CRACKING THE MYSTERY OF HIGH YOUNG ADULT MORTALITY DURING THE 1918 FLU PANDEMIC

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Young adults are not usually very susceptible to death from influenza. This is the reason why they are not typically the primary focus of seasonal flu vaccinations campaigns. Yet, along with the very young and the very old, adults aged 20 to 40 were the hardest hit by the infamous H1N1 virus during the 1918 Spanish flu pandemic. The resulting 'W-shaped' mortality curve is arguably the foremost characteristics of this pandemic, and remains to this day an unsolved mystery. However, easily accessible data, such as mortality tables by single year of age (the number of deaths at age 1, 2, 3, 4, etc.), may help researchers understand the unusual impact of the 1918 pandemic on young adults. Such single year data helps us realize that individuals with the highest risk were likely exposed at a very young age to an earlier pandemic influenza virus. Would exposure to pandemic influenza very early in life increase the risks of death from a subsequent influenza pandemic? Mortality rates by year of birth during more recent outbreaks, such as during the 2009 swine flu influenza pandemic, also appear to support this possibility. To find out how this relationship between two influenza pandemic viruses works, let us go back one hundred years.

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In the aftermath of the Spanish flu pandemic, the US Department of Commerce published "Special tables of mortality from influenza and pneumonia" for September to December 1918[1]. According to this report, in Philadelphia, one of the hardest hit cities in the US, "[...] the highest rate [per 100,000], 5,383 for females, was for those 1 year of age, and the next highest, 4,660, was for those aged 28." Although Canadian sanitary authorities were quite aware of the unusually high susceptibility of young adults, no single year age mortality tables were tabulated for Canada, nor, to our knowledge, for any other place in the world. But there was, at least for women in Philadelphia, a tantalizing peak of influenza mortality at the precise age of 28. The people who died at age 28 from Spanish Flu were born around 1890 (1918 – 28 years) -- when another great influenza pandemic, the "Russian flu," raged throughout the world, in the closing months of 1889 and the early months of 1890.

This intriguing coincidence suggests that exposure to an influenza virus early in life may increase the risk of death upon re-exposure to another influenza virus later in life. Such a conjecture, however, would have sounded silly to any knowledgeable investigator in 1918. The idea simply made no sense because the principle of "acquired immunity" was well understood. The beneficial effects of previous exposure to a pathogen through inoculation and vaccination, which conferred immunity, had been well understood since Edward Jenner invented his smallpox vaccine in 1796.

Hence, physicians naturally would have expected that a previous exposure to influenza in 1890

1 Davis, W. H. & Mitchell, J. B. Special tables of mortality from influenza and pneumonia: Indiana, Kansas, and Philadelphia, Pa. September 1 to December 31, 1918, Department of Commerce, U.S. Bureau of Census. (Govt. print. off., 1920).

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should have helped survival during the 1918 pandemic, not increased mortality. In France, for example, a doctor at the Académie Médicale wrote on October 1, 1919: "[...] people from a certain age were spared, which seems to indicate that exposure [to influenza] in 1889-1890 conferred a sensible immunity" (our translation from "[...] les personnes d'un certain âge ont été respectées, ce qui semble indiquer que le fait d'avoir été atteint en 1889-1890 a conféré une immunité sensible")[2]. This is the fundamental principle of acquired immunity, and it is still largely understood that previous exposures to a virus should help ward off a new infection from the same virus, just as it does for measles or smallpox.

As the years went by, single year mortality data on influenza, such as those tabulated in the US for the 1918 pandemic, were replaced with tabulations using 5-year, 10-year or even larger age groups (as an example, instead of being considered separately, ages 25, 26, 27, 28, and 29 can be lumped into the "25-29 age group"). Most of what we know about the foremost characteristic of the 1918 influenza pandemic – its well-known W-shaped mortality signature – comes from such tabulations. Even today, surveillance programs such as Canada's FluWatch[3] usually report data on influenza cases or hospitalisations using large-bin age categories (eg., 0-4; 5-14; 15-39; 40-64, 64+). This emphasis on lumping single year ages together into large age groups has resulted in an unfortunate loss of precision and insight. In our opinion, this approach would be analogous to biologists today trading their modern electron microscopes for Antonie van Leeuwenhoek's late 17th century single-lens model!

There is a strong argument to be made for studying influenza mortality using single-year age data instead of age groups. Figure 1 shows estimates of mortality rates by single years of birth for the city of Toronto (red) and the Catholic population in Montreal (blue) during the month of October 1918, at the height of the Spanish flu pandemic. The data used to prepare this figure were collected in censuses as well as in civil and parish registers by a group of students and researchers at the University of Montreal, and McMaster and Western Universities.[4] The familiar W-shaped mortality pattern reported by all previous inquiries is obvious when looking at the smoothed lines passing through the dots for each city. But this figure brings a critical observation: there is a peak at the age of 28 for both cities. Although there are exceptions, this finding has been replicated in various other locations, including New York, New Zealand, and Sweden. Our research group is currently using data from the Human Mortality Database[5] to show this peak in a number of countries in Europe (see also [6,7]).

2 Morel, P. & Quétel, C. La grippe 'espagnole' de 1918 à Caen et son impact au Bon-Sauveur. Ann. Normandie **27,** 205–217 (1977).

3 FluWatch website: https://www.canada.ca/en/public-health/services/diseases/flu-influenza/influenza-surveillance.html.

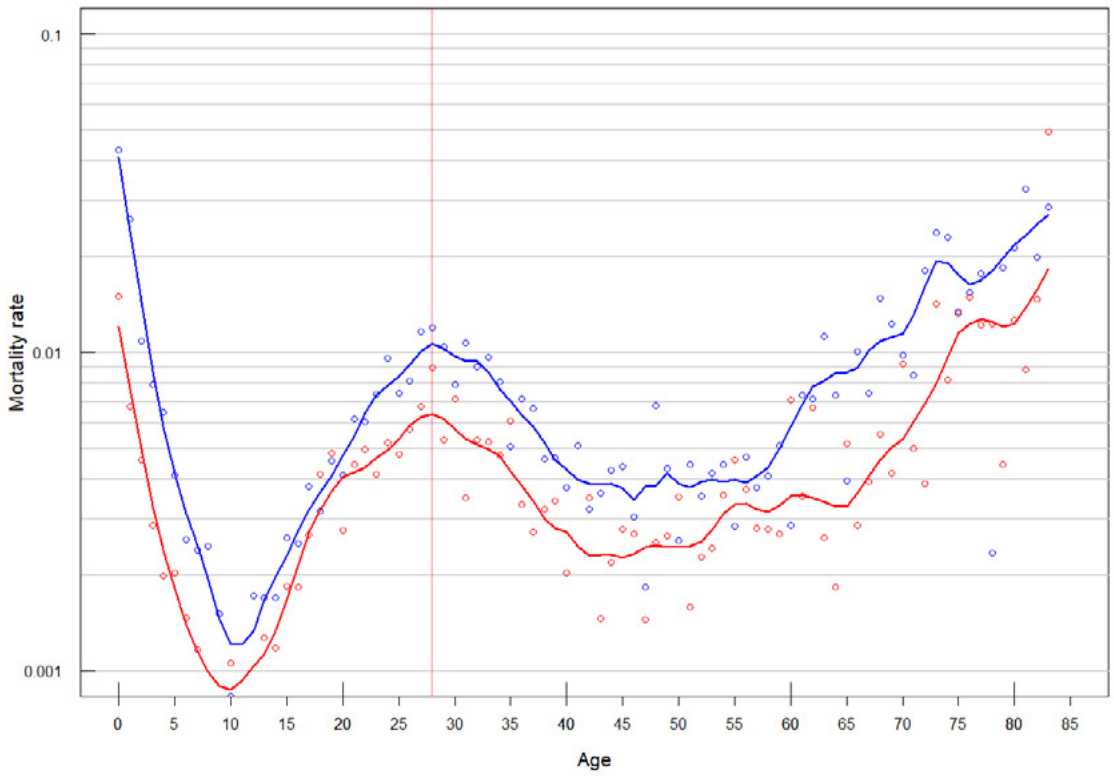
4 Hallman, S. The Demographic Links Between the 1890 and 1918 Influenza Pandemics in Ontario. Electron. Thesis Diss. Repos. (2015).

5 Human Mortality Database. University of California, Berkeley (USA), and Max Planck Institute for Demographic Research (Germany). Available at www.mortality.org or www.humanmortality.de.

6 Oeppen, J. & Wilson, C. Epidemiological evidence for viral exposure in childhood as a risk-factor in subsequent influenza pandemics. Population Association of America, Los Angeles, March 30-April 1 2006. in (2006).

7 Gagnon, A. et al. Age-Specific Mortality During the 1918 Influenza Pandemic: Unravelling the Mystery of High Young Adult Mortality.

Figure 1. Rates of mortality by age in Montreal (blue) and Toronto (red) during the month of October 1918



Why this increased risk for young adults? Pioneering work by early investigators provides useful insights into the answers to this question. In the 1950s, a group of immunologists led by Thomas Francis Jr. put forward the doctrine of "original antigenic sin" (OAS)[8]. According to this idea, your first influenza infection conditions your immune reaction to the virus for the rest of your life. They arrived at this conclusion based on their analysis of serum samples from field studies of people with influenza infections. Their studies revealed a surprising finding: the serum samples showed that the people in the study had minimal immunological responses against the current viral strain but, instead, a response directed towards a strain *they had previously encountered as children*. In fact, the doctrine of OAS was called upon to explain another distinctive feature of the Spanish flu pandemic. Although the elderly were at high risk of death in 1918 (as clearly seen in Figure 1), their risk was nevertheless lower relative to previous years' seasonal outbreaks. Referring to the OAS doctrine, many investigators thus speculated that older individuals were partly spared during the

PLoS ONE 8, e69586 (2013).

8 Francis, T., Jr. On the Doctrine of Original Antigenic Sin. Proc. Am. Philos. Soc. **104,** 572–578 (1960).

1918 H1N1 influenza pandemic because they gained protection as children from an exposure to an H1-like virus, which would have circulated in the decades that preceded the Russian flu outbreak of 1889-1890. This would make a lot of sense: early life exposure to a specific strain of the influenza virus would condition the immune system to respond to that specific strain or to a similar one. But what if the strains are widely different?

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Let us return to the relationship between the 1918 Spanish flu and 1889-90 Russian influenza pandemic. Recall that the peak in influenza mortality at age 28 meant that these people were born in 1890. As it turns out, people born around 1890 were likely first infected with a strain of pandemic influenza that researchers believe was H3N8[9]. This strain is very different from the H1N1 virus, known to be responsible for the 1918 influenza pandemic. According to OAS, the immune systems of those people were "primed" to respond to a very different virus (H3N8) early in their lives. Consequently, when, later in life, they encountered the infamous H1N1 strain in 1918, they mounted an inadequate immune reaction.

This observation helps making sense of the apparent lack of acquired immunity to influenza for young adults in 1918 that we noted above. In general, acquired immunity does not work so well with the influenza virus because it is constantly mutating through a process that experts call "antigenic drift," and this is basically why you need a new vaccine to gain protection every year. At times, however, the virus gains new DNA segments from its animal "reservoirs" such as pigs or waterfowl birds, and invades its hosts, who have no to little immunity to it, and quickly spreads around the globe. This process, which is called "antigenic shift," leads to pandemics and brings about a virus to which those born during the previous pandemic respond inadequately; they would have a "built-in" susceptibility, preventing their immune system to mount an adequate defense.

The precise immunological mechanism behind this inadequate immune response is largely unknown. Yet evidence is rapidly accumulating that the phenomenon may not be unique to the 1918 pandemic. As recently demonstrated by our research group, people born at the time of the 1957 H2N2 "Asian flu" pandemic had excess mortality (in comparison with usual seasonal flu outbreaks) in both the US and Mexico during the 2009 H1N1 "swine flu" pandemic, caused by a close relative – indeed a descendant – of the 1918 H1N1 virus[10]. Similarly, people born around 1918, thus aged about 50 years in 1968, had the highest excess mortality during the Hong Kong flu pandemic that year, caused by H3N2, still in circulation[11].

9 Worobey, M., Han, G.-Z. & Rambaut, A. Genesis and pathogenesis of the 1918 pandemic H1N1 influenza A virus. Proc. Natl. Acad. Sci. 201324197 (2014). doi:10.1073/pnas.1324197111

10 Gagnon, A. et al. Pandemic Paradox: Early Life H2N2 Pandemic Influenza Infection Enhanced Susceptibility to Death during the 2009 H1N1 Pandemic. mBio **9,** e02091-17 (2018).

11 Gagnon, A., Acosta, J. E., Madrenas, J. & Miller, M. S. Is Antigenic Sin Always "Original?" Re-examining the Evidence Regarding Circulation of a Human H1 Influenza Virus Immediately Prior to the 1918 Spanish Flu. PLoS Pathog **11,** e1004615 (2015).

In addition to helping to crack the mystery of the W-shaped curve of mortality during the 1918 influenza pandemic, these studies of influenza mortality by single age – rather than by large age groupings– are highly relevant for risk assessment and immunization campaigns in contemporary public health. They provide key information for medical authorities setting priorities for treating infected patients and may help to convince people of specific ages to seek vaccination based on their early life influenza signature.