Loose Ends Surrounding the Spanish Flu: Explaining the Extreme Mortality in Young Adults

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Introduction
Over 100 years after the iconic 1918 influenza pandemic many questions still remain unanswered. One being the pandemic’s signature pattern of high death rates in young adults and low death rates in the elderly. We took another look at the evidence of the characteristic age-related pattern of death during the 1918 pandemic in Copenhagen and relate this to the “original antigenic sin” hypothesis.1

Methods
We analyzed death patterns of tight 5-year to 10-year age-cohorts in Copenhagen in 1918. We specifically searched for break-points in the age-profile of deaths and look for evidence of past epidemics that, with the “original antigenic sin” hypothesis in hand, may explain the patterns we see in mortality statistics.

Data were derived from detailed, long time series of age-stratified monthly death records along with population census statistics.2

Incidence rates, and incidence rate ratios were calculated for each of the 4 pandemic waves in Copenhagen. We calculated a baseline mortality rate for the pandemic period as the interpolation between pre- and post-pandemic years 1917 and 1921. Excess mortality was calculated as the ratio of mortality during the pandemic wave to the baseline mortality rate.

Outstanding questions
• What is the exact role of childhood exposure to major phylogenetic clades for influenza A hemagglutinin, and risk of future influenza infectio or mortality?
• How can pandemic preparedness be adapted with insights from knowing priming experience with influenza - the antigenic sin?
• Can population exposure surveillance be used to help predict risk groups for the next pandemic?
• How can influenza virus subtypes were circulating pre-1918, that can explain the mortality patterns we see during the pandemic?
• What can we learn from serology studies done in the 1950s in this regard?

Key messages
• Infants had no meaningful elevated risk of death. The risk gradually increased with age, peaking for young adults 20–34 years of age and dropping sharply for adults ages 35–44 years. The break point is likely around 40-years (also confirmed in Kentucky data).3
• Those born before 1878 or after 1908 were not at increased risk of dying of 1918 influenza A hemagglutinin, and risk of future influenza infection or mortality.
• Outstanding questions

Figure 1. All deaths in Copenhagen 1910-1924, by month and age-group. The pandemic only stands out in young adults aged 10 to 44.

Figure 2. Weekly number of reported influenza outpatient illnesses in Copenhagen, Denmark 1889-1923. The pandemic is clearly visible, but the 1889-1890 pandemic much less so. Also little evidence of other major pandemics.

Figure 3. Relative age-specific mortality ratios in the 4 pandemic waves in Copenhagen. Clear peak in mortality risk for those aged 10-44 (born 1873-1908).

“Original antigenic sin” Early childhood exposure to specific influenza subtypes may determine risk of dying of influenza encountered later in life.

Evidence from Gostic et al4 and Worobey et al4 suggests that the major phylogenetic clade of influenza A hemagglutinin segment, Group 1 (H1, H2, H5) or Group 2 (H3, H7), encountered early in life may determine the risk of dying to a novel influenza infection.