Epidemiol. Infect. (2010), **138**, 1135–1145. © Cambridge University Press 2010
doi:10.1017/S0950268809991506

Trends for influenza and pneumonia hospitalization in the older population: age, period, and cohort effects

S. A. COHEN[1,2*], A. C. KLASSEN[3], S. AHMED[2], E. M. AGREE[2], T. A. LOUIS[4] AND E. N. NAUMOVA[1]

[1] *Tufts School of Medicine, Department of Public Health and Community Medicine, Boston, MA, USA*
[2] *Johns Hopkins Bloomberg School of Public Health, Department of Population, Family, and Reproductive Health, Baltimore, MD, USA*
[3] *Johns Hopkins Bloomberg School of Public Health, Department of Health, Behavior, and Society, Baltimore, MD, USA*
[4] *Johns Hopkins Bloomberg School of Public Health, Department of Biostatistics, Baltimore, MD, USA*

(*Accepted 30 November 2009; first published online 8 January 2010*)

SUMMARY

Birth cohort has been shown to be related to morbidity and mortality from other diseases and conditions, yet little is known about the potential for birth cohort in its relation to pneumonia and influenza (P&I) outcomes. This issue is particularly important in older adults, who experience the highest disease burden and most severe complications from these largely preventable diseases. The objective of this analysis is to assess P&I patterns in US seniors with respect to age, time, and birth cohort. All Medicare hospitalizations due to P&I (ICD-9CM codes 480-487) were abstracted and categorized by single-year of age and influenza year. These counts were then divided by intercensal estimates of age-specific population levels extracted from the US Census Bureau to obtain age- and season-specific rates. Rates were log-transformed and linear models were used to assess the relationships in P&I rates and age, influenza year, and cohort. The increase in disease rates with age accounted for most of the variability by age and influenza season. Consistent relationships between disease rates and birth cohorts remained, even after controlling for age. Seasonal associations were stronger for influenza than for pneumonia. These findings suggest that there may be a set of unmeasured characteristics or events people of certain ages experienced contemporaneously that may account for the observed differences in P&I rates in birth cohorts. Further understanding of these circumstances and those resulting age and cohort groups most vulnerable to P&I may help to target health services towards those most at risk of disease.

Key words: Epidemiology, influenza, pneumococcal infection, prevention, statistics.

INTRODUCTION

The objective of this study is to examine three related demographic effects – age, period, and cohort – on influenza and pneumonia hospitalization rates in the older population. Over the past century, influenza has been responsible for more than 50 million deaths worldwide [1]. Despite extensive research and population-wide preventive measures, influenza still presents a major global public health threat. The older population is particularly vulnerable to influenza and its effects, especially during peak periods of disease

* Author for correspondence: Dr S. A. Cohen, Tufts School of Medicine, Department of Public Health and Community Medicine, 136 Harrison Avenue, Boston, MA 02111, USA.
(Email: steven_a.cohen@tufts.edu)

that typically occur in winter [2]. Although influenza is a self-limited disease of the upper respiratory tract, influenza infection enables other, more serious, diseases to develop in older adults, such as pneumonia [3], which is one of the most common infections in the population aged $\geqslant$65 years [4]. On average, there are more than 1·6 million annual hospitalizations attributable to pneumonia and influenza (P&I), 65% of which list pneumonia or influenza as the primary diagnosis [5]. Each year, over 36000 deaths in the USA attributable to P&I occur [6], most of which occur in the older population.

The biology of influenza and pneumonia is well-understood. Influenza is largely a seasonal infection, peaking in the winter months and varying annually in the intensity and duration of the influenza season [7]. Three types of influenza virus are known to exist – types A, B, and C, based on the serological responses to internal proteins [8]. Influenza types A and B cause the most severe illnesses in humans. Although there is some genetic variability observed in influenza B virus strains, type A influenza mutates rapidly through antigenic drift and shift [8]. Often, new subtypes of influenza type A viruses emerge in the human population, which are thought to permeate from wild or domestic animals, and are then transmitted to humans [9], as in the case of the recent swine-originated H1N1 influenza epidemic [10]. The predominant influenza subtypes can vary from season to season, producing the well-documented 'period effect', and predicting which subtype will be most dominant is a continual challenge for the development of appropriate vaccine strains [11]. This, ultimately, poses major challenges for the provision of public health, given that the primary means of prevention is through annual vaccination of those most at risk of influenza [12]. The rapid genetic changes that occur in the influenza virus translate to large-scale year-to-year variability in the severity of seasonal influenza [13]. Methods to analyse seasonality in influenza and influenza-related disease cases or rates have been developed [14] and subsequently modified to account for this season-specific variation in the magnitude of influenza and pneumonia [15].

There is a small, but growing body of evidence to suggest that these three distinct, but related demographic characteristics (age, period, and cohort) impact disease rates, especially in older adults. The relationship between P&I and age has served as a major focus of research, especially in older adults. Overall, P&I rates and mortality increase exponentially in the older population with age [16], which may be due to declines in immunological function with age. Biologically, older people who are vaccinated against influenza exhibit less of an immune response than younger people [17]. These findings have been validated by several studies of vaccine efficacy in older adults [18, 19]. However, it is important to note that several factors may alter immune decline with age. After controlling for age, high levels of comorbidity in older patients were associated with decreased immune function [20], and functional status in older adults may further confound the association of influenza vaccine and mortality [21]. Thus, there is extensive research on P&I morbidity and mortality by age, as well as season-specific, or period, changes in the genetic composition and severity of seasonal influenza and associated diseases.

However, there are comparatively few studies examining and quantifying the possibility that age and period effects are augmented by cohort effects. Our analysis expands upon prior research [22] and simultaneously evaluates the relationships between season, age, and P&I rates, as well as between cohort and P&I, to account for the potential for certain birth cohorts to have experienced P&I differently than others. The age-period cohort model allows for the possibility that three related, but separate parameters – age, period, and cohort – are associated with patterns of morbidity and mortality [23] and can be mathematically assessed using linear models accounting for each of these factors separately [24]. Thus, this study will describe patterns in P&I hospitalizations in the USA, using a modified age-period cohort model by single-year of age for 13 influenza seasons to assist aetiological research on influenza and pneumonia and provide the basis for specific hypothesis generation for future work in this area of study.

METHODS

Data sources

Hospitalization records from the Centers for Medicare and Medicaid Services' (CMS) databases containing all Medicare-eligible hospitalizations in the USA from July 1991 to June 2004 were used for this analysis. About 96% of all adults aged $\geqslant$65 years are enrolled in CMS [25]. As of 2005, there were $\sim$42·4 million Medicare beneficiaries in the USA [26]. All

https://doi.org/10.1017/S0950268809991506 Published online by Cambridge University Press

claims records of hospitalizations associated with P&I (ICD-9CM codes 480–487) [27, 28] were abstracted from these CMS databases and tabulated by single-year of age and influenza year, defined as July to June of the following year. This process was repeated for influenza only (ICD code 487). All data abstractions were performed only for the population aged 66–99 years. Those claims from patients aged $\geqslant$100 years were excluded because population counts by single-year of age were not publicly available, and those aged 65 years were excluded because of the temporary increase in overall hospitalizations that occur at that age, probably because Medicare eligibility begins at age 65 years for the majority of the population. Corresponding US population counts were obtained using national US Census mid-year population counts for each year (1991–2004) provided by the Population Estimates Program. Using these data, age-specific hospitalization rates were estimated for each single-year of age for the 13 influenza years of study (1991–2004) and then transformed using the natural logarithm.

Data analysis and visualization

Preliminary data analysis included univariate summaries of variables, including influenza rates, P&I rates, and related statistics overall and by gender. Age-acceleration coefficients were obtained for each influenza year from the slope of the line representing the log of P&I rates plotted against age. To evaluate the relationships between log-transformed P&I rates and age, period, and cohort, linear regression models were fitted, including functions of the explanatory variables of interest. Each demographic variable type was modelled in a unique way. Age was treated as a continuous variable in each of the models containing functions of age. Adjusted R^2 values were used to determine how age should most appropriately be modelled. Several modelling schemes were considered, including simple linear, exponential, logarithmic, and polynomial functions of age.

Periods were defined as individual 12-month influenza years, and their relationships with P&I hospitalization rates were assessed through the use of indicator variables for each period. Thus, a linear association between influenza year and P&I rate was not assumed. To address cohort effects, each group was assigned to a single-year birth cohort using indicator variables spanning the 12-month period between July and the following June, based on age and influenza year. Data for complete birth cohorts were available for those born beginning in July 1905, because this was the first birth-cohort year in which all 13 seasons of P&I rates could be studied in this analysis. The youngest birth cohort for which all 13 seasons of data were available was those born between July 1926 and June 1927. This is considered to be a partial age-period cohort analysis because data are available for 35 specific ages, but only 13 influenza seasons; in this way it is not possible to follow one single-year birth cohort for all ages given the limited time period of data availability.

The regression strategy employed for this analysis was based on that employed in Thygessen and colleagues [29]. The basic model equation is shown here:

$$\log(\text{P\&I rate}_{ap}) = \alpha_a + \beta_p + \gamma_c.$$

The parameters α_a, β_p, and γ_c, represent age, period, and cohort effects, respectively. Since, by definition, the sum of age and cohort effects equals the period effect using all possible age, period, and cohort effects, this model was modified to account for the perfect collinearity that would result from such a model. Multiple indicator variables for cohort were omitted from the model in order to reduce the possibility of collinearity from the identity properties of age, period, and cohort.

Linear regression models using the log-transformed outcome variables were constructed. Seven models were ultimately produced for each outcome variable: influenza alone and pneumonia and influenza combined. Groups of predictive variables were assessed individually to form an age model, a period model, and a cohort model. The age model included the best model using only functions of age as described above. The period model included only terms indicating period, using the 1991–1992 season as the reference period.

The cohort model included the indicator variables for cohort with the 1892–1893 birth cohort used as a reference, as well as a linear term representing cohort number (from youngest to oldest) to account for the issue of different birth cohorts of different ages. For example, the 1905–1906 birth cohort was represented by ages 86–98 years, while the 1906–1907 birth cohort was represented by ages 85–97 years. Because P&I increases with age, the 1905–1906 birth cohort could show overall higher rates than the 1906–1907 birth cohort, not because the age-specific rates are higher, but because the ages represented by this cohort are higher.

https://doi.org/10.1017/S0950268809991506 Published online by Cambridge University Press

The next step involved formulating three additional models with two factors each included age and period, age and cohort, and cohort and period together. The demographic variable groups were modelled in the same way as in the individual demographic variable models described above. In the final model, cohort relationships were assessed after age and period associations were taken into account.

P&I rates were displayed by use of Lexis surfaces [30] overall and by gender. Residuals from each model were used to demonstrate differences between several of the key component age-period cohort models for P&I rates overall and by gender, influenza rates, and the proportion of all P&I cases due to influenza. SPSS version 15.0 (SPSS Inc., USA) was used for all statistical analyses.

RESULTS

Longitudinal trends

Total hospitalizations increased between 1991 and 2003 (Table 1). Rates also tended to increase overall, but there were year-to-year exceptions. This trend was evident in females, although in males, P&I rates actually declined between the 1997–1998 and 2000–2001 influenza years. The national population of people aged $\geqslant 65$ years also increased between 1991 and 2003. Influenza alone varied substantially by influenza year. The total number of hospitalized influenza cases ranged from ~ 7000 cases (in 2000–2001) to 40 915 cases in the most severe season (2003–2004). There was no significant association between overall influenza rate and ratio of gender-specific influenza rates ($P = 0{\cdot}288$).

Age acceleration of P&I rates peaked in the late 1990s and decreased slightly thereafter. For influenza alone, age acceleration also peaked in the late 1990s and early 2000s, but tended to fluctuate during the peak seasons. There were no significant associations between age acceleration and overall P&I rate ($P = 0{\cdot}913$) or between age acceleration and influenza rate ($P = 0{\cdot}856$). Figure 1 shows influenza rates by age for each of the 13 seasons. In general, influenza rates increase with age, and this increase is roughly exponential throughout the younger population of older adults. However, around age 90 years, the degree of 'increase with age' decreases. At the oldest ages, influenza rates become increasingly unstable, which may be due to the small population size in this age group, or possibly due to a deceleration of the risk of contracting influenza and pneumonia by age.

There are substantial differences in the severity of influenza in the older population over time. Age-specific influenza rates were generally 4–5 times higher in the 2003–2004 season compared to the previous season. Although influenza rates increase with age, each season has a characteristic age pattern. To illustrate, the influenza rate of the population aged 65 years in the 1993–1994 season – 0·401 cases per thousand – was the third-highest of all seasons at that age. Yet, the influenza rate of 97-year-olds in that season is the seventh-highest overall, as the increase in influenza with age was comparatively small in that season. These characteristics were more pronounced for influenza alone than for the outcome of combined P&I.

Age-period cohort models

Parameter estimates for age and period based on the full age-period cohort model are shown in Table 2, and illustrated in Figure 2. For influenza alone and combined P&I, age and age-squared terms were both significantly and positively associated with disease rates. The relationship between age and disease rates was higher for males than for females. Similarly, the relationship between age-squared and disease rates was higher for females than for males. Age-cubed was negatively associated with disease rates in each of these models.

For all P&I, the period relationships were consistent over most of the seasons examined. However, the relationship between influenza alone and influenza year was much more variable. These were generally consistent by gender, with a few notable exceptions. Compared to the reference season, 1991–1992, the 1998–1999 season had significantly higher influenza rates for males. However, no statistically significant difference existed between the two seasons overall, and for females. Similar results were found in the 1997–1998 season.

The age-period cohort models isolated several potential cohort effects (Figs 3, 4). Combined P&I was negatively associated with each of the birth cohorts between 1921–1922 and 1934–1935. For males, this extended to the 1915–1916 birth cohort, while for women, these significant negative relationships occurred only in those birth cohorts between 1922–1923 and 1934–195. Perhaps of greater interest were the observed associations between P&I rates and

https://doi.org/10.1017/S0950268809991506 Published online by Cambridge University Press

Table 1. *Summary statistics by influenza season for influenza and pneumonia in the US population aged ⩾65 years*

	Season	1991–1992	1992–1993	1993–1994	1994–1995	1995–1996	1996–1997	1997–1998	1998–1999	1999–2000	2000–2001	2001–2002	2002–2003	2003–2004
Population	Total	31 772 840	32 316 749	32 861 160	33 289 176	33 725 982	34 097 708	34 354 869	34 571 562	34 749 013	35 026 769	35 280 628	35 541 227	35 901 386
	Females	18 970 203	19 271 264	19 562 211	19 783 919	19 998 713	20 181 766	20 300 434	20 390 316	20 457 998	20 581 505	20 683 225	20 790 182	20 951 062
	Males	12 802 637	13 045 485	13 298 949	13 505 257	13 727 269	13 915 942	14 054 435	14 181 246	14 291 015	14 445 264	14 597 403	14 751 045	14 950 324
Hospitalized influenza cases	Total	19 927	12 594	22 195	9554	10 427	16 545	22 498	22 198	35 190	7145	15 179	6151	40 915
	Females	12 731	8257	14 269	6124	6663	10 446	14 155	13 710	21 736	4511	9203	3724	24 821
	Males	7196	4337	7926	3430	3764	6099	8343	8488	13 454	2634	5976	2427	16 094
Hospitalized P&I cases	Total	930 230	969 435	1 046 762	1 089 923	1 098 657	1 204 091	1 230 195	1 229 724	1 236 264	1 201 743	1 309 860	1 302 092	1 438 444
	Females	490 564	510 111	556 224	578 937	584 891	646 723	665 422	668 256	676 685	656 822	718 695	711 254	792 728
	Males	439 666	459 324	490 538	510 986	513 766	557 368	564 773	561 468	559 579	544 921	591 165	590 838	645 716
Influenza rates per 100 000	Total	62·7	39·0	67·5	28·7	30·9	48·5	65·5	64·2	101·3	20·4	43·0	17·3	114·0
	Females	67·1	42·8	72·9	31·0	33·3	51·8	69·7	67·2	106·2	21·9	44·5	17·9	118·5
	Males	56·2	33·2	59·6	25·4	27·4	43·8	59·4	59·9	94·1	18·2	40·9	16·5	107·6
P&I rates per 100 000	Total	2928	3000	3185	3274	3258	3531	3581	3557	3558	3431	3713	3664	4007
	Females	2586	2647	2843	2926	2925	3204	3278	3277	3308	3191	3475	3421	3784
	Males	3434	3521	3689	3784	3743	4005	4018	3959	3916	3772	4050	4005	4319
Influenza cases per 1000 P&I cases	Total	21·4	13	21·2	8·8	9·5	13·7	18·3	18·1	28·5	5·9	11·6	4·7	28·4
	Females	26	16·2	25·7	10·6	11·4	16·2	21·3	20·5	32·1	6·9	12·8	5·2	31·3
	Males	16·4	9·4	16·2	6·7	7·3	10·9	14·8	15·1	24	4·8	10·1	4·1	24·9
Age acceleration	Influenza	5·8	5·88	5·6	6·38	6·66	7·15	8·17	7·78	7·47	8·18	7·84	7·77	7·09
	P&I	7·75	7·56	7·41	7·97	8·13	8·17	8·29	8·29	8·23	8·17	7·94	7·56	7·28

P&I, Pneumonia and influenza.

Table 2. *Model estimates of the effects of age and period for influenza and pneumonia models*

		Pneumonia and Influenza			Influenza		
		Total	Males	Females	Total	Males	Females
Age	Age	5·41 (0·29)***	6·64 (0·33)***	4·25 (0·28)***	2·83 (0·60)***	2·74 (0·81)***	2·25 (0·69)**
	Age-squared	0·22 (0·02)***	0·20 (0·02)***	0·28 (0·02)***	0·23 (0·04)***	0·35 (0·06)***	0·20 (0·05)***
	Age-cubed	−0·01 (0·001)***	−0·01 (0·001)***	−0·01 (0·001)***	−0·004 (0·001)***	−0·007 (0·001)***	−0·004 (0·001)**
Period	1992–1993	1·15 (1·24)	1·75 (1·42)	0·96 (1·20)	−48·63 (2·58)***	−51·03 (3·49)***	−47·45 (2·97)***
	1993–1994	6·14 (1·24)***	5·88 (1·42)***	6·87 (1·20)***	3·72 (2·59)	2·57 (3·50)	4·16 (2·98)
	1994–1995	10·29 (1·24)***	11·27 (1·42)***	10·42 (1·21)***	−78·04 (2·60)***	−80·60 (3·51)***	−77·67 (2·99)***
	1995–1996	9·74 (1·25)***	10·06 (1·43)***	10·14 (1·21)***	−71·15 (2·61)***	−69·27 (3·53)***	−71·78 (3·00)***
	1996–1997	17·19 (1·26)***	16·29 (1·44)***	18·47 (1·22)***	−25·98 (2·63)***	−21·1 (3·55)***	−28·27 (3·02)***
	1997–1998	18·45 (1·27)***	16·28 (1·45)***	20·49 (1·23)***	5·24 (2·65)*	8·87 (3·58)*	3·05 (3·05)
	1998–1999	17·50 (1·28)***	14·58 (1·47)***	20·09 (1·24)***	2·95 (2·68)	10·33 (3·62)**	−0·72 (3·08)
	1999–2000	16·90 (1·30)***	12·78 (1·49)***	20·29 (1·26)***	48·71 (2·71)***	55·22 (3·66)***	45·50 (3·12)***
	2000–2001	12·80 (1·30)***	7·99 (1·49)***	16·29 (1·26)***	−107·50 (2·72)***	−107·02 (3·67)***	−108·46 (3·13)***
	2001–2002	19·08 (1·31)***	12·92 (1·50)***	23·34 (1·27)***	−35·87 (2·73)***	−29·42 (3·69)***	−39·88 (3·14)***
	2002–2003	16·31 (1·31)***	9·38 (1·50)***	20·73 (1·27)***	−125·79 (2·74)***	−119·47 (3·71)***	−129·95 (3·15)***
	2003–2004	23·94 (1·32)***	14·82 (1·51)***	29·63 (1·28)***	59·86 (2·76)***	64·67 (3·72)***	56·93 (3·17)***

Reference group is the 1991–1992 influenza season.
* $P<0·05$, ** $P<0·01$, *** $P<0·001$.

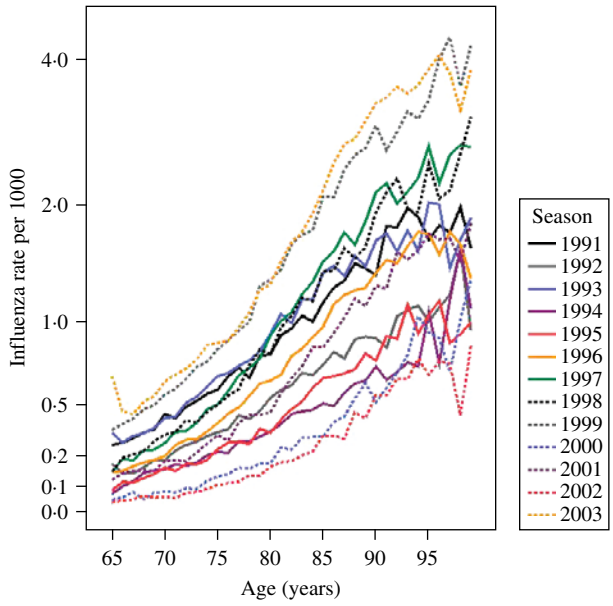

Fig. 1. Influenza rates by individual influenza season and age.

three earlier birth cohorts – 1898–1899, 1899–1900, and 1902–1903. For influenza, there were significant and positive associations between birth cohort and disease rates for all cohorts between 1898–1899 and 1927–1928, and these relationships were observed in females for about the same time frame, and about 1 year earlier for males.

The panels in Figures 3 and 4 illustrate the decomposition of age, period, and cohort relationships with P&I outcomes. Log-transformed pneumonia rates by age and influenza year are shown in Figure 3. Figure 3*a* illustrates the actual rates by age and year, with darker shades indicating higher rates. There appears to be a consistent trend of increasing P&I rates with increasing age, and the residuals from the age-only model are shown in Figure 3*b*. Age accounts for a substantial portion of the variation in P&I rates (99%), yet the residuals from this model are not evenly dispersed over time and age. The age-period model (Fig. 3*c*), shows that the magnitude of residuals decreased from the age-only model when period terms were added to the model. Additionally, the vertical stripes and patterns observed in the age-only model do not seem as evident in the age-period model. However, there are notable diagonal patterns remaining in the residuals of the age-period model, suggesting the potential for associations with birth cohort. The full age-period cohort model residuals (Fig. 3*d*), depicts the lowest overall residuals in magnitude, and some potential weak patterns in the direction of residuals. For the oldest ages in the last two or three seasons, there were consistently large, negative residuals throughout nearly all models examined, indicating that assuming the same P&I increase with age for all influenza seasons may not be the most appropriate approach in modelling P&I rates.

For influenza alone, the relative annual variability was generally higher than that of P&I combined (Fig. 4*a*). The residuals from the age model (Fig. 4*b*) show that after accounting for age, there are still notable period associations with influenza rates. After

https://doi.org/10.1017/S0950268809991506 Published online by Cambridge University Press

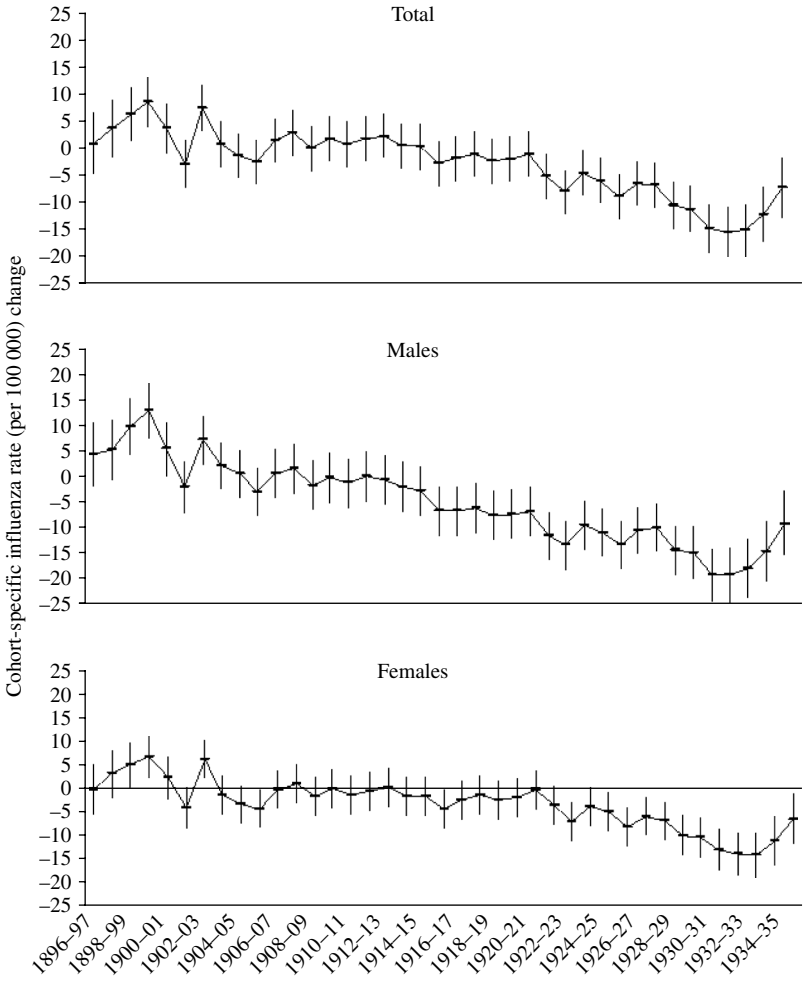

Fig. 2. Illustration of cohort effects for pneumonia and influenza rates after adjustment for age and period effects overall, and by gender.

age and period associations are taken into account, the magnitude of residuals decreased sharply from $\pm 1{\cdot}32$ to $\pm 0{\cdot}57$ (Fig. 4*c*). The full age-period cohort (Fig. 4*d*) models showed less discernible patterns to the residuals, and overall reduced residual magnitude compared to the age-period and age-only models.

DISCUSSION

Our findings suggest the benefits of considering not only period effects, but also age and cohort effects when studying P&I morbidity in older adults. This study is among the first to use a formal age-period cohort approach for P&I in the US older population, in which P&I are common causes of morbidity and mortality.

Age effects account for substantial variability in seasonal influenza and in combined P&I rates. The disease rates increase with age almost exponentially, but decelerate at the oldest ages. The age-period cohort models highlight the importance of age in determining P&I rates in the older population. Age may not be an independent cause of the infections, but rather a meaningful surrogate for physiological conditions and changes [31]. However, in this aggregate national analysis, age accounts for the most variability in hospitalization rate when compared to the other two factors, period and cohort (99% for P&I combined, 65–81% for influenza alone). The period effect shows dramatic fluctuations over time, particularly for influenza alone, which generally exhibits large changes in magnitude across years. These period effects are consistent with previous research on influenza seasonality [13–16], but are relatively less intense for P&I combined. The severity of the influenza strain for older adults generally correlates to the severity of the observed period effect [5]. In the full age-period cohort model, the residual still showed

https://doi.org/10.1017/S0950268809991506 Published online by Cambridge University Press

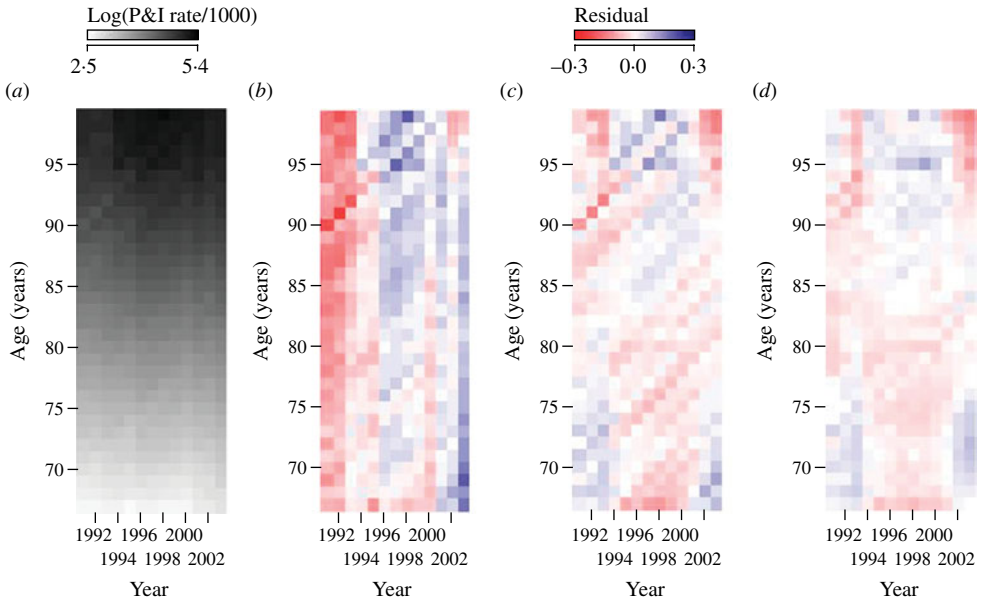

Fig. 3. (*a*) Log-transformed pneumonia and influenza rates and (*b–d*) residuals from variations of the age-period cohort model by age and season: (*b*) age model, (*c*) age-period model, (*d*) age-period cohort model. Colours and intensities represent magnitude and direction of residual: red and blue represent positive and negative residuals, respectively.

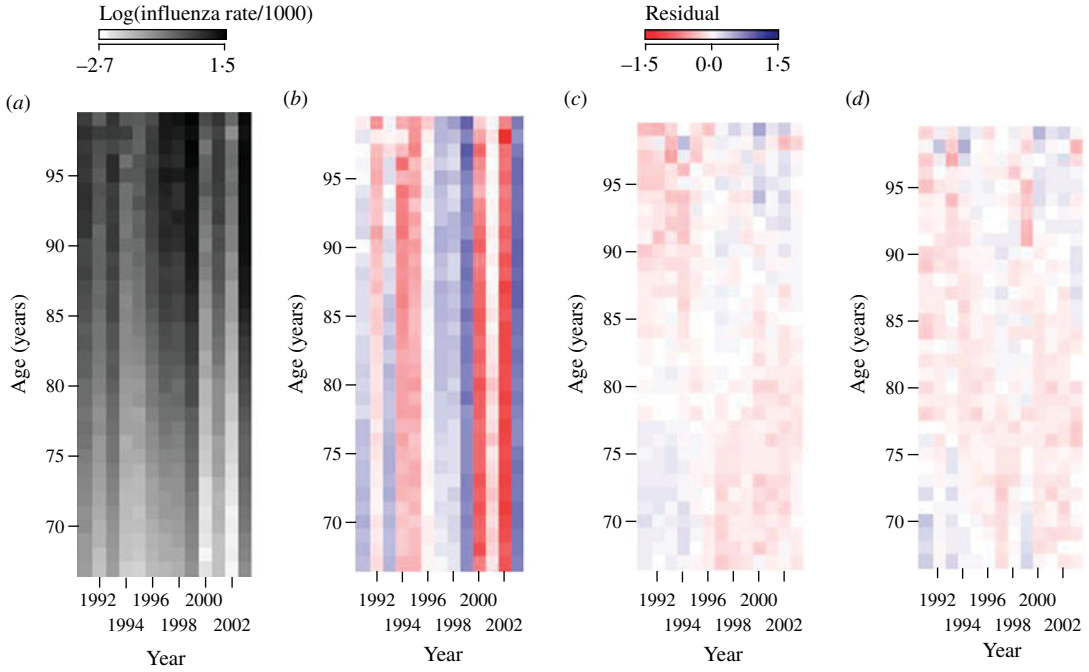

Fig. 4. (*a*) Log-transformed influenza-only rates and (*b–d*) residuals from variations of the age-period cohort model by age and season: (*b*) age model, (*c*) age-period model (*d*) age-period cohort model. Colours and intensities represent magnitude and direction of residual: red and blue represent positive and negative residuals, respectively.

some differences by period. For example, for P&I combined, three distinct influenza seasons – 1993–1994, 2002–2003, and 2003–2004 – had similar residual patterns. In the younger seniors, there was a discernible positive peak in residuals between ages 69 and 75 for all three years. During the same seasons, residuals exhibited negative bands at the highest age groups, primarily above age 92 years. Similar, but less noticeable residual patterns were observed in the 1992–1993 season. In contrast, the seasons between

https://doi.org/10.1017/S0950268809991506 Published online by Cambridge University Press

1994–1995 and 2001–2002 had the opposite pattern, with negative residual bands in the younger age groups and higher residuals in the oldest ($\geqslant$90 years) group. This demonstrates that the relationship between P&I and age is more complex than allowed for by the model, in that this relationship varies from year to year. It may also suggest additional age effects for which the models do not adjust. To improve the additive age-period cohort model used in this analysis, models might incorporate interaction terms that allow for the relationship between age and P&I to vary by influenza season. However, for the influenza-only model these residual patterns were not as evident.

The most notable finding was that cohort-specific morbidity patterns were present even after adjusting for age and period trends. Consistent, positive associations existed between P&I and three birth cohorts – 1898–1899, 1899–1900 and 1902–1903 – for the population as a whole, and by gender. For females, the 1901–1902 birth cohort was associated with a significant decrease in P&I rates. The reasons why these non-contiguous birth cohorts exhibit such anomalous behaviour with respect to P&I rates is not clear. Given the consistency across genders, chance alone may not be the most likely explanation for this irregularity. Further research is needed to elucidate the source of these patterns.

The age-period cohort model for P&I had a region of significantly negative terms for the cohorts born around and after 1920 (slightly earlier for males). This could be a result of several factors. First, these findings could reflect the type of model used. That is, since the younger cohorts are represented by younger ages in these models, these cohorts would naturally exhibit lower P&I rates than their older counterparts. Perceivably, the model may not fully account for the entire age effect, suggesting that the observed cohort relationships are, indeed, remaining age effects. However, this model does account for the overall increase in P&I rates with increasing age, and these relationships remain even after including a linear term representing birth-cohort group to control this potential confounding by age. Thus, another scenario is that these cohort effects may reflect a real decline in influenza by birth cohort, perhaps due to increased vaccination coverage, for instance. Additional data on these cohorts are needed to test this hypothesis, including prior data on the earlier cohorts to discern their P&I burden during their younger years, and future data on the younger birth cohorts for analogous reasons.

For the influenza-only models, disease rates showed significant positive associations with birth cohorts between the late 1890s and mid-1920s, peaking in the early 1910s. Although theses associations changed direction in the youngest birth cohorts, none were statistically significant. These associations may be due to the modelling procedure and may, in fact, represent residual age effects, or could be attributed to true cohort trends. The anomalous birth cohorts observed in the P&I models discussed above were also evident in the influenza-only model, as well as a small decline in the relationship for the 1905–1906 birth cohort. The explanations for these observations are not entirely clear. There is uncertainty as to exactly how potential cohort effects influence disease dynamics in the population. One explanation suggests that any given birth cohort is influenced by certain exogenous or endogenous factors, which can be related with the overall health and viability of the individuals in that birth cohort, directly or indirectly [31]. Alternatively, a cohort can be considered not as a cause, but a group of proxies for a set of underlying conditions common to people who experience events contemporaneously and at similar ages. Another possibility is a cohort-inversion effect. The premise of this theory is that population cohorts that experience particularly good or unfavourable conditions early in life will show an inverse response in morbidity and/or mortality later in life [32], which is consistent with an emergent body of research that suggests that childhood conditions are associated with later-life health outcomes [33]. In the case of P&I, cohort effects may occur via pre-existing immunity to cohorts through exposure during previous epidemics, as in the case of the 1918–1919 Spanish influenza epidemic [34, 35]. Discerning the specific set of good or unfavourable conditions experienced by these cohorts that resulted in this atypical morbidity pattern requires more detailed research.

Generally, the age-period cohort studies of other health issues and diseases demonstrate the importance of assessing these three related, but distinct, demographic dimensions of disease and mortality patterns [36, 37]. The age-period cohort approach allows for the analysis of several potential population-level influences – namely age and cohort – that would otherwise be overlooked using the more traditional period-based approach. In this study, the age-period cohort approach allows for the possibility that some cohorts have irregularly high or low levels of P&I than would be expected if there were no differences

between cohorts. Cohort effects in age-period cohort analyses can be thought of as period effects that only occur to a particular age or age group. Consider, for example, that, in a given year, occupational or environmental exposures occur, to toxic chemicals that could potentially damage the respiratory system. However, the exposure may be differentially detrimental to particular age groups, such as children, who might be particularly susceptible to such an exposure because their respiratory systems are in the developmental stages. Such exposures could have consequences later in life, but only to those people of a particular birth cohort who were exposed at a vulnerable age. In our study, we cannot definitively ascertain the set of specific factors that contribute to the observed patterns of P&I. More detailed hypotheses can be explored to elucidate those cohort-related factors that are related to the observed differences found between cohorts. This approach also allows for the modelling of the complex relationship between age and P&I, which is often analysed as a nuisance parameter, and may be masked by standardization of rates [38] or by grouping older adults into age categories [13, 22].

Additionally, the models may underestimate true age effects, due to the outcome data source. The outcome is based on hospitalized cases of P&I, not all cases of these diseases. Excess influenza-attributable hospitalizations that are not coded as P&I would probably increase the overall levels of P&I cases if they had been included in the CMS hospitalization data. If, for example, the older an individual is, the less likely they are to be tested for influenza, then this discrepancy between hospitalized cases and actual cases would increase with age in older adults, suggesting that the age effects would be underestimated in these models. Healthcare utilization itself varies over time and space. For example, there are considerable rural–urban gradients in the distribution of the older population in the USA [39], and in healthcare utilization [40, 41]. There is evidence to suggest that the overall increase in P&I over the past several decades is due, in part, to increased frequency of coding influenza and pneumonia in Medicare data. One study found that up to 5% of the increase in P&I observed between 1987 and 1999 was due exclusively to an increase in coding frequency of P&I [42]. The increase in coding may contribute to the period effects observed.

Extending this analysis before the 1991–1992 season and beyond the 2003–2004 season to provide complete coverage for birth cohorts from ages 66–99 years would help to determine whether the observed cohort effects are, in fact, real, or if these are related to the different ages of the cohorts. Additional research is necessary to explore the potential influence of specific living conditions, availability of resources, event experiences, or other factors related to the observed differences between birth cohorts for P&I rates. Furthermore, if such factors did contribute to differences in P&I, they would need to occur not only at some period of time, but they would also, by definition, need to affect only people of a certain age at that time. Further exploration into these effects is important to better understand the potential factors that contributed to differences in birth cohorts, to ultimately reduce the potential for those conditions or events from increasing susceptibility to these deadly diseases in future birth cohorts.

ACKNOWLEDGEMENTS

We acknowledge our funding source, NIH-NIAID U19 AI62627 and HHSN266200500032C. We also thank Drs Kenneth Chui, Jyotsna Jagai, and Janet Forrester, and Ms. Julia Wenger of Tufts School of Medicine for their assistance with this research.

DECLARATION OF INTEREST

None.

REFERENCES

1. **Potter CW.** A history of influenza. *Journal of Applied Microbiology* 2001; **91**: 572–579.
2. **Fleming DM, Elliot AJ.** The impact of influenza on the health and health care utilization of elderly people. *Vaccine* 2005; **23** (Suppl. 1): 1–9.
3. **Maxwell ES, Ward TG, Van Metre TE.** The relation of influenza virus and bacteria in the etiology of pneumonia. *Journal of Clinical Investigation* 1948; **28**: 307–318.
4. **Cunha BA.** Pneumonia in the elderly. *Clinical Microbiology and Infection* 2001; **7**: 581–588.
5. **Thompson WW, *et al.*** Influenza-associated hospitalizations in the United States. *Journal of the American Medical Association* 2004; **292**: 1333–1340.
6. **Thompson WW, *et al.*** Mortality associated with influenza and respiratory syncytial virus in the United States. *Journal of the American Medical Association* 2003; **289**: 179–186.
7. **Dowell SF, Ho MS.** Seasonality of infectious diseases and severe acute respiratory syndrome – what we don't know can hurt us. *Lancet Infectious Diseases* 2004; **4**: 704–708.

8. **Zambon MA.** Epidemiology and pathogenesis of influenza. *Journal of Antimicrobial Chemotherapy* 1999; **44**: 3–9.
9. **Nicholson KG, Wood JM, Zambon M.** Influenza. *Lancet* 2003; **362**: 1733–1745.
10. **Smith GJ, *et al.*** Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza A epidemic. *Nature* 2009; **459**: 1122–1125.
11. **Palese P.** Influenza: old and new threats. *Nature Medicine* 2004; **10**: S82–87.
12. **Couch RB.** Prevention and treatment of influenza. *New England Journal of Medicine* 2000; **343**: 1778–1787.
13. **Simonsen L, *et al.*** Impact of influenza vaccination on seasonal mortality in the US elderly population. *Archives of Internal Medicine* 2005; **165**: 265–72.
14. **Serfling RE.** Methods for current statistical analysis of excess pneumonia-influenza deaths. *Public Health Reports* 1963; **78**: 494–506.
15. **Lofgren E, *et al.*** Influenza seasonality: underlying causes and modeling theories. *Journal of Virology* 2007; **81**: 5429–5436.
16. **Cohen SA, Naumova EN.** Population dynamics in the elderly: the need for age-adjustment in national biosurveillance systems. *Lecture Notes in Computer Science* 2007; **4506**: 47–58.
17. **Kang I, *et al.*** Age-associated change in the frequency of memory CD4+ T cells impairs long term CD4+ T cell responses to influenza vaccine. *Journal of Immunology* 2004; **173**: 673–681.
18. **Goodwin K, Viboud C, Simonsen L.** Antibody response to influenza vaccination in the elderly: A quantitative review. *Vaccine* 2006; **24**: 1159–1169.
19. **Voordouw BC, *et al.*** Influenza vaccination in community-dwelling elderly: impact on mortality and influenza-associated morbidity. *Archives of Internal Medicine* 2003; **163**: 1089–1094.
20. **Castle SC, *et al.*** Comorbidity is a better predictor of impaired immunity than chronological age in older adults. *Journal of the American Geriatrics Society* 2005; **53**: 1563–1569.
21. **Jackson LA, *et al.*** Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors. *International Journal of Epidemiology* 2006; **35**: 345–352.
22. **Olson DR, *et al.*** Monitoring the impact of influenza by age: emergency department fever and respiratory complaint surveillance in New York City. *PLoS Medicine* 2007; **4**: 1349–1361.
23. **Sacher GA.** On the statistical nature of mortality with special reference to chronic radiation mortality. *Radiology* 1956; **67**: 250–257.
24. **Collins JJ.** The contribution of medical measures to the decline of mortality from respiratory tuberculosis: an age-period-cohort model. *Demography* 1982; **19**: 409–427.
25. **Fisher ES, *et al.*** Overcoming potential pitfalls in the use of Medicare data for epidemiologic research. *American Journal of Public Health* 1990; **80**: 1487–1490.
26. **The Henry Kaiser Family Foundation.** Medicare (http://www.statehealthfacts.org/cgi-bin/healthfacts.cgi?action=compare&welcome=1&category=Medicare). Accessed 20 March 2007.
27. **Viboud C, *et al.*** Synchrony, waves, and spatial hierarchies in the spread of influenza. *Science* 2006; **312**: 447–451.
28. **Simonsen L, *et al.*** The impact of influenza epidemics on mortality: introducing a severity index. *American Journal of Public Health* 1997; **87**: 1944–1950.
29. **Thygessen LC, Knudsen LB, Keiding N.** Modelling regional variation of first-time births in Denmark 1980–1994 by an age-period-cohort model. *Demographic Research* 2005; **13**: 573–596.
30. **Scherbov S, van Vianen H.** Marriage in Russia: a reconstruction. *Demographic Research* 2004; **10**: 28–60.
31. **Derrick VPA.** Observations of (1) errors of age in the population statistics of England and Wales and (2) the changes of mortality indicated by national records. *Journal of the Institute of Actuaries* 1927; **58**: 117–159.
32. **Hobcraft J, Menken J, Preston S.** Age, period, and cohort effects in demography: a review. *Population Index* 1982; **48**: 4–43.
33. **Blackwell DL, Hayward MD, Crimmins EM.** Does childhood health affect chronic morbidity later in life? *Social Science & Medicine* 2001; **52**: 1269–1284.
34. **Ahmed R, Oldstone MB, Palese P.** Protective immunity and susceptibility to infectious diseases: lessons from the 1918 influenza pandemic. *Nature Immunology* 2007; **8**: 1188–1193.
35. **Graham JE, Christian LM, Kiecolt-Glaser JK.** Stress, age, and immune function: toward a lifespan approach. *Journal of Behavioral Medicine* 2006; **29**: 389–400.
36. **Cayuela A, *et al.*** Age-period-cohort analysis of breast cancer mortality rates in Andalucia (Spain). *Annals of Oncology* 2004; **15**: 686–688.
37. **Wilmoth J, Vallin J, Caselli G.** When does a cohort's mortality differ from what we might expect? *Population: an English Selection* 1990; **2**: 93–126.
38. **Rizzo C, *et al.*** Trends for influenza-related deaths during pandemic and epidemic seasons, Italy, 1969–2001. *Emerging Infectious Diseases* 2007; **13**: 694–699.
39. **Cohen SA.** A review of demographic and infrastructural factors and potential solutions to the physician and nursing shortage predicted to impact the growing US elderly population. *Journal of Public Health Management and Practice* 2009; **15**: 352–362.
40. **Arcury TA, *et al.*** The effects of geography and spatial behavior on health care utilization among the residents of a rural region. *Health Service Research* 2005; **40**: 135–155.
41. **Adams EK, *et al.*** Predicting hospital choice for rural Medicare beneficiaries: the role of severity of illness. *Health Service Research* 1991; **26**: 583–612.
42. **Hebert PL, McBean AM, Kane RL.** Explaining trends in hospitalizations for pneumonia and influenza in the elderly. *Medical Care Research and Review* 2005; **62**: 560–582.