***InForMID*: Tufts Initiative for the Forecasting and Modeling of Infectious Diseases**

Examining the Role of Viral Evolution on Seasonal Influenza Incidence

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Study Objectives

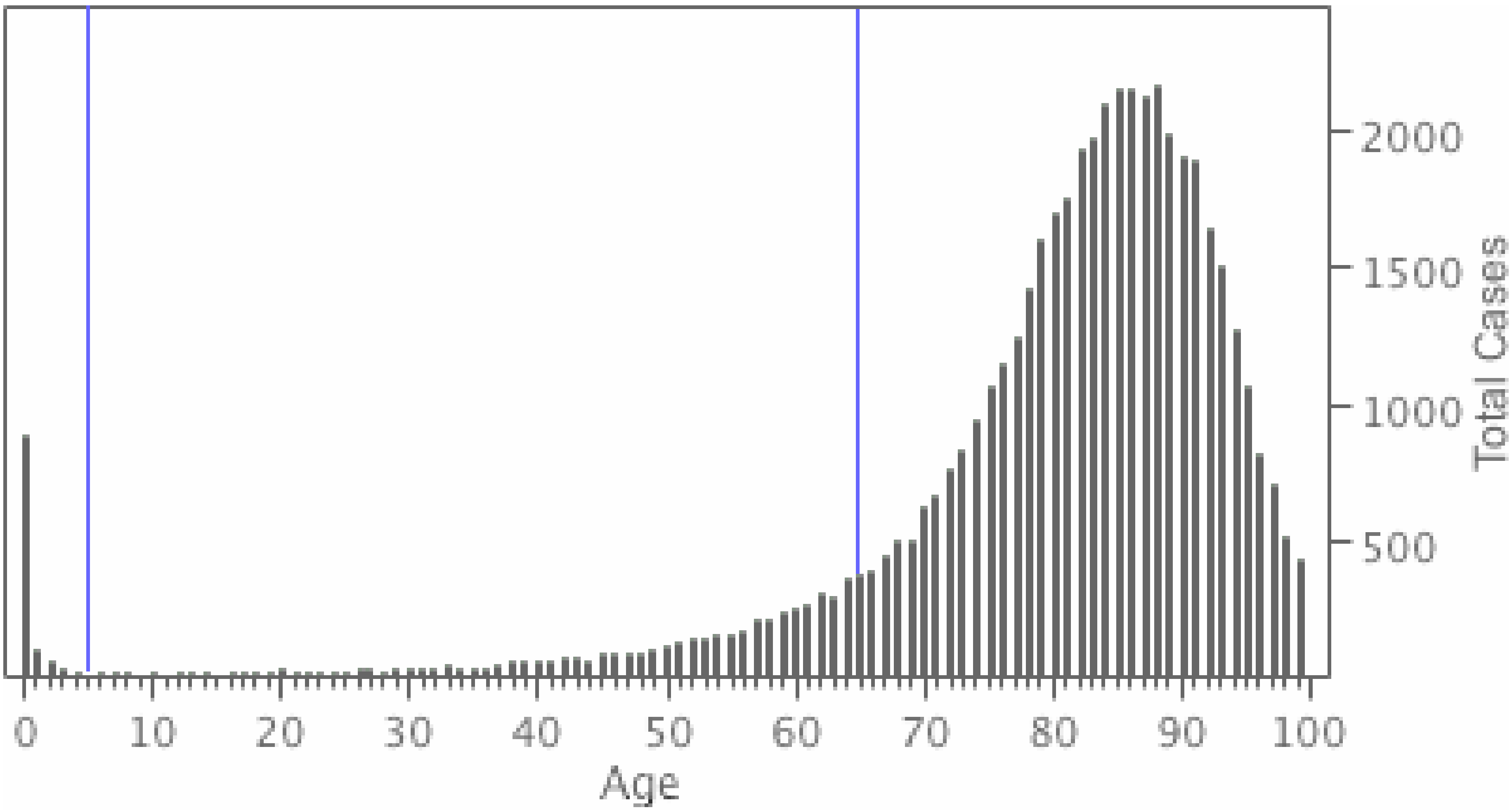
Goal: To examine the seasonal variations in Pneumonia and Influenza (P&I) mortality and its association with viral evolution of influenzas A (H1N1, H3N2) and B.

Methods: Utilize Poisson regression models adapted for time series analysis to characterize seasonal influenza epidemic curves and allow for statistical comparison between years and circulating strains.

Data Sources:

- 51,536 deidentified deaths with Pneumonia or Influenza listed as a cause of death in Wisconsin between 1967 and 2004
  - Stratified into 3 distinct population subgroups: Elderly (65+ years of age), General Population (6-64 years of age) and Children (0-5 years of age). Children additionally subcategorized into an Infant category (0-1 year of age).
- Population estimate based on Census 1970, 1980, 1990 and 2000 with linear interpolation. Infant population estimate derived from birth and death records (Births + Last Years Births - Deaths).
- Circulating virus strain based on WHO Weekly Epidemiological Report's recommended vaccine strain and MMWR reports on seasonal influenza activity.

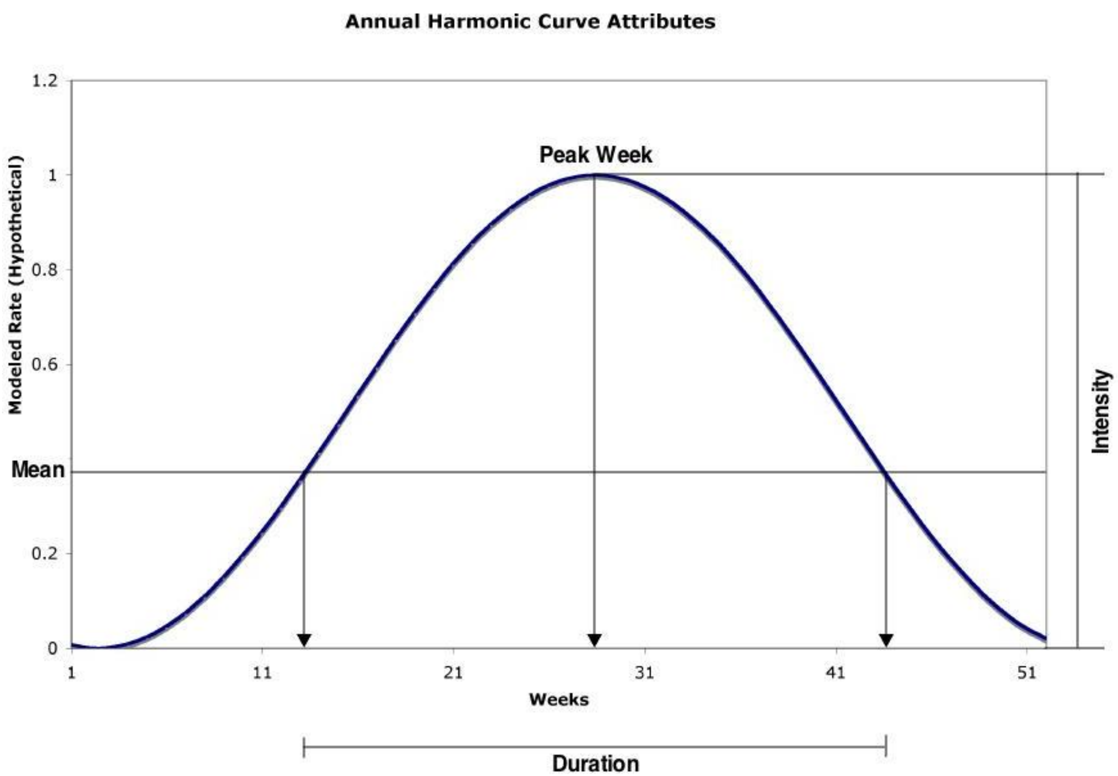
Influenza Mortality by Age, 1967-2004



The Model

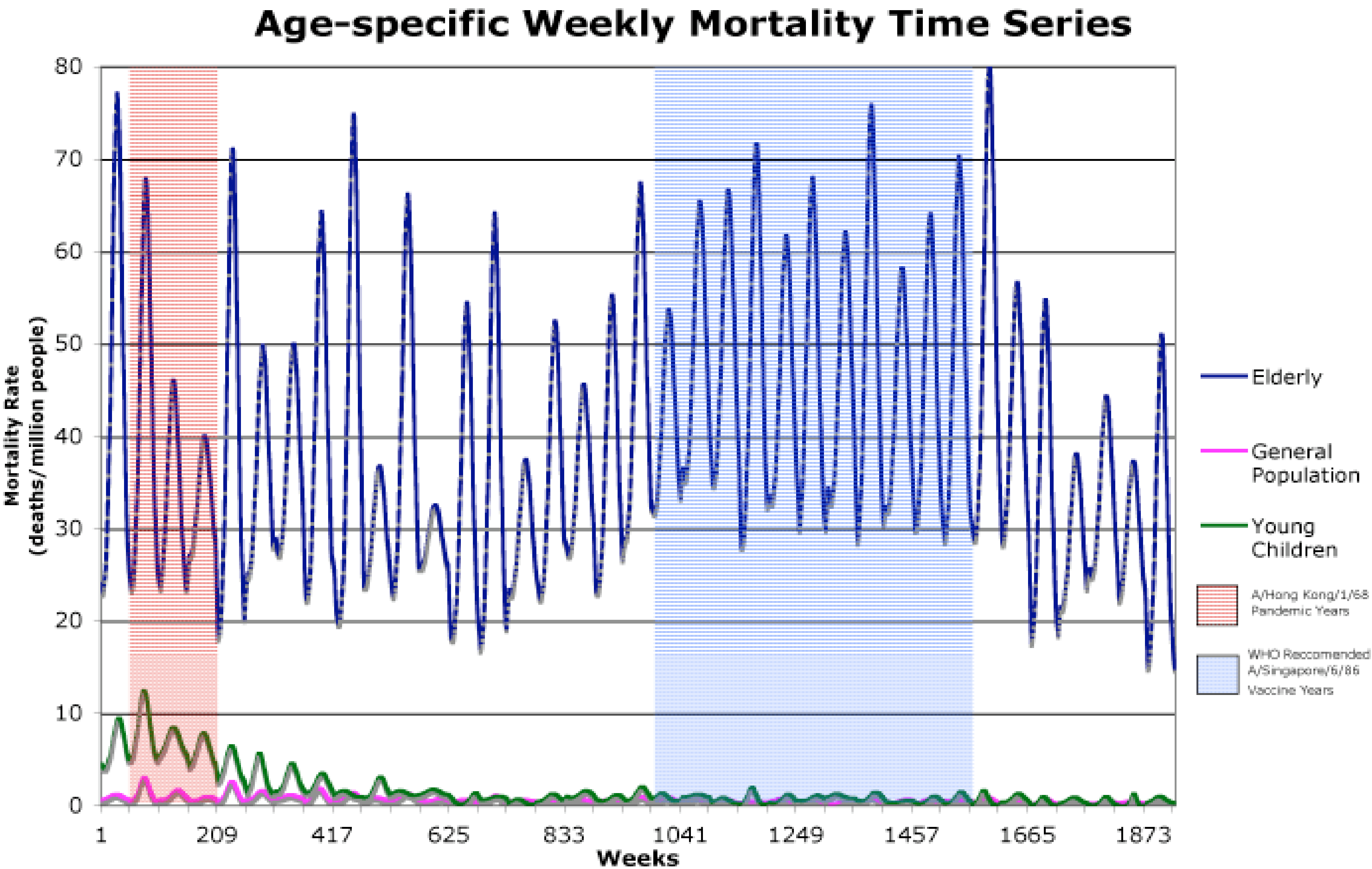
- Annual Harmonic Regression is a modified Serfling-type regression model to characterize variation between epidemic curves

$$Y(t)_i = \exp\{\beta_{0,i} + \beta_{1,i}\cos(2\pi\omega t) + \beta_{2,i}\sin(2\pi\omega t) + \varepsilon\}$$



- Advantages:
  - Improved model fit over traditional Serfling methods
  - Can capture complex non-linear trends
  - Curve attributes can be used to evaluate inter-year variation with simple statistical techniques
- Disadvantages:
  - Purely descriptive model, no predictive ability
  - Not a truly continuous model

Time Series Results



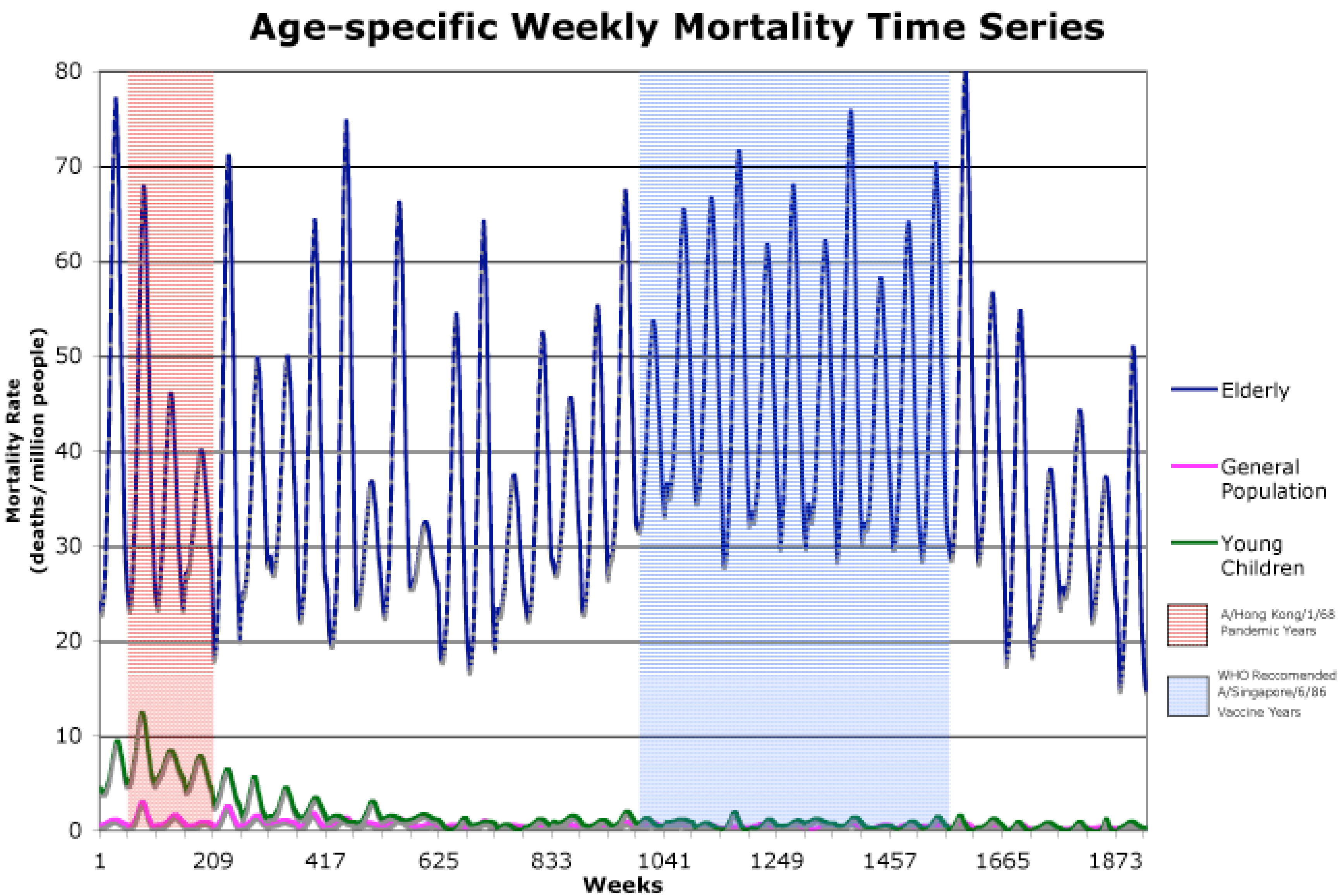
Seasonal Curve Attributes

Population	Total Cases	Model Fit (p-Value)	Peak Week (±SD) (Weeks)	Intensity (±SD) (deaths/million)	Duration (±SD) (Weeks)
Whole Series	51536	r^2=0.765 ($p<0.001$)	30.75 (±2.07)	4.37 (±1.72)	24.36 (±0.58)
Children	1258	r^2=0.501 ($p<0.001$)	27.92 (±6.73)	1.59 (±1.59)	23.42 (±1.86)
Infants	1000	r^2=0.484 ($p<0.001$)	27.78 (±7.26)	3.44 (±3.57)	23.47 (±1.97)
Elderly	45388	0 r^2=0.566 ($p<0.001$)	30.82 (±2.26)	32.23 (±12.88)	24.34 (±0.59)
General Population	4890	r^2=0.370 ($p<0.001$)	29.73 (±4.75)	0.57 (±0.52)	24.23 (±1.15)

Pandemic Influenza

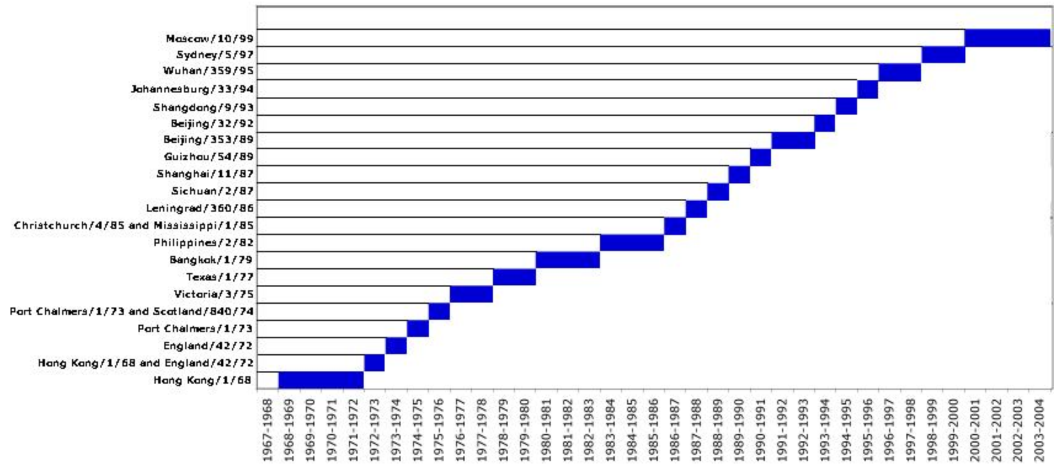
- Time series includes the several year A/Hong Kong/1/68 pandemic
  - Children and Infants have significantly higher intensity of seasonal influenza outbreaks during the pandemic ($p=0.012$ and $p < 0.005$ respectively).
  - General population's seasonal intensity is borderline non-significant ($p=0.07$).
  - Elderly population has no significant increase in intensity during the pandemic years ($p=0.48$).
- Agrees with previous reports of disproportionately higher influenza incidence during pandemics among the young and adults
  - May have biological cause, a result of the harvesting effect, or another - as yet unknown - cause.

Viral Evolution and the Elderly

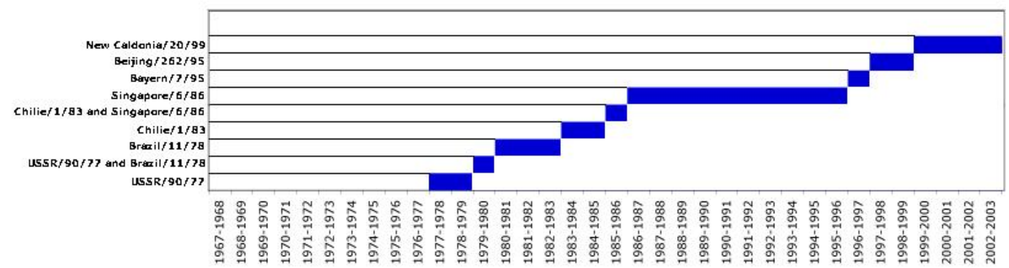


Circulating Virus Strain

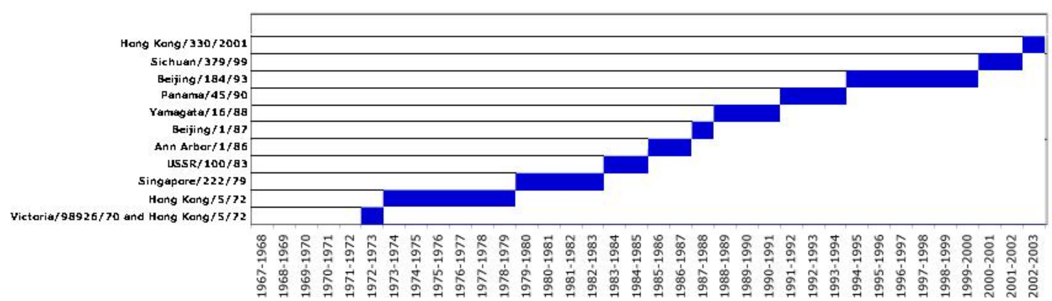
Dominant Circulating H3N2 Strain



Dominant Circulating H1N1 Strain

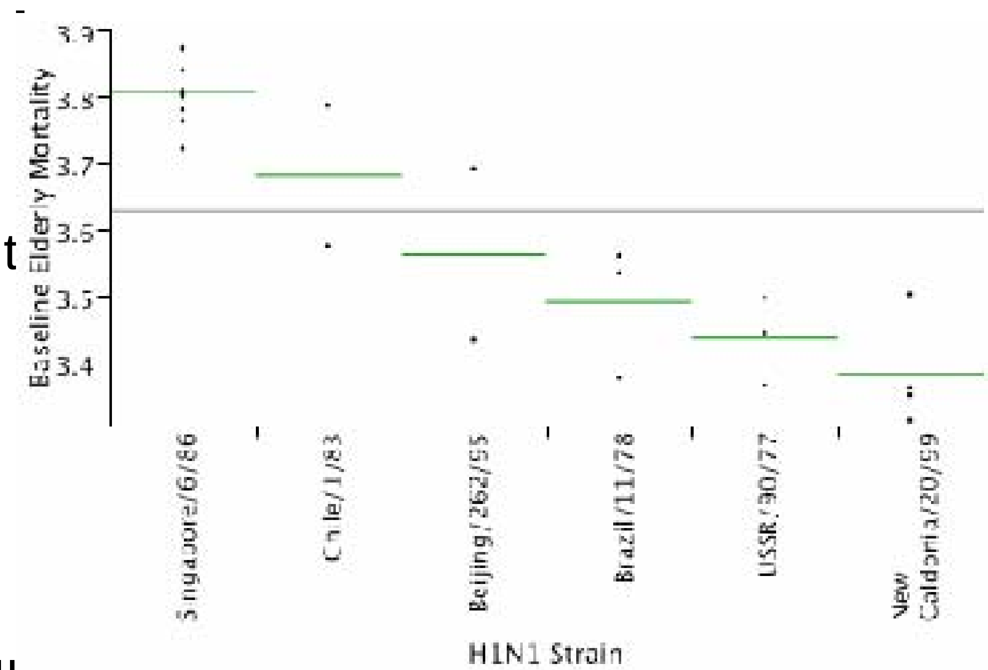


Dominant Circulating B Strain



A/Singapore/6/86

- Seasonal epidemic curve characteristics analyzed by circulating strain using ANOVA.
- Elderly subpopulation had statistically significant variation in baseline seasonal severity ($F=23.67$, $p<0.001$).
- Pairwise comparison showed that these differences were not due to a pandemic strain.
  - Particularly long circulating strain of H1N1, A/Singapore/6/86
  - Mean baseline seasonal severity for the strain (3.807 deaths/million persons per year) is higher than the overall rate of 3.626 deaths/million persons per year, and higher than all other strains save for that immediately preceding.



Nonpandemic Strain Specific Variation

- Strain specific increases in seasonal influenza mortality suggests a subtle relationship between viral evolution and influenza seasonality
  - Singapore/6/86 represents a substantial evolutionary departure from previously circulating H1N1 strains, possibly resulting in reduced population immunity or a less effective vaccine
  - Likely **not** due to the kind of strain novelty that results in pandemics - population at risk had been exposed to both the 1918 Pandemic and reemergence in Russia in 1977

Seasonality and Evolution: Developing an Understanding

- Small increases in strain-specific severity could result in a large increase in influenza mortality and morbidity, especially in long circulating strains
- Vigilance, and a monitoring of viral evolution is essential not only for pandemic influenza, but its annual seasonal counterpart

Acknowledgements and More Information

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- More Information:
  - InForMID: http://www.tufts.edu/med/informid/
  - Eric Lofgren: Eric.Lofgren@unc.edu
  - AHR: Lofgren et. al. *Assessing Seasonal Variation in Multisource Surveillance Data: Annual Harmonic Regression.* LNCS 4506. (2007)