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# 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.<sup>1</sup>

## 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.<sup>2</sup>

Incidence rates, and incidence rate ratios were calculated for each the 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 and this baseline.

## The Spanish Flu in Copenhagen

There were 4 pandemic waves in Copenhagen during 1918-1920<sup>2</sup>:

- 1st wave: July - August 1918, mild herald wave
- 2nd wave: October - November 1918, main autumn wave
- 3rd wave: January - February 1919, winter wave
- 4th wave: January - February 1920, recrudescence wave

Already in June 1918 the Danish national newspapers reported on Spanish Sickness. In July, the pandemic broke out in both Copenhagen and Roskilde. Initially, due to the mild nature of the summer wave, doctors advised people not to worry. The subsequent autumn wave killed about 0.3% of the Danish population, lower relative to other countries but still severe since most deaths occurred in young adults.

## "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 al<sup>3</sup> and Worobey et al<sup>4</sup> 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.

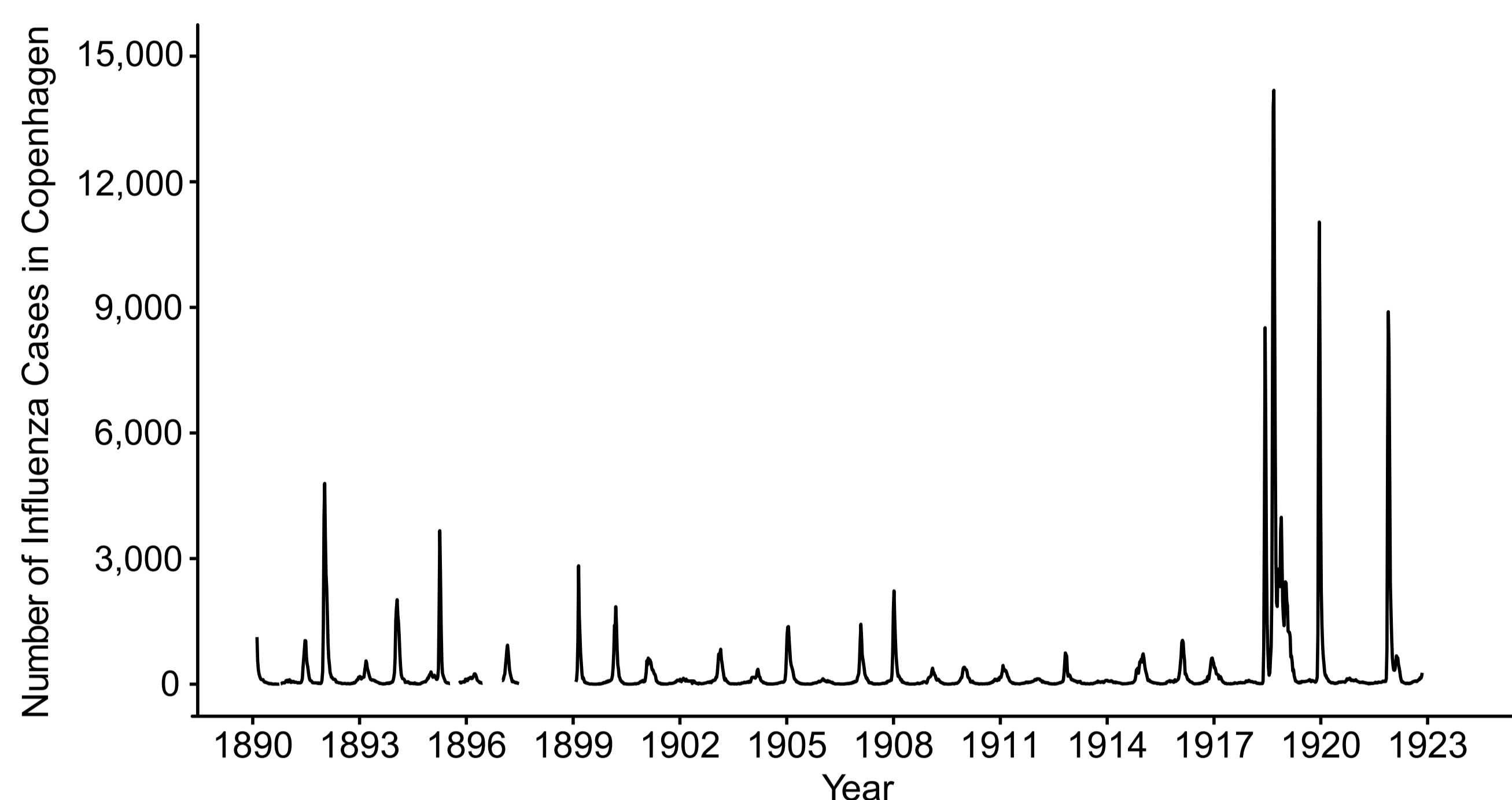


Figure 2. Weekly number of reported influenza outpatient illnesses in Copenhagen, Denmark 1889-1923. The pandemic is clearly visible, but the 1889-1890 pandemic much less so. Also little evidence of other major pandemics.

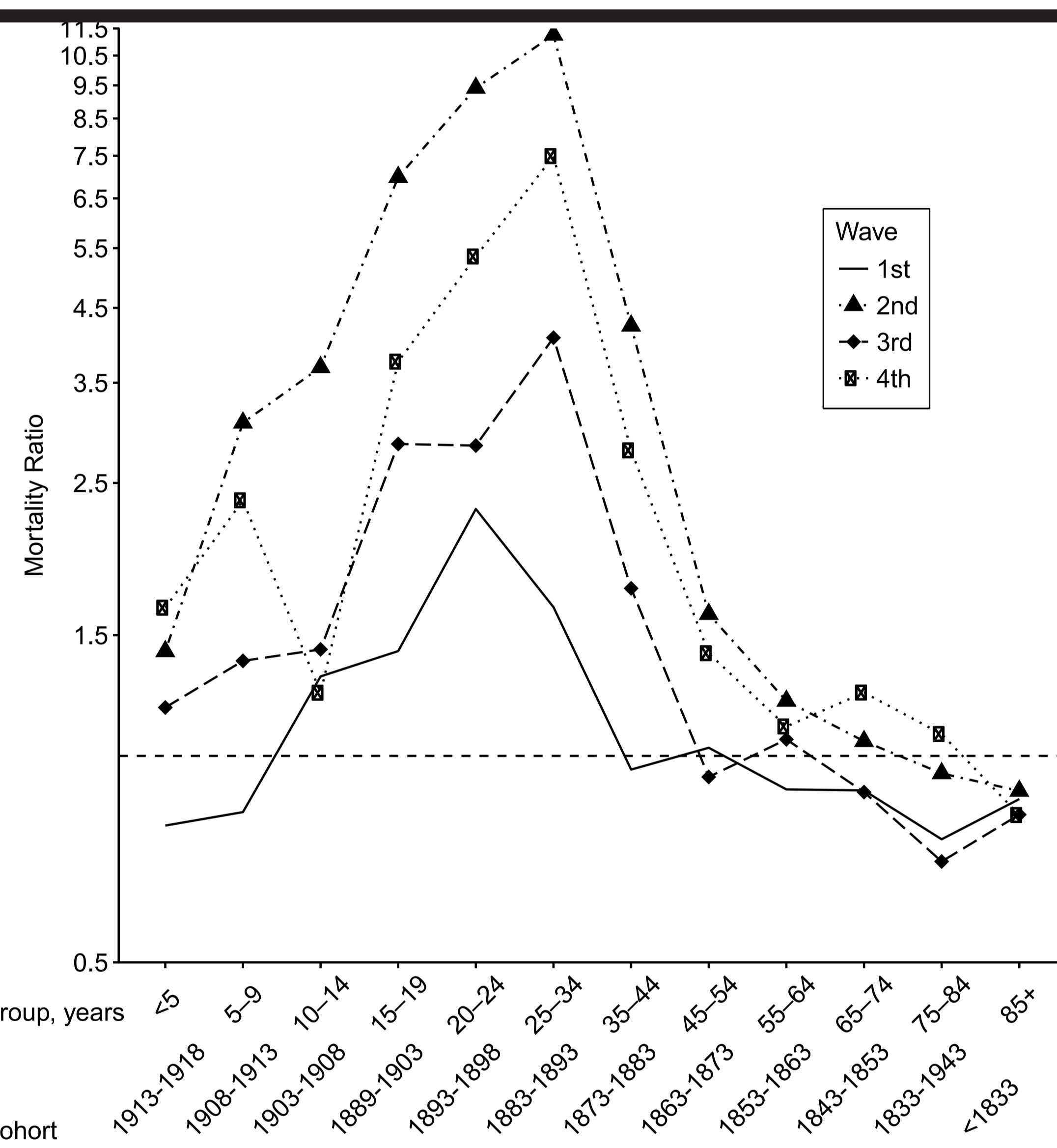


Figure 3. Relative age-specific mortality ratios in the 4 pandemic waves in Copenhagen. Clear peak in mortality risk for those aged 10-44 (born 1873-1908).

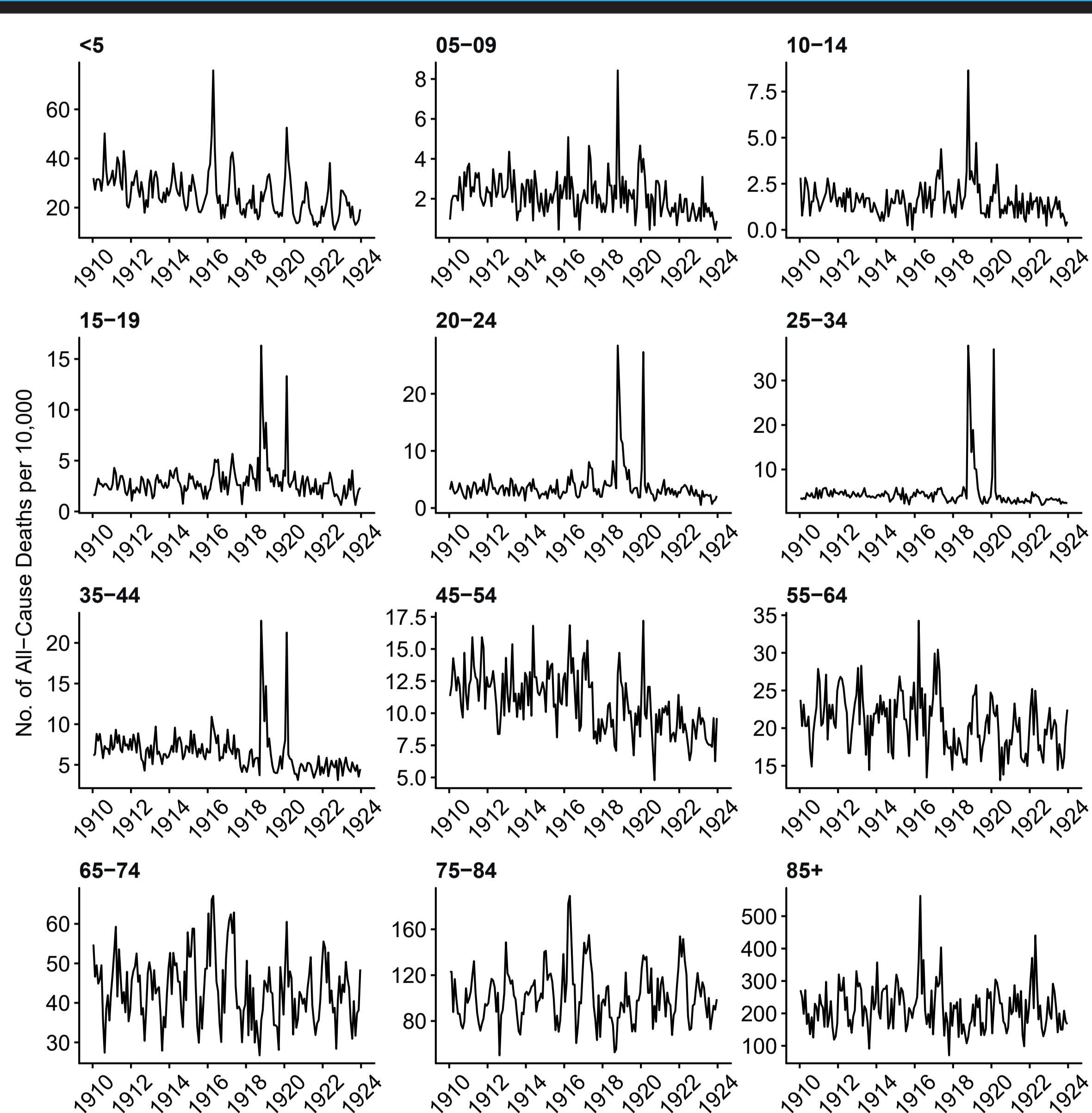


Figure 1. All deaths in Copenhagen 1910-1924, by month and age-group. The pandemic only stands out in young adults aged 10 to 44.

Christiansfeld  
July 2th 1918:  
An outbreak is reported in Christiansfeld (at that time part of Germany). Possibly introduced by a postman returning from another part of Germany.

July 7th 1918:  
A circus artist, who had been to Oslo (Norway) where the pandemic had already started, travels by train to Roskilde to join a circus. He falls ill and infects a police officer and possibly others.

July 10th 1918:  
A group of soldiers stationed at a hotel in Taarbæk fall ill.

July 9th 1918:  
The torpedo boat *Tumleren* goes out on patrol in the morning between Copenhagen and Helsingør. During the day the crew starts falling ill with influenza. They moor in Copenhagen and are admitted to the marine hospital.

Summer 1919:  
A ship from Denmark eaves for Greenland. When it arrives, some of the passengers have fallen ill with influenza, which then spreads along the west and south coast.

## 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<sup>5</sup>)
- Those born before 1878 or after 1908 were not at increased risk of dying of 1918 pandemic influenza.
- The break point of maximum risk elevation corresponds to around birth year 1878, a pandemic-free period.
- Those with the highest risk, 25-34 years, correspond to those born around the 1889 pandemic.
- Diverging childhood exposure to first flu may explain the mortality risk patterns in 1918: birth cohorts before 1878 may have been exposed to Group 1 influenza. Birth cohorts from 1878-1908 may have been exposed to Group 2 influenza. Birth cohorts after 1908, may be exposed to re-emerging Group 1 influenza.

## Outstanding questions

- What is the exact role of childhood exposure to major phylogenetic clades for influenza A hemagglutinin, and risk of future influenza infection 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?
- Which influenza virus subtypes were circulating pre-1918, that can explain the mortality patterns we see during the pandemic<sup>3</sup>?
- What can we learn from serology studies done in the 1950s in this regard?

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