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

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New Zealand, February 7 & 8, 2018
Pandemic preparedness
Learns from historical Pandemics
1918 is “poster child”
So important to get it right

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

BILL GATES
1918 influenza pandemic
1-2% of global population died
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:

**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
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
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

Frozen cadaver lung tissue
Jeffery Taubenberger and Ann Reid

By 2005: complete genome sequenced

1918 viral gene sequencing

X
FAILED
evolutionary distance from known avian strains. Here we present sequence and phylogenetic analyses of the complete genome of the 1918 influenza virus, and propose that the 1918 virus was not a reassortant virus (like those of the 1957 and 1968 pandemics), 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. A total of
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,
Influenza A Virus Pandemics and Circulation for a Century

1889 Russian Influenza
1918 Spanish Influenza
1957 Avian influenza
1968 Hong Kong influenza
2009 H1N1p

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

122 cities weekly P&I mortality data

%P&I deaths

Severe
Fujian
2003-04

Observed P&I ratio
Predicted Baseline

2009 Pandemic
2nd wave fall’09
Modeling Global 1918 Burden:
62M deaths in today’s population; 95% of these in low income countries

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

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

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

Viboud et al, Plos Currents 2009
2009 Pandemic -- A Perplexing Situation

- **Risk scenario: disaster**
  - 1918-like risk scenario: ~2% 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

Seniors
≥65 years

Young Adults
15-44 years

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\textsuperscript{1,2}, Peter Spreeuwenberg\textsuperscript{3}, Roger Lustig\textsuperscript{4}, Robert J. Taylor\textsuperscript{5}, Douglas M. Fleming\textsuperscript{5}, Madelon Kroneman\textsuperscript{5}, Karla O. Van Kerkhove\textsuperscript{3,6}, Anthony W. Mounts\textsuperscript{5}, W. John Paget\textsuperscript{5}, the GLaMOR Collaborating Teams\textsuperscript{3}

2009 Pandemic age shift
Pneumonia mortality in Mexico
Chowell et al, NEJM, August 2009

Younger adults die
Elderly spared
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)

<table>
<thead>
<tr>
<th>Copenhagen</th>
<th>1918 summer wave</th>
<th>1918 fall wave</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population: 540,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excess Illness</td>
<td>25,000</td>
<td>61,000</td>
</tr>
<tr>
<td>Excess Deaths</td>
<td>85</td>
<td>1,300</td>
</tr>
<tr>
<td>Case Fatality</td>
<td>0.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td>% occurred in young &lt;65</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>Transmissibility Ro</td>
<td>&gt;2</td>
<td>1.3</td>
</tr>
</tbody>
</table>

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

**SUMMARY**

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

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, Jaluit 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
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,1,2 Daniel S. Chertow,3 Xavier Ambrogi,1 Sherman McCall,1 Ronald M. Przygodzki,2 Robert E. Cunningham,2 Olga A. Maximova,3 John C. Kash,2 David M. Morens,” and Jeffery K. Taubenberger

“Viral Pathogenesis and Evolution Section, Laboratory of Infectious Diseases, “Bioinformatics and Computational Biosciences Branch, “Office of the Chief, Laboratory of Infectious Diseases, and Office of the Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892; “Clinical Pathology Laboratory, US Army Medical Research Institute of Infectious Diseases, Fort Detrick, MD 21702; “Department of Veterans Affairs, Washington, DC 20420; and *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 and John F. Brundage

Table 2. Postmortem bacterial lung culture results in 1918

<table>
<thead>
<tr>
<th>Culture Result (Current Preferred Nomenclature)</th>
<th>No./Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcus (Streptococcus pneumonia)</td>
<td>22/42 (52.4)</td>
</tr>
<tr>
<td>Pneumococcus, Serotype I</td>
<td>2/42 (4.8)</td>
</tr>
<tr>
<td>Pneumococcus, Serotype II</td>
<td>5/42 (11.9)</td>
</tr>
<tr>
<td>Pneumococcus, Serotype III</td>
<td>7/42 (16.7)</td>
</tr>
<tr>
<td>Pneumococcus, Serotype IV*</td>
<td>5/42 (11.9)</td>
</tr>
<tr>
<td>Pneumococcus, not serotyped</td>
<td>3/42 (7.1)</td>
</tr>
<tr>
<td>Streptococcus, hemolytic (Streptococcus pyogenes)</td>
<td>4/42 (9.5)</td>
</tr>
<tr>
<td>Streptococcus, nonhemolytic</td>
<td>1/42 (2.4)</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>4/42 (9.5)</td>
</tr>
<tr>
<td>Friedländer’s bacillus (Klebsiella pneumonia)</td>
<td>1/42 (2.4)</td>
</tr>
<tr>
<td>Bacillus coli (Escherichia coli)</td>
<td>1/42 (2.4)</td>
</tr>
<tr>
<td>Diplococci observed in sections</td>
<td>1/42 (2.4)</td>
</tr>
<tr>
<td>Mixed cultures</td>
<td>6/42 (14.3)</td>
</tr>
<tr>
<td>Pneumococcus + Streptococcus</td>
<td>2/42 (4.8)</td>
</tr>
<tr>
<td>Pneumococcus + Staphylococcus</td>
<td>1/42 (2.4)</td>
</tr>
<tr>
<td>Streptococcus + Staphylococcus</td>
<td>2/42 (4.8)</td>
</tr>
<tr>
<td>Pneumococcus + Staphylococcus + Friedländer’s bacillus</td>
<td>1/42 (2.4)</td>
</tr>
</tbody>
</table>

*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

CONTENDERS

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

Wilson et al, Emerg Inf Dis 2012
TB is a leading cause of death in young adults.

Around 1918, many young adults were latently infected or had active TB.

**FIGURE 5.** Age-standardized death rate, ASDR, for tuberculosis (all forms), males and females, 1900–60.
Birth year as a risk factor?

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) with 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 bases only 13 data points, extrapolations, but so much variability and so much not measured

- **Young adults at extreme risk, why?**

- **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?**
What Comes Next?

& collaboration mechanisms to fight against them
Acknowledgments

- Cecile Viboud
- Gerardo Chowell
- Don Olson
- Viggo Andreasen
- Kåre Mølbak
- John Barry
- Robert Taylor
- Martha Nelson
- Mark Miller
- Tom Reichert
- Magnus Gottfredsson
- Wladimir Alonso/Cynthia Schuck
- Bryan Grenfell
- Ellis McKenzie
- And many more students and colleagues over the years
  - Fogarty MISMS and RAPIDD international networks of mathematical modeling

Support:
- RAPIDD fellowship: Fogarty-NIH and Dept Homeland Security
- Danish Medical Research Council,
- Lundbeck Foundation
- World Health Organization
- EU/Horizon2020 Marie Curie Action