Title: Epidemiological evidence for viral exposure in childhood as a risk-factor in subsequent influenza pandemics.

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Please Note: this text analyses the 1918 pandemic in detail. The final version will examine the role of childhood exposure to influenza and its impact on mortality experience in pandemics from the 1830s to 1969, as a guide to the possible impact of future pandemics.

Structured Abstract:

Context After four decades of decline, influenza re-emerged in the 1891 pandemic, thought to be the result of an antigenic shift in the virus. The next major pandemic in 1918 was the worst in statistically documented history and has been the focus of considerable scientific attention, especially as a guide to the risks associated with emerging diseases. In 1918 the adaptive immune system is thought to have protected older cohorts through prior exposure to a similar virus, but its unique lethality amongst young adults is unexplained.

Objective To investigate the hypothesis that excess mortality risk in 1918 can be understood as an interaction between the new virus and cohort-specific immunological experience.

Design and Setting A multi-national, cohort study using a population-level, epidemiological method applied to new data from the Human Mortality Database. Female cohorts are used to limit wartime effects.

Main Outcome Measure We estimate the effect of the virus on each female birth cohort in 1918, after controlling for age, by calculating the Relative Risk between

the pandemic mortality rate and the “normal” rate from 1913 to 1917 for women of the same age.

Results Cohorts born after 1891 were at much higher relative risk in 1918. For all cohorts, the closer their birth year was to 1891 the higher the relative risk. As expected**,** older cohorts had risk ratios close to unity.

Conclusion Excess mortality in 1918 is better understood as a cohort phenomenon than as an age effect. The extreme virulence of 1918 for young adults is associated with their cohort experience of the 1891 virus. Explaining these powerful adverse cohort effects poses a major challenge for research in immunology, virology and epidemiology. Identifying specific cohorts that may react badly to future viruses would have significant policy implications.

Keywords: influenza A | 1918 pandemic | virulence | birth cohort

Text:

The emergence of new diseases, or new variants of familiar ones, is widely regarded as a major potential health risk. In this context, the 1918 global pandemic of influenza, the so-called “Spanish flu”, is invariably cited as an example. The exact number of deaths caused worldwide by the 1918 pandemic is unknown, since few countries outside Europe, North America and Australasia had accurate registration. Estimates of the global toll range from 20 million to 100 million or more. Even the lower estimate, however, makes the 1918 flu

by far the most costly epidemic in terms of human life for at least the last 150 years. Understandably, given so huge a loss of life, the 1918 episode has received considerable attention from scholars of many disciplines in an attempt to understand how so lethal an epidemic could occur.

In recent years there has been significant improvement in our understanding of the 1918 virus; many of its molecular characteristics have now been identified, and its lethality confirmed by animal tests.[1-4] Complementary research focuses on host-virus interaction; either in the laboratory, or via epidemiological studies. The former is illustrated by the retrospective analysis of sera (sero-archaeology).[5] Among the latter, a recent study shows that the transmissibility of the 1918 virus was not unusual, but it was the extremely high case fatality proportion, particularly among young adults, that made 1918 unique.[6]

We offer a new demographic perspective on this mystery of the 1918 epidemic: why it affected people of different ages to varying degrees. Most demographic research for 1918 has used broad age groups and has often presented rather indirect measures, such as the total number of deaths in each age group. Moreover, no previous study has considered the age pattern of mortality in 1918 in a broader perspective that integrates the effects of age, time-period, and cohort of birth with characteristics of influenza. In this paper we make use of data by single year of age that have only recently become available for general analysis as part of a wider collation of detailed mortality statistics.[7] Our analysis shows that the virulence of the 1918 pandemic displays a very strong cohort-specific profile related to

the 1891 pandemic and provides new insights into the relationship between the 1918 virus and its victims.

The Dynamic Nature of the Virus. The influenza A virus, the type responsible for the most serious epidemics in human populations, is an RNA virus capable of very high rates of mutation, possibly 10,000 times as high as for a DNA virus.[8] Different subtypes of the virus are designated on the basis of antigenic relationships of the proteins haemagglutinin (HA) and neuraminidase (NA), for example H1N1 for the 1918 flu, H3N2 for the 1968 "Hong Kong" flu, and so on. In addition to changes concerning these two surface proteins, there may also be significant differences in responses to the virus within the cell. The virus undergoes two forms of genetic change. Within a subtype, new variants emerge every few years, arising from progressive and cumulative mutation of the virus. This process of gradual change, or limited jumps, in the make-up of the virus is termed *antigenic drift*. In contrast, more radical changes to the virus occur intermittently (the gaps ranged from 9 to 39 years in the 20th century) and almost always result from gene reassortment. This larger change is called *antigenic shift*.[9]

Many of the largest human epidemics, including the 1918 pandemic, are believed to have followed antigenic shifts. Indeed, some authors argue that the term 'pandemic' should only be used for a global epidemic following a shift. Until the 1970s the appearance of each new subtype led to the replacement of the previous form of the virus. However, since 1977

strains of both H1 and H3 have been in circulation. The influenza virus was first identified in 1933 and assessments of which subtype was present at earlier dates are mostly derived from antibody studies carried out in later years. It is generally believed that an H1 strain was prevalent in the years down to c.1850, with an H2 strain taking over around 1890 and an H3 version around 1900. However, there is still a substantial degree of uncertainty attaching to assessment of the antigenic identity of many of the pre-1918 strains. Thus Dowdle has argued that an H3 epoch began c.1890.[5] Evidence concerning the type of the virus in circulation between c.1850 and c. 1890 remains ambiguous.[10]

Conceptual framework

It is possible to derive a number of clear expectations concerning age-specific mortality from these dynamic characteristics of influenza. There is no reason to believe that the virus targets individuals of any particular age, and it can be assumed that exposure is virtually universal in epidemics. Thus the main determinant of mortality is likely to be the resistance of each individual when faced with the challenge of a new virus. In this context, we can distinguish three main effects: first exposure, recent exposure and frailty.[11-12]

First Exposure. The first strain of the virus to which an individual is exposed leaves an indelible immunological imprint, and later exposure to a closely related variant produces an anamnestic (remembered) response.[13-14] For a disease such as influenza, which is effectively omnipresent, this first exposure occurs shortly after birth. It can thus best be

thought of as a *cohort effect* – being born in a particular year will give an individual's immune system a lifelong capacity to respond more effectively when again confronted with the same subtype of the virus that was prevalent when he was born. However, this beneficial response will not occur when exposed to a different subtype. A slight variation of this effect can be termed 'early exposure', in that exposure to a strain during childhood might entail a different immune response from that of an adult, with enduring consequences.

Recent exposure. Antigenic shift and drift can both be regarded as producing *period effects*, since they present a new challenge that is not inherently age- or cohort-specific. Between antigenic shifts, the amount of change in the virus from one year to the next is modest, and thus an immune response triggered by recent exposure is likely to be helpful when facing a new variant. Immunity after an antigenic shift depends on prior exposure to the new subtype.

Frailty. The ability of an individual to respond effectively to the influenza virus is partly determined by their age. Generally speaking, older individuals are frailer and thus more likely to succumb to the negative effects that the virus produces. In some situations, infants and young children may also be more susceptible than others to die following infection. This is a classic *age effect*.

Age, Period and Cohort. Demographers classify mortality along three primary dimensions: age, period and (birth) cohort. Each has a corresponding immunological interpretation: first exposure (cohort), recent exposure (period) and frailty (age). Age is the number of completed years at the start of the period, in this case the calendar year. Cohort is the calendar year of birth. The three dimensions are logically interconnected: age = period – cohort. The overall pattern of mortality will be produced by interactions between these three effects. In most circumstances, in both epidemic and non-epidemic years, the frailty effect predominates, and influenza mortality rises steeply with age.

However, apparent age (frailty) effects can arise from interactions between period (recent exposure) and cohort (first exposure). From our own research we know that first-exposure and recent-exposure effects can be clearly detected in some influenza epidemics, certainly for 1957/8 and 1968/9.

This distinction between age, period and cohort effects, and their close relationship to features of the virus, is fundamental to a fuller understanding of the 1918 pandemic. Although the three are interrelated, it is possible to test their importance.

Data and Methods

Data. Data for the 1891 and 1918 pandemics are drawn from the Human Mortality Database (HMD), which provides the most rigorously comparable international statistics.[7]

These data are specifically constructed to avoid the arithmetic confounding of age, period and cohort effects. Eight countries are available for both 1891 and 1918: Denmark, England and Wales, Finland, The Netherlands, New Zealand (Non-Maori population), Norway, Sweden and Switzerland. France is only available for 1918. As advised by the HMD, we excluded Spain from both analyses, and Italy from the 1891 study, because their data are more seriously affected by age misreporting than the other available countries. Only female age-specific mortality is analysed because of inconsistencies between countries in the reporting of deaths among military personnel in World War I. In the non-combatant countries, males and females show very similar patterns, so this restriction raises no problems with interpretation of the results.

Total versus influenza mortality. The results presented here refer to mortality from all causes, rather than from influenza alone. Influenza often triggers deaths from other causes, including pneumonia and heart disease, and cause of death classification in the past was often inaccurate. It is also not available for so many countries, or in such detailed age-groups, as overall mortality. In all the epidemics we have examined for which reliable death rates for influenza, or influenza plus pneumonia, are available, the patterns of mortality change are consistent with the results based on all-cause mortality.

Relative Mortality Risk. Age-specific relative mortality risk is defined here as the risk in the epidemic year divided by the comparable risk in "normal years" – in this paper the five preceding years - holding age constant. Relative Risk has a long pedigree in demography

and epidemiology, but has rarely been used in influenza studies.[15-17] It enables us to remove the normal age-specific pattern of deaths and focus on the differences that arise during the epidemic year. Relative risk also provides a population-level analog (based on millions of individuals) to the retrospective analysis of smaller samples by sero-archaeology. The relative risk can be thought of as related to the proportion of a cohort born in a given year having an ineffective immune response to a given sub-type of the virus.

Relative risk measures proportional, rather than absolute, changes. Proportional change in risk is suited to understanding the process by which the immune system responds to challenge, whereas additive excess deaths are appropriate for impact studies. In the Figures, a horizontal line at 1.0 is what would be expected if the mortality risk in the epidemic were exactly the same for the age-group as that prevailing in normal years. A value of 2.0 indicates that mortality was double the normal, and so on. A horizontal line is to be expected if the epidemic simply worsened the normal age-specific pattern to the same degree for all cohorts.

Results

Figure 1 shows the relative risk of dying in 1918 compared with five normal years (1913-1917) for England and Wales (20 million women) and the pooled set of ten countries (with a total female population of 69 million). The risk is given for each year of birth. Although taking annual cohorts leads to some irregularity in the results, this is greatly preferable to

aggregating the data, as it allows both smooth progression and turning points in the curves to be seen more clearly. Departures from the horizontal indicate that some cohorts suffered disproportionately during 1918. The graph also shows vertical lines at 1847, 1891 and 1900, which are thought to be the dates of antigenic shifts.

Two features stand out. First, the increase in the relative risk is enormous for some cohorts. Whereas for any other influenza epidemic over the last 140 years, the highest relative risk was usually less than 1.2 (implying at worst a 20% increase in mortality), the peak for 1918 is almost 3 for England and Wales and over 3 for the pooled data (indicating a tripling of death rates). The other immediately obvious point is the striking shape of the curves. Apart from infants, all childhood and young adult ages experienced much worse mortality, with a marked peak for those born around 1891: the year of the last major epidemic of influenza before 1918. The relative risk declines smoothly and rapidly for earlier cohorts, and in England and Wales for most women born before the 1850s mortality was actually lower in 1918 than might have been expected. This strongly suggests that an H1 strain of the virus (more closely related to the 1918 version) was the predominant form before the 1850s.

The advantage of presenting the results according to single years of birth is also clearly demonstrated. The results for each of the nine countries (not plotted here) show closely related patterns. The somewhat higher risk for the pooled data is largely produced

by higher rates in Italy. Although the relative risk is highest for those born from 1891 on, cohorts born during the 1880s were also at higher risk than older individuals. This may reflect the proportion of each cohort that escaped infection before 1891, but it is also consistent with the idea that exposure to a new virus during childhood, even if it is not the very first exposure, has a more lasting impact on the immune system than adult exposure. There is little variation from country to country in the values before 1890, but more in later cohorts, with England and Wales having the sharpest decline after 1891. In all nine countries the relative risk was high for all cohorts born between 1890 and 1917. There is no marked change in the relative risk around 1900, and thus no evidence from these data that a hypothesised antigenic shift at that time affected mortality in 1918.

When faced with the challenge of the 1918 flu, the immune systems of different birth cohorts responded in very different ways. What needs to be explained is thus not an age-effect, but this cohort effect. As is apparent from Figure 1, far from being a general effect for all young adults, as is often implied in the literature, the risk has a striking inflection around 1891. This strongly suggests some association between the two epidemics, or more generally between the variant of the virus that was in circulation between 1891 and 1918 and the new strain. At present there is no clear evidence why this arose. Thus, understanding more about the 1891 epidemic may provide the key to unraveling the mystery of the 1918 strain's exceptional virulence. The next two figures explore the context and the relative risk of the 1891 epidemic.

Figure 2 presents the death rate from influenza for England and Wales from 1838 (when civil vital registration began) to 2000. The data were collated from the original sources and Langford.[18] The figure is plotted on a log scale and refers to both sexes; where we were able to check, the trends for each sex are virtually identical. From a level of around 100 per million in the 1850s the influenza death rate fell to almost zero by the 1880s, long before the introduction of influenza vaccination, antivirals or antibiotics. The values in the 1880s might be understated because physicians may have under-diagnosed so rare a cause of death. However, no adjustment for under-reporting in the 1880s could mask the scale and suddenness of the return of influenza as a major cause of death in 1891. The reported death rate rose over 100-fold, from 2-3 per million to 200-300. It then remained at about this level throughout the period until 1918, when the pandemic produced a rate of 3000 per million. Since 1918, influenza mortality has declined and is now approaching the low point seen in the 1880s.

England and Wales was the only large population to report influenza deaths before the 1890s, but data from several smaller countries, regions and cities confirm the abrupt reemergence of influenza worldwide at this time. Contemporary authors all agreed that a global epidemic of influenza occurred in the years 1888-1892. Indeed scholars writing in the period between 1890 and 1918 often regarded the resurgence of influenza around 1890 as the most important event in the history of the disease.[19]

Figure 3 presents the relative risk of dying in 1891 compared with five normal years before the return of high influenza death rates (1884-1888) in the eight countries for which data are available. The total female population was 25 million. Since England and Wales dominates the pooled set there is little value in showing it separately, as was done for 1918. It is obvious that the pattern of mortality increase in 1891 was very different from that seen in the 1918 epidemic. Firstly, the earlier episode was much less severe than 1918: the highest relative risk implies only a 15% worsening of mortality. Also unlike 1918, the young were at no disadvantage in 1891. Most of the people born after the 1850s had lower mortality in 1891 than in normal years. In contrast, cohorts born before about 1850 suffered the highest increase in mortality in 1891, whereas they experienced no significant worsening in 1918. Taken together, the graphs for the two epidemics almost certainly indicate that the form of the virus in circulation prior to c. 1850 was closely related to the 1918 flu, in all likelihood an H1 virus. Figure 3 also makes clear that what matters most is viral exposure during childhood. Simply being exposed to a strain of influenza during adult life between c. 1850 and 1890 was of little help to people born in the H1 era before c. 1850 when faced with the more lethal 1891 strain.

The nature of the influenza in circulation between c. 1850 and c. 1890 is still a mystery. The fact that young cohorts were at an advantage in 1891 suggests that the resurgence of influenza mortality c. 1890 was not brought about by an antigenic shift in the

virus. However, the 1889-1891 epidemic did usher in a new era of greatly elevated risk of dying from influenza after four decades of sharply declining virulence. Thus, whatever the subtype in circulation from c. 1890 to 1918, people born during that period were at much greater risk when faced with the return of an H1 type in 1918. The people born at the time when this new regime was being established around 1891 were the most vulnerable of all in 1918.

Discussion

Age is usually by far the most important factor determining an individual's ability to resist an infection. As a result, strategies for coping with new strains of influenza (or with new diseases) focus on age as the key variable. Moreover, in statistical modelling of influenza data, age is usually included by assuming a simple linear relationship, or arbitrary age groups. Most analysis takes no account of cohort effects. However, the 1918 pandemic shows that these can play a crucial role in determining lethality. Without the powerful cohort effect identified here, the 1918 epidemic would have been far less severe. By focusing on the relative increase in risk in 1918, rather than overall deaths, our analysis makes clear the interactions between the 1918 virus and its victims.

Each birth cohort develops a unique immunological history, reflecting the particular strains of influenza it encounters. The first exposure is especially important in shaping the immune system. One possible explanation for the smoothly rising curve towards 1891 in

Fig. 1 is that it reflects the proportion of each cohort whose first infection was the 1891 virus. Certainly, the strains of flu that were in circulation from 1891 to 1917 left the people born in those years with immune responses that were inadequate when faced with the 1918 version. The decline in relative risk after 1891 may indicate that the effect was ameliorated by antigenic drift.

The strains of flu circulating between 1891 and 1917 preconditioned these birth cohorts to exceptional vulnerability to the 1918 strain. There may be analogous relationships between flu strains that could lead to similarly enhanced risks for specific birth cohorts in future epidemics. If new research could expose the mechanism that made the 1891-1917 cohorts so vulnerable in 1918, then as each new strain of flu emerged we could assess which cohorts were especially at risk. Such an understanding could lead to a very significant advance in preventive strategies.

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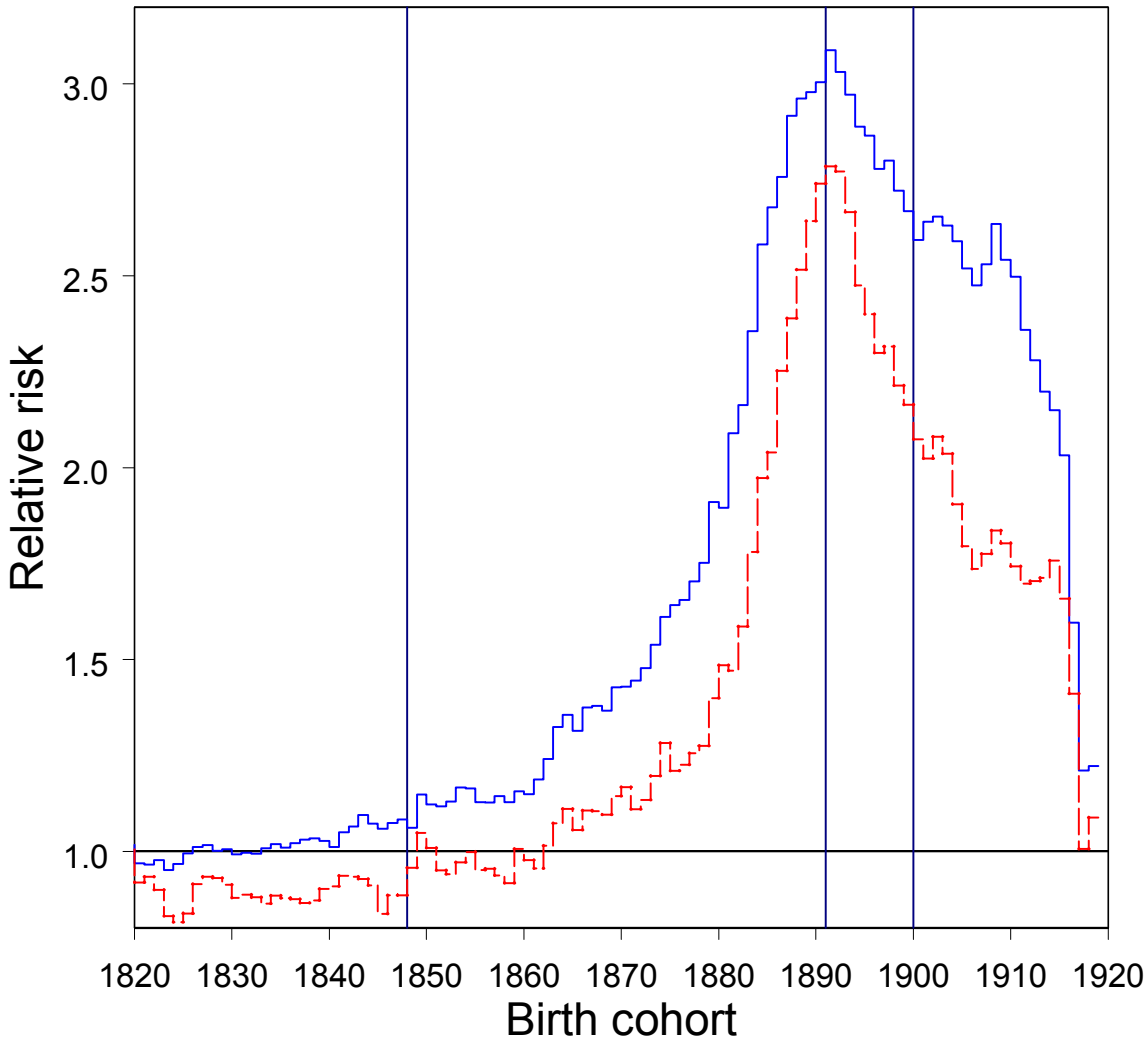
Figure titles.

Fig. 1. Female relative mortality risk in the 1918 influenza pandemic by birth cohort.

Fig. 2. Male and female influenza mortality rate in England and Wales from 1838.

Fig. 3. Female relative mortality risk in the 1891 influenza pandemic by birth cohort.



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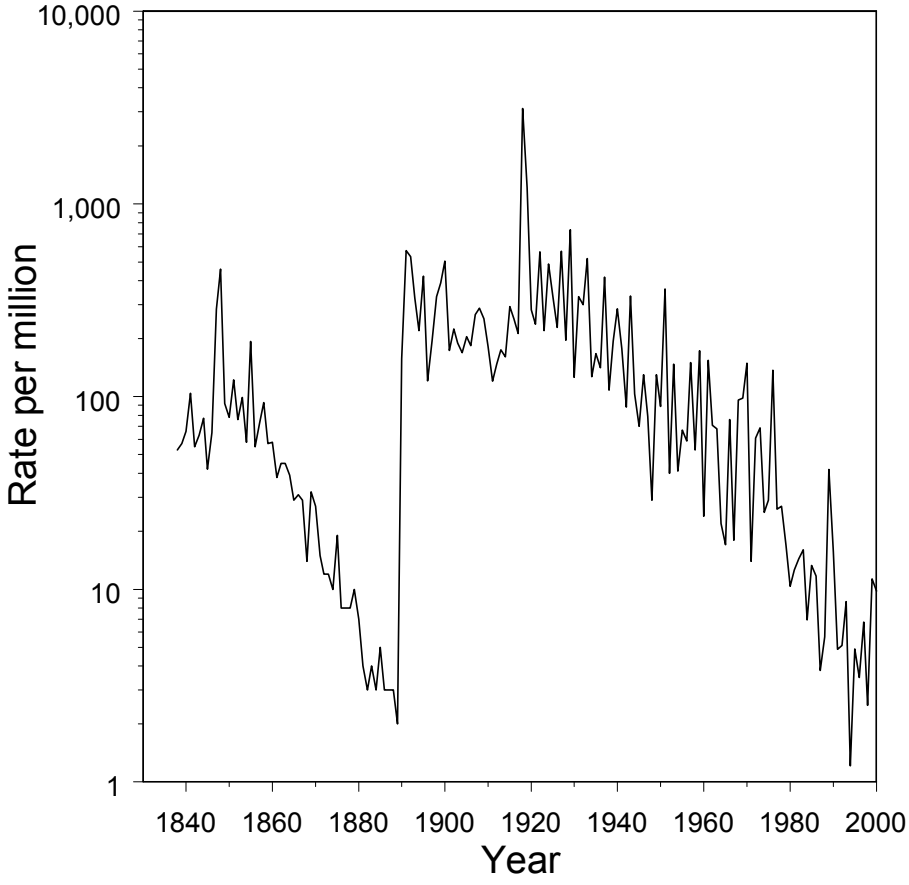

Fig. 2. Male and female influenza mortality rate in England and Wales from 1838.

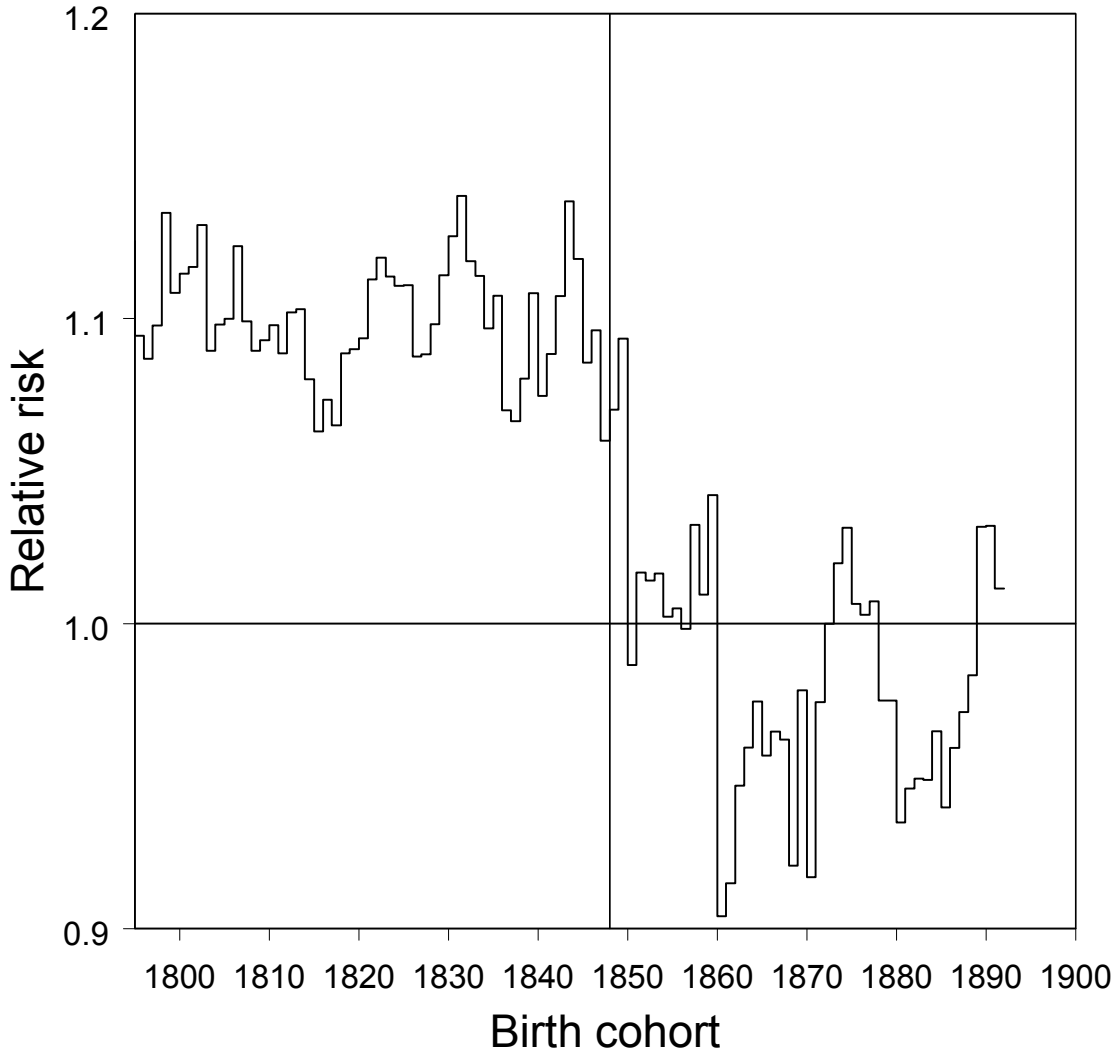

Fig. 3. Female relative mortality risk in the 1891 influenza pandemic by birth cohort.

Figure Legends.

Fig. 1.

Age-specific all-cause mortality in 1918 divided by the risk for the same age in the preceding 5 years. Nine countries combined (solid line) and England and Wales (dashed line). Vertical lines mark the three supposed antigenic shifts preceding 1918.

Fig. 2.

Mortality is defined as the number of influenza deaths per million of the total population and is plotted on a log scale. The relative increase in 1891 exceeds that of the 1918 pandemic.

Fig. 3.

Age-specific all-cause mortality for England and Wales in 1891 divided by the risk for the same age in the preceding 5 years. The vertical line marks the supposed antigenic shift preceding 1891.