Original Antigenic Sin and the 1918 influenza pandemic

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Influenza A virus

- Antisense RNA virus
- Major coat proteins = haemagglutinin (H1 – H14) neuraminidase (N1-N9) (the major antigens, by which subtypes named e.g. H5N1)
- 8 part genome (10 genes) - allows recombination between subtypes infecting a host.
Influenza A strains change via

- 'Viral drift' - step mutations within a subtype (cause annual epidemics)

- 'Viral shift' - sudden change in subtype, due to:
  - recombination between subtypes
  - Mutations allowing species jump (e.g. avian flu in 1918)
    - Associated with pandemics
• **Interpandemic periods** are dominated by a single influenza A subtype that undergoes gradual mutation
• **Pandemics** are caused by novel subtypes
• *Each new subtype tends to replace previous*
In interpandemic years, influenza mortality risk is related to

- age
- underlying chronic disease, especially
  - heart disease
  - respiratory problems (asthma, tuberculosis etc)
- pregnancy
- immunity (previous infection by same subtype - may diminish with age or with viral drift)
In normal years influenza has a U-shaped mortality pattern.
The 1918 pandemic was characterised by:

- unusual age pattern of mortality
- high male mortality

![Female influenza mortality](image1)
![Male influenza mortality](image2)

England & Wales
Infection rates were high at all ages, but mortality was highest in young adults.

Relative risk captures age-specific effects of 1918 pandemic

Relative risk = death rate 1918/mean death rate 1913-17

Relative risk of influenza and pneumonia mortality in 1918, by age
Relative risk in 1918 was highest for cohorts born around 1891

Relative risk = death rate 1918/mean death rate 1913-17

Relative risk of influenza and pneumonia mortality in 1918, by cohort

England & Wales
‘Original antigenic sin’
(Davenport et al. 1953)

- Studies of antibody responses to flu infection indicate that individuals
  - show greatest antibody response to ‘original’ subtype (subtype to which they were first exposed)
  - may produce antibodies to original subtype in response to a different subtype by ‘cross-reaction’,
Immunity provided by past exposure with no subtype recycling (A) or recycling (B)

A

1 2 3 4

- oldest age group: no recycling
- middle age group
- younger age group
- youngest age group (naive)

B

1 2 3 1

- oldest age group: recycling of original subtype
- middle age group
- younger age group
- youngest age group (naive)

Youngest cohort should always show least immunity

(Francis, 1953)
Relative risk was lowest in oldest adults and infants.

Maternal immunity was unlikely to provide high protection since women of fertile age were at highest risk.

Relative risk of influenza and pneumonia mortality in 1918, by age.
Original antigenic sin may also cause susceptibility greater than naïve.

- Early evidence for reduced primary response to new viral subtype after prior infection with another subtype (Fazekas & Webster, 1966).

- Immune enhancement (non-neutralising cross-reacting antibodies enhance viral replication in macrophages)

- Evidence for cytotoxic T lymphocyte (CTL) anamnestic (OAS) response
  - Mice previously infected showed lower levels of specific CTL response to new subtype, and slower recovery, than naïve animals (Klenerman & Zinkernagel, 1998)

- Inappropriate CTL response also implicated in excessive inflammatory response in dengue HF.

Young adults susceptible due to first infection with 1891 pandemic subtype?
Modelled the predicted risk if exposure to 1889-91 subtype increased risk.

• Assumed constant rate of annual infection of previously unexposed, no age structure to infection.
• Calculate proportion first infected at each age with 1889-91 subtype.

![Seroprevalence graph](image)

**first infected with 1889 subtype (1918)**
(assuming 1889 subtype persisted 1889-1917)
Assuming constant annual infection rates cannot fit relative risk distribution

Lower rates of infection post-1891 pandemic?
Influenza infection rates unlikely to have decreased after 1891

Did 1889 subtype decline in prevalence?
An H3 subtype is the most likely candidate for the 1889-91 pandemic, with subsequent drift or reduction in infection rate. H1 and H2 subtypes may have co-circulated with H3 sometime before 1918.
Relative risk in 1918 may depend on original H3 infection

H1
- male risk
- female risk

H2
- male risk
- female risk

H3
- male risk
- female risk
Relative risk in 1918 may depend on original H3 infection

- E&W P&I
- U.S. P&I
- Dutch P&I
- Noncombatant, all-cause
Does this OAS phenomenon occur in other pandemics?

<table>
<thead>
<tr>
<th>Year</th>
<th>Strain</th>
</tr>
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<tbody>
<tr>
<td>1891</td>
<td>H3?</td>
</tr>
<tr>
<td>1957</td>
<td>H2N2</td>
</tr>
<tr>
<td>1968</td>
<td>H3N2</td>
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1957 (H2N2 'Asian flu')

Unusual age pattern of mortality, but less notable than 1918.
1957 (H2N2)

- Peak risk 10-25 year olds
- Higher relative risk for females
- Low risk to those born before 1891
- Highest risk to cohorts first infected with H1’N1?

Relative risk of death from flu or pneumonia (E&W)

by age

by year of birth

England & Wales
French data show 1947 peak, but pattern is less obvious.
1969 (H3N2: ‘Hong Kong flu’)

- Middle-aged at highest risk
- No real sex differences
- Protective effect of H2N2 (N2?)
- Highest risk to cohorts born in H1 eras?

Relative risk of death from flu or pneumonia (E&W)

by age

by year of birth

• Middle-aged at highest risk
• No real sex differences
• Protective effect of H2N2 (N2?)
• Highest risk to cohorts born in H1 eras?
French relative risk much higher than E&W in 1969, but similar pattern
Conclusions

• Pandemic influenza is characterised by an unusual age pattern of mortality

• In 1918 mortality risk was apparently related to first infection with the 1889-91 subtype (possibly an H3 type)

• Some immune cross-reaction between the 1889-91 and 1918 subtypes may have resulted in an extreme inflammatory response, increasing risk.

• Could be tested by measuring immune responses in early cases, for targeting of vaccines by age?
Future work

• Digitise cause of death datasets for other countries

• Investigate interactions between influenza and other causes of death, esp. heart disease and tuberculosis.

Collaborators

• Jim Oeppen, MPI for Demography, Rostock
• Ian Timaeus, London School of Hygiene & Tropical Medicine
Reported H5N1 cases show an unusual age pattern

Thai P&I mortality (1997-2002) and H5N1 rates