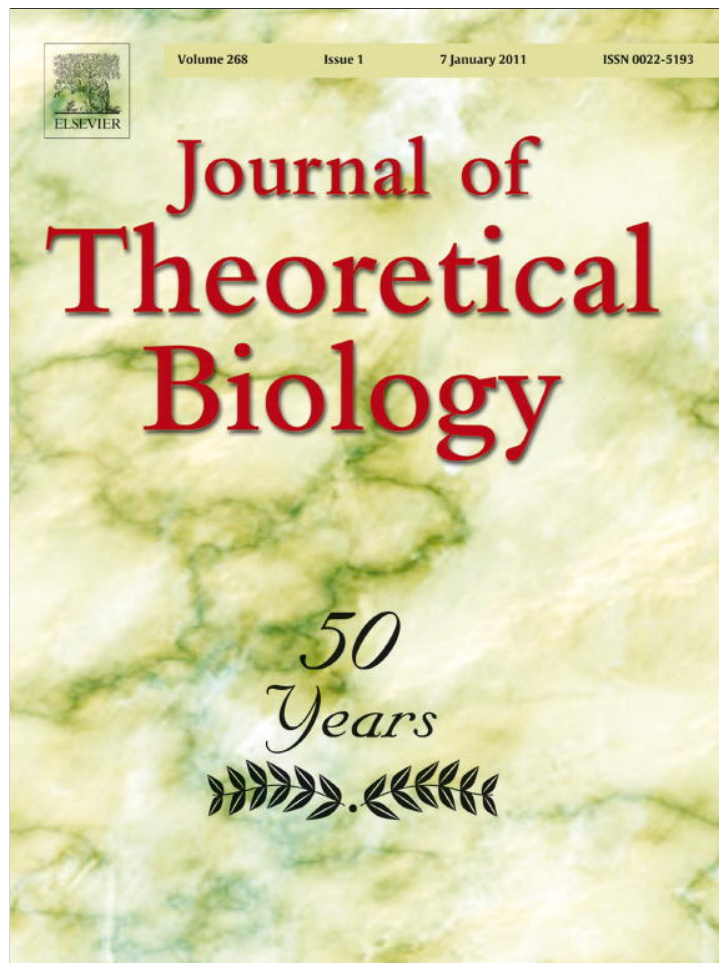


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## Age-specific mortality risk from pandemic influenza

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### ABSTRACT

Younger age groups account for proportionally more mortality in influenza pandemics than in seasonal influenza epidemics. Mechanisms that might explain this include young people suffering from an over-reactive immune system (“cytokine storm”), older people benefiting from cross-immunity from a wider variety of previous influenza infections (“antigenic history”), and lifetime immune responses in all people being shaped by their first influenza A infection (“antigenic imprinting” or “original antigenic sin”). We examined whether these mechanisms can explain age-specific influenza mortality patterns, using the complete database of individual deaths in Canada from 1951 to 1999. The mortality pattern during the 1957 pandemic indicates that antigenic imprinting plays an important role in determining age-specific influenza virulence and that both shift years and major drift years contribute significantly to antigenic imprints. This information should help pandemic planners to identify age groups that might respond differently to novel influenza strains.

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### 1. Introduction

Who is at greatest risk of death from influenza?

Deaths attributed to influenza are typically caused by complications, which often involve pneumonia. For this reason, patterns of influenza mortality are most commonly studied beginning from combined pneumonia and influenza (P&I) deaths. In typical non-pandemic influenza seasons, the relationship between age and P&I mortality is U-shaped, indicating highest risk for the very young and the very old, and much lower risk for intermediate ages (Glezen, 1996; Simonsen et al., 1998). In contrast, the 1918 influenza pandemic led to an unusual W-shaped curve for age-specific P&I mortality (Glezen, 1996; Taubenberger and Morens, 2006). In Fig. 1, we show the age-specific P&I mortality in the United States for 1915 (typical U-curve, grey) and 1918 (W-curve, black). In 1918, there was unusually high mortality especially in individuals between 20 and 40 years of age. The rising tail of the 1918 W-curve is almost identical to the tail of the U-curves in non-pandemic years, meaning that mortality in individuals over 65 was similar to non-pandemic years and hence

that the elderly were “spared” in the 1918 pandemic (Andreasen et al., 2008; Olson et al., 2005).

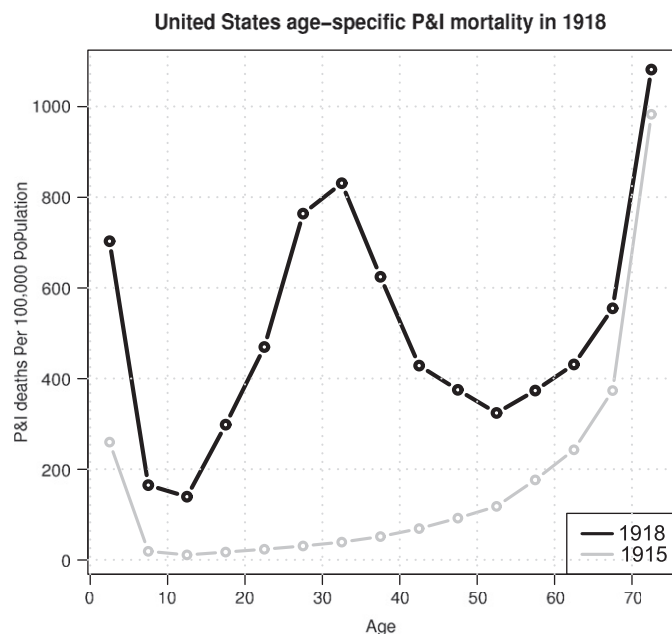
While a W-curve *per se* has not been reported for other pandemics, it has been shown that the proportion of P&I deaths occurring in persons < 65 years of age was elevated in both the 1957 and 1968 pandemics (Simonsen et al., 1998), and the majority of people who died of pneumonia during the early weeks of the 2009 pandemic of influenza A/H1N1 (pH1N1) in Mexico were under 50 (Chowell et al., 2009). The cause of elevated mortality in middle age categories during pandemics has not been clearly established (Morens and Fauci, 2007).

A relatively recent hypothesis that aims to explain P&I age-mortality relationships concerns what is known as a *cytokine storm* (Ferrara et al., 1993; Kobasa et al., 2004; Osterholm, 2005), a potentially fatal immune response caused by positive feedback between cytokines and immune cells. Healthy young people, who have the strongest immune responses to novel pathogens, may have experienced an especially high frequency of cytokine storms in response to the H1N1 influenza that caused the 1918 pandemic. The cytokine storm hypothesis has also been suggested to explain high mortality rates from SARS (Huang et al., 2005) and H5N1 “bird flu” (Szretter et al., 2007).

Much earlier, Thomas Francis, Jr. (Francis, 1953) argued that the decrease in P&I mortality in 1918 for people over 40 (evident in our Fig. 1) indicated that individuals older than 40 had some protective immunity from earlier epidemics caused by viruses

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**Fig. 1.** US P&I age-specific mortality in 1918 (black, W curve) and 1915 (grey, U curve). The age bins contain 5 year intervals up to age 70 and a single bin for ages 70 and above. The mortality data come from the published vital statistics of the United States, which include annual age-specific pneumonia and influenza (P&I) mortality throughout the 20th century (United States Bureau of the Census). We calculated age-specific rates using age-specific population estimates for 1910, found in the 1920 United States Census (United States Bureau of the Census, 1920, Table 1).

with similar antigenic properties. This hypothesis would be consistent with his observation that 1918 influenza incidence also decreased with age after 40. We refer to the idea that previous exposures to related—but currently non-circulating—influenza strains could explain pandemic age–mortality relationships, as the *antigenic history* hypothesis.

Francis (Francis et al., 1953; Francis, 1955, 1960) also framed another hypothesis, based more specifically on the very first influenza strain to which an individual is exposed. Serological studies (Davenport et al., 1953; Fazekas de StGroth and Webster, 1966) have shown that, regardless of how different a new “challenging strain” of influenza A virus is from the “first-exposure strain”, our immune system always produces the largest number of antibodies to the first-exposure strain. Francis dubbed this phenomenon *original antigenic sin*. Perhaps because this name does not clearly convey its meaning, it is often confused with antigenic history. We suggest that it may be helpful to refer to this mechanism as *antigenic imprinting*. Imprinting implies that when an antigenic shift occurs, individuals may be most strongly protected if their *first* influenza A infection was caused by a similar strain (and most weakly protected if their first-exposure strain was very different).

Both the antigenic history and antigenic imprinting hypotheses involve immunity to influenza strains that have not circulated for many years. Very long lasting immunity (and evidence of previous circulation of apparently new viral subtypes) has been demonstrated in a number of serological studies. For example, during the 1957 pandemic (which introduced the A/H2N2 influenza subtype) antibodies to H2 were discovered in sera taken before the pandemic from individuals who were over 60 in 1957 (Mulder and Masurel, 1958; Francis, 1960), and during the 1968 pandemic (which introduced A/H3N2) antibody to H3 was detected in sera from individuals over 75 who were sampled before the pandemic began (Simonsen et al., 2004).

The 2009 pH1N1 pandemic (Butler, 2009; Cohen and Enserink, 2009; Lipsitch et al., 2009) appears to provide some specific support for the antigenic imprinting hypothesis. People born before 1957, most of whom were first exposed to A/H1N1, showed proportionally lower mortality than those born after 1957 (Chowell et al., 2009). Given that descendants of the pre-1957 A/H1N1 influenza strain have been circulating since 1977 (Nakajima et al., 1978; Hayashida et al., 1985), it seems unlikely that the 2009 pH1N1 mortality pattern could have resulted primarily from antigenic history (though combined effects of antigenic history and cytokine storms could perhaps produce this pattern). In contrast, antigenic imprinting alone might be adequate to explain the observed pH1N1 pattern; almost everybody born before 1957 would have had their *first* exposure to H1N1, whereas most born since then would have had their first exposure to H2N2 or H3N2.

In modern terms, antigenic imprinting implies that mortality risk from influenza infection can be expected to be higher in individuals whose first-exposure strain has a greater antigenic distance (Smith et al., 2004) from the new strain. Population-level effects of antigenic imprinting should be most evident if we compare mortality patterns before and after influenza seasons that are distinguished by a large antigenic change, i.e., an antigenic shift or an unusually large degree of antigenic drift (Earn et al., 2002). We should see an epidemiological signature of this phenomenon in the age–mortality curve for the population as a whole.

In this paper, we examine mortality patterns since 1951 in Canada and find a strikingly unusual age–mortality relationship during the 1957 pandemic. We argue that this relationship is most easily explained as a population-level effect arising from antigenic imprinting.

## 2. Methods

### 2.1. Canadian mortality categorized by cause and influenza year

Most published mortality data are aggregated by calendar years, which mix pandemic deaths (which tend to occur at the end of a calendar year) with deaths that occurred during the previous influenza year (but the beginning of the same calendar year). To study age-specific effects of influenza, we worked with Statistics Canada to obtain the number of deaths at each age in each “influenza year” (from August to July) from their (confidential) Canadian Mortality Database (CMDDB) containing each digitized Canadian death record from 1951 to 1999, including date of death and causes of death. In the United States, individual records are available only since 1959, making it impossible to investigate the 1957 influenza pandemic.

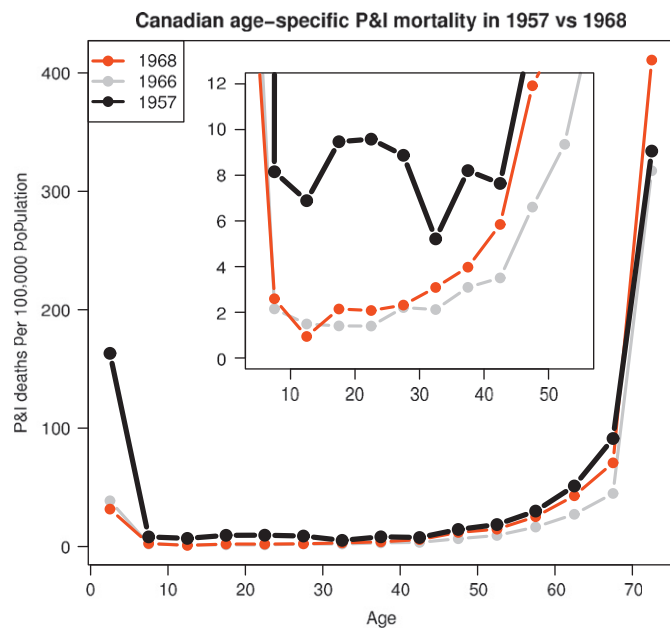
We identified P&I deaths by extracting records that list at least one of pneumonia or influenza as the underlying cause of death, i.e., records containing at least one of the International Classification of Diseases (ICD) codes in Table 1. We used only death records that listed the date of birth of the deceased, so that individuals could be unambiguously categorized both by the influenza year of birth and influenza year of death (this classifies

**Table 1**  
ICD codes used to extract influenza and pneumonia deaths.

ICD version	Years in use in Canada	Codes for pneumonia	Codes for influenza
ICD 6&7	1951–1968	490–493	480–483
ICD 8	1969–1978	480–486	470–474
ICD 9	1979–1999	480–486	487

individuals according to the first influenza year in which they could have been infected, but does not account for the complications of maternally acquired immunity or other delaying effects). Specifically, we tabulated deaths from all causes (AC) and P&I for all records with reported birth date from August 1870 to July 1970, by age, in each influenza year from 1951 to 1999.

It would be useful to have deaths aggregated at a finer time scale than a year, so that the number of pneumonia deaths not related to influenza could be estimated from the number of P&I deaths in months that influenza is not present, using baseline methods (e.g., Serfling, 1963; Thompson et al., 2003). However, we did not extract data at a finer scale for this study, because of confidentiality issues (Statistics Canada requires censoring of cells with small numbers of deaths).



**Fig. 2.** Age-specific P&I mortality rates for pandemic years, 1957 (black) and 1968 (red), and a non-pandemic year, 1966 (grey). The boxed region containing the intermediate age range is expanded in the inset, which reveals a W in 1957 (but not in 1968). Five year age bins are used for ages below 70 and a single bin is used for ages 70 and above. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

## 2.2. Age-specific P&I mortality

We calculated age-specific mortality rates for Canada (Fig. 2) using age-structured population sizes from the 1956 Canadian census (Statistics Canada, 1956) for 1957 mortality, and from the 1966 Canadian census (Statistics Canada, 1966) for 1966 and 1968 mortality.

A traditional method to impute influenza deaths from P&I deaths is to use the “excess” mortality, calculated by first estimating a “pneumonia baseline”—an estimated number of P&I deaths that would occur in the absence of an influenza epidemic. The most commonly used baseline is the Serfling baseline (Serfling, 1963), calculated by fitting a sinusoidal curve with a linear trend to P&I deaths from months without influenza epidemics (see Thompson et al., 2003). Unfortunately, we do not have access to the monthly age-stratified data that would be necessary for a Serfling analysis (or the simpler differencing method of Dushoff et al., 2006). It is also not clear if these methods would be robust to the noisiness of our fine-scale age classes. For the purpose of inter-annual comparisons, however, we believe that a straightforward proportional approach will capture much of the relevant signal, since the sinusoidal part of the Serfling baseline tends to average out on the time scale of a whole year.

Our age-specific P&I mortality measure is the fraction of deaths at age  $a$  due to P&I in year  $y$ , which we denote  $P\&I/AC_{a,y}$ , i.e.,

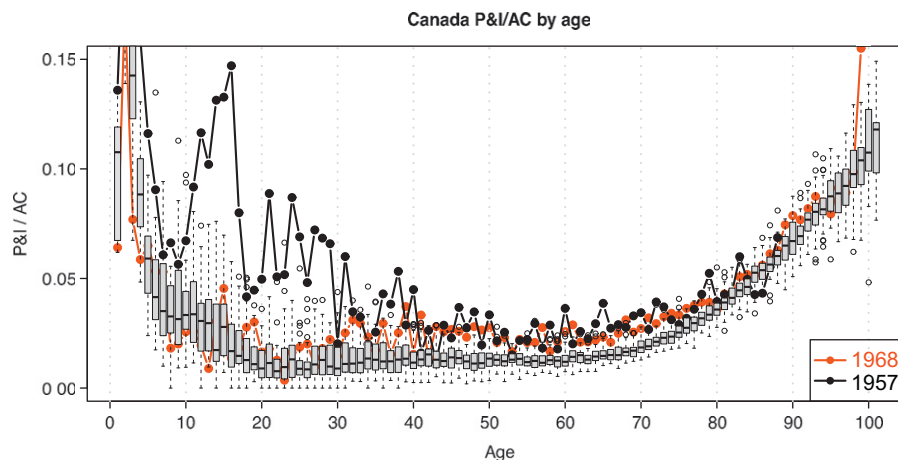
$$P\&I/AC_{a,y} = \frac{\text{number of P\&I deaths at age } a \text{ in year } y}{\text{total number of deaths at age } a \text{ in year } y}. \quad (1)$$

Thus, for example,  $P\&I/AC_{39,1957} = 0.05$  means that among 39-year-olds who died in 1957, 5% were recorded as having died from pneumonia or influenza.

## 2.3. Risk profile across age cohorts

We use a simple measure to quantify the risk of death (from P&I) associated with being age  $a$  during influenza year  $y$ . The relative risk for age  $a$  in year  $y$  is a ratio: the fraction of deaths at age  $a$  due to P&I in year  $y$  ( $P\&I/AC_{a,y}$ ) relative to that fraction in an average non-pandemic year (i.e., relative to the median of  $P\&I/AC_{a,y}$  over years 1951–1999, excluding 1957 and 1968). Thus

$$\text{Relative risk for age } a \text{ in year } y = \frac{P\&I/AC_{a,y}}{\text{Median of } P\&I/AC_{a,y} \text{ for non-pandemic years}}. \quad (2)$$



**Fig. 3.** Age distributions of Canadian P&I mortality ( $P\&I/AC$ ) for the 1957 pandemic (black), the 1968 pandemic (red), and all non-pandemic years from 1951 to 1999 (box plot). In the box plot, black horizontal lines are drawn at the medians, the grey boxes cover the inner quartiles, the error bars show the 5% and 95% quantiles, and all data points outside these quartiles are plotted with open circles. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

For example, the relative risk for age 39 in year 1957 was 4, which means that a 39-year-old person (born in 1918) was four times more likely to die from P&I in 1957 than 39-year-olds in typical non-pandemic influenza years.

### 3. Results

In Fig. 2, we show the age-specific Canadian P&I mortality for 1957 (black) and 1968 (red), and also for a typical non-pandemic year (1966, grey). Consistent with the results of Simonsen et al. (1998) who examined 20th century P&I mortality in the US, we find considerable excess P&I mortality in people under the age of 65 in both the 1957 and 1968 influenza epidemics in Canada. However, close examination (the inset of Fig. 2) indicates that the age ranges that suffered the most unusually high mortality were different in 1957 and 1968 (individuals under 40 were strongly affected in 1957—yielding a W—but not in 1968). But due to the aggregation of deaths into 5-year age bins, these curves cannot reveal any effects of antigenic imprinting on pandemic mortality.

Fig. 3 shows P&I mortality as a proportion of all-cause mortality ( $P\&I/AC$ , see Eq. (1)) for the 1957 and 1968 pandemics in Canada. The mortality data shown in this figure are aggregated only by the influenza year of death, rather than the 5-year age bins used in Fig. 2, so the age–mortality patterns are revealed in finer resolution. We compare  $P\&I/AC$  as a function of age for the 1957 pandemic (black) and the 1968 pandemic (red) with all non-pandemic years in the database (box plot of  $P\&I/AC$  for 1951–1999, excluding 1957 and 1968). We now see that the pattern of P&I mortality across age is very different in 1957 and 1968: in terms of the proportion of deaths due to P&I, 1957 was the highest year for most ages between 10 and 80, with the most dramatic elevation occurring between ages 11 and 39 (normalized P&I deaths in ages under 10 were also much higher in 1957 than in 1968, but the deviation from the typical seasonal variation is less pronounced in this age range). The 1968 mortality was in the upper quartile (and was often one of the two highest values) for almost all ages between 40 and 80, but was not consistently high for ages below 40. Neither pandemic displayed an unusual mortality pattern for ages above 80.

In Fig. 4, we examine the risk of dying—as a function of age—during an influenza pandemic, relative to the risk during non-pandemic influenza seasons (the risk profile defined by Eq. (2)). We show the age-specific relative risk of death from

P&I for 1957 and 1968 (together with box plots of relative risk for all other years for comparison). For almost all ages, the relative risk in 1957 was greater than 1, meaning that almost all age cohorts died more from P&I in 1957 than in typical non-pandemic years. Serological studies show that major antigenic changes occurred in influenza years 1918, 1928 and 1946 (HopeSimpson, 1992); ages corresponding to these birth years are highlighted in Fig. 4 with squares, circles and diamonds respectively. Compared with other age groups, people born before 1918 or after 1946 showed only moderate elevation in 1957 P&I mortality risk, with relative risk between 1 and 2 for most ages. People born in 1918 or the few years after 1918 were more likely to die from P&I in 1957 than older individuals born before 1918. A drastic increase in relative risk occurred in people born in the few years following 1928 (until 1946), who were at least five times more likely to be killed by P&I in 1957 than in typical non-pandemic years.

### 4. Discussion

The data we have analyzed show that the ages that were at greatest risk of death from P&I were different in each 20th century influenza pandemic. The most striking new result is the 1957 age-specific mortality risk (Fig. 4). How can we explain this? In particular, should we attach special significance to the changes in relative risk at ages of approximately 11, 28 and 39 years (corresponding to people born in 1946, 1928 and 1918, respectively)? We consider each of the hypotheses discussed in Section 1.

In the context of 1957, the antigenic history hypothesis is that an H2 subtype similar to the H2N2 strain that invaded in 1957 circulated before 1918, providing at least partial protective immunity to people born before 1918. This can explain increased risk for individuals below a certain age, but not increased risk for individuals above a certain age.

The cytokine storm hypothesis is that young people (perhaps older children and young adults in particular) suffered a higher death rate in 1957 than in non-pandemic years because they displayed a dangerously strong immune response when infected with the novel H2N2 influenza strain. This theory could explain elevated risk in a particular age range, but it cannot explain sharp changes in risk near ages corresponding to births during previous pandemics and severe epidemics. Moreover, P&I mortality risk for intermediate ages peaks at different age groups in 1918 (25–40;

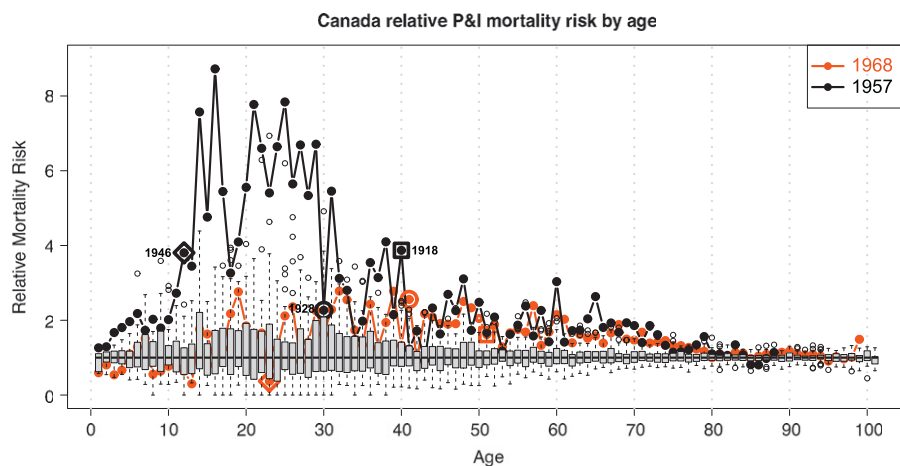


Fig. 4. Age-specific relative risk of P&I mortality in Canada in 1957 (black), 1968 (red), and all other years from 1951 to 1999 (box plot). Points corresponding to births in influenza years 1918, 1928 and 1946 (in which there were major influenza epidemics) are highlighted with squares, circles and diamonds, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 1) and 1957 (15–30; Fig. 3), suggesting that cytokine storm cannot be the only immune response relevant to influenza virulence.

Observed mortality risk depends on contact rates, the probability of infection given contact, and the probability of death given infection. To the extent that observed mortality patterns reflect age-specific patterns in contact rates, we would not expect previous exposure to be a factor. School children are believed to have generally higher contact rates (Reichert et al., 2001; Longini and Halloran, 2005; Loeb et al., 2010) and have higher infection rates during pandemics (Bansal et al., 2010; Miller et al., 2010). Age-specific infectivity would not explain high observed mortality risk in young adults, however, nor the differences in age-specific mortality risk between pandemics and seasonal epidemics.

It may be that antigenic history and cytokine storms together can explain observed pandemic mortality patterns. However, given that mortality data alone can never provide unequivocal evidence to support any specific immunological mechanism, we are inclined to use Occam's razor. We suggest that antigenic imprinting (traditionally referred to as original antigenic sin) is a more parsimonious explanation of the observed changes in age-specific P&I mortality risk in 1957. Unlike the cytokine storm theory, antigenic imprinting predicts that the largest changes in relative risk should occur at ages corresponding to major antigenic changes in influenza before the year in question. And unlike the antigenic history theory, antigenic imprinting can explain why protective changes that occur at such ages might apply over a limited age range (rather than applying to everyone born on or before a given date). The population-level signature of antigenic imprinting appears to be written on the Canadian mortality data for 1957.

What about 1968? Fig. 2 does not show a W-curve in 1968, and Fig. 4 shows no evidence for sharp changes in relative risk at any age. This lack of a clear indication of antigenic imprinting in 1968 may simply reflect generally lower virulence of the invading strain in 1968, especially among young people. Fig. 4 makes clear that P&I mortality risk was much lower in 1968 than in 1957; and in 1968, the mortality risk for people under 30 years old is no different from that in seasonal years. So sampling noise may be obscuring age-virulence effects in 1968. In principle, if we had morbidity rather than mortality data for 1968 then we might be able to detect evidence of antigenic imprinting. It is also possible that modern serological approaches, applied to samples from people born before 1955, after 1968, and in between, could unravel the importance of imprinting in determining immune responses.

The 2009 pH1N1 pandemic displayed elevated mortality among those born after 1957, indicating that antigenic imprinting may be the major cause of protection (Chowell et al., 2009). This hypothesis could be tested by comparing specific mortality rates for people born before and after H1N1 was reintroduced in 1977; at least some of those born after 1977 will have had H1N1 as their first influenza infection, so this group should be protected relative to the group born before 1977. The reported pattern of deaths from severe pneumonia during the first 5 weeks of the pH1N1 epidemic in Mexico (see Fig. 3 in Chowell et al., 2009) did not appear to indicate higher risk for individuals born between 1957 and 1977. However, the (fortunately) low mortality rate from pH1N1 in 2009 implies that pH1N1 mortality data are very noisy and of limited use for the types of inferences that we have attempted to draw here. If individual-level hospitalization data become available for the 2009 pandemic, it would be enlightening to examine those data through the lens of our approach in this paper. Our mortality risk formula (2) can also be adapted for analysis of serological studies (Miller et al., 2010; McVernon et al., 2009) in order to estimate detailed patterns of age-specific attack

rates. However, serological studies are usually strongly limited by sample size, potentially making them even more sensitive to demographic noise.

Our results suggest that, at the introduction of a novel influenza strain that can cause severe illness and/or high case fatality, antigenic imprinting may be an important factor in age-specific mortality risk. It is likely that similar patterns would hold for morbidity risk. Pandemic planners can prospectively categorize ranges of birth years as falling into different original antigenic classes (defined by the most recent major influenza epidemic before a given birth year), to maximize the chance that potentially important effects of antigenic imprinting will be detected.

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