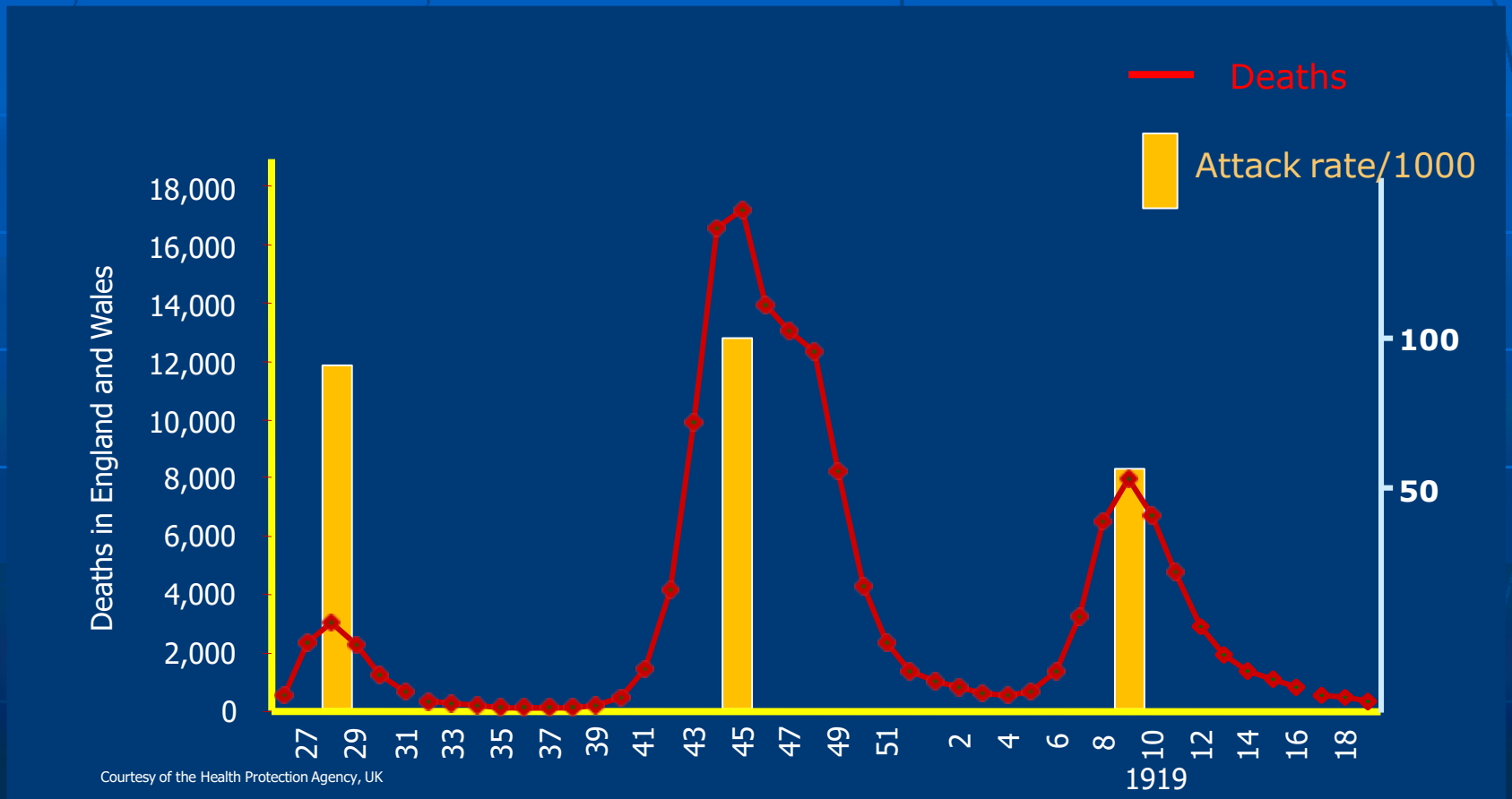
# Twentieth Century Pandemic 1: 1918-19

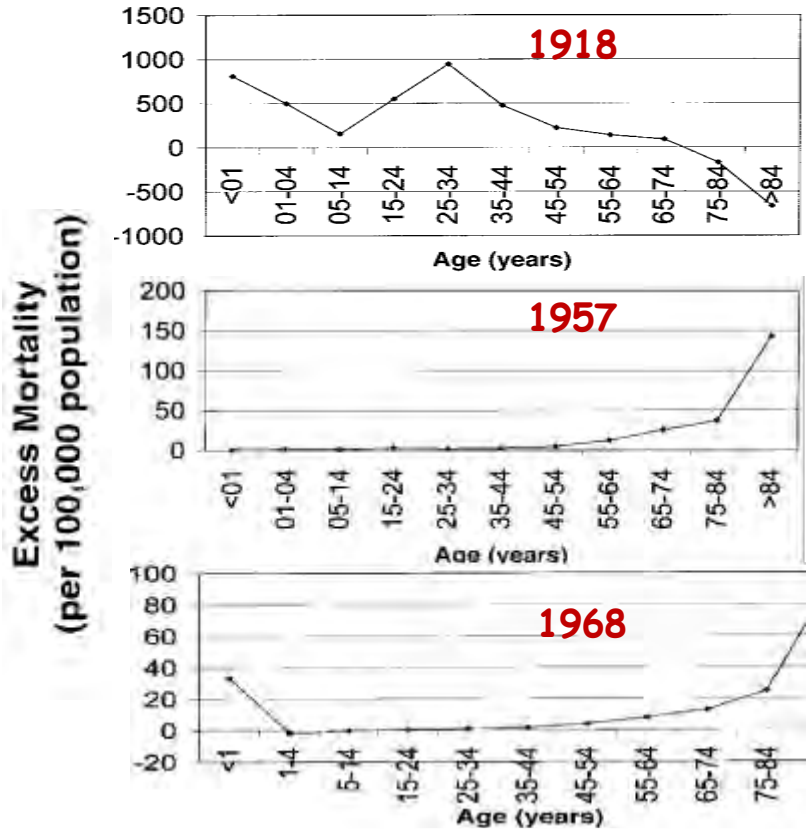
- Unusual 'W' shaped mortality curve
  - Three waves of differing mortality



# Twentieth Century Pandemic 1: 1918-19

- Unusual 'W' shaped mortality curve
  - Three waves of differing mortality
  - Sparing of older adults – analysis of **excess mortality** suggests protection by earlier infection (Luk et al 2001) possibly 1830-33 pandemic (Worobey et al 2014.

Excess mortality by age in USA – in 3 pandemics




From Luk et al CID (2001):**33**, 1375

# Twentieth Century Pseudo- Pandemic 1947

- Originally thought to be a pandemic due to:
  - high morbidity worldwide
  - vaccine failures
  - major antigenic differences in the HI test

**Table 15.1** Antigenic Variation and Pandemic Severity[a]

| Year | Virus[b] | Change[c] | Extent of change | Result |
|---|---|---|---|---|
| 1918 | HswN1 | ? | ? | Pandemic (severe) |
| 1928 | H0 N1 | H | ++ | (?) Pandemic |
| | | N | + | (?) Year of H0N1 introduction |
| 1946 | H1 N1 | H | ++ | Pandemic (mild) |
| | | N | + | |
| 1957 | H2 N2 | H | +++ | Pandemic (severe) |
| | | N | +++ | |
| 1968 | H3 N2 | H | +++ | Pandemic (moderate) |
| | | N | 0 | |

[a] Modified from Kilbourne (1973a). *J. Infec. Dis.* **127**, 478–487. Copyright 1973, University of Chicago Press. Reproduced by permission.

[b] Single vertical lines indicate slight antigenic relatedness. Double vertical lines indicate close antigenic similarity. Dashed lines indicate relatedness only through anamnestic response.

[c] H, hemagglutinin; N, neuraminidase.

Kilbourne 1973

TABLE 1

*Titrations of antigens prepared from different strains of influenza virus with ferret antisera*

| Antigen | | Serum titers* | | | | |
|---|---|---|---|---|---|---|
| Virus type | Strain | FM1 | LF1 | PRS | Swine | Lee |
| A | FM1 | 3,048* | 1,024 | 16 | 0 | 16 |
| | LF1 | 1,024 | 512 | 32 | 0 | 16 |
| | SF1 | 1,024 | 128 | 64 | ND | 16 |
| | PRS | 64 | 0 | 4,096 | 0 | 16 |
| | Weiss | 16 | 8 | 512 | 0 | ND |
| Swine | | 32 | 16 | 64 | 1,024 | ND |
| B | Lee | 32 | 16 | 16 | ND | 2,048 |

# Twentieth Century Pseudo- Pandemic 1947

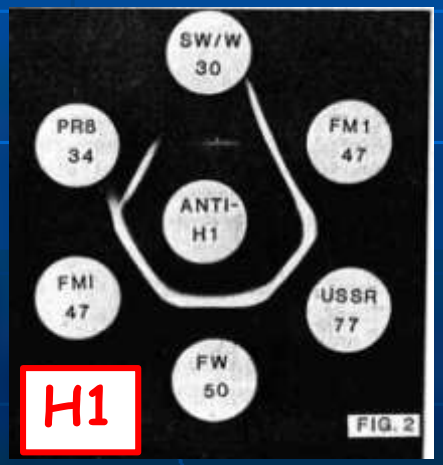
Comp. Immun. Microbiol. infect. Dis., Vol. 3, pp. 5–15.
Pergamon Press Ltd., 1980. Printed in Great Britain

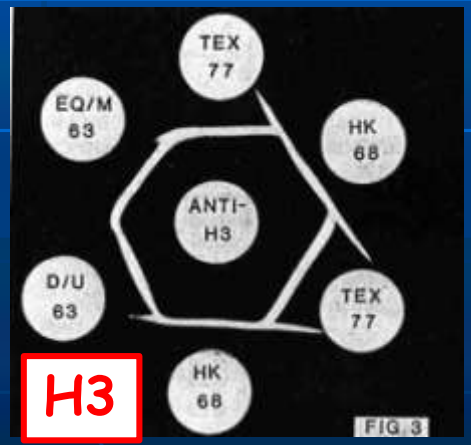
## ANTIGENIC ANALYSIS OF INFLUENZA A VIRUS SURFACE ANTIGENS: CONSIDERATIONS FOR THE NOMENCLATURE OF INFLUENZA VIRUS

G. C. SCHILD*, R. W. NEWMAN*, R. G. WEBSTER‡, DIANE MAJOR* and VIRGINIA S. HINSHAW‡

*National Institute for Biological Standards and Control, Holly Hill, Hampstead, London, NW3 6RB, U.K. and ‡Laboratories of Virology, St Jude Children's Research Hospital, P.O. Box 318, Memphis, TN 38101, U.S.A.

**Abstract**—The surface antigens of a comprehensive collection of prototype and other strains of influenza A virus of human, swine, equine and avian origin were studied in immuno-double-diffusion tests with antisera to purified hemagglutinin and neuraminidase antigens. These tests were selected because of their ability to reveal antigenic relationships which may not be apparent by




Schild et al 1980

*Memoranda*
*Mémorandums*

***Memoranda*** *are statements concerning the conclusions or recommendations of certain WHO scientific meetings; they are signed by the participants in the meeting.*

*Les* ***Mémorandums*** *exposent les conclusions et recommandations de certaines réunions scientifiques de l'OMS; ils sont signés par les participants à ces réunions.*

*Bulletin of the World Health Organization*, 58(4): 585–591 (1980)

## A revision of the system of nomenclature for influenza viruses: a WHO Memorandum*

*In February 1980, the World Health Organization convened a meeting to consider information relevant to the nomenclature of influenza viruses and to make definitive*

**Table 1. Proposed subtypes of haemagglutinin antigens of influenza A viruses**

| Proposed subtypes | Previous subtypes (1971 system) |
|---|---|
| H1[a] | H0, H1, Hsw1 |
| H2 | H2 |
| H3 | H3, Heq2, Hav7 |
| H4 | Hav4 |
| H5[a] | Hav5 |
| H6 | Hav6 |
| H7 | Heq1, Hav1 |
| H8 | Hav8 |
| H9 | Hav9 |
| H10 | Hav2 |
| H11 | Hav3 |
| H12 | Hav10 |

# Twentieth Century Pseudo- Pandemic 1947

## The total influenza vaccine failure of 1947 revisited: Major intrasubtypic antigenic change can explain failure of vaccine in a post-World War II epidemic

Edwin D. Kilbourne*†, Catherine Smith‡, Ian Brett‡, Barbara A. Pokorny‡, Bert Johansson‡, and Nancy Cox‡

Although vaccine-induced immunity to influenza A virus is continually challenged by progressively selected mutations in the virus's major antigens (antigenic drift), virus strains within a subtype (e.g., H1N1) are antigenically cross-reactive. Although cross-immunity diminishes as further mutations accumulate, necessitating frequent changes in vaccine strains, older vaccines are usually partially protective. The post-World War II epidemic of 1947 is notable for the total failure of a vaccine previously effective in the 1943–44 and 1944–45 seasons. We have combined extensive antigenic characterization of the hemagglutinin and neuraminidase antigens of the 1943 and 1947 viruses with analysis of their nucleotide and amino acid sequences and have found marked antigenic and amino acid differences in viruses of the two years. Furthermore, in a mouse model, vaccination with the 1943 vaccine had no effect on infection with the 1947 strain. These findings are important, because complete lack of cross-immunogenicity has been found previously only with antigenic shift, in which antigenically novel antigens have been captured by reassortment of human and animal strains, sometimes leading to pandemics. Although the 1947 epidemic lacked the usual hallmarks of pandemic disease, including an extensive increase in mortality, it warns of the possibility that extensive intrasubtypic antigenic variation (coupled with an increase in disease severity) could produce pandemic disease without the introduction of animal virus antigens.

Materials and Methods

Viruses and Their Genealogy. Strains of A/Fort Monmouth/1/47 (H1N1) (FM-1) from three laboratories were compared serially and found to be similar in antigenicity and HA sequence. Therefore, one studied, based on the most passes in the laboratory of one of us (E.D.K.) since 1980 and used previously in immunologic studies. This strain was known to be avirulent for mice and presumably was almost homogeneous in the mass initially isolated in eggs in 1947. A/Weiss/43 (H1N1) was a component together with A/PR/8/34 (H1N1) and B/Lee/40 of the 1947 vaccine. A second 1947 strain, A/Marton/47, was generously provided as lyophilized virus by H. F. Maassab (University of Michigan Ann Arbor), and two others, A/Hawaii/1/50 and A/Taiwan/1/86, were from the files of the Centers for Disease Control. It is important to note that although both

PLoS PATHOGENS

## Multiple Reassortment Events in the Evolutionary History of H1N1 Influenza A Virus Since 1918

**Martha I. Nelson[1], Cécile Viboud[2], Lone Simonsen[3], Ryan T. Bennett[4], Sara B. Griesemer[4], Kirsten St. George[5], Jill Taylor[4], David J. Spiro[5], Naomi A. Sengamalay[6], Elodie Ghedin[7], Jeffery K. Taubenberger[8], Edward C. Holmes[1,2]**

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**Abstract**

The H1N1 subtype of influenza A virus has caused substantial morbidity and mortality in humans first documented in the global pandemic of 1918 and continuing to the present day. Despite this disease burden, the evolutionary history of the A/H1N1 virus is not well understood, particularly whether there is a virological basis for several notable epidemics of unusual severity in the 1940s and 1950s. Using a data set of 71 representative complete genome sequences sampled between 1918 and 2006, we show that segmental reassortment has played an important role in the genomic evolution of A/H1N1 since 1918. Specifically, we demonstrate that an A/H1N1 isolate from the 1947 epidemic acquired novel PB2 and HA genes through intra-subtype reassortment, which may explain the abrupt antigenic evolution of this virus. Similarly, the 1951 influenza epidemic may also have been associated with reassortant A/H1N1 viruses. Intra-subtype reassortment therefore appears to be a more important process in the evolution and epidemiology of H1N1 influenza A virus than previously realized.

InterFlu

# Twentieth Century Pandemic 2: 1957-58
## 'Asian Flu'

- Outbreaks started in Kweichow province (Guizhou), China in February
- Spread globally within ~6 months

# Twentieth Century Pandemic 2: 1957-58
## 'Asian Flu'

- Unrelated to previous strains in HI test
  - Later serological studies and then molecular analyses indicated avian origin of HA, NA and PB1 genes reassorted with previous H1N1 virus.

TABLE II. Comparison of Far East Influenza A Isolates with Prototype Strains in Hemagglutination-Inhibition Tests

| Chicken antisera against viruses: (type and strain) | Hemagglutination-inhibition titers obtained in tests with antigens: Far East viruses: A-Japan 305-57 | A-Japan 307-57 | A-Hong Kong 304-57 | A-Malaya 309-57 | A-Malaya 310-57 | A-Malaya 311-57 | Prototype viruses: A-AA, 1-57 | A-Denver 2-57 | A-Japan 301-56 | A-Hawaii 303-56 | A-AA, 4-56 | A-FLW, 1-52 | A-FW, 1-50 | A-PM1 (1947) | A-PR8 (1934) | A-WS (1933) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Far East viruses* | | | | | | | | | | | | | | | | |
| A-Japan-305-57 | | | | | | | | | | | | | | | | |
| #9488 | 100 | 400 | 400 | 400 | 400 | 200 | <25 | <25 | <25 | <50 | <25 | <25 | <25 | <25 | <25 | <25 |
| #B 891 | 200 | " | " | 800 | " | 400 | " | " | " | " | " | " | " | " | " | " |
| A-Malaya-311-57 | 100 | 800 | " | " | " | " | <50 | <50 | <50 | " | | <50 | <50 | <50 | <50 | <50 |
| *Prototype viruses* | | | | | | | | | | | | | | | | |
| A-Japan-301-56 (Dec.) | <50 | | <50 | <25 | <25 | <50 | 400 | | | | | | | | | |
| -Hawaii-303-56 | <25 | <25 | " | " | " | " | | 400 | | | | | | | | |
| -AA-4-56 | " | " | " | " | " | " | | | 400 | | | | | | | |
| -FLW-1-52 | " | " | " | " | " | " | | | | 800 | | | | | | |
| -FW-1-50 | " | " | " | <50 | " | " | | | | | 800 | | | | | |
| -FM1 (1947) | <50 | | " | <25 | " | " | | | | | | 800 | | | | |
| -PR8 (1934) | " | <50 | " | " | " | " | | | | | | | 800 | | | |
| -WS (1933) | " | | " | " | " | " | | | | | | | | 1600 | | |

# Twentieth Century Pandemic 2: 1957-58
## 'Asian Flu'

- Two waves in many places – late autumn then winter-spring
- High morbidity, moderate mortality
  - Highest morbidity in children
  - Excess mortality reported in pregnant women

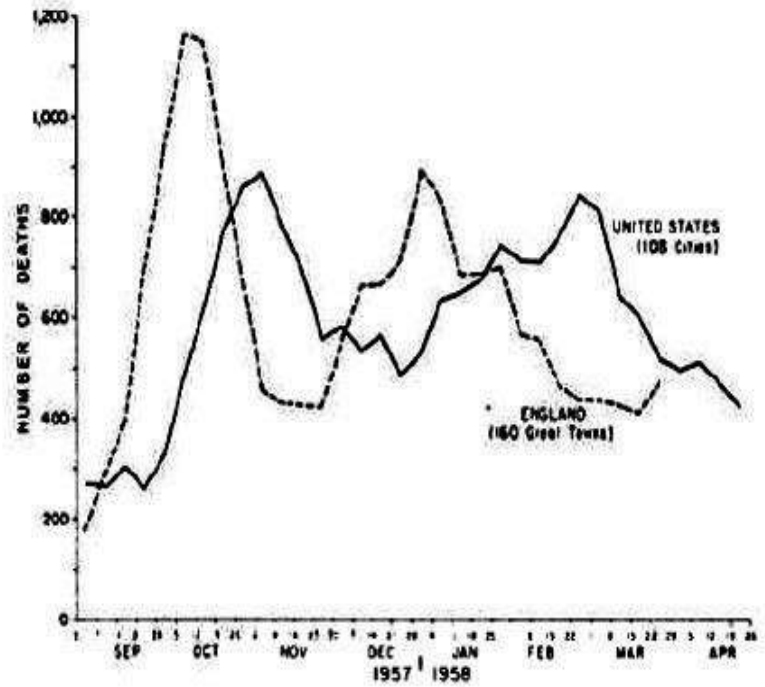
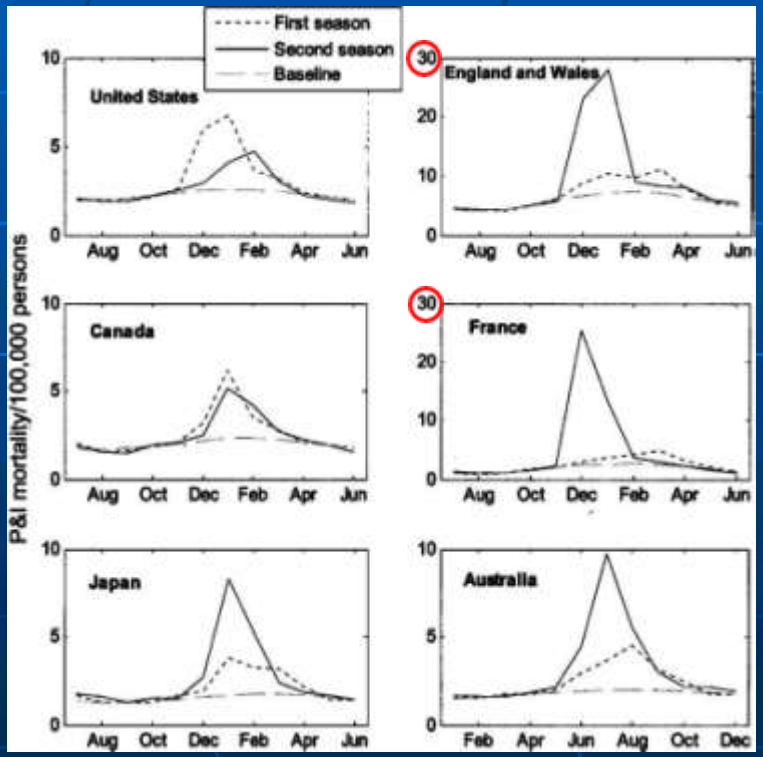
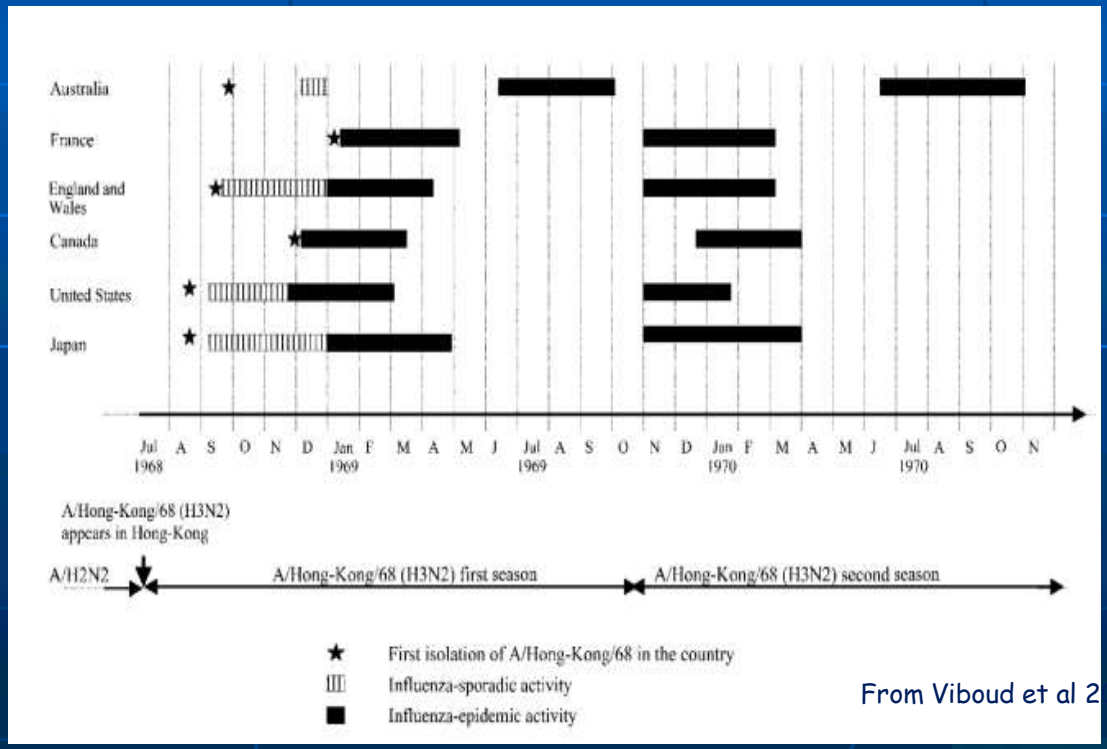



Fig. 19. Weekly influenza and pneumonia deaths in England and in the United States, 1957–1958.

# Twentieth Century Pandemic 3: 1968-69
## 'Hong Kong Flu'

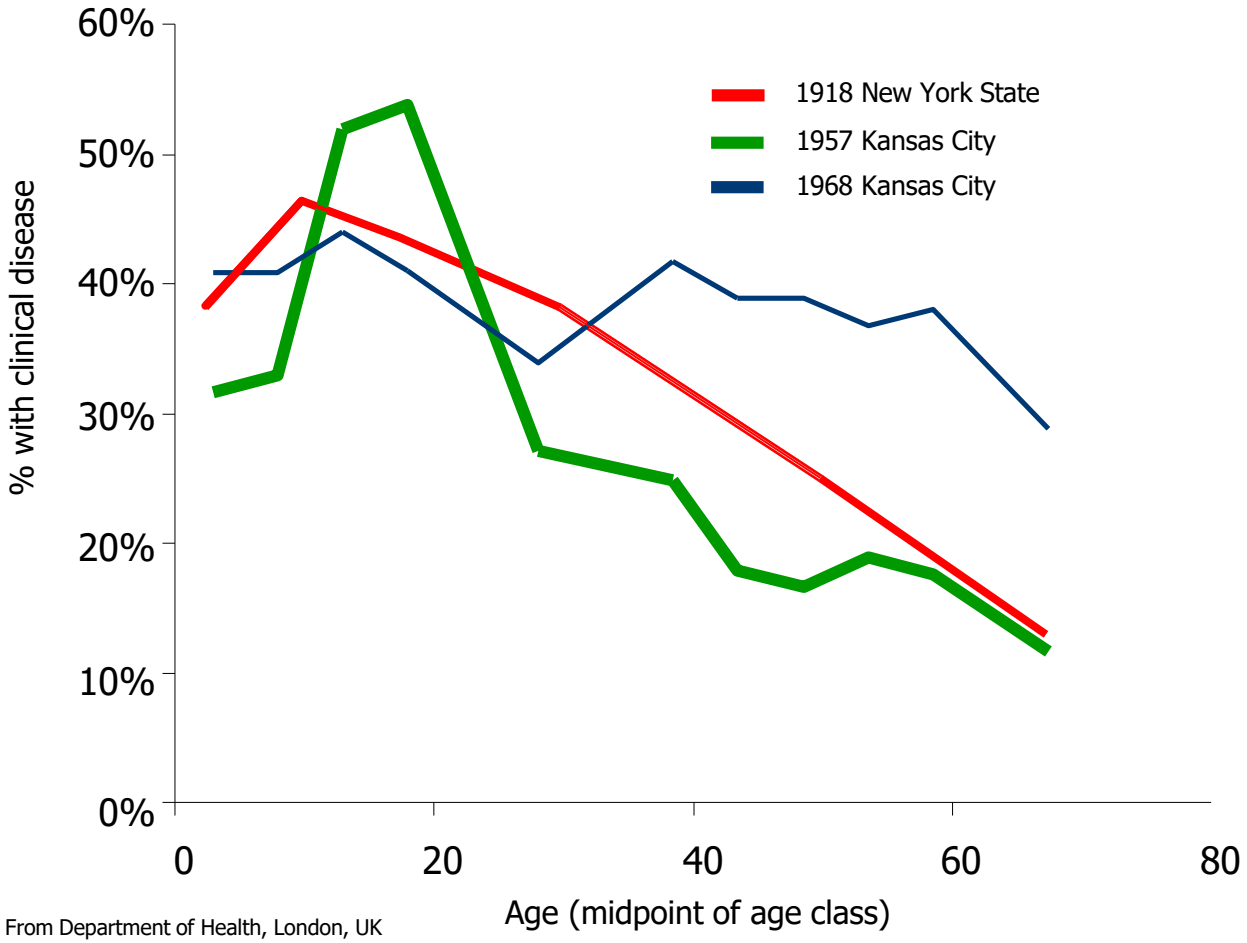
- Origin S.E.China? Outbreak in Hong Kong July 1968.
- Serologically different HA subtype but NA close to H2N2 strains.
- Spread quickly, two pandemic seasons, differing impact North America vs other regions- recently re-analysed by Viboud et al.
  - Possible impact of 1968 H2N2 outbreak in Australia




From Viboud et al 2

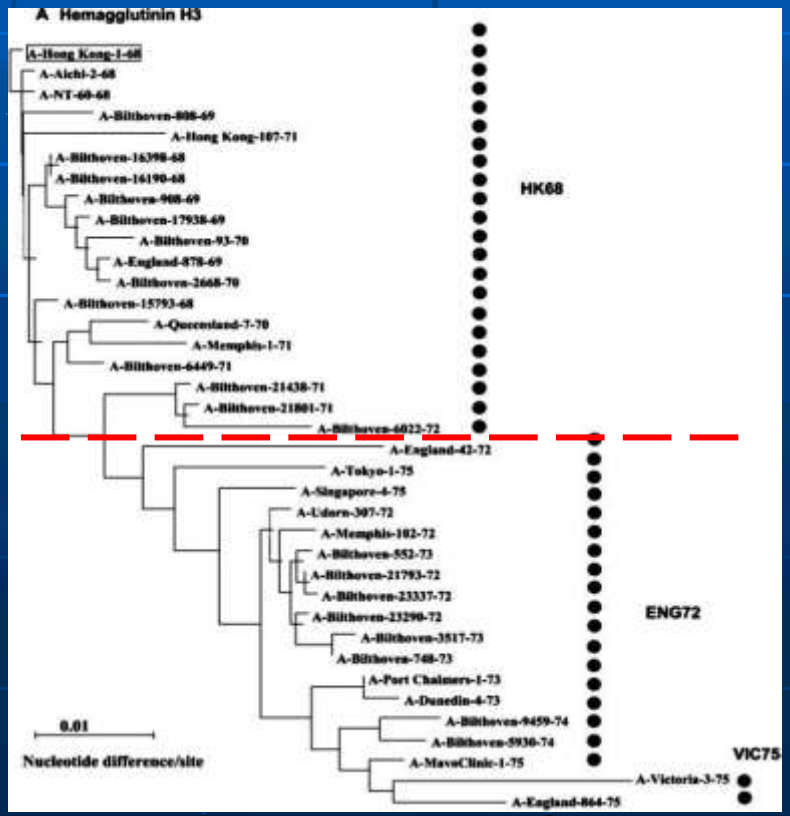
# Twentieth Century Pandemic 3: 1968-69
## 'Hong Kong Flu'

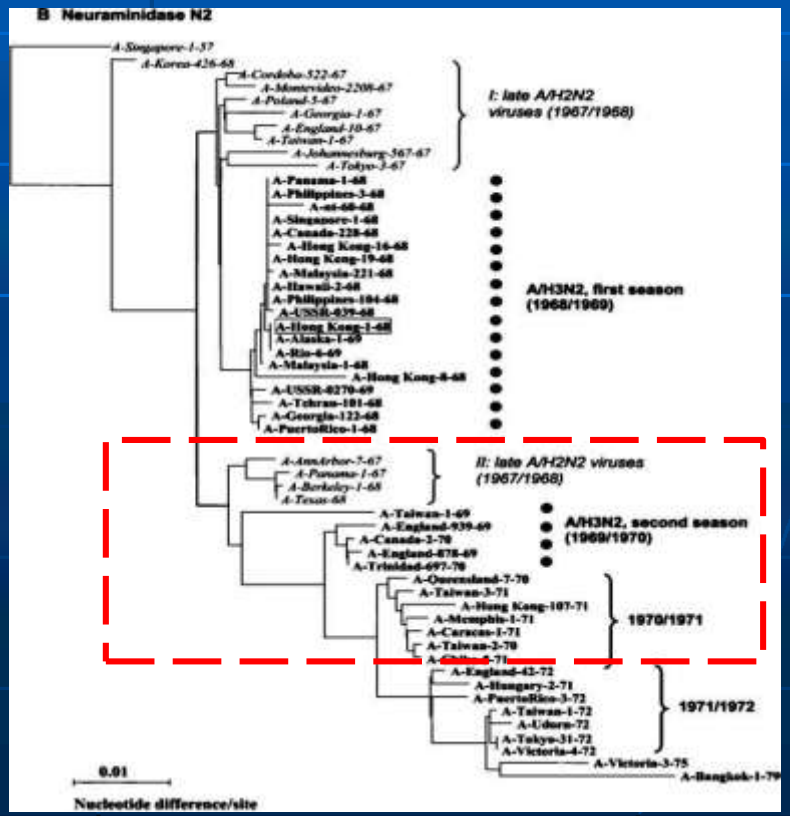



From Department of Health, London, UK

# Twentieth Century Pandemic 3: 1968-69
## 'Hong Kong Flu'

- Neuraminidase antibody from prior H2N2 infection probably protective.
  - ? Effect on epidemiology eg Australia
- HA constant over first two seasons.
- Neuraminidase drifted or second lineage between first and second outbreaks – possible effect on pathogenicity or immunity?
- Subsequent genetic analysis shows 6 gene segments from H2N2 with avian HA and PB1



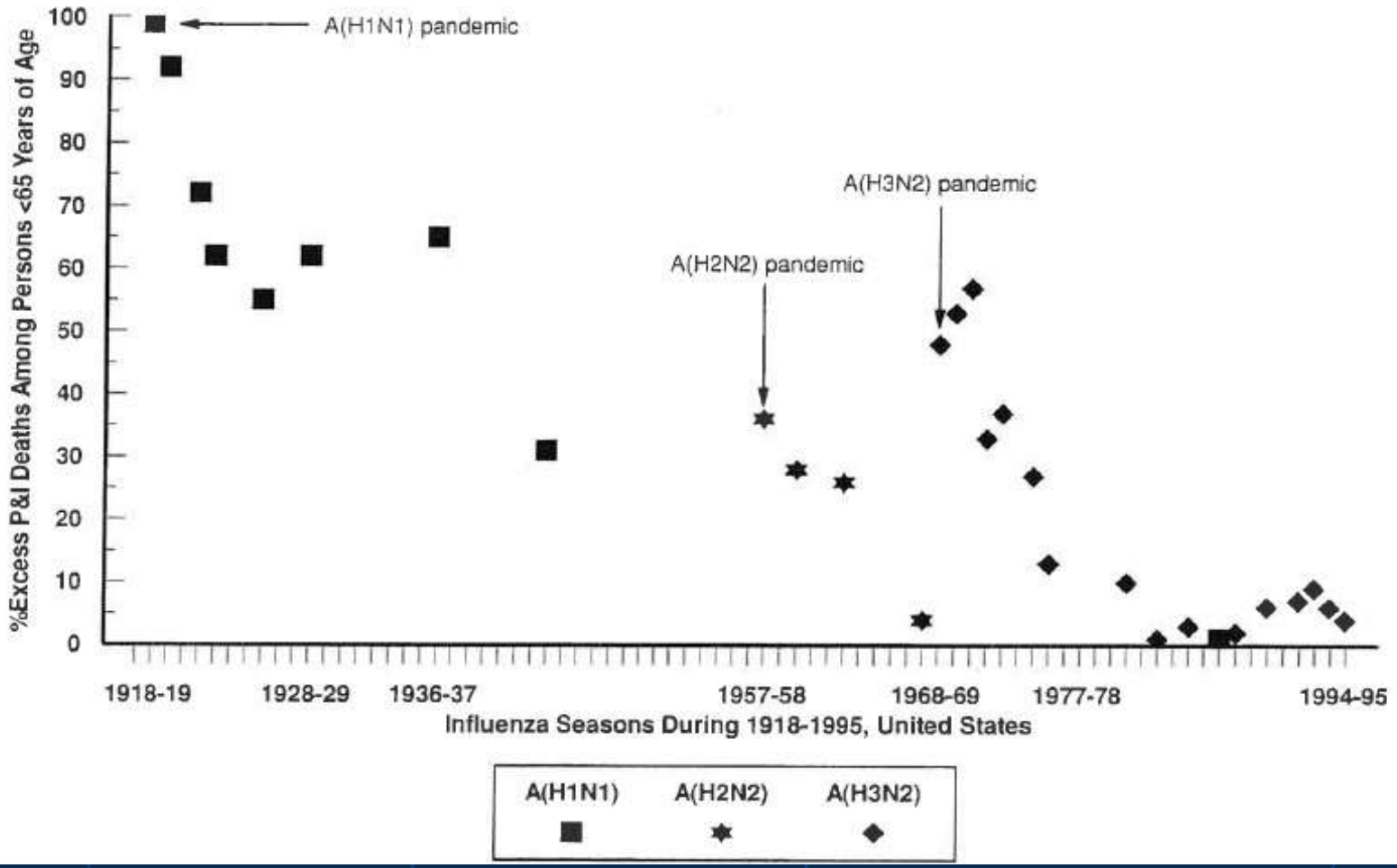



# Comparison of Mortality in Twentieth Century Pandemics 1-3

JID 1998;178 (July)
Simonsen et al

## Relative age shift in excess mortality





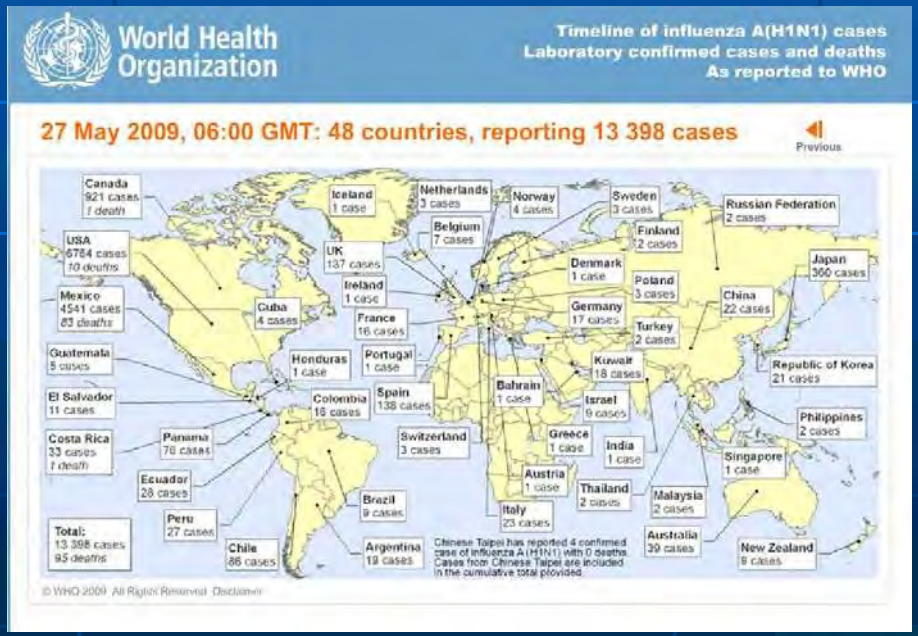
# Twentieth Century Pandemic 4: 1977-78

## 'USSR Flu' or the children's pandemic.

- First reported in Norther China May-June 1977.
- Spread to far eastern USSR by November 1977 then globally through 1978.
- Infection predominantly in children and young adults <26 years old – attack rates up to 70% reported in students, no excess mortality.
- Serologically both the HA and NA were closely related to earlier H1N1 viruses – specifically to a 1950 lineage rather than later strains. (Kendal et al 1978)
- Genetically all genes closely related to the 1950 'Scandinavian' strains. (Scholtissek et al 1978).
- Conclusion: not a natural event but one with human intervention.
- Unlike previous recent pandemics the circulating subtype (H3N2) was not replaced.
- Continued circulation as seasonal influenza with sporadic epidemics, antigenic drift and increasing impact in older adults until 2009.

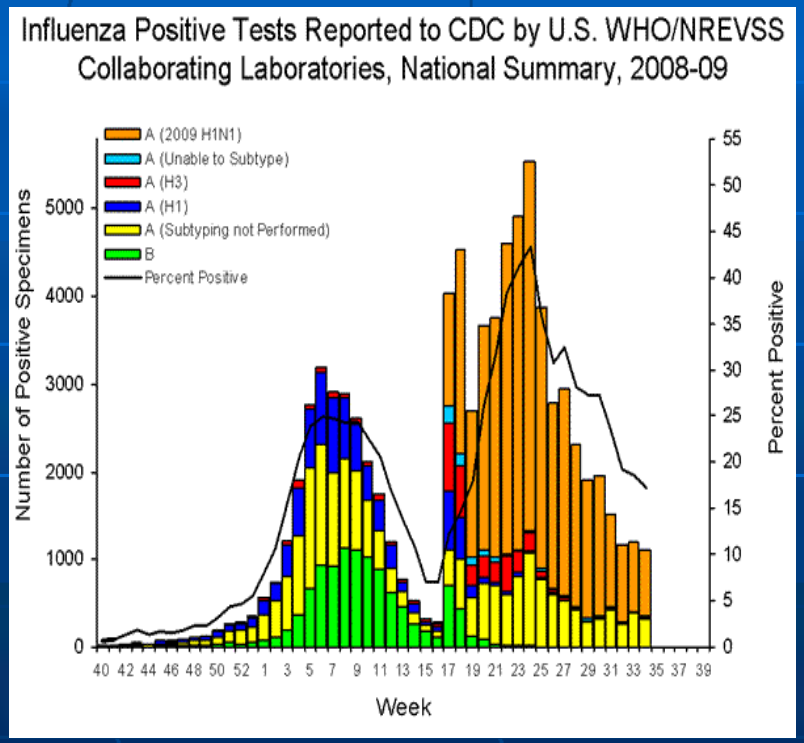
# Twenty First Century Pandemic 1: 2009-10
## 'Swine Flu or A(H1N1)pdm09'

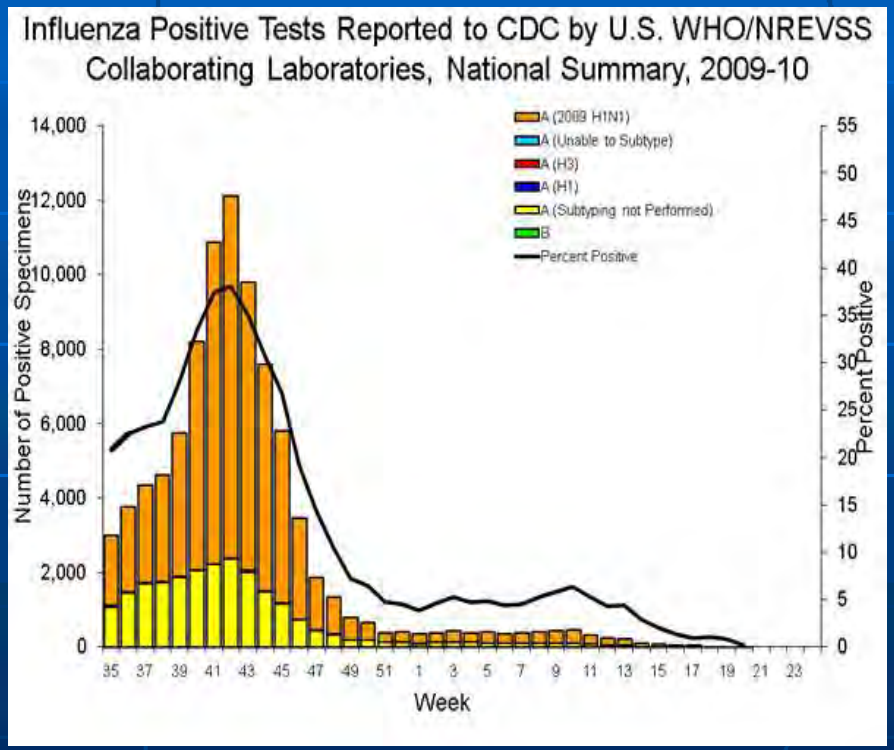
- First cases of swine-like H1N1 diagnosed 15 April in USA
- Mexican origin quickly recognised, eventual indications near Mexico City Jan-Feb 2009.
- Early indications of severe disease in Mexico.
- Rapid increase in reports to WHO from late April through early May
  - Interactive maps at http://www.who.int/csr/disease/swineflu/interactive_map/en/

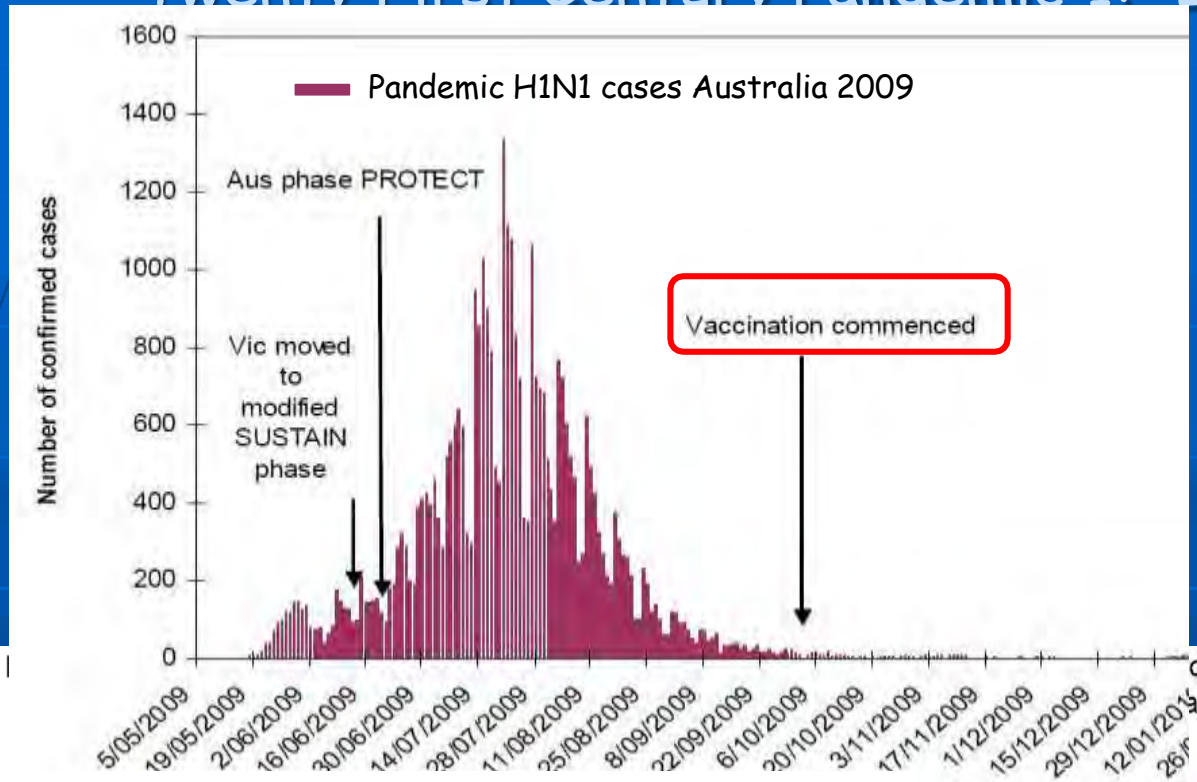
# Twenty First Century Pandemic 1: 2009-10
## 'Swine Flu or A(H1N1)pdm09'

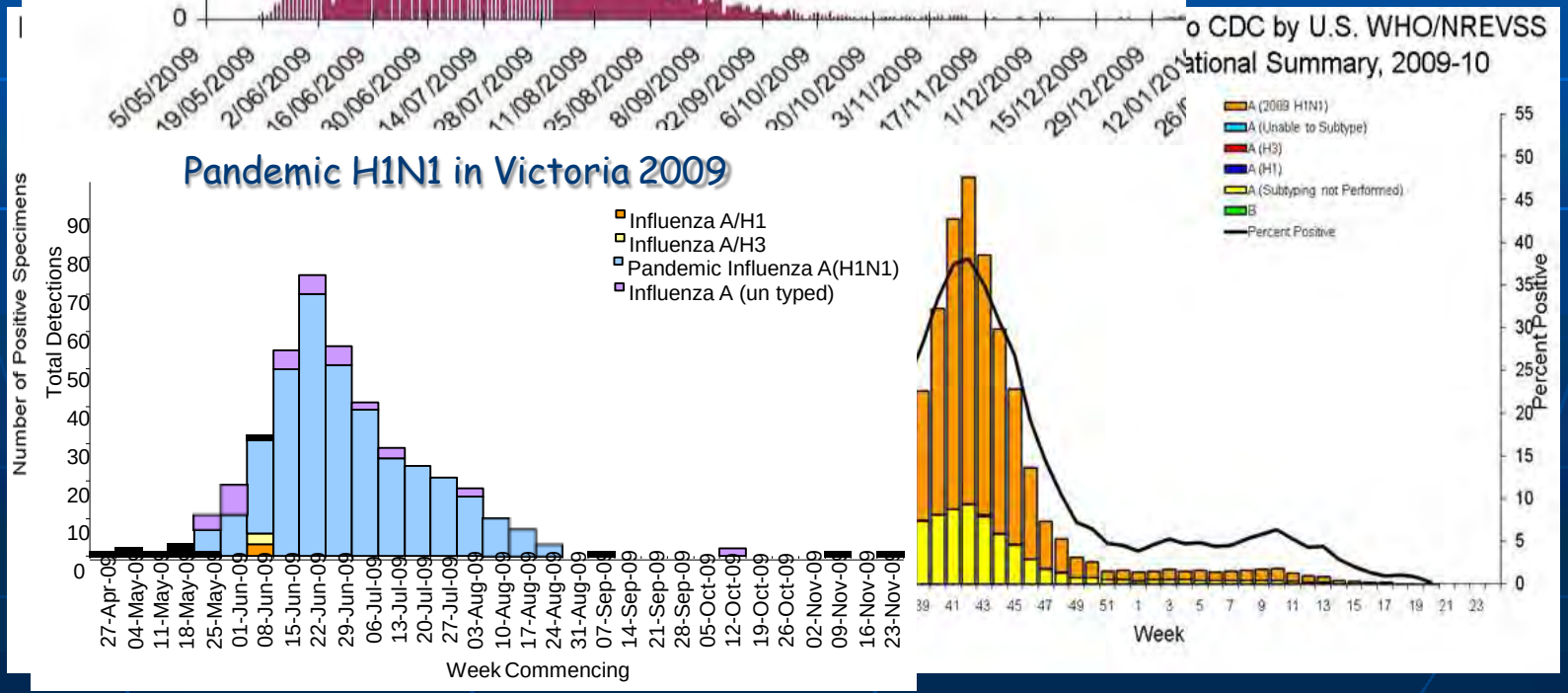
- Non-seasonal in some regions
  - eg North America.



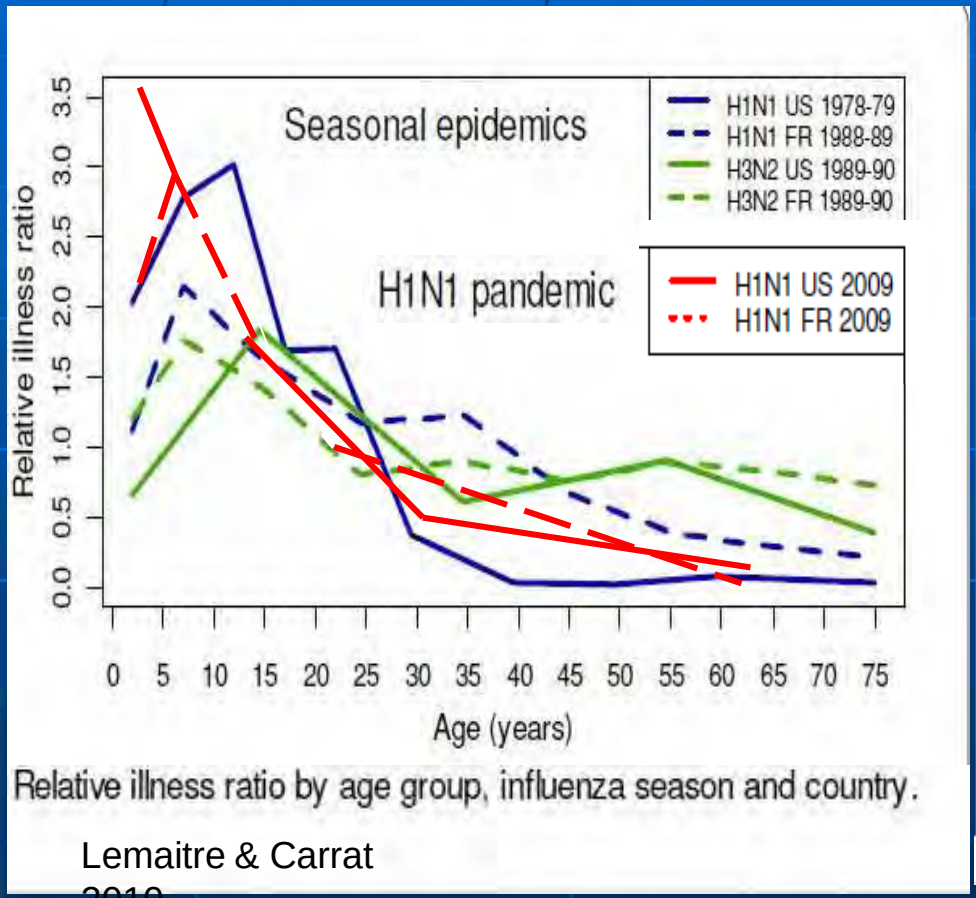
# Twenty First Century Pandemic 1: 2009-10



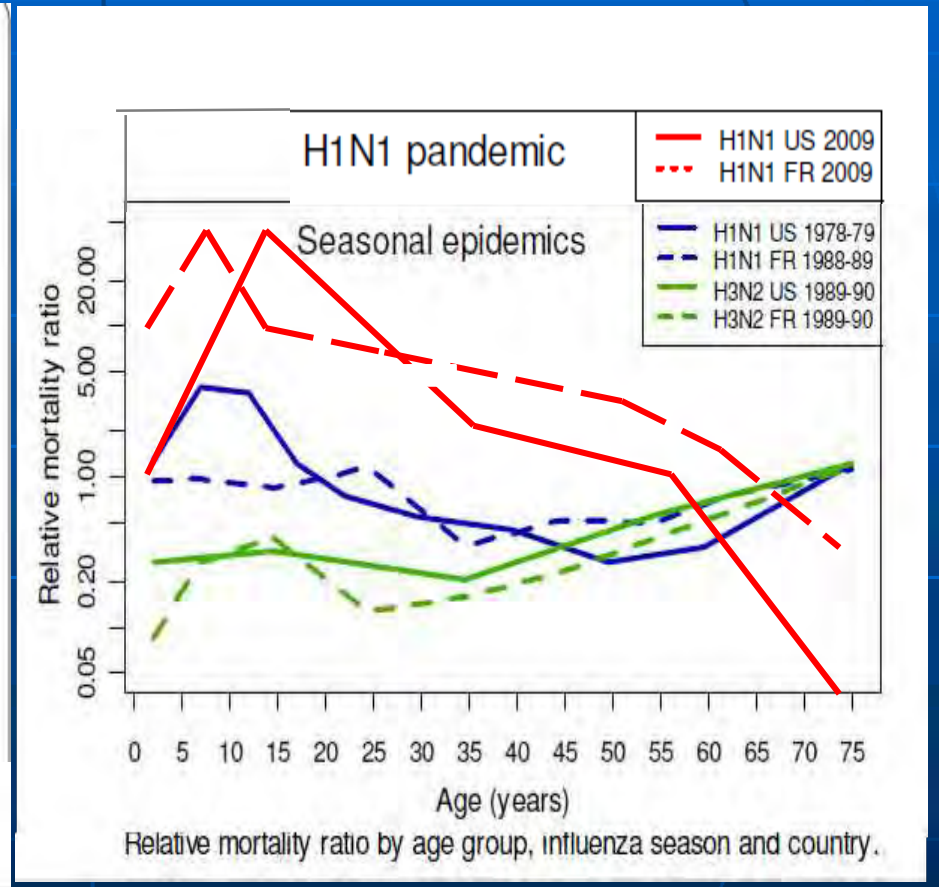
# Twenty First Century Pandemic 1: 2009-10
## 'Swine Flu or A(H1N1)pdm09'

- Morbidity pattern differs slightly from seasonal flu.



Relative illness ratio by age group, influenza season and country.

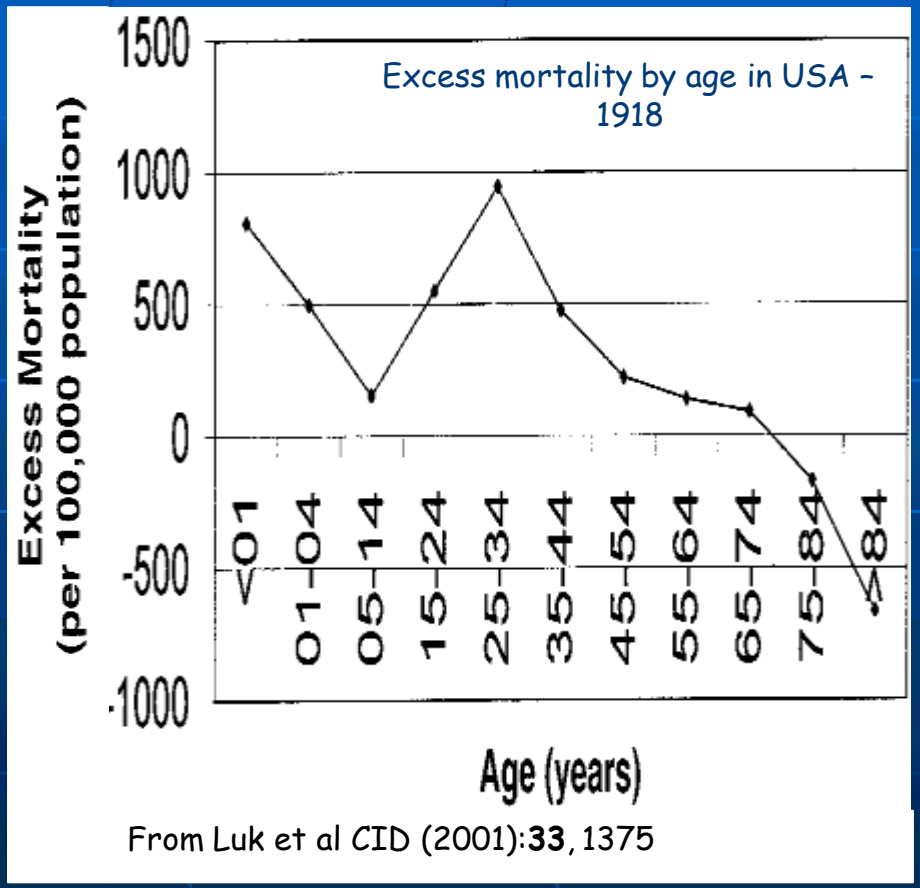
Lemaitre & Carrat 2010



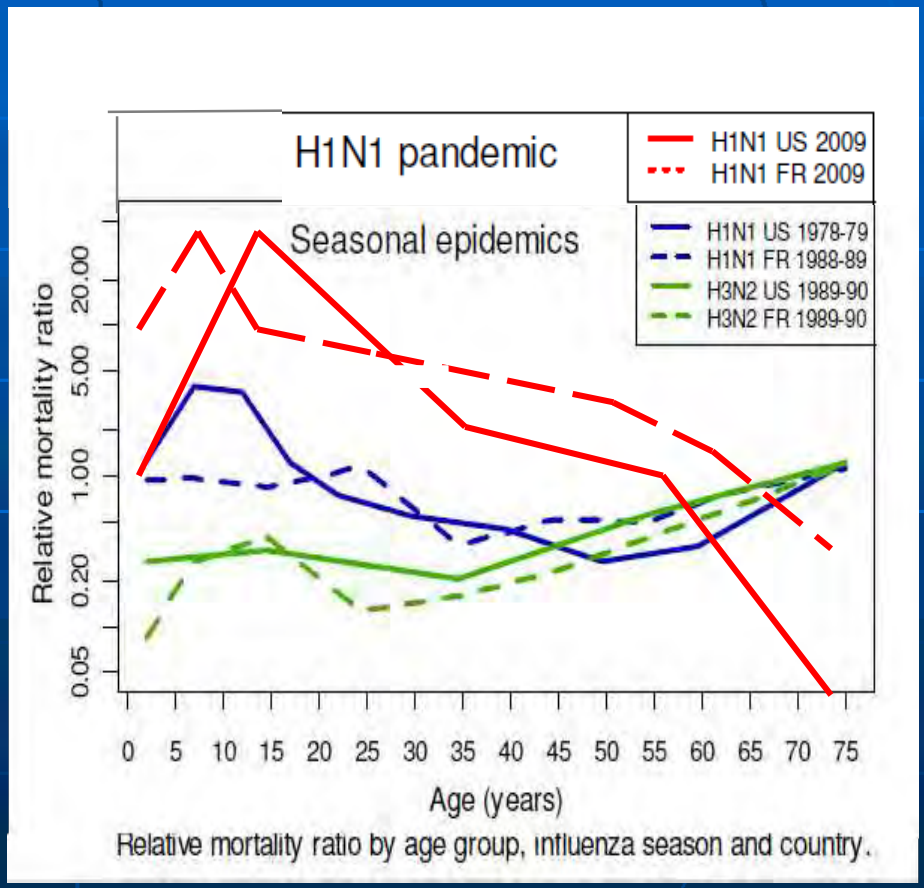
Relative mortality ratio by age group, influenza season and country.

# Twenty First Century Pandemic 1: 2009-10
## 'Swine Flu or A(H1N1)pdm09'

- Mortality pattern significantly different and reminiscent of 1918 pandemic



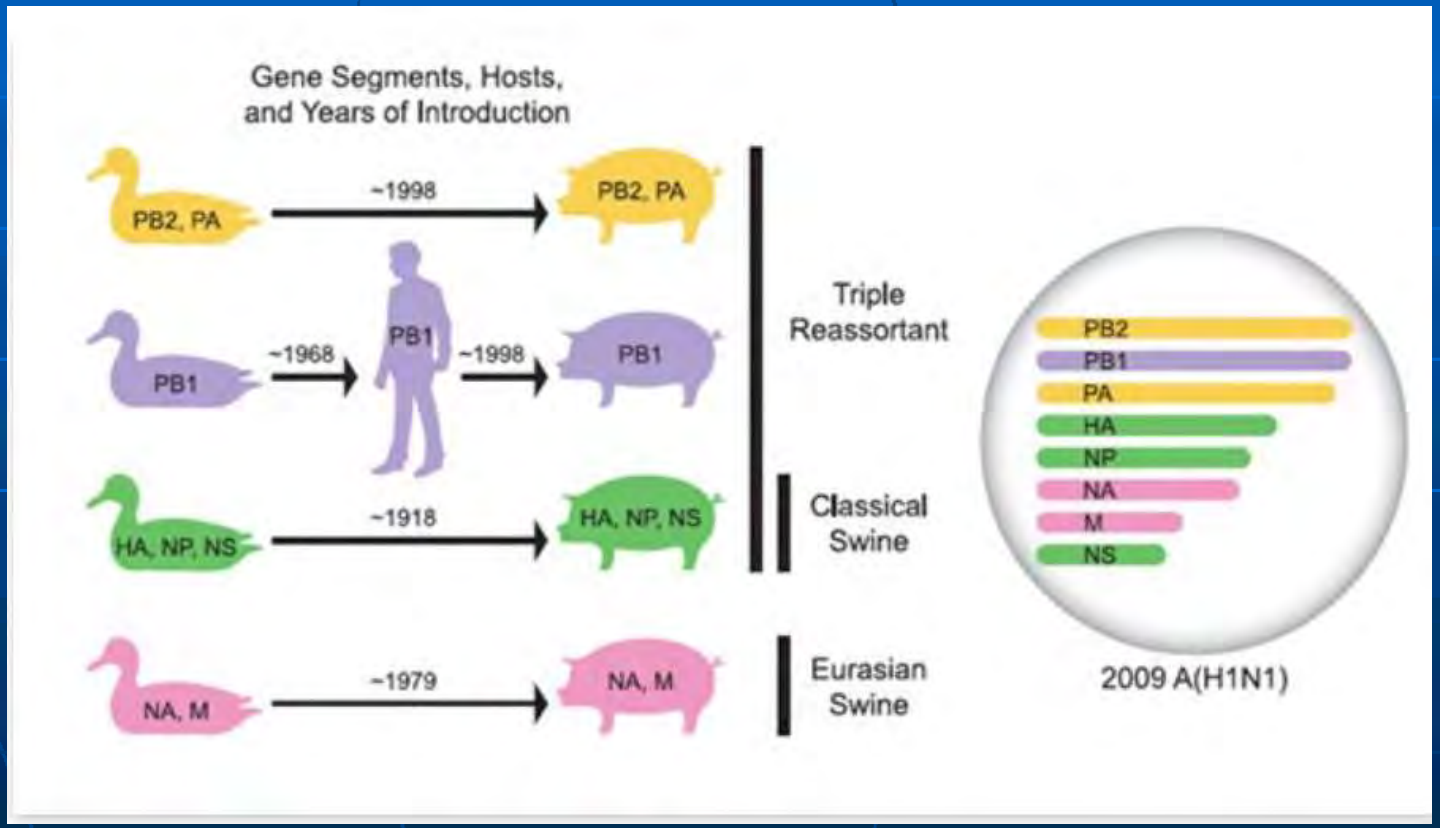

From Luk et al CID (2001):**33**, 1375




Relative mortality ratio by age group, influenza season and country.

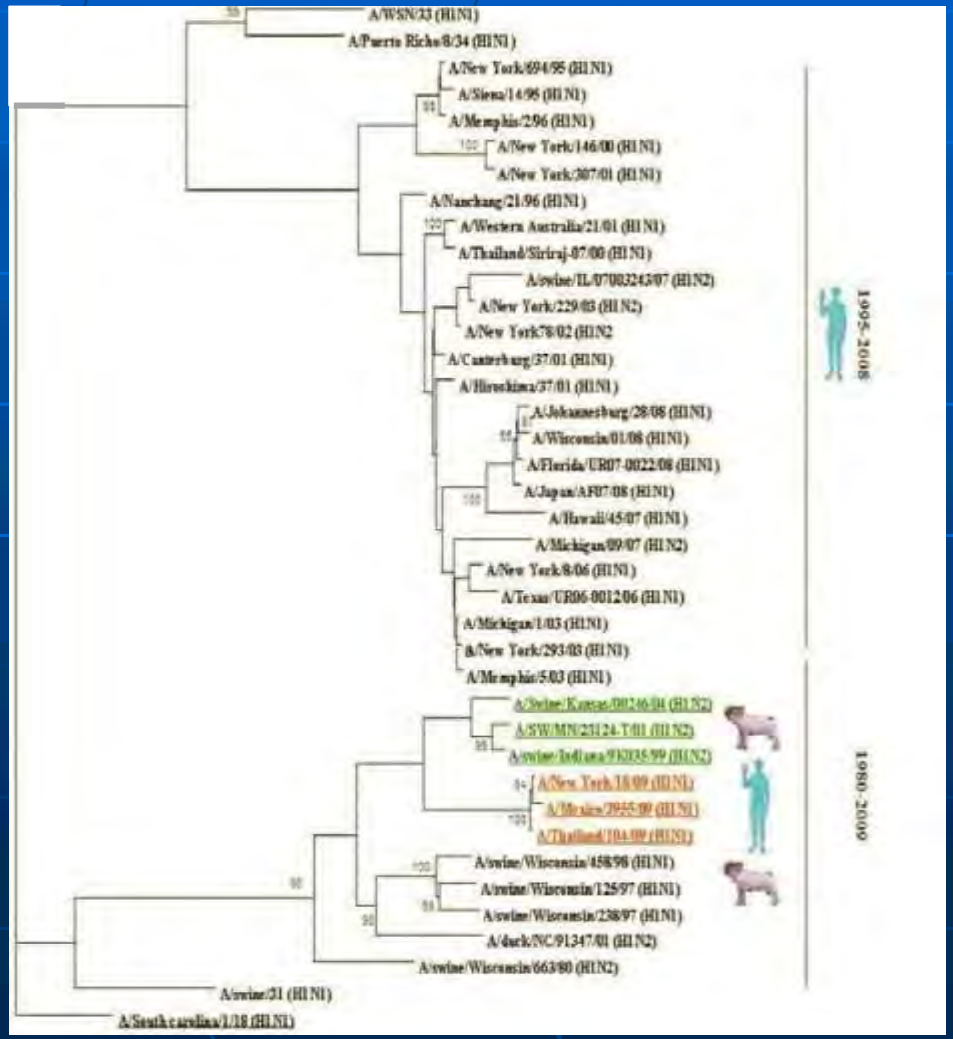
# Twenty First Century Pandemic 1: 2009-10
## 'Swine Flu or A(H1N1)pdm09'

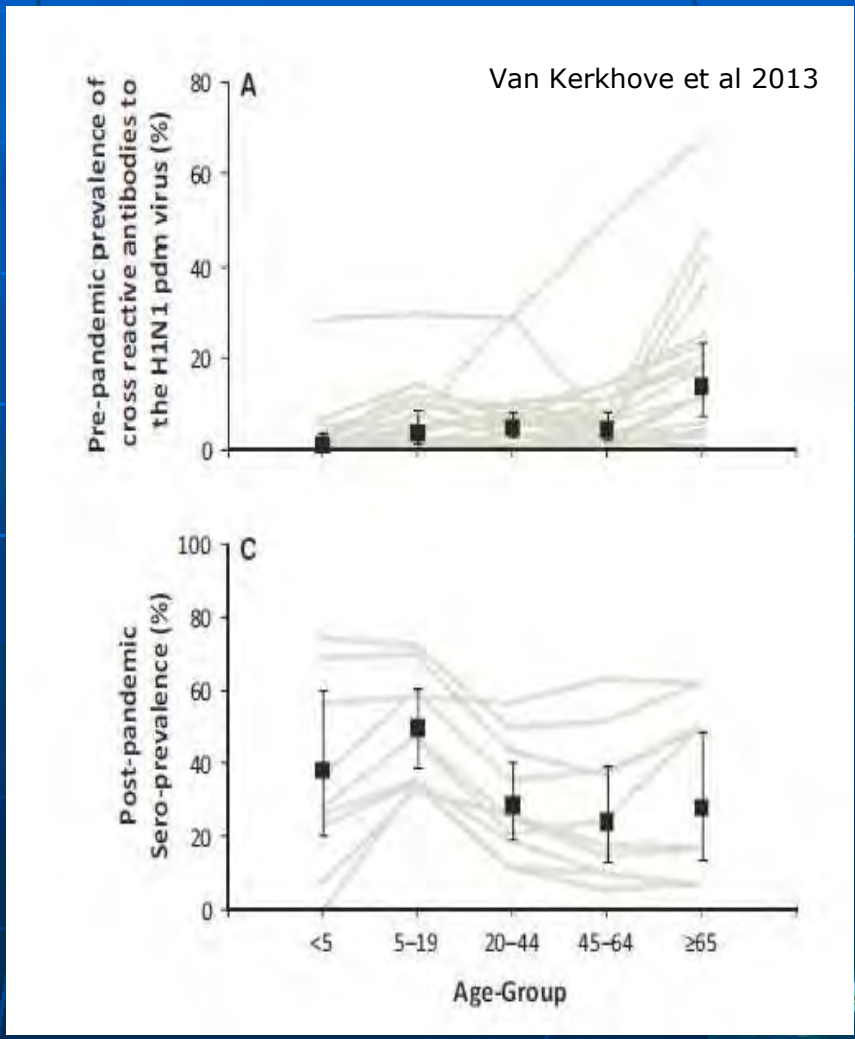
- The virus was a reassortant containing gene segments from a variety of sources.



# Twenty First Century Pandemic 1: 2009-10
## 'Swine Flu or A(H1N1)pdm09'

- While there appeared to be immunity in older adults:
  - The HA was quite distantly related to early H1N1 of the 1930s-1957 era.
  - Serological studies showed only a little pre-existing antibody in older adults



# What Can be Learned?

- Nothing particularly novel from pandemics predating 20th century – but does reinforce observations from the more recent pandemics.
  - Often 2-3 waves with higher mortality in second wave
  - Shift to younger age mortality
  - Severity in pregnant women
  - Can have high morbidity with low mortality
  - Can deviate from usual seasonality
  - Spread at the speed of human travel
  - Most common apparent source China
  - A number of potential sources
    - Reassortment of current human virus with avian/animal virus
    - Emergence from animal/avian host
    - Intentional or unintentional release of virus from laboratory
- Can be a 'novel' virus within a circulating sub-type
- With current vaccines there is virtually no chance of a matched vaccine ahead of the first wave.

*‘the student of influenza is constantly looking back over his shoulder and asking "what happened"? in the hope that understanding of past events will alert him to the catastrophes of the future’*