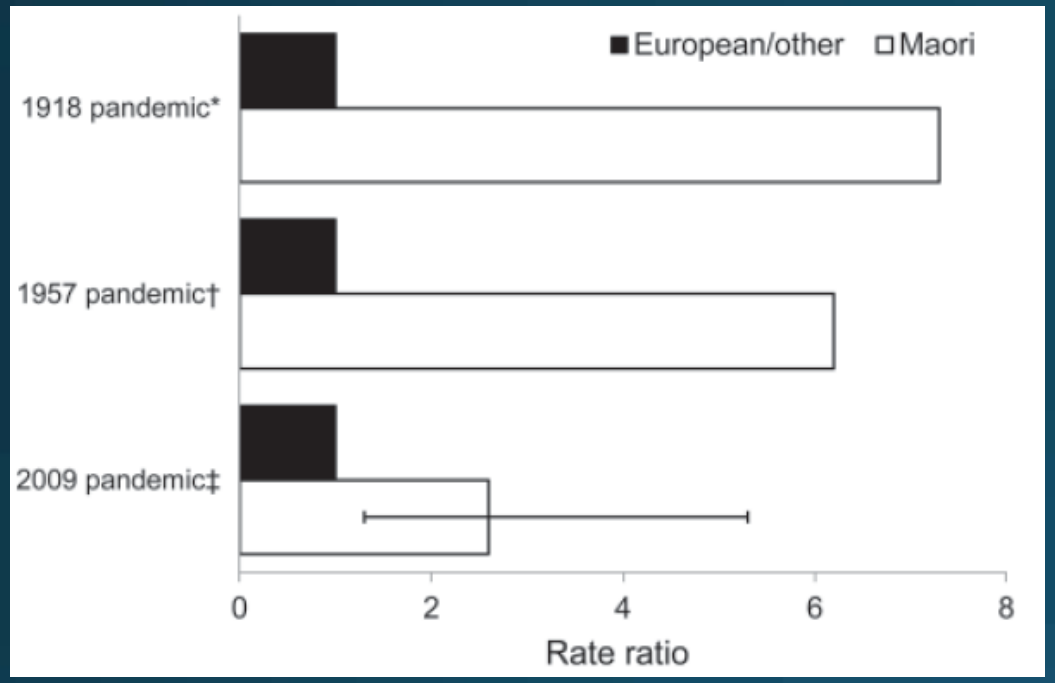
Table 2. Postmortem bacterial lung culture results in 1918

1918 culture result (current preferred nomenclature)	No./total (%)
Pneumococcus (*Streptococcus pneumonia*)	22/42 (52.4)
Pneumococcus, Serotype I	2/42 (4.8)
Pneumococcus, Serotype II	5/42 (11.9)
Pneumococcus, Serotype III	7/42 (16.7)
Pneumococcus, Serotype IV*	5/42 (11.9)
Pneumococcus, not serotyped	3/42 (7.1)
Streptococcus, hemolytic (*Streptococcus pyogenes*)	4/42 (9.5)
Streptococcus, nonhemolytic	1/42 (2.4)
Staphylococcus	4/42 (9.5)
Friedländler's bacillus (*Klebsiella pneumonia*)	1/42 (2.4)
Bacillus coli (*Escherichia coli*)	1/42 (2.4)
Diplococci observed in sections	1/42 (2.4)
Mixed cultures	6/42 (14.3)
Pneumococcus + *Streptococcus*	2/42 (4.8)
Pneumococcus + *Staphylococcus*	1/42 (2.4)
Streptococcus + *Staphylococcus*	2/42 (4.8)
Pneumococcus + *Staphylococcus* + Friedländler's bacillus	1/42 (2.4)
Negative	2/42 (4.8)

*Serotype IV in 1918 included a number of polysaccharide capsular types that were subsequently assigned to newly identified types (43).

Ethnicity as a risk factor?

New Zealand Maori population was at 7 x 1918 pandemic mortality risk



Wilson et al, Emerg Inf Dis 2012

CONTENDERS

- Genetic predisposition?
- Previous influenza exposure less in remote populations?
- Differences in background mortality levels?

Tuberculosis as a risk factor?

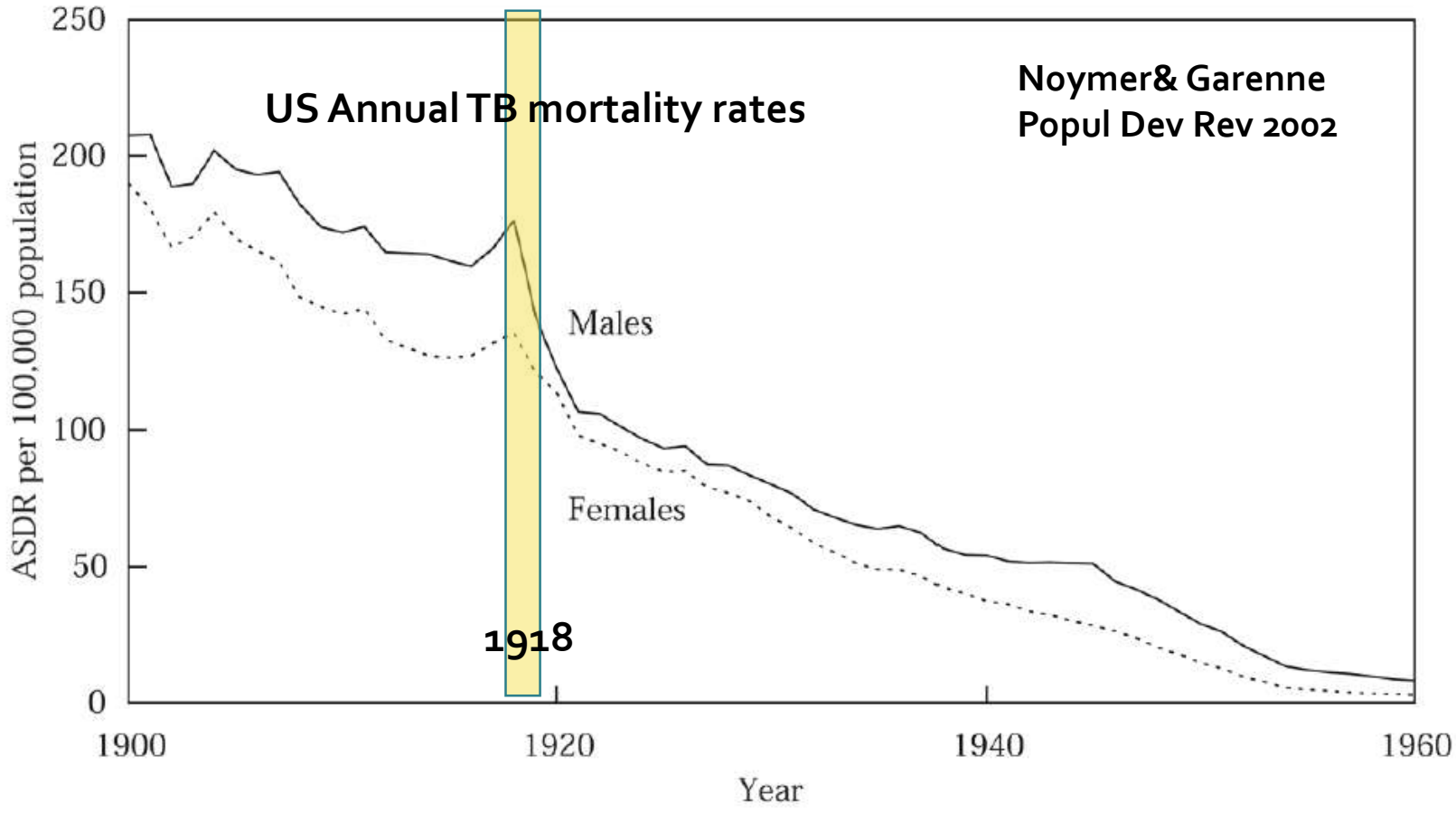


FIGURE 5.
Age-standardized death rate, ASDR, for tuberculosis (all forms), males and females, 1900–60

Birth year as a risk factor?

First flu is forever

A change in the properties of influenza virus in 1968 has left a profound mark on population immunity

By Cécile Viboud[1] and Suzanne L. Epstein[2] | A/H5N1 and A/H7N9 reported glo

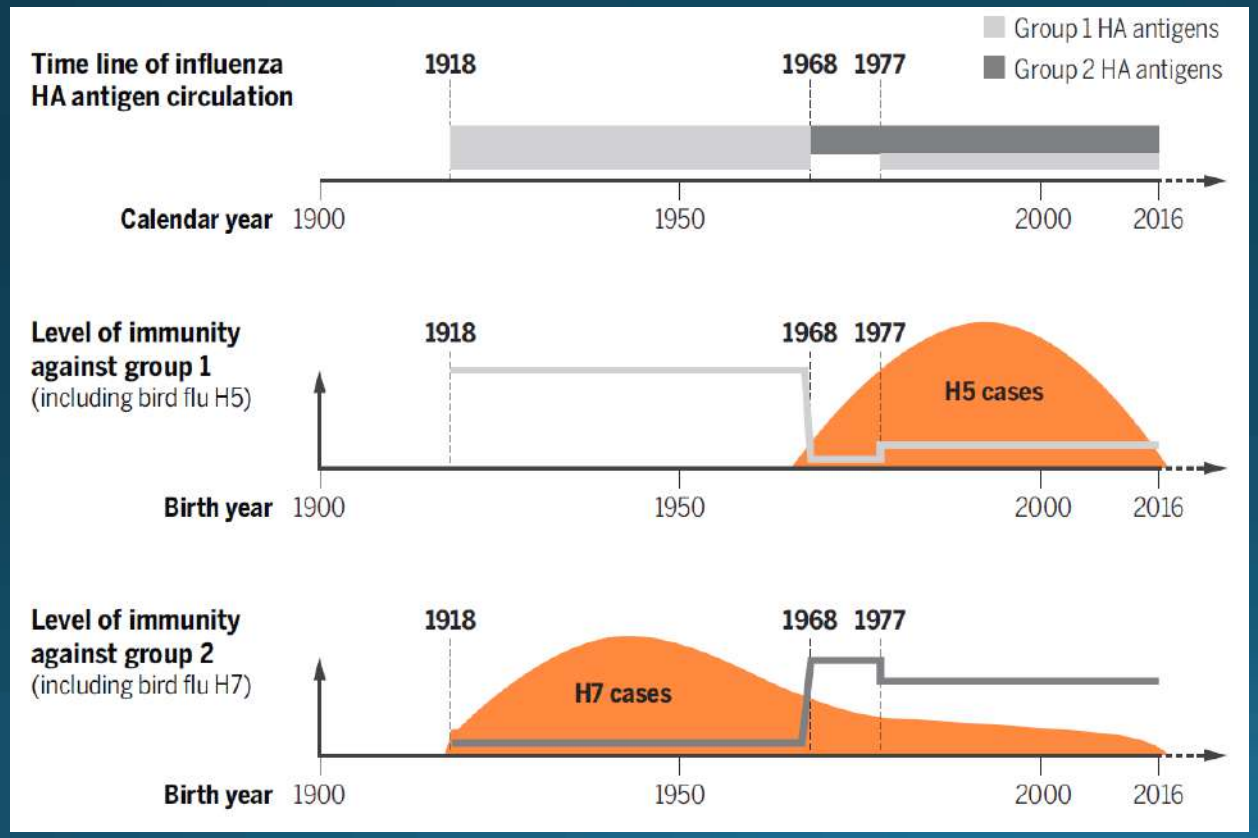
RESEARCH ARTICLE

INFLUENZA EPIDEMIOLOGY

Potent protection against H5N1 and H7N9 influenza via childhood hemagglutinin imprinting

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

Science 2016



Two Influenza HA types

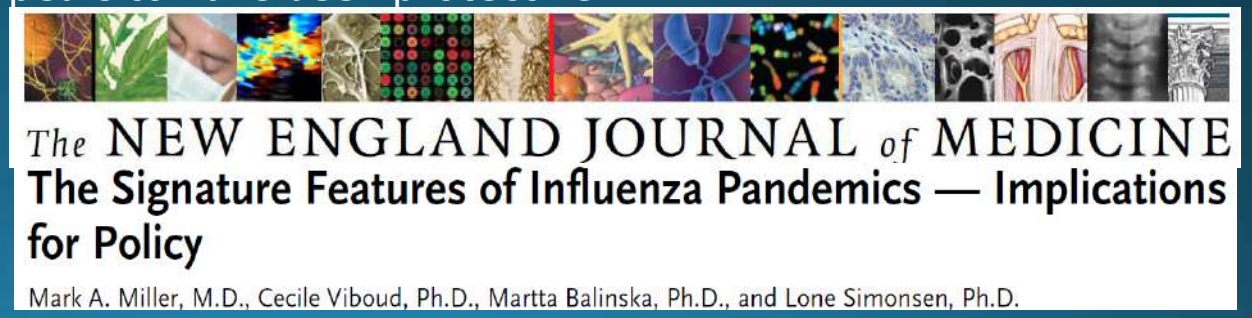
-Type1: H1, H2, H5

-Type2: H3, H7

Cases and Deaths, by birth year, for two avian influenza viruses, one of each type

What we now know about 1918 Pandemic "Signature Features"

- Novel influenza A H1N1 virus (sequenced)
- High transmissibility (Ro>2; susceptible population)
- rapid global dissemination; disrespects typical seasonality
- High mortality (1-2% of population) w unusual age pattern
  - Young adults at extreme risk
  - Seniors often spared
- Geographical heterogeneity in mortality burden
  - 30-fold differences between countries
- Multiple waves 1918-1921
  - Mild 1st wave that appears to have been protective

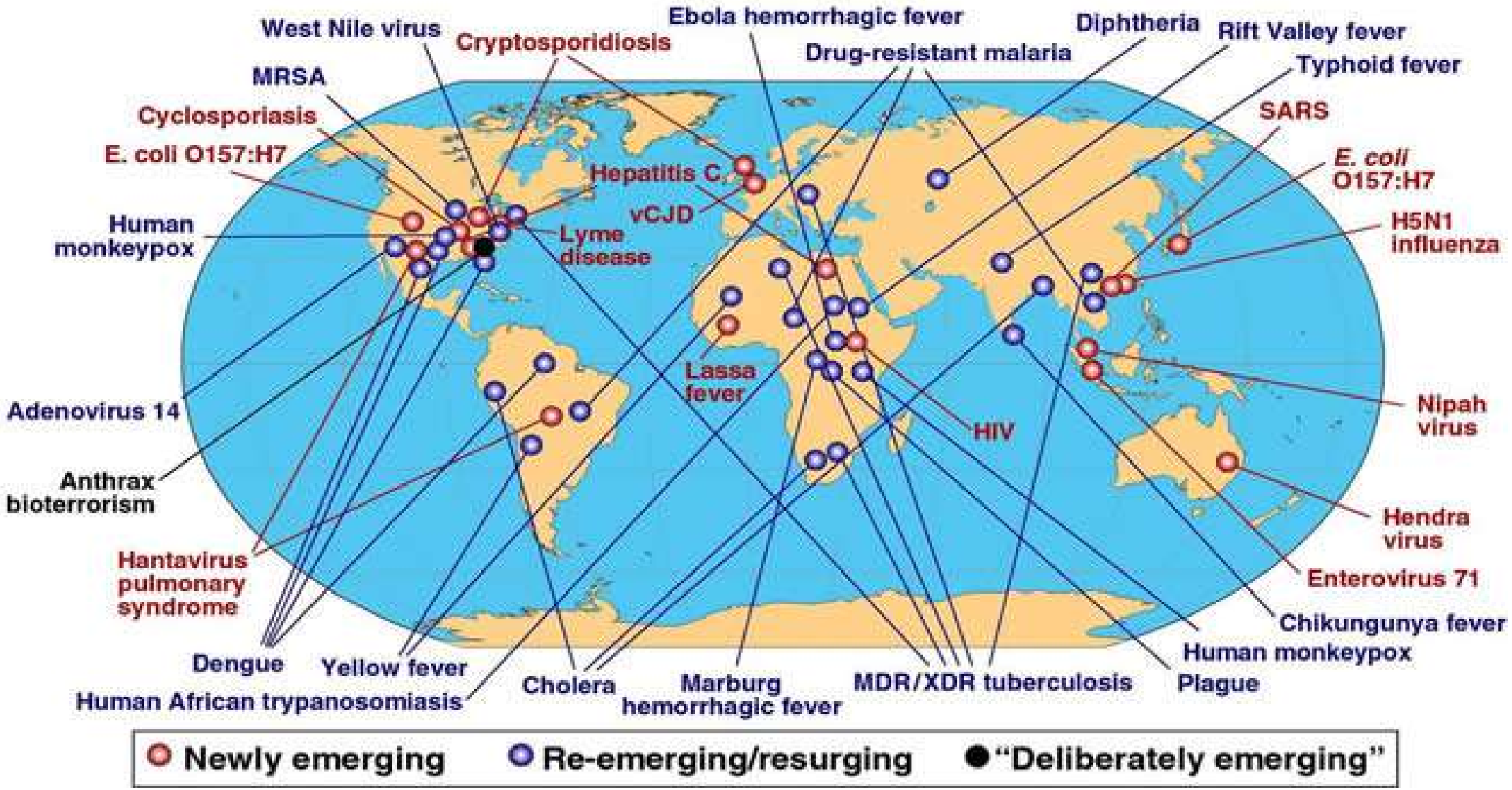


Remaining Puzzles I

- **Origin of pandemic virus**
  - To be or not to be an all-avian virus
- **Role of the Military**
  - Origin in WW1 trenches? Spread via troop movements?
- **1918 pandemic mortality global estimates correct?**
  - Murray Lancet study bears on only 13 data points, extrapolations, but soo much variability and soo much not measured
- **Young adults at extreme risk, why?**
  - Immune imprinting in 1870 and 1889 ? Cytokine storm? Monsalvo, Nature Medicine and Jackie Katz, NEJM
- **Elderly sparing – why not everywhere?**
  - recycling in connected locations most parsimonious…same "type" seen in childhood
- **Mild 1st Wave – what was missing?**
  - Wrong time of year? H1N1 evolved to higher virulence? Missing bacterial co-factor?
- **Role of TB co-morbidity?**
  - Tuberculosis as a risk factor? leading cause of death at the time in young adults
- **Why were some ethnic populations at high mortality risk?**

World Health Organization

What Comes Next?



& collaboration mechanisms to fight against them

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