Age-specific incidence of influenza A responds to change in virus subtype dominance

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Abstract

When H3N2 replaced H1N1 as the dominant influenza subtype during the 2018-19 season, the pattern of age-specific influenza incidence shifted due to the lingering effects of antigenic imprinting. The characteristic shape that imprinting leaves on influenza susceptibility could foster important advances in understanding and predicting the epidemiology of influenza.

Keywords

Influenza incidence; antigenic imprinting; cohort effect; age-specific analysis

Text

In a recent paper[1], we used on incidence of influenza in Quebec (Canada) to show that the elderly had a relatively low incidence of influenza during recent seasons dominated by the H1N1 subtype, most likely because they gained protection from repeated early life exposure to the H1N1 viruses that circulated from 1918 to 1956. We also speculated that priming to the H3N2 subtype for those born at the time of the 1968 "Hong Kong Flu" pandemic and before the return of H1N1 in 1977 could explain the "dip" in influenza incidence for those aged 40-49 during the 2016-17 and 2017-18 seasons, dominated by the H3N2 subtype.

These results were recently corroborated by three studies. A group from the CDC reported lower rates of incidence, hospitalisations, and mortality for the elderly during seasons dominated by the H1N1 in comparison with seasons dominated by H3N2 in the US. The 1968-81 cohorts also had lower hospitalisation rates during recent seasons dominated by H3N2, relative to seasons dominated by H1N1 [2]. Researchers from the University of Chicago reported a reduction in medically-attended infection risk to a specific influenza subtype for those whose primary infection was caused by that same subtype [3]. A third study, also addressing the epidemiology of seasonal influenza, additionally provided evidence that imprinting acts through protection to specific HA or NA subtypes [4], thereby adding to a series of recent empirical studies highlighting the role of antigenic imprinting in the epidemiology of influenza virus [5–10].

According to the antigenic imprinting hypothesis, one's first influenza virus infection conditions the immune system for life, as memory cells primed to the responsible virus are hierarchically locked in the first position in the immune repertoire, and expand as a result of back-boosting during subsequent influenza seasons [11]. Here, we provide further evidence for this phenomenon, which results in characteristic cohort effects that can be observed in any age-

specific data reporting influenza incidence, provided that these data have not been lumped into large age groups [1].

We used the sentinel data from the Institut national de santé publique du Québec (INSPQ), which reports weekly numbers of positive tests samples for influenza A and B cases by age group (0; 1-4; 5-9; 10-14; 15-19; 20-29; 30-39; 40-49; 50-59; 60-69; 70-79; 80-89; and 90+) [12]. To estimate weekly rates of influenza A incidence by age group, the total numbers of cases for each period under observation were divided by the total population size for that age group in Quebec and by the number of weeks covered (shortened to "incidence" hereafter; see Figure 1, Panel A). Although this is an underestimation of overall incidence (because the sentinel network does not cover the entire Quebec population), these estimates faithfully reproduce the age-specific trend of incidence by subtype.

In what can be described as a natural experiment, influenza virus subtype dominance completely shifted during the winter of 2019 in Canada, as H3N2 viruses progressively replaced H1N1, the dominant subtype for the first portion of the season. In January, FluWatch Canada reported that the majority of influenza A viruses were A(H1N1)pdm09 [13]. Yet, by the end of February: "Detections of influenza A(H3N2) have been steadily increasing since mid-January and accounted for 58% of subtyped influenza A detections this week"[13]. This proportion has then steadily increased to about 80-90% at the end of March, and remained at that level for the whole month of April (see Figure 1, Panel B). It is important to note that FluWatch reports do not contain information on subtype from influenza viruses isolated in Quebec. Yet, we show here that the progressive shift in subtype dominance can actually be captured by a close examination of the distribution of influenza A cases by age in the province, even without data on subtype dominance.

Figure 1 about here

It is clear from Figure 1 that age-specific incidence is patterned by subtype dominance. As reported previously [1–4], younger individuals generally demonstrate increased susceptibility to H1N1 relative to H3N2, while H3N2 disproportionally targets older individuals. The most striking feature of Figure 1A, however, is the notable change in the shape of age-specific incidence as H3N2 progressively replaced H1N1 during the 2018-19 season.

In December 2018, H1N1 was by far the most frequent influenza A virus subtyped in Canada (Figure 1, Panel B) and, correspondingly, the slope depicting the increase of influenza A incidence with age is not very steep during that period (Figure 1, panel A, solid blue line). However, as the fraction of H3N2 infections increased, so did the slope. At the same time, the trough for the 40-49 years age group, noted earlier for the 2017-18 season[1] and visible in Figure 1 (red dotted line), suddenly appeared (blue dashed line), and deepened late in the influenza season (blue dotted line). Based on a test of comparison of proportions, incidence rates of individuals aged 40-49 were found significantly different from that of their younger or older counterparts aged 30-39 or 50-59, with $P<0.001$ and $P<0.02$, respectively. The corresponding figures for the 2017-18 season were, respectively, $P<0.02$ and $P<0.001$.

By April 2019, overall influenza incidence had appreciably decreased, while the proportion of H3N2 – relative to H1NI – viruses detected by the Canadian sentinel programs had increased to about 80-90%. This pattern was similar to the 2017-2018 pattern, when H3N2 was also dominant. Note how the two dotted lines are nearly linear and parallel after age 60, demonstrating that the rate of increase of incidence with age is constant for H3N2, regardless of overall incidence. Data from previous influenza seasons reproduce these results with striking similarity in Supplementary Figure S1. A trough for the 40-49 age group is observable during

the H3N2-dominated 2016-17 season, whereas the increase of incidence with age is flatter during the 2015-16 season, as would be expected given H1N1 subtype dominance. When both subtypes co-circulate without either being overtly dominant, as was the case between Jan 12th and March 23th, 2019 (dashed blue line in Fig.1), the rate of increase lies in-between the two extremes. Note, however, that the slope increases after age 75 during periods of co-circulation, reflecting the increased proportion of H3N2 infections among the elderly.

Concluding remarks

The 2018-19 influenza season provided a unique opportunity to observe the effects of imprinting on age-specific incidence in a season wherein there was a late shift in the dominant subtype of influenza A virus that circulated. As H3N2 replaced H1H1, the drop in incidence for the 40-49 years age group noted during the previous 2017-18 season reappeared, while the incidence for older individuals rose markedly with age. These results are consistent with the antigenic imprinting hypothesis: during the 2017-18 and 2018-19 seasons, individuals aged 40-49 years were born in 1968-78 and in 1969-79, respectively, and were thus most likely imprinted by H3N2 (the probability is about 85-90% for those aged 40-49 in 2017-18 according to [3]). Alternatively, the pattern depicted in Figure 1A could signal an "age-effect" for the 20-49 years old, rather than a trough for the 40-49 years old due to a "cohort effect," as proposed here. The "hump" could arise due to increased susceptibility for parents who have young children [14]. The H3N2/H1N1 ratios presented in Figure S2, which neutralize such an age effect [1], support a protective role for imprinting. We also feel that this effect is unlikely to be caused by heterosubtypic interference (whereby individuals first infected with a subtype would gain cross protection to the other), since incidence by age remains relatively constant from

week-to-week even in seasons when no change in subtype is observed. Given the relatively low vaccination rates in Quebec (relative to the US, for example), it is also unlikely that age-specific differences in vaccination coverage could explain the shift observed.

The consistency of the slope marking an exponential increase of incidence with age is remarkable, and has not yet been reported to our knowledge. Immuno-senescence, for instance, may exponentially increase with age, while other factors affecting the spreading of the virus and the infection rates across all age groups would mainly shift the overall level up or down, as a scale parameter. A steeper slope, on the other hand, could indicate a larger fraction of H3N2 relative to H1N1, and vice-versa. In turn, this framework could eventually be used to help predict the most at-risk populations, based on circulating influenza A virus subtypes.

Finally, careful scrutiny of influenza A incidence by age could represent an invaluable tool to detect the occurrence of an antigenic shift, practically in "real-time," without relying upon genetic or immunological analyses. Existing databases could be updated daily with information on age as patients seek medical assistance, or simply report flu-like symptoms. Surveillance projects involving public participation through anonymous report of symptoms on the Internet already exists and could integrate single age data into their platform, while maintaining high standards of confidentiality. Taken together, the natural experiment that occurred as a result of the shift in dominant influenza A subtype during the 2018-19 influenza season demonstrates the predictive power of age-specific analyses under the framework of antigenic imprinting.

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Conflicts of interest

M.M. reports advisory board member fees from Sequaris and Medicago, outside the submitted work. All other authors have no potential conflicts.

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Figure caption

Figure 1. Weekly rate of incidence of influenza by age in Quebec as a function of subtype dominance. Panel A shows estimates of incidence of influenza A by age group in Quebec during the peak of the 2017-2018 influenza season (in red), along with the corresponding rates for three distinct stretches of the 2018-19 season (in blue), chosen to capture the progressive shift in dominance that occurred during that season. Although originally distributed in discrete age categories, the rates were placed in a line graph in the middle of the age-group intervals (e.g., age 25 for the 20-29 years age group), and were joined by linear interpolation. The rate for the open-ended age group (90+) was placed at age 92, (an estimate of the average age of cases in this age group). To facilitate interpretation, a solid line is used when H1N1 was the dominant subtype, a dotted line when H3N2 was the dominant subtype, and a dashed line to represent an intermediary situation. The two grey arrows point to reduced susceptibility in the 40-49 age group. The two shaded diagonals indicate that the rate of increase of incidence with age is nearly constant after age 65 when H3N2 dominates (see text). Since the proportions of positive tests by specific subtype (H3, H1,...) for influenza A were not available for Quebec, we used data from the national FluWatch sentinel program, which reports the numbers of positive tests by subtype for other provinces in Canada, to derive subtype dominance statuses by week (**panel B**).