Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Commentary

Reporting and evaluating influenza virus surveillance data: An argument for incidence by single year of age

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1. Main text

The observation that past exposures to influenza virus shape the outcome of subsequent exposures has been recognized since the 1950s – when Thomas Francis Jr. described the concept of "original antigenic sin" [1], according to which the immune system preferentially boosts the response to the first strain of influenza virus against which an individual was infected upon later encounters with antigenically-related strains. Since that time, the concept has been met with varying degrees of support and skepticism [2]. However, in recent years strong evidence has accumulated that the year of birth conditions one's risk of severe influenza infection later in life [3–8]. This concept is becoming so well-established, that it is now recognized even within the realm of popular science.

Indeed, the magazine *New Scientist* dedicated an article to pandemic influenza in their first issue of 2018, writing: "Our strongest immunity is to the first kind of flu we caught. Between 1918 and 1968, no H3N2 viruses circulated as winter flu, so people born before 1968 would have a weaker immunity to it" [9]. This clearly points to a "cohort effect" for people born during specific years. Yet, most sentinel programs and agencies that track seasonal influenza circulation report data in a way that depicts risk exclusively as the result of an "age effect." The U.S. Centers for Disease Control and Prevention (CDC), for example, usually report data based on large-bin age categories (e.g., 0–4; 5–14; 15–39; 40–64, 64+), which fail to account for differences in exposures from one cohort to another based on year of birth. This same propensity often extends to scientific studies of particular cohorts. As the next vaccination campaigns are being planned, it is useful to step back, reflect, and perhaps question the "status quo" for reporting influenza virus infection and surveillance data.

Currently, the ability to observe cohort effects that result from priming to a particular strain or subtype based on current reporting relies almost entirely on serendipity. This may have been the case, for instance, during this past 2017–2018 influenza season, at least based on virus circulation data in 5-year or 10-year age groups made available by the sentinel program of the *Institut national de santé publique du Québec* (INSPQ) [10]. By browsing the distribution of confirmed cases broken down by age, we noted that people aged 40 to 49 at the time of writing this paper (Summer 2018) were born between 1968 and 1977 (i.e., between the emergence of the H3N2 virus and the return of H1N1).

Interestingly, as shown in Fig. 1, these cohorts seemed to have lower rates of influenza A cases than the surrounding cohorts born just before (between 1958 and 1967 - the 50–59 year olds), or just after (i.e., between 1978 and 1987 - the 30–39 years olds). Since H3N2 dominated the 2017–2018 influenza A season in Quebec, as it did elsewhere in North America, a tempting interpretation would be that, having been primed to H3N2 between 1968 and 1977, these cohorts benefited from better protection against the circulating strain of that virus during this past season. However, before speculating on the eventual presence of such "cohort effect," it would be necessary to establish first whether there are "inflection points" in incidence levels for these specific years of birth, and this would require much higher resolution data (i.e., single year data). Alternatively, the data reported in Fig. 1 could just as easily support the alternative interpretation that it is instead the young adults born between 1978 and 1997 (aged 20–39) that have an increased influenza A risk relative to those born before or after, as highlighted by the comparison with influenza B rates, also reported in Fig. 1.

Supposing that young adults aged 20–39 truly had an increased influenza A risk this past season, whether this "hump" results from an age effect or a cohort effect is still unclear. For instance, age effects on incidence rates are expected to occur as a result of varying densities of social contacts by age [11], or through differential immune susceptibility, consistent with the "honeymoon period hypothesis [12]." Were the data to be reported by single years, however, it would be much easier to differentiate between age and cohort effects. Cohort effects will create specific risk profiles to individuals born during a specific year (i.e., when a new strain appears through antigenic shift or drift), while age effects are expected to affect incidence rates in a more diffuse manner, affecting whole age groups without anticipated peaks or troughs at specific ages [13].

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https://doi.org/10.1016/j.vaccine.2018.08.077
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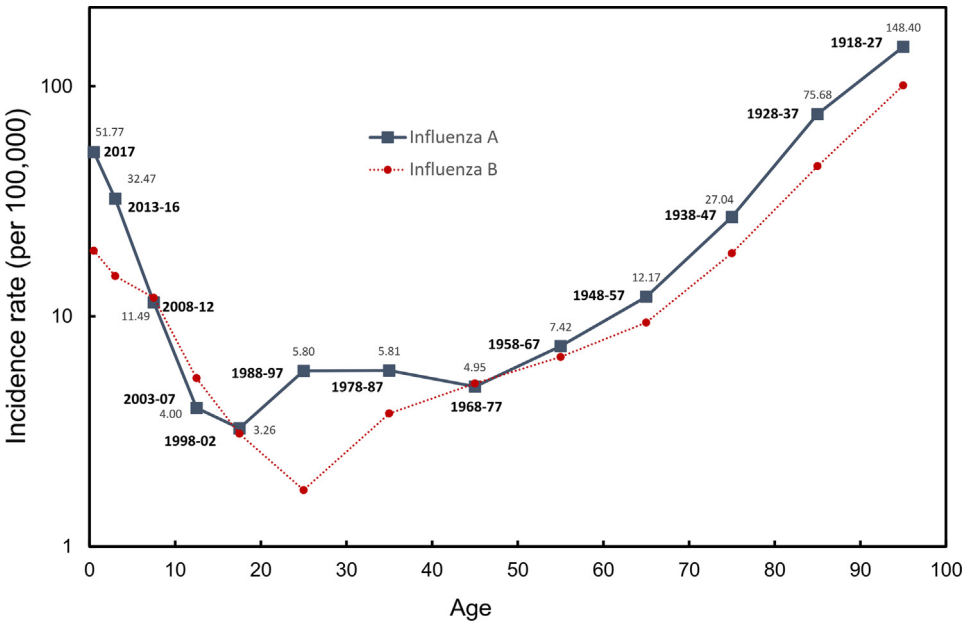

Fig. 1. Rate of incidence of influenza by age in Quebec, 2018. Data were extracted from the weekly reports of December 30 to February 10 from the INSPQ sentinel program, which provides numbers of positive test samples for influenza A and influenza B at age 0 and by 5-year age groups from ages 1 to 19 and then by 10-year age groups for older ages. Approximate birth cohorts are reported in bold along the square marks depicting rates of incidence by age group, which were estimated by dividing the number of positive tests for influenza A by the population size of that age group. As the subtypes (H3, H1. . .) for influenza A are not available, we assume that influenza A samples were all of the H3N2 subtype, the dominant strain in Quebec this year.

One alternative way of appreciating the possible role of imprinting early in life is to establish ratios of incidence by age from influenza seasons dominated by different influenza A strains, such as "H3/H1 ratios." Since similar age effects are to be expected irrespective of the strain of influenza A virus that is circulating during specific seasons, variations in these ratios across age groups can be interpreted as originating from strain-specific cohort effects, rather than age effects. Fig. 2 reports H3/H1 ratios of tested cases

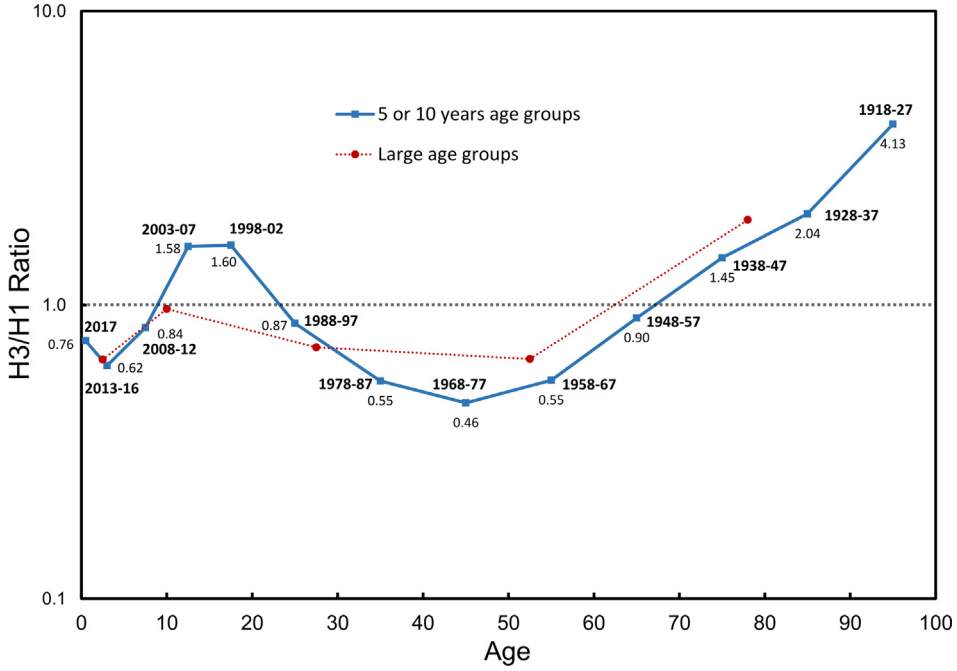

Fig. 2. Ratios of H3 to H1 incidence rates of influenza by age in Quebec during recent epidemic seasons (2015–18). Data were extracted from the INSPQ sentinel weekly reports. Rates of incidence by age group were estimated by dividing the number of positive tests for influenza A by the population size of that age group. H1N1 was the dominant subtype during the 2015–16 epidemic season whereas H3N2 was dominant during both the 2016–17 and 2017–18 seasons. For each season, we selected the three to four weeks for which overall influenza intensity was at its peek; choosing different weeks affects levels of ratios, but not the general pattern, with a trough for the 1968–77 generations (plain blue line, squares). Approximate birth cohorts are reported in bold along the square marks depicting H3/H1 ratios based on the INSPQ's age grouping. Larger age groups used to plot the red dotted line are: 0–4; 5–14; 15–39; 40–69; and 70 + years (red dotted line, circles). In both cases, we plotted the ratios at the midpoint value of the interval (e.g., 2.5 years for the 0–4 age group, 25 years for the 20–29 age group, and so on), except for the open-ended age intervals, for which we used the average age of cases in those intervals, i.e., 92 years and 78 years respectively.

Please cite this article in press as: Gagnon A et al. Reporting and evaluating influenza virus surveillance data: An argument for incidence by single year of age. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.08.077