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# Loose Ends in the Epidemiology of the 1918 Pandemic: Explaining the Extreme Mortality Risk in Young Adults

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In the century since the 1918 influenza pandemic, insights have been sought to explain the pandemic's signature pattern of high death rates in young adults and low death rates in the elderly and infants. Our understanding of the origin and evolution of the pandemic has shifted considerably. We review evidence of the characteristic age-related pattern of death during the 1918 pandemic relative to the "original antigenic sin" hypothesis. We analyze age-stratified mortality data from Copenhagen around 1918 to identify break points associated with unusual death risk. Whereas infants had no meaningful risk elevation, death risk gradually increased, peaking for young adults 20–34 years of age before dropping sharply for adults ages 35–44 years, suggesting break points for birth cohorts around 1908 and 1878. Taken together with data from previous studies, there is strong evidence that those born before 1878 or after 1908 were not at increased risk of dying of 1918 pandemic influenza. Although the peak death risk coincided with the 1889–1892 pandemic, the 1908 and 1878 break points do not correspond with known pandemics. An increasing number of interdisciplinary studies covering fields such as virology, phylogenetics, death, and serology offer exciting insights into patterns and reasons for the unusual extreme 1918 pandemic mortality risk in young adults.

1918 Spanish flu; age patterns; antigenic sin; excess mortality; pandemic influenza

Abbreviation: WWI, World War I.

This year marks the 100th anniversary of the iconic 1918 influenza pandemic. Over the years, the impact of the pandemic on death, demography, society, and its general characteristic features have been studied in depth. Although many questions have already been resolved, answers to some key questions continue to elude us, such as the origin of the virus, the role of World War I (WWI), the economic and societal impacts, and, most importantly, the unusual death-rate pattern in young adults.

In this article, we review some of these outstanding questions, focusing on the origin of the pandemic as well as its "signature" age pattern of an extremely high death rate among young adults, whereas the elderly tended to be spared. We address the hypothesis of "original antigenic sin" (1)—that early childhood exposure may determine death risk during influenza pandemics encountered later in life—which may explain why some age cohorts fared differently in this pandemic. This hypothesis has brewed for some time (2), and detailed analyses of 1918 data from Kentucky (3) as well as analysis of the dramatically different age patterns among victims of avian H5N1 and H7N9 influenza who were born before and after the 1968 pandemic (4–6) have brought new steam to this old question.

To further investigate the age-related patterns of death rates and risk change points in 1918, we analyzed monthly all-cause and age-stratified mortality data from Copenhagen to address the antigenic sin hypothesis. Specifically, we reviewed data on 12 age groups from the 1918 pandemic and sought to pinpoint change points in relative risk elevation. We also sought to link these change points to particular years when the so-called original sin would have occurred. For this purpose, we used weekly surveillance for outpatient influenza-like illness in Copenhagen and looked for unusual influenza activity.

## EVIDENCE OF THE ORIGIN AND EVOLUTION OF THE 1918 INFLUENZA PANDEMIC

### Clinical evidence

It has been argued that the 1918 H1N1 virus originated in the context of WWI efforts in the trenches and army camps in England and France in 1916; affected persons received a diagnosis of "purulent bronchitis." The reports of an unusual clinical picture of young men with respiratory febrile illness, heliotrope cyanosis, and bloody coughing are strong support for this hypothesis (7–9). Others have argued that it all started in a military camp in Kansas in early March 1918; again, military doctors saw a similar unusual picture of hemorrhage and edematous lungs on autopsy among enlisted men who had clinical symptoms of influenza (10, 11). According to a third theory, the pandemic originated in inner northern China, where in 1917–1918, an epidemic of "pneumonic plague" (12) may have been pandemic influenza that then spread to Europe via Chinese migrant workers (13). Although we cannot resolve these different views, the evidence of unusual cyanotic respiratory illness in young men that was later a signature clinical feature in the severe autumn 1918 pandemic supports the idea that the emerging H1N1 pandemic virus had festered in immune-suppressed WWI army populations for some time before it gained effective transmissibility. Indeed, it may have been WWI troop movements that brought the emerging virus to the United States and it was there that the first documented epidemics took place. The central role of WWI troop movements has previously been documented in a study of Brazilian naval ships whose personnel became infected with pandemic influenza after an encounter with the British fleet along the African coast in the early summer of 1918 (14).

### Phylogenetic evidence

Meanwhile, the genetic origins of the H1N1 pandemic virus have been studied through phylogenetic analysis of fully sequenced viral RNA isolated from lung specimens of victims of the 1918 pandemic. Taubenberger et al. (15) concluded that the pandemic virus emerged as an all-avian virus crossing over to human populations in 1918. However, evidence from Smith et al. (16) suggests the virus arose through multiple reassortment events among circulating swine, avian, and human strains in the decade before the pandemic. In 2014, contradictory evidence was brought forth by Worobey et al. (6), who argued that the H1N1 virus was not all avian but rather was assembled by reassortment of a human H1 hemagglutinin and avian viral segments shortly before 1918. They concluded that the hemagglutinin segment had already emerged in human strains around 1907 and that about a decade later, the H1N1 pandemic virus fully formed in a single event when the human H1 strain reassorted with an avian source. Taken together with clinical evidence, it is not easy to reconstruct the actual reassortment timeline. It is possible that the unusual occurrence of cyanotic respiratory illness in WWI army camps was, in fact, a manifestation of the H1 reassortant circulating in the years before the pandemic virus had fully formed and gained the ability to spread effectively.

### Epidemiologic evidence

Epidemiologists have long analyzed death time series to study the signature age patterns of the 1918 pandemic influenza, characterized by extreme death rates in young adults while seniors were spared (17–19). Using unique influenza outpatient and death time-series data from Copenhagen, we demonstrated the existence and the mild nature of the first pandemic wave in the summer of 1918 (18, 20) and we recently reviewed all evidence of herald waves in 1918 (21). Why this first summer wave was milder than the following fall and winter waves remains unclear. It is possible that the virus had not yet acquired the virulence mutations before autumn, or that important bacterial cofactors were not present during the summer wave.

The devastating impact of deaths resulting from the 1918 pandemic was due to a combination of high attack rates (50%–70%), high case-fatality rates (2%–4%), and the unusual age distribution: An estimated 95% of pandemic deaths occurred in young adults (22). The unique 1918 pandemic age pattern holds important clues about the meeting of the pandemic virus with the immune landscape of the human population that was shaped by decades of experience with influenza. So far, the observation that adults older than 45 years suffered no excess mortality in cities like New York City and in Copenhagen has been interpreted as evidence of "recycling" of the H1 antigen that age group had encountered during their childhood some 50 years earlier (18, 20). Meanwhile, the extreme death rate in young adults suggests that having been born between the 1900 (pseudo) pandemic and the 1889 Russian pandemic resulted in that age group's "antigenic sin" (2). The exact break points on the age-risk pattern have been elegantly studied using individual-level 1918 death records from Kentucky (3). Viboud et al. (3) found several change points in age-specific excess death rates: a minimum at approximately 10 years of age, followed by a steep increase that peaked at ages 24–26 years and another minimum at ages 56–59 years. Viboud et al. hypothesized that these peaks and valleys in the corresponding birth years (cohorts born during 1859–1862, 1892–1894, and 1908–1909) should correspond with known dates of historic pandemics. However, they found that this was not the case.

### Evidence from historically remote populations

The large geographical discrepancies in age patterns provide additional clues. It was found in studies of death patterns in South American populations that elderly people were not spared from pandemic influenza; in fact, all age groups seemed to be at highly elevated risk (23, 24). Similarly, observations of high pandemic impact in remote populations such as Inuits in Newfoundland and the Maoris in New Zealand can be interpreted in the same way (25, 26). For example, the Maoris were 7-fold more likely to die during the 1918 influenza pandemic than were the New Zealand population who were of European descent. Although far higher death risk in ethnic populations could also be interpreted as a consequence of genetic risk factors, we think a more parsimonious explanation is the remoteness of these ethnic populations in their childhood some 20–50 years earlier. These findings of high risk for death associated

with pandemic influenza in elderly adults living in remote settings would then support the recycling hypothesis.

### Relaxing the recycling hypothesis

Gostic et al. (4) brought new evidence to this immunity age-signature puzzle. They demonstrated that victims of H5N1 and H7N9 avian influenza had very different age distributions, such that birth cohorts born before and after the 1968 pandemic had completely opposite risk profiles for these 2 zoonotic viruses (4). Their findings expand on the fascinating possibility proposed earlier by Worobey et al. (6) that it is the phylogenetic group of influenza A hemagglutinin segment (group 1 or group 2) that may determine death risk of a novel influenza infection. Members of these groups may elicit cross-immunity because their subtypes (H1, H2 and H5, belonging to group 1, and H3 and H7 belonging to group 2) are from the same major hemagglutinin phylogenetic clade. Thus, the recycling hypotheses can be relaxed to having experienced an original sin of group 1 versus group 2 influenza A hemagglutinin in childhood, rather than requiring that the original exposure had to be the exact same hemagglutinin subtype. The high young adult death rate during the 1918 pandemic may be due to different imprinting between age groups.

## METHODS

### Investigating age break points in death risk in Copenhagen

All-cause, age-specific death patterns can help us determine which age groups were more affected by the 1918 pandemic and thus help uncover clues about the evolutionary history of the virus. Therefore, we looked at the death patterns of different age cohorts in Copenhagen in 1918 and sought to place these patterns in the context of long time series of outpatient records of influenza-like illness.

### Data sources

We used detailed, long time series of age-stratified monthly death records from Copenhagen along with population census statistics (see Andreasen et al. (20) for more information on the data sources) to look for break points in the age profile of cases during the various seasons of the 1918 pandemic (Figure 1). We took the same general approach as Viboud et al. (3), but rather than look at excess death rates, we studied the relative death risk over the baseline level for each age group.

### Statistical analysis

All-cause death data with a 5- to 10-year age resolution were available from 1879 through 1923 through annual reports from the medical officers of Copenhagen. As a baseline for 1918 and 1919 data, we interpolated the death rates for each month between 1917 and 1921 and calculated incidence rates (the baseline) during each of the 4 pandemic waves. All rates were expressed as all-cause deaths per 10,000 individuals (linearly interpolating between successive census data). We then computed the incidence ratio as the ratio of incidence rates for each wave over the baseline.

## RESULTS

### Timeline for the 1918 influenza pandemic in Denmark

There were 4 pandemic waves in Copenhagen during 1918–1920: a milder first (herald) wave in July to August 1918, followed by the main wave peaking in October to November. This was followed by a winter wave peaking in January to February 1919, and a fourth recrudescent wave in January to February 1920.

Already in June 1918, the Danish national newspapers began reporting on the "Spanish sickness" (27–29). In the second week of July, the pandemic broke out in both Copenhagen and the town of Roskilde, 30 km to the west of Copenhagen. Although the source of the outbreak in Copenhagen is impossible to track, in Roskilde, it was likely introduced by a circus artist arriving from Oslo, Norway, where the first wave had already reached epidemic levels a week earlier (Table 1). Interestingly, before the outbreak in Copenhagen and Roskilde, an outbreak occurred in the town of Christiansfeld just south of the Danish border in Jutland, apparently introduced by a postal clerk returning from Germany (30, 31).

It was widely accepted among physicians in Copenhagen at the time that the outbreak was a novel, atypical form of influenza and they likened it to the influenza that had caused substantial impact in Madrid, Spain, in June (19, 29). Also, they commented on the outbreak's mildness and suggested that people should not worry—unfortunate advice, in hindsight, because the subsequent autumn wave killed 0.2% of the Danish population and 1%–2% of the entire world population (20, 22).

### Death patterns

Across the study period, the 1918 pandemic death rate in young adults stood out dramatically in the severe autumn 1918 wave (the second wave) and the recrudescent (fourth) wave during winter 1919–1920. In contrast, young children as well as older adults did not have unusual excess death in the 1918–1920 period (Figure 1; Web Figure 1, available at https://academic.oup.com/aje).

During the severe autumn 1918 pandemic wave, the risk ratio was highest for persons in age groups between approximately 10 and 44 years, reiterating earlier findings in other studies (Figure 2). The risk ratio steadily increased to more than 11-fold of baseline for the 25–34-years age group during the autumn of 1918. The incidence ratio then dropped sharply for the 35–44-years age group and reached a risk ratio of approximately 1 for older age groups, consistent with no risk elevation during the pandemic. The exact risk break point is likely approximately 40 years of age, judging by the steep decline in this group compared with the surrounding age groups. A similar risk-ratio pattern was seen in all 4 pandemic waves, in particular in the second and fourth waves.

We next looked for evidence of pandemic-level activity in the decade before 1918 in long time series of weekly influenza outpatient morbidity data available since 1889 when influenza was added to the list of notifications (Figure 3). We could not identify any standout epidemics between the 2 pandemics of

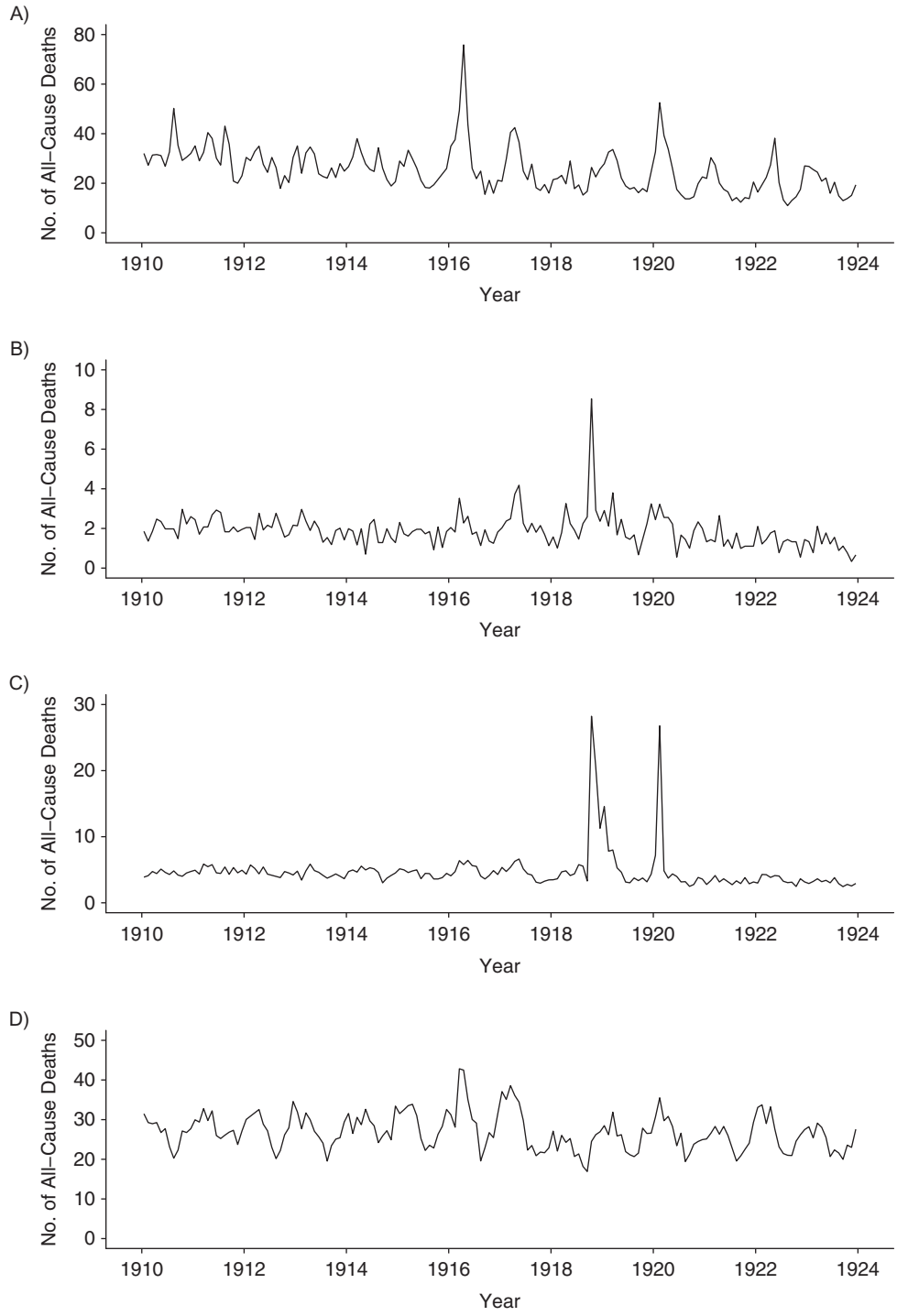


**Figure 1.** Time series of monthly all-cause mortality rate per 10,000 persons aggregated to 4 broad age groups,Copenhagen, Denmark, 1910–1922. Age groups with similar patterns in 1918 have been aggregated for plotting purposes: A) 0–4 years; B) 5–14 years; C) 15–44 years; D) 45 years or older.

1889 and 1918. Unfortunately, these morbidity data did not allow us to go back further to check for epidemics around 1873. We next perused annual medical reports for Denmark and found that influenza, in fact, was noted and discussed during 1876–1883 but without mention of pandemic or severe activity before 1889. One physician commented that there had been no notable influenza in the years between the pandemic in the 1830s and 1889 (32).

**Table 1.** Tracing the Origin of the 1918 Pandemic Influenza in Denmark

| Event | Date | Location | Source | Reference No. |
|---|---|---|---|---|
| Outbreak of possible influenza | July 2, 1918 | Christiansfeld | Postman from Germany | 39 |
| Outbreak of influenza begins | July 7, 1918 | Roskilde | Circus artist from Oslo | 40 |
| Outbreak on torpedo boat *Tumleren* | July 9, 1918 | Copenhagen | Military | 41 |
| Outbreak in hotel Taarbæk | July 10, 1918 | Taarbæk | Military | 42 |

## CONCLUSION

Reviewing the evidence that has accumulated from various disciplines, including medical history, quantitative epidemiological analyses, seroepidemiology, virology, and phylogenetics, answers to key questions about the 1918 pandemic still elude us. However, we are moving closer, in particular regarding the unusual age pattern of deaths.

The recycling hypothesis was first put forward to explain the 1918 patterns and has since been investigated for more recent pandemics. Age-specific excess death rates were used in a study to review age-groups data to identify points at which pandemic protection begins. Such change points have been found for persons older than 77 years during the 1968 pandemic, corresponding to those born before the pandemic in 1889 (2). For the recent 2009 pandemic, middle-aged and older adults born before the 1957 pandemic were nearly completely spared and showed evidence of preexisting cross-reactive antibodies (33, 34). Thus, there is good reason to believe that adult protection relates to exposure to pandemics in childhood. For the 1918 pandemic, such an inquiry can only be done with epidemiologic excess death data, because of the absence of seroepidemiology from blood sampled before that pandemic and the absence of virologic evidence from the 19th century.

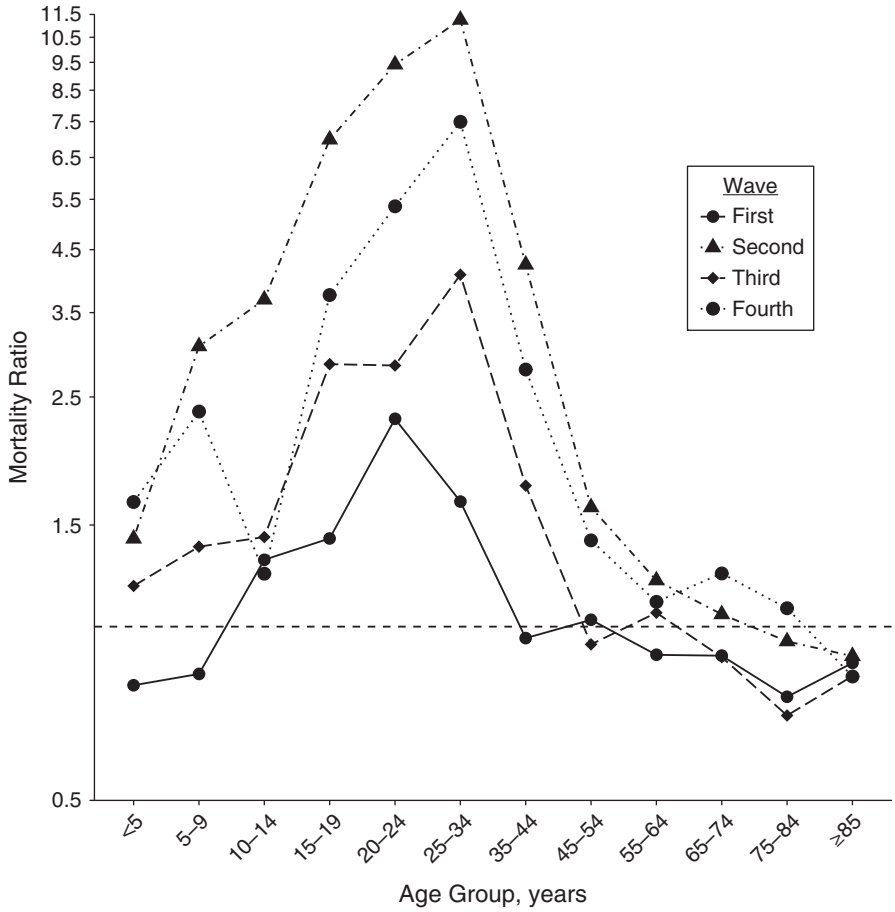


**Figure 2.** Relative age-specific mortality risk in the 4 pandemic waves, Copenhagen, Denmark, 1918–1922. The first wave was in the summer of 1918; the second wave was in the autumn of 1918; the third wave was in the winter of 1918–1919; and the fourth, recrudescent wave was in the winter of 1919–1920. The birth years for the age groups ranging from <5 years of age through those ≥85 years of age in 1918 were, respectively: 1913–1918, 1908–1913, 1903–1908, 1898–1903, 1893–1898, 1883–1893, 1873–1883, 1863–1873, 1853–1863, 1843–1853, 1833–1843, and 1833 or earlier.

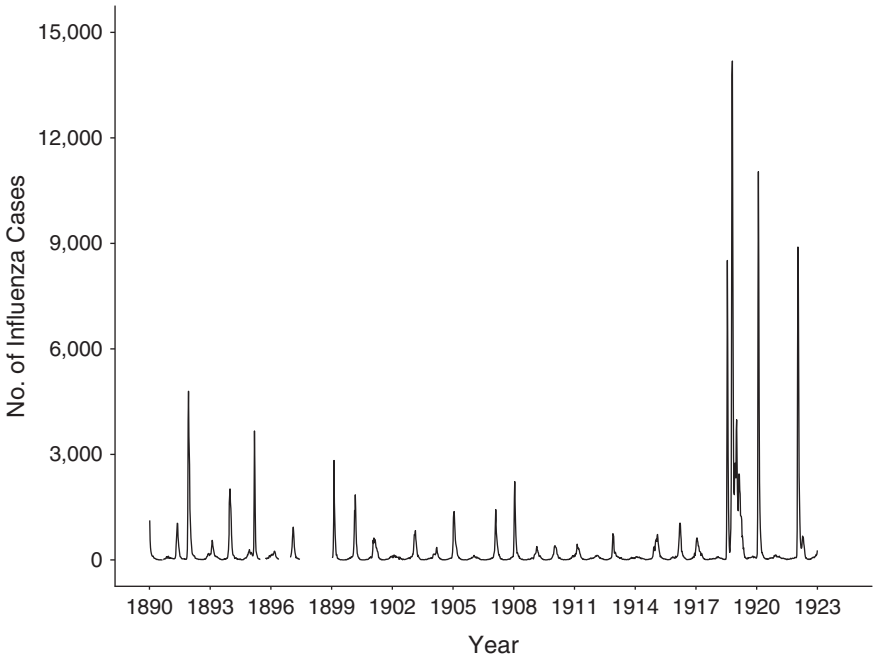


**Figure 3.** Weekly number of reported influenza outpatient illnesses, Copenhagen, Denmark, 1889–1923.

In our analysis of Copenhagen data, we managed to pinpoint the break point from high to low death risk at approximately 40 years of age (in the middle of the 35–44-years age group). This corresponds to having been born around 1878 (range, 1873–1882), which is curiously a pandemic-free period in humans as far as we know (there was a severe pandemic in horses (35)). In Denmark, certainly, there is no mention in the medical literature of a human pandemic event in that period. However, our finding that the maximum death risk occurred in the 25–34-years age group (probably at approximately 29 years of age) is consistent with having been born around the time of the 1889–1892 pandemic, as if exposure to the 1889 emerging pandemic virus led to enhanced risk later in life.

Unfortunately, we could not pinpoint with accuracy a particular break point in terms of risk among the pediatric age groups; rather, we found a gradual increase in the incidence ratios, starting with the 5–9-years age group. Explanations for the lack of a steep cutoff could be the limited total number of deaths in the toddler and schoolchildren age groups, or the resolution of the age groups. Infants were at no particular

**Table 2.** Hypothesized Scenario of Circulating Influenza A Hemagglutinin Group 1 and 2, Which May Explain the Characteristic Age Patterns for the 1918 Pandemic in Copenhagen, Denmark, and Kentucky, United States

| Location | Age Group, years, and Birth Cohort | | | | |
|---|---|---|---|---|---|
| | 0–4 (1913–1918) | 5–9 (1908–1913) | 10–19 (1898–1908) | 20–44[a] (1873–1898) | ≥45 (1873 or Earlier) |
| Copenhagen | | | | | |
| Risk profile during 1918 | Low risk | Medium risk | Medium to high risk | High risk | Low risk |
| Kentucky | | | | | |
| Risk profile during 1918 | High risk | Low risk | Medium risk | High risk | Low risk |
| Suggested original antigenic sin for Copenhagen and Kentucky[b] | | | | | |
| Possible circulating influenza A HA group | Group 1 | Groups 1 and 2 (group 2 dominant) | Groups 1 and 2 (group 2 dominant) | Group 2 | Group 1 |
| Possible circulating HA subtypes | H1 | H1 and H3 | H1 and H3 | Possibly H3 | Possibly H1 |

Abbreviation: HA, hemagglutinin.

[a] In this broad age group, the peak risk occurred in the 25–34-years age group, whereas the age group 35–44 years had a steep decline in risk, suggesting a break point at age 40 years in the Danish data.

[b] Evidence from seroepidemiology, phylogenetics, and epidemiology (6, 36, 43).

increased risk relative to the baseline level. This is not to say that there were no infant deaths due to the pandemic—rather, those would be few compared with the overall background number of deaths.

Our results are remarkably similar to those of Viboud et al. (3), given the lower resolution of our data (Table 2). Whereas in Kentucky it was clear that those approximately 10 years of age were at the lowest risk for death associated with the pandemic, our analysis points to children under 5 being at lower risk than those in other pediatric age groups. However, it is also clear that those 5–9 years of age were at a relatively low risk compared with those 10–44 years old. The highest risk in Kentucky was in people between 20 and 30 years old—similar to data from Copenhagen. In Kentucky, the excess death declined steadily after 25 years; in Copenhagen, this decline was sharper and mainly evident in the age groups older than 35 years.

These results suggest diverging antigenic sins between birth cohorts. Birth cohorts born before 1873 may have been exposed predominantly to group 1 influenza A hemagglutinin, whereas those born between 1873 and 1908 may be been exposed to group 2 influenza A hemagglutinin, and those born after 1908 may have an antigenic sin related to reemerging group 1 influenza A hemagglutinin, very likely of the H1 subtype. It is possible that H1 was also circulating around 1873, which would explain the low risk among the elderly.

Seroepidemiology, epidemiologic, and phylogenetic evidence seem to point to the same time period around 1907 (Table 2) (3, 6, 36). The possibility of a 2-step assembly raised by Worobey et al. (37) in a newer phylogenetic analysis is in disagreement with earlier phylogenetic analyses by Taubenberger et al. (15) and Reid et al. (38), who concluded that the 1918 pandemic was an all-avian zoonosis. Although these hypotheses disagree on the origin of the pandemic and its reassortment history, they are consistent with the idea that H1 (of avian or human origin) was already circulating well before the 1918 pandemic arose and was likely introduced in humans between 1900 and 1907. It is possible that the pandemic virus was assembled in multiple steps: Around 1907, the virus acquired H1 by recombination (6). This precursor virus may have been circulating for a decade or more before the 1918 pandemic, along with the previous group 2 influenza virus, thereby explaining the intermediate risk profile for those born between 1908 and 1913 (some would have experienced a group 1 infection and others a group 2 infection as their first influenza illness). Certainly, a consolidating view on this issue, and of the possible contribution of other segments, like neuraminidase, would be most helpful to elucidate the likely human immunity landscape at the time.

The nature, origin, and timing of a future pandemic may be unknown; however, it is clear from historical accounts that one will occur again. Pandemic preparedness relies on our understanding of what might happen given our pandemic experiences; in particular, our understanding of patterns of severity and high-risk age groups. Studying historical influenza pandemics is only natural, therefore, and may resolve important conundrums about the interaction between population immunity and pathogen evolution. Although some aspects of events such as the H1N1 1918 outbreak and other pandemics of the 20th and 21th centuries still elude us, they provide invaluable insights for informing pandemic planning whatever the next threat may be.

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