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Original Article

Disproportional effects in populations of concern for pandemic influenza: insights from seasonal epidemics in Wisconsin, 1967–2004

Eric T. Lofgren,[a] Julia B. Wenger,[b] Nina H. Fefferman,[c,d] David Bina,[e] Steve Gradus,[e] Sanjib Bhattacharyya,[e] Yuri N. Naumov,[f] Jack Gorski,[g] Elena N. Naumova[b]

[a]UNC Gillings School of Global Public Health, Department of Epidemiology, Chapel Hill, NC, USA. [b]Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, MA, USA. [c]Department of Ecology, Evolution, and Natural Resources, Rutgers University, New Brunswick, NJ, USA. [d]Center for Discrete Mathematics and Theoretical Computer Science (DIMACS), Rutgers University, Piscataway, NJ, USA. [e]City of Milwaukee Health Department, Milwaukee, WI, USA. [f]Department of Pathology, University of Massachusetts Medical School, Worcester, MA, USA. [g]Blood Research Institute, BloodCenter of Wisconsin, Milwaukee, WI, USA.
Correspondence: Elena N. Naumova, PhD, Professor, Tufts University School of Medicine, Department of Public Health and Community Medicine, 136 Harrison Avenue, Boston, MA 02111, USA. E-mail: elena.naumova@tufts.edu

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Background Influenza infections pose a serious burden of illness in the United States. We explored age, influenza strains, and seasonal epidemic curves in relation to influenza-associated mortality.

Methods The state of Wisconsin death records for the years 1967–2004 were analyzed for three distinct populations: children, general population, and elderly. Yearly parameters of duration, intensity, and peak timing were obtained from Annual Harmonic Regression coefficients.

Results Overall, elderly had the highest rate and intensity of influenza mortality. The children and infant subpopulations showed an earlier and wider range in duration of peak timing than elderly. During A/Hong Kong/1/68 pandemic years, the elderly subpopulation showed no change in mortality rates while a sharp increase was observed for the children and infant subpopulations. In epidemic years such as 1966–1969, children and infants showed a dramatic decrease in the severity of influenza outbreaks over time. The elderly had increased baseline mortality in years (1986–1987) where predominant strain was characterized as A/Singapore/6/86.

Conclusions Our findings indicate that the younger populations may have benefited from the lack of a major shift in viral strains for a number of decades. Furthermore, we demonstrate considerable heterogeneity in the spread of seasonal influenza across age categories, with implications both for the modeling of influenza seasonality, risk assessment, and effective distribution and timing of vaccine and prophylactic interventions.

Keywords Children, elderly, epidemic, influenza, seasonality.

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Background

Viral respiratory infections such as influenza pose a serious burden of illness annually in the United States.[1] Many factors including age group variability, population dynamics, timing of vaccination, and public health interventions have been shown to affect influenza-related mortality. Our research explores the role of age, circulating influenza strains, genetic evolution, and the seasonal epidemic curve in relation to influenza-associated mortality.

Although influenza viruses can cause disease at any age, the very young and very old have traditionally experienced more severe disease; influenza mortality is highest among those aged 65 and older as well as children younger than 2 years of age.[2–4] Current World Health Organization (WHO) vaccine recommendations for all children and young adults from age 6 months to 18 years, and persons over the age of 50 reflect the uneven distribution of influenza-related disease in the general population.[5] While periods of epidemic seasonal influenza follow this traditional age pattern, during periods of pandemic influenza, such as in 1918, 1957, 1968, and currently in 2009, those under the age of 65 experienced the highest rate of excess deaths because of influenza-associated disease, therefore "disproportionately" affecting the young.[6] Indeed, several of the pandemic years, while causing comparatively major increases in intensity in the child and general populations, were relatively mild for the elderly population. This variability has been linked to differences in transmissibility and virulence of influenza circulating strains as well as previous

exposure to antigenically similar strains.[6] This pattern is being mirrored in the current pandemic (H1N1) 2009. It therefore continues to be of obvious importance to understand the different risks to specific demographic groups from ever-shifting strains of influenza and the critical differences in epidemiologic behavior of pandemic versus seasonal outbreaks.

While the association between influenza circulating strains and differing mortality rates among age subpopulations has been explored, the role of viral evolution from antigenic drift on seasonal, non-pandemic influenza has been less frequently studied. What is currently known is that influenza-related mortality is highest in seasons where H3N2 influenza A viruses predominate in comparison with H1N1 influenza A or B viruses.[7,8] In temperate climates, seasonality plays a role in the intensity of various influenza seasons. Seasonality refers to the cyclic appearance of events over a period of time. Influenza seasonality is characterized by a seasonal peak, amplitude, and duration as defined by the shape of the seasonal curve. These seasonal patterns vary annually among different subpopulations because of diverse circulating strains and various environmental factors.[9,10]

The current study aims to examine the effects of specific strains and their evolution during seasonal epidemics in relation to modeling of mortality rates among various age categories. These questions are typically well studied in the elderly, but it is possible that subtle but important infection dynamics in other demographic categories are missed because of the dominant effect of the elderly immune status in seasonal mortality. As these other categories are of growing concern, but their sensitivity to influenza's natural seasonal infection cycle is less well understood, we present analysis across a wide range of demographics. This approach allows us to explore questions where a focus on a particular demographic group would yield an incomplete picture.

We parameterized influenza seasonality based on 37 years of mortality records using the δ-method which has been validated on a number of infections with well-pronounced seasonal structures.[11,12] Comparison of seasonal curves of influenza-related mortality between age groups with respect to predominant circulating strain provides insight into the complex phenomenon of temporal oscillations in the clinical diagnosis of influenza and associated fatality.

Methods

Population and mortality data

The analyzed data consisted of 51 536 de-identified death records from 1967 to 2004 in Wisconsin, USA provided by the Wisconsin Department of Health Services. Records were considered if they included influenza, pneumonia or influenza-like illness as a primary or underlying cause of death (ICD-10 codes J10, J11, J12.9, J15, and J18 or equivalent codes in earlier classification systems). The deaths were categorized as part of three distinct population subgroups, children (0–5 years of age), general population (6–64 years of age), and elderly (65 years of age and older) and abstracted to a weekly time series. Children were further subdivided to include an infant category (0–1 year of age). The children and general population categories were chosen as points where influenza in young people ceases to be a major burden and subsequently when it becomes a major source of illness in older populations (Figure 1).

Population adjustment was made by converting the weekly mortality counts into rates per million persons, using decennial census with interpolation between years for the children, general population and elderly subgroups, and a yearly population estimate for the infant subgroup, calculated as: infant population = new births + last years births − last years infant deaths, based on vital records data where no age-specific census information was available. Because of a lack of population estimate data for the 1967–1968 influenza season, the infant subpopulation was omitted for that year.

Vaccine selection and circulating virus strain

The WHO's recommended vaccine strains[13] were used as a proxy variable for the predominant circulating influenza viruses for viral subtypes A and B, while the predominant disease-causing strains were obtained from Morbidity and Mortality Weekly Reports (MMWR) of influenza activity within the United States for a given year[14] (Figure 2). The duration of the A/Hong Kong/1/68 pandemic was determined by consulting the WHO Weekly Epidemiological Record[15] for dispatches detailing considerable outbreaks of A/Hong Kong/1/68 influenza.

Time-series and statistical analysis

The seasonal epidemic curve was described by analyzing the mortality time series with the Annual Harmonic Regression model to obtain yearly parameters quantifying the duration (period in weeks in which the epidemic curve exceeds the median mortality rate for that year) and absolute intensity (difference between the minimum and maximum mortality rates for that year) of the epidemic, as well as the week in which the epidemic peaked.[11,12,16] Yearly influenza epidemics are fitted to a unique curve expressed as:

$$Y(t)_{\mathrm{i}} = \exp\{\beta_{0,\mathrm{i}} + \beta_{1,\mathrm{i}}\cos(2\pi\omega t) + \beta_{2,\mathrm{i}}\sin(2\pi\omega t) + \varepsilon\}$$

where $Y(t)_{\mathrm{i}}$ is disease incidence at time t within a particular flu season i (expressed as weekly cases per million popula-

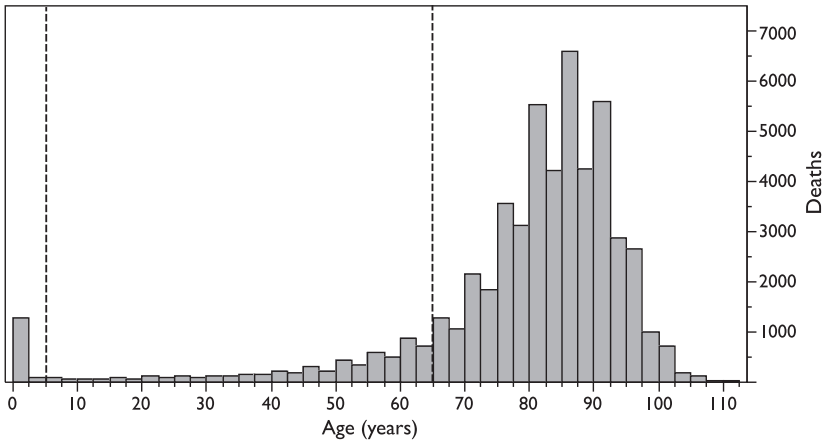

Figure 1. Population distribution of seasonal influenza mortality in Wisconsin by age group aggregated from 1967 to 2004. Reference lines at 5 years of age and 65 years of age mark changes in subpopulation categorization.

tion). β_o represents the intercept of the yearly epidemic curve or a baseline level of infection; β_1 and β_2 are the respective coefficients of the harmonic; $\omega = 1/M$, where M is the length of one cycle. This model, is similar to Thompson *et al.*[17,18] and modified as in Ref. [16], provides sufficiently good fit with r^2 values exceeding those which can be obtained from Serfling-type methodology.[19] Smoothed predicted values of weekly rates were obtained from this model; to produce a continuous model fit, the last 2 weeks of a season and the beginning 2 weeks of the next season were interpolated. Yearly parameters of duration, intensity, and peak timing (and the corresponding values for the 95% confidence intervals) were obtained from the regression coefficients using the δ-method.[11] The δ-method allows for the examination of the variability in seasonal influenza outbreaks beyond that of excess mortality.

This concept is easy to express via model (1) as follows:

$$\log(E[Y(t)]) = \gamma\cos(\omega t + \psi) + e(t), \quad (1)$$

where $Y(t)$ is a time series, the periodic component has a frequency of ω, an amplitude of γ, and a phase angle of ψ, and $\{e(t),\ t = 1,\ 2,\ldots,n\}$ is an i.i.d. sequence of random variables with $E[e(t)] = 0$ and $\mathrm{Var}[e(t)] = \sigma^2$. From a user stand point, this model offers a highly desired property as being easy to interpret. The model describes a seasonal curve by a cosine function with symmetric rise and fall over a period of a full year. As shown in Ref. [11], this model is equivalent to model (2)

$$\log(E[Y(t)]) = \beta_0 + \beta_1\sin(2\pi\omega t) + \beta_2\cos(2\pi\omega t) + e(t), \quad (2)$$

which is more convenient to fit as a log-linear regression model or as generalized linear model with the Poisson assumption for the outcome (the results of the latter are presented in the article), both procedures are available in many commercial statistical software. The essence of the δ-method is in estimation of the amplitude γ and phase ψ along with their variance using β_1 and β_2 regression coefficients and then to formally compare via standard statistical tests (for proofs see Ref. [11]).

For the amplitude, the estimates are $\gamma = (\beta_1^2 + \beta_2^2)^{1/2}$ (3)

and $Var(\gamma) = (\sigma^2_{\beta_1}\beta_1^2 + \sigma^2_{\beta_2}\beta_2^2 + 2\sigma_{\beta_1\beta_2}\beta_1\beta_2)/(\beta_1^2 + \beta_2^2)$. (4)

The phase angle estimate is $\psi = -\arctan(\beta_1/\beta_2)$ (5)

and corresponding variance estimate is

$$Var(\psi) = (\sigma^2_{\beta_1}\beta_2^2 + \sigma^2_{\beta_2}\beta_1^2 - 2\sigma_{\beta_1\beta_2}\beta_1\beta_2)/(\beta_1^2 + \beta_2^2)^2. \quad (6)$$

Using the estimates of the amplitude and the phase angle, as well as the model intercept, a number of the seasonality characteristics can be estimated and formally compared:

1. Seasonal peak, or the average maximum value on the seasonal curve of disease incidence, $\max\{Y(t)\} = \exp\{\beta_0 + \gamma\}$;
2. Seasonal nadir, or the average minimum value on the seasonal curve of disease incidence, $\min\{Y(t)\} = \exp\{\beta_0 - \gamma\}$;
3. Average intensity, the difference between maximum and minimum values on the seasonal curve or incidence of disease, $I = \exp\{\beta_0 + \gamma\} - \exp\{\beta_0 - \gamma\}$;
4. Average peak timing (in weeks), a position of the maximum point on the seasonal curve of exposure or disease incidence, $P = 52.25(1 - \psi/\pi)/2$;
5. Baseline level, or median annual rate, $S = \exp\{\beta_0\}$.

These estimates were computed for each age group and each influenza season and used for comparisons and an examination of autocorrelation with lags for 0–10 influenza seasons. All analyses were conducted in JMP 6.0 (SAS Institute, Cary, NC, USA).

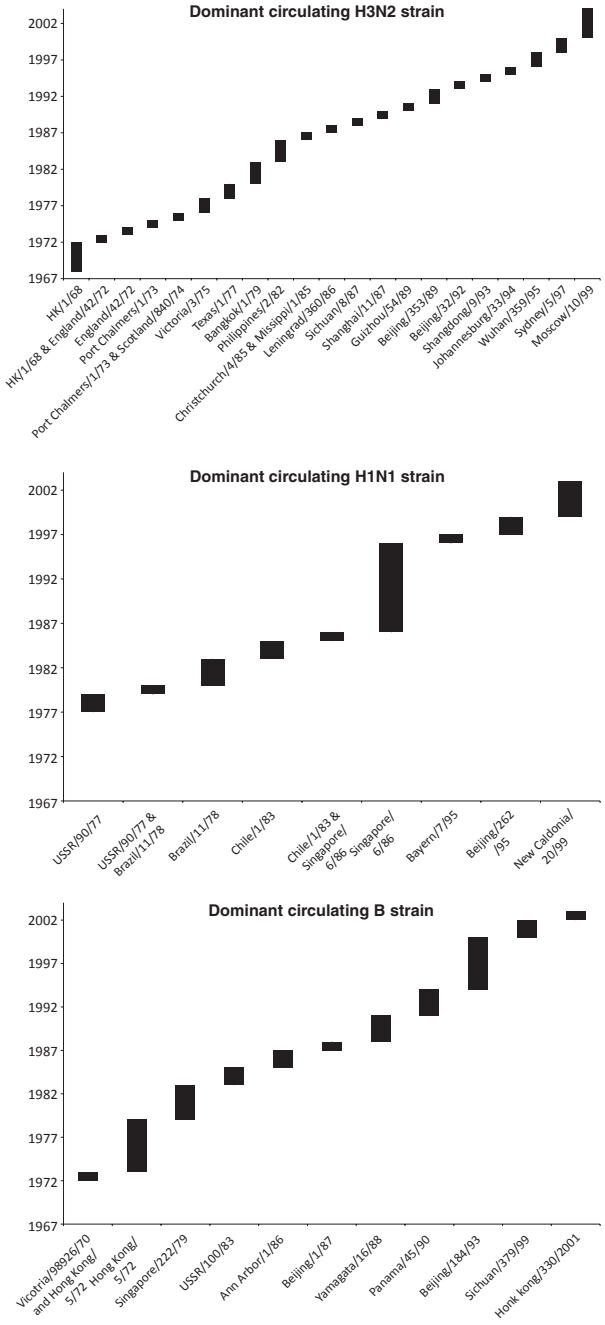

Figure 2. Circulating influenza virus strain by subtype. Considerable evolution in the form of genetic drift and the turnover of circulating virus strains exists over the study period.

Results

The yearly smoothed time series (Figure 3) shows considerable variation in the shape and nature of the epidemic curve both between influenza seasons and across population subgroups, as summarized in Table 1. The elderly subpopulation, as expected, had the highest rate of influenza mortality, accounting for 88% of the total mortality for the series, and possessing an intensity nearly 10 times higher than that of infants. The children and infant subpopulations showed an earlier peak and wider duration than elderly.

Intensity of influenza seasons during pandemic periods

The 1967–2004 period includes a 3-year period where the A/Hong Kong/1/68 pandemic can be considered in full force (1966–1969), and two additional years where it is circulating but no longer a major source of reported epidemics. While the elderly subpopulation showed no statistically significant change in any parameter values, the same is not true of the children and infant subpopulations. In these two subpopulations, the intensity of the epidemic was significantly higher during years when A/Hong Kong/1/68 was in circulation (two-tailed t-test assuming unequal variance comparing intensity in pandemic versus non-pandemic seasons, $t = 4{\cdot}23$, d.f. = 4·16, $P = 0{\cdot}012$ and $t = 5{\cdot}16$, d.f. = 4·35, $P<0{\cdot}005$ for children and infants, respectively). While the general population did not exhibit a statistically significant difference, there was an increase in seasonal intensity as well (t-test, $t = 2{\cdot}36$, d.f. = 4·11, $P = 0{\cdot}075$).

Trends in seasonal influenza by age group

Seasonal influenza in children and infants shows the greatest change in the annual epidemic curve and severity over the length of the time series. At the start of the time series, periodic childhood epidemics showed a clear, cyclical seasonality, less severe than the elderly seasonal epidemics. Later in the series, influenza in children had a more sporadic pattern with less-pronounced seasonality (see Figure 3). While it is tempting to assign responsibility for this pattern to the circulating pandemic influenza strain at the beginning of the series, it is important to note that this period of pronounced seasonality extends 10 seasons into the series, four generations of influenza A (H3N2) after the Hong Kong pandemic strain. Child and infant seasonal influenza epidemics are characterized by steadily declining durations, indicating more sporadic, short-term outbreaks, and geometrically decreasing intensities, indicating a dramatic decrease in the severity of influenza outbreaks over time (Figure 4). After the initial 10-year period, the seasonal burden of influenza in children drops to levels near those of the general subpopulation. Both the general and elderly subpopulations exhibit no trends over time in any of the three curve parameters.

In addition to the trends in intensity and duration, the child and infant subpopulations exhibit other seasonal epidemic behaviors not present in the older subpopulations. Peak timing exists in an alternating, quasi-cyclical

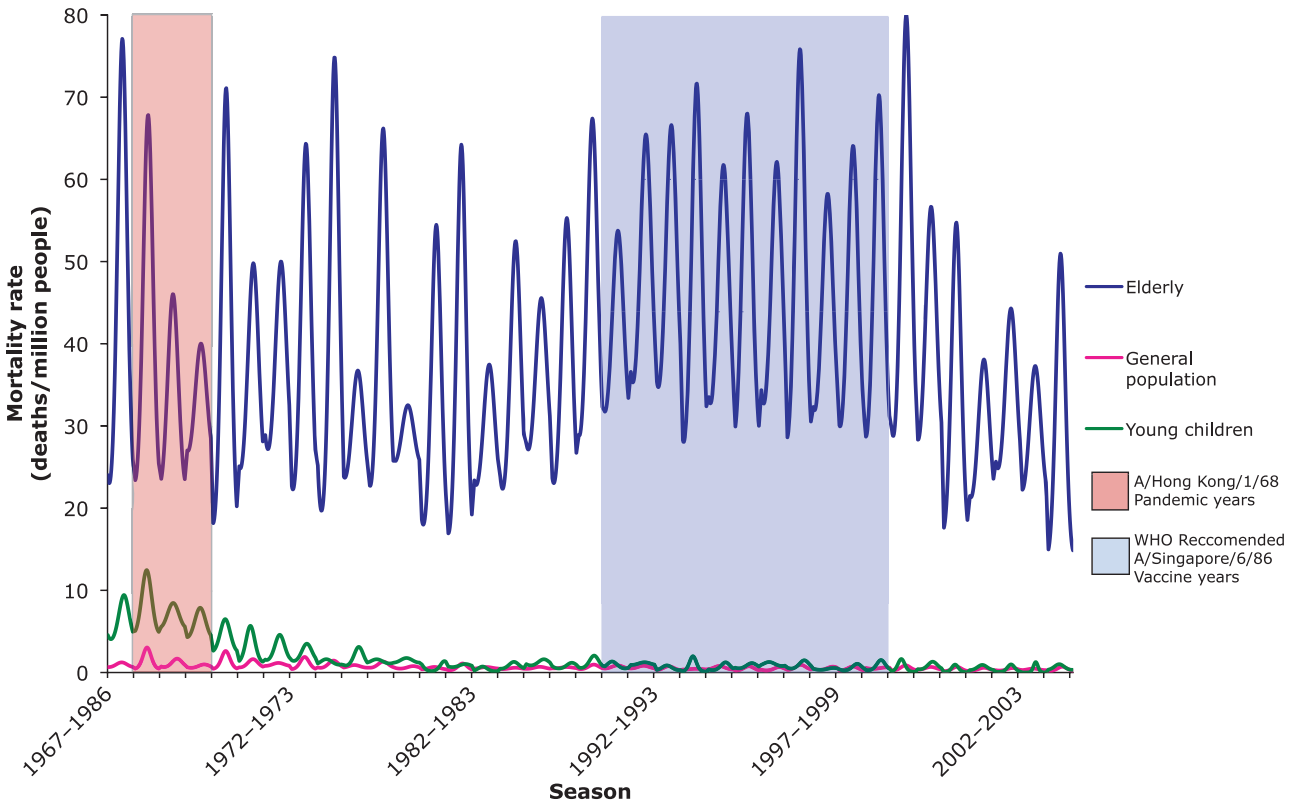

Figure 3. Smoothed harmonic time series for three population subgroups produced with Annual Harmonic Regression model. Periods of the pandemic circulation of A/Hong Kong/1/68 and the epidemic circulation of A/Singapore/6/86 are highlighted.

pattern of early peak and late peak years. In children, this pattern exists as an extremely strong negative autocorrelation between the timing of a season's peak and the timing of the peak before it, indicating frequent and significant alternations in peak timing ($r_{lag1} = -0{\cdot}51$, $P < 0{\cdot}05$) (Figure 5). Although in infants the relationship is somewhat more complex and less strong, it is never the less present. This relationship appears to be independent of any other epidemic curve attributes or circulating viral strains.

Viral evolution and seasonal influenza

While there were no statistically significant associations between viral strain and duration, intensity, or peak timing of seasonal epidemics, there was a statistically significant difference in the intercept ($\beta_{0,i}$) of a given year's smoothed model for all population subgroups. The intercept is as a proxy for a baseline level of severity of the influenza season in conjunction with intensity, representing higher or lower rates of influenza mortality over the whole year. While in

Table 1. Summary of influenza time series 1967–2004; peak week, intensity, and seasonal duration show considerable variation within and between subpopulation categorizations

Population	Total cases	Model fit (*P*-value)	Peak week (±SD) (weeks)	Intensity (±SD) (deaths/million)	Duration (±SD) (weeks)
Infants	1000	$r^2 = 0{\cdot}484$ ($P < 0{\cdot}001$)	27·78 (±7·26)	3·44 (±3·57)	23·47 (±1·97)
Children	1258	$r^2 = 0{\cdot}501$ ($P < 0{\cdot}001$)	27·92 (±6·73)	1·59 (±1·59)	23·42 (±1·86)
General population	4890	$r^2 = 0{\cdot}370$ ($P < 0{\cdot}001$)	29·73 (±4·75)	0·57 (±0·52)	24·23 (±1·15)
Elderly	45 388	$r^2 = 0{\cdot}566$ ($P < 0{\cdot}001$)	30·82 (±2·26)	32·23 (±12·88)	24·34 (±0·59)
Total	51 536	$r^2 = 0{\cdot}765$ ($P < 0{\cdot}001$)	30·75 (±2·07)	4·37 (±1·72)	24·36 (±0·58)

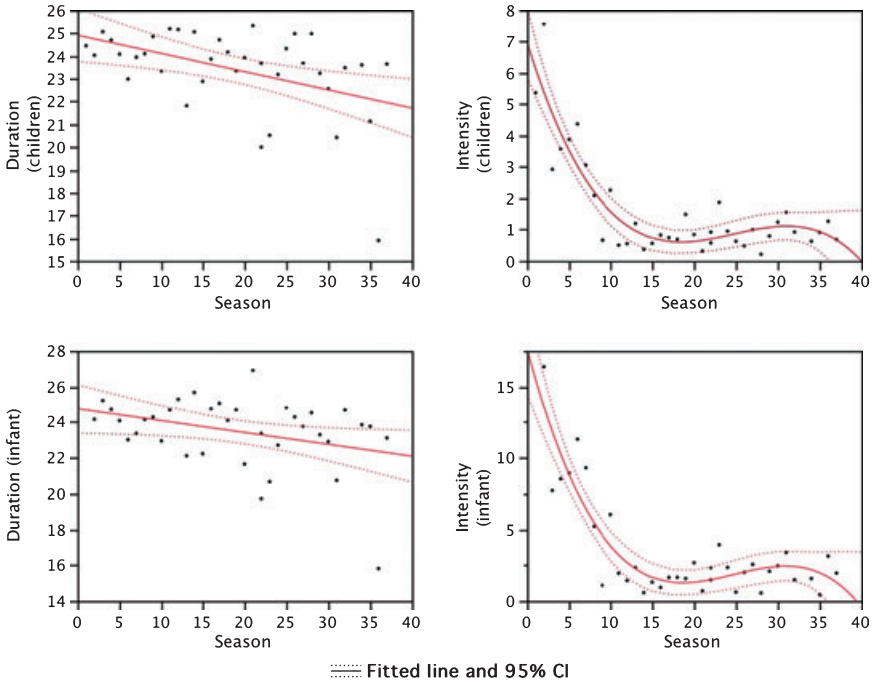

Figure 4. Trends in childhood influenza seasonality. Duration estimates are shown in weeks; intensity estimates are shown in difference units: (maximum deaths – minimum deaths)/million; trend is approximated by a polynomial curve. The indicator for seasons corresponds to years in Figures 2 and 3. The shape of the yearly epidemic curve transitions from periodic, pronounced epidemics to more sporadic, rare events.

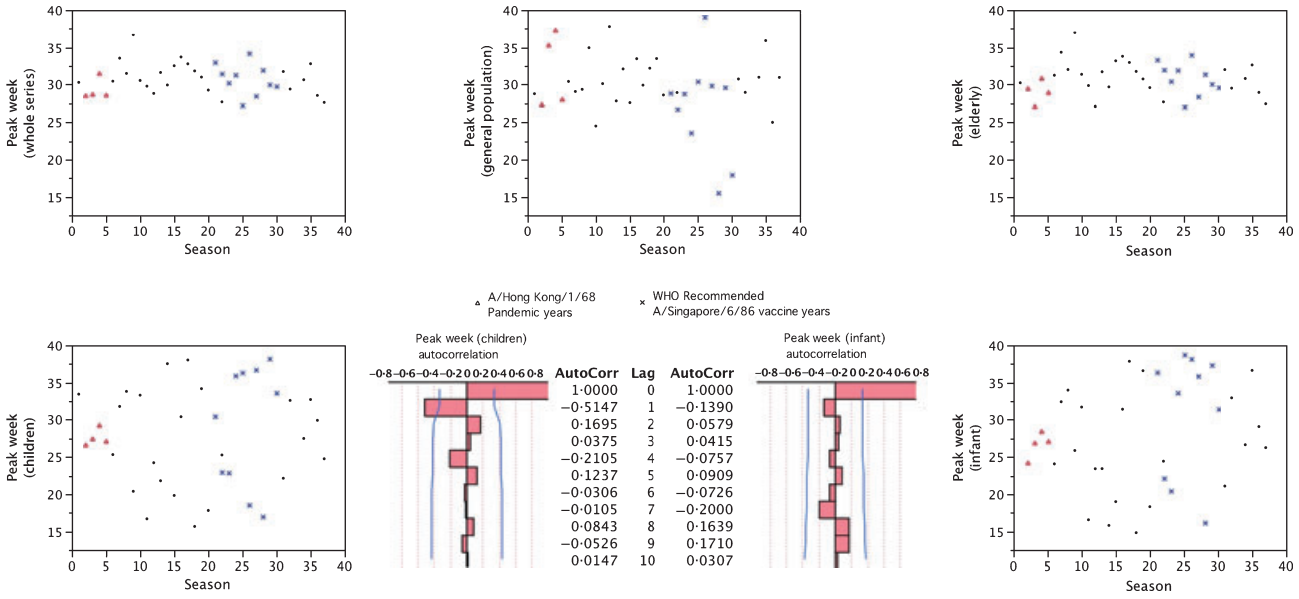

Figure 5. Peak timing (in weeks) for four population subgroups and the population as a whole. Pandemic A/Hong Kong/1/68 and epidemic A/Singapore/6/86 years are highlighted in red. The indicator for seasons corresponds to years in Figures 2 and 3. The graphs for child and infant peak timing are accompanied by plots of autocorrelation functions for lag 0–10 seasons to better demonstrate their quasi-cyclical nature.

the general, child, and infant subpopulations these differences are almost entirely because of the A/Hong Kong/1/68 season, there also exists a statistically significant (ANOVA, F-ratio = 23·67, $P < 0·001$) difference in the baseline mortality level in the elderly subpopulation with respect to circulating viral strain. Based upon pairwise comparisons (Tukey's HSD, $\alpha = 0·10$), this difference is not because of pandemic flu strains.

The 1986–1987 influenza season saw the circulation of a particularly long-lasting strain of influenza A (H1N1), A/Singapore/6/86, with the high mortality rate in the elderly. The baseline mortality for this strain of H1N1 in the

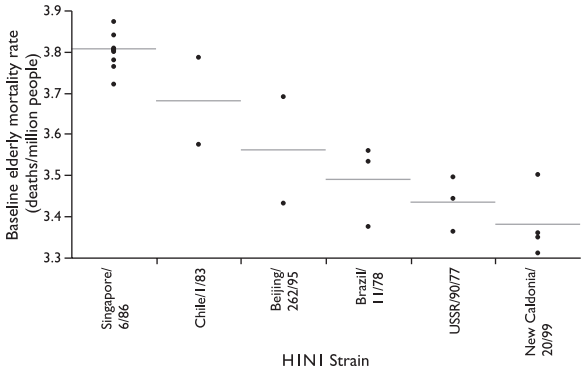

Figure 6. Increase in elderly seasonal epidemic severity because of the circulation of A/Singapore/6/86 (r^2 = 0·120, P = 0·038).

elderly subpopulation models (mean = 3·807 deaths/million persons) is considerably higher than that of the average level for all strains (mean = 3·626 deaths/million persons) and significantly higher than all other strains aside from A/Chile/1/83, the immediately preceding strain (Figure 6). A single strain that circulated for <2 years was not included in the analysis, as the study was examining the long-term impact of viral evolution and strain selection. Prior to its exclusion, this strain was not a significant source of higher model intercept in population subgroup.

Conclusion

Viral evolution as a driving force in seasonal influenza

The impact of viral evolution of influenza on infrequent pandemics because of antigenic shift is widely studied.[23] However, the role of viral evolution in the form of antigenic shift on seasonal, non-pandemic influenza is also of clear importance.[24,25] In the elderly population, which has proven resistant to changes in the timing and severity of seasonal epidemics over the 37-year period of the study, it appears that particular strains of influenza are capable of producing higher rates of mortality without altering the underlying shape of the epidemic. The higher baseline mortality associated with A/Singapore/6/86 is puzzling. The virus has not previously been noted for virulence, although there is some suggestion that the recommended WHO vaccine strain only partially protected against the strain circulating in some years.[26,27] As a member of the H1N1 subtype, Singapore/6/86 appeared nearly a decade after the reemergence of H1N1 into the circulating virus pool in the form of A/USSR/90/77, and the majority of the individuals in the elderly cohort during the period would have been exposed in their youth to the pandemic H1N1 strain of 1918. The lack of any increase in seasonal severity in the child or general subpopulations suggests a lack of ''pandemic potential''.

The role of viral evolution in the seasonality of influenza clearly warrants further research because of the unexplained rise in seasonal mortality concurrent to the circulation of A/Singapore/6/86. It is possible that an underlying biological mechanism is responsible or it may be as a result of a poorly targeted vaccine. Regardless of its cause, it seems extremely likely that such viruses – lacking pandemic potential yet capable of causing significant health problems – will arise in the future. Advancing the understanding of potentially subtle changes in viral genomes, as well as detecting continuing circulation of the H1N1 strain responsible for the current pandemic relies on expanding laboratory and surveillance capabilities to track infections of multiple strains of influenza virus and non-influenza respiratory infections. Significant research and monitoring of the antiviral resistance of the locally circulating predominant strains are critical for the efficacy and use of antiviral medications as well as tracking newly mutated viral evolution.

The decline of influenza as a common severe childhood disease

While still among the most at-risk populations for severe seasonal influenza-related complications,[5] significant progress has been made in the last few decades in decreasing the burden of seasonal influenza on young populations. The strong downward trends in both duration and intensity of the seasonal epidemics represent childhood influenza transitioning from an ''elderly-like'' state of frequent, recurrent seasonal epidemics to a more ''general'' state, where influenza mortality, while still seasonal, is more sporadic, less severe on a population level, and generally indicative of greater health problems rather than a common occurrence. Clinicians and public health agencies would be advised to enhance the monitoring and treatment of childhood influenza as a serious disease, as well as ensure public awareness of the potential severity of the disease, mandate cases of potential pandemic influenza as reportable, and making mass vaccinations available.[20]

The quasi-cyclical pattern of peak timing in childhood influenza is somewhat more puzzling. This pattern has not been widely reported, and as such little evidence for a biological source exists.[21,22] The presence of the pattern when examining the entire newborn to 5 years of age population suggests that this cycle is not a product of the harvesting effect in newborns and the subsequent replenishment of a susceptible population in the oncoming year. Instead, it seems possible that this cycle is the result of complex interactions between infections from parents, siblings, and the maturing immune systems of newborns as they move into late childhood and a less immunologically vulnerable stage of their life.

The careful balance between demography, antigenic strain, pandemic history, and seasonal influenza

The analysis of this particular time series is ideally positioned to examine the last pandemic of influenza in light of its subsequent decades of epidemic circulation and to help inform perspectives on modeling future pandemics and seasonal epidemics, in light of the ongoing, novel, global pandemic (H1N1) 2009. As this work has demonstrated, exploring demographically sensitive models,[28] even within age groups not typically of specific focus for concern, can lead to novel insights into the epidemic behavior of circulating strains and potential risk for severe influenza-associated disease.

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