Pandemic versus Epidemic Influenza Mortality: A Pattern of Changing Age Distribution

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Almost all deaths related to current influenza epidemics occur among the elderly. However, mortality was greatest among the young during the 1918–1919 pandemic. This study compared the age distribution of influenza-related deaths in the United States during this century's three influenza A pandemics with that of the following epidemics. Half of influenza-related deaths during the 1968–1969 influenza A (H3N2) pandemic and large proportions of influenza-related deaths during the 1957–1958 influenza A (H2N2) and the 1918–1919 influenza A (H1N1) pandemics occurred among persons <65 years old. However, this group accounted for decrementally smaller proportions of deaths during the first decade following each pandemic. A model suggested that this mortality pattern may be explained by selective acquisition of protection against fatal illness among younger persons. The large proportion of influenza-related deaths during each pandemic and the following decade among persons <65 years old should be considered in planning for pandemics.

The epidemiology of influenza in temperate climate zones is characterized by the annual or near-annual occurrence of regional or national epidemics of influenza [1]. The virologic basis for recurrent epidemics is a continual process of antigenic change (antigenic drift) among circulating influenza viruses [2]. Between 1972 and 1992, influenza epidemics claimed an average of 21,000 lives each season (range, 0–47,000 deaths) in the United States [3]. In recent seasons, 80%–90% of influenza-related deaths have occurred among persons ⩾65 years old [4]. Mortality was highest during seasons in which influenza A (H3N2) viruses predominated [1, 3, 4].

In contrast to annual epidemics, worldwide pandemics of influenza occur infrequently in association with the unpredictable emergence of new influenza A virus subtypes [5–7]. Pandemics lead to widespread increases in influenza-related morbidity and mortality and have occurred three times in this century: in 1918–1919 ''Spanish influenza,'' A (H1N1); in 1957–1958 ''Asian influenza,'' A (H2N2); and in 1968–1969 ''Hong Kong influenza,'' A (H3N2) [1]. Influenza A (H1N1) viruses stopped circulating in 1957 and then reappeared in 1977; influenza A (H2N2) viruses disappeared from the human population in 1968 [1]. In recent years, strains of influenza A (H1N1), A (H3N2), and B viruses have cocirculated [3, 8].

Nearly half of the influenza-related deaths during the 1918–1919 pandemic occurred among young (20–40 years of age) and previously healthy adults for reasons that have never been explained adequately [9]. This devastating pandemic led to >500,000 deaths in the United States and 20 million deaths worldwide [1]. The striking contrast in mortality patterns between recent influenza epidemics and the 1918–1919 pandemic led us to compare the age distribution of deaths between this century's three influenza A pandemics and the epidemics that followed.

Materials and Methods

Because influenza illness and related deaths are incompletely ascertained [10], ''seasonal excess mortality'' is calculated to assess the impact of influenza on mortality [1]. Excess mortality is typically estimated as the sum of deaths during the influenza season above a baseline of deaths that would be expected in the absence of influenza epidemics. Over the years, investigators usually have reported either excess in pneumonia and influenza (P&I) mortality or excess in mortality due to any cause (''all-cause'' excess mortality) to measure the impact of influenza on mortality [1, 3].

1968–1995: estimating age-specific excess mortality by using national vital statistics. We used multiple-cause-of-death data from the National Center for Health Statistics, Centers for Disease Control and Prevention, to identify P&I-related deaths during 1968–1995 [11]. We defined a P&I death as any death in which pneumonia or influenza (ICDA-8 codes 474 and 480–486 and ICD-9 codes 480–487) was listed on the certificate as the single underlying cause of death [12–14]. A recently developed statistical model [3] was applied to weekly numbers of P&I deaths to estimate

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The computer simulation model is available from L. Simonsen as an Excel spreadsheet file. Please make requests by email (Lonesimon@msn.com).

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seasonal excess P&I deaths among persons <65 years old and ≥65 years old for 1972–1995.

Because weekly mortality data were not available for 1968–1972, an alternative approach was developed that used monthly data. A baseline of expected deaths in winter months (i.e., deaths in the absence of influenza) was constructed by calculating 3-month moving averages of P&I deaths in 25 influenza-free November months between 1968 and 1995. To raise this line to best fit the 6 influenza-free December months, we iteratively added a constant to the 3-month moving average estimates until the squared distance between these raised November estimates and the actual December estimates was minimized. The sum of P&I deaths above this baseline during the months with documented influenza virus activity was considered excess P&I mortality. The use of monthly mortality data was validated by comparing our estimates for 1972–1992 with previously published P&I excess mortality estimates for the same period [3]. Results using both methods were very similar (Pearson $r = .9$, $P < .05$).

1918–1968: estimating age-specific excess mortality from literature sources. For 1918–1968, we used published age-specific excess mortality estimates for influenza A seasons in the United States. Some authors reported excess mortality in terms of P&I deaths, while others reported excess deaths due to any cause (all-cause excess mortality). Census data from the preceding year were used to convert rates of excess mortality to absolute numbers of excess deaths for each age group.

Studies by Collins [9, 15, 16] provided data for the 1918–1919 influenza A (H1N1) pandemic and the seven severe influenza epidemics during 1919–1944. Collins calculated excess P&I mortality rates by calendar year for 1918–1929, so we converted these into seasonal mortality rates based on the periods with excess mortality [17]. Five additional influenza A (H1N1) seasons (1945–1946, 1946–1947, 1949–1950, 1950–1951, and 1952–1953) were associated with excess mortality [17] but could not be studied because age-specific mortality data were not available. Studies by Houseworth and Spoon [18] provided age-specific all-cause excess mortality for the 1957–1958 influenza A (H2N2) pandemic, three severe influenza A (H2N2) epidemics between 1959 and 1968, the 1968–1969 influenza A (H3N2) pandemic, and the 1969–1970 A (H3N2) season. Data for 1974–1981 and 1968–1983 were obtained from studies by Lui and Kendal [4] and by Stroup et al. [19], respectively.

Analysis of the age distribution of excess mortality related to influenza. For each influenza A season, we calculated the proportion of excess deaths accounted for by persons <65 years of age, the relative risk of excess mortality among elderly versus younger persons, and the absolute risk of influenza-associated mortality in the years following a pandemic. Changes in risk of mortality following a pandemic were calculated for each age group by dividing the excess mortality rate associated with each pandemic by the mortality rates of later severe influenza seasons in which the same virus subtype predominated.

Use of computer simulations to explain observed mortality patterns. We searched for factors that might account for the observed pattern of age-related mortality during and after the 1968–1969 influenza A (H3N2) pandemic by constructing a model that used US census data for two age groups (the young, <65 years old; the old, ≥65 years) and contained the following parameters: (1) proportion who acquired protection against fatality, A_{young} and A_{old}, (2) the infection rate, P for pandemic seasons, E for epidemic seasons, and (3) the proportion that die, M_{young} and M_{old}. The model exposed the census population to a simulated influenza epidemic based on varying combinations of these parameters for each season during 1968–1995, when influenza A (H3N2) viruses circulated and caused epidemics in the United States. We explored these effects for a realistic range of infection rates [20], from 40% to 50% for the pandemic season and from 15% to 30% for subsequent epidemics, and from 15% to 25% for acquired protection against fatality. Each simulation was initiated by choosing a pandemic infection rate P, and then the probability of death given infection of a susceptible young or old person (M_{young} and M_{old}) was adjusted so that the simulation produced the observed number of P&I deaths for each age group for the 1968–1969 pandemic.

In the base model, persons of any age who survived their first A (H3N2) infection would gain full protection against fatal disease from A (H3N2) viruses in future seasons ($A_{young} = A_{old} = 100\%$). In subsequent simulations, the parameters were altered in an attempt to mimic the observed pattern of declining excess P&I deaths among the <65-year-old population. For all simulations, M_{young} and M_{old} were fixed once established, and those <65 years old were fully protected from death once infected ($A_{young} = 100\%$).

Results

Seasonal age distribution of excess deaths. Overall, excess mortality rates during influenza A epidemics declined from 1918 to 1995 among groups <65 years and ≥65 years old. There were large fluctuations among individual seasons (tables 1–3). During each of the three pandemics in this century, persons <65 years of age initially accounted for a high proportion of all influenza-related deaths and then proportionally fewer deaths during subsequent epidemics in the following decade (figure 1, tables 1–3).

Influenza A (H1N1). The 1918–1919 influenza A (H1N1) pandemic was unique in that the absolute risk of influenza-associated mortality was higher among persons <65 than those ≥65 years old (table 1). In that pandemic, persons <65 years of age accounted for 99% of all excess influenza-related deaths. During subsequent A (H1N1) epidemics, however, persons <65 years of age accounted for progressively fewer of such deaths. This group accounted for about 30% of influenza-related mortality in the 1940s, and 0–5% in the 1980s. After the reappearance of influenza A (H1N1) in 1977, the 1986–1987 season was the only season in which A (H1N1) viruses predominated (accounting for 99% of the isolates); therefore, this was the only season in which it was possible to definitely attribute influenza-related deaths to A (H1N1) viruses.

These figures correspond to a 10-fold decrease in the absolute risk of influenza-associated mortality after 1 decade (by 1928–1929) and a 44-fold decrease in the absolute risk after 2 decades (by 1936–1937) among the younger age group. By contrast, the risk of influenza-related mortality among persons ≥65 years of age increased >3-fold just after 1 decade of A (H1N1) circulation and decreased to 74% of its initial level after 2 decades.

Table 1. Age-specific excess mortality related to influenza A (H1N1), United States.

Season	Influenza subtype	P&I data source*	Excess mortality rate/100,000† for			Risk ratio ≥65:<65	Proportion (%)‡ of excess deaths in persons <65 years old
			All ages	Persons ≥65 years old	Persons <65 years old		
1918–1919	**H1N1**	[16]	529 (546,000)	166 (8000)	546 (538,000)	0.3:1	99
1919–1920	H1N1	[16]	93 (96,000)	175 (8000)	89 (88,000)	2:1	92
1921–1922	H1N1	[16]	16 (17,000)	93 (5000)	12 (12,000)	8:1	72
1922–1923	H1N1	[16]	37 (41,000)	280 (16,000)	24 (25,000)	12:1	62
1925–1926	H1N1	[16]	26 (30,000)	221 (14,000)	15 (16,000)	15:1	55
1928–1929	H1N1	[16]	84 (102,000)	594 (39,000)	55 (63,000)	11:1	62
1936–1937	H1N1	[16]	18 (23,000)	101 (8000)	12 (15,000)	8:1	65
1943–1944	H1N1	[15]	14 (19,000)	123 (13,000)	4.8 (6000)	26:1	31
1977–1978§	H1N1		3.8 (8300)	30 (7100)	0.6 (1200)	50:1	14
	H3N2	[19]	3.7 (8200)	31 (7400)	0.4 (800)	79:1	9
		[4]	3.3 (7300)	26 (6300)	0.5 (1000)	50:1	14
1983–1984	H1N1, B		1.5 (3500)	16 (4400)	0 (0)	Infinite	0
1986–1987	H1N1		0.7 (1800)	5.7 (1700)	0 (0)	Infinite	0
1988–1989	H1N1, B		2.1 (5100)	15 (4400)	0.1 (200)	131:1	5

NOTE. Pandemic season is in bold. Listed influenza epidemics before 1933 were probably caused by influenza A (H1N1) viruses, but this could not be directly verified because influenza isolation and subtyping only began after 1933. Recently, molecular analysis has confirmed that 1918–1919 pandemic was caused by influenza A (H1N1) virus [26]. P&I = pneumonia and influenza.

* Collins [15, 16] used different P&I definition than did Lui and Kendal [4], Stroup et al. [19], and us. Thus, excess P&I mortality estimates during 1918–1944 are not directly comparable to those for seasons after 1977. Entries without references are estimates from this study and from Simonsen et al. [3].

† No. of excess deaths is given. Seasonal rate for 1918–1919 was calculated as combination of Collins's yearly rates for 1918 and 1919; 1919–1920 was 1920 yearly rate; 1921–1922 was 1922 yearly rate; 1922–1923 was 1923 yearly rate; 1925–1926 was combination of 1925 and 1926 yearly rates; 1928–1929 was combination of 1928 and 1929 yearly rates.

‡ Percents were calculated by using sum of excess deaths in age groups as total excess estimate.

§ During 1977–1978 season there were high levels of confirmed influenza A (H1N1) as well as A (H3N2) activity [1]. Relative contribution of 2 subtypes of viruses to excess mortality cannot be determined. Similarly, contribution of influenza B viruses cocirculating with A (H1N1) during 1988–1989 season to excess mortality cannot be determined.

Influenza A (H2N2). During the 1957–1958 influenza A (H2N2) pandemic, persons <65 years old accounted for 36% of all excess influenza-related deaths. Over the next decade this proportion decreased to 4%, corresponding to a 28-fold reduction in the absolute risk (table 2). The reduction in absolute risk in the ≥65-year age group was 2-fold during the same period.

Influenza A (H3N2). During the 1968–1969 influenza A (H3N2) pandemic, persons <65 years old accounted for 48% of all influenza-related excess deaths (table 3). This proportion decreased to 10% after 1 decade (1980–1981 season) and has averaged approximately 5% during later influenza A (H3N2) seasons. These figures correspond to a 7-fold decrease in risk among persons <65 years old after 1 decade (by the 1980–

Table 2. Age-specific excess mortality related to influenza A (H2N2), United States.

Season	Influenza subtype	All-cause data source*	Excess mortality rate/100,000† for			Risk ratio ≥65:<65	Proportion (%)‡ of excess deaths in persons <65 years old
			All ages	Persons ≥65 years old	Persons <65 years old		
1957–1958	**H2N2**	[18]	39 (66,000)	273 (42,000)	15 (24,000)	18:1	36
1959–1960	H2N2	[18]	18 (32,000)	145 (23,000)	5.6 (9000)	26:1	28
1962–1963	H2N2	[18]	25 (46,000)	198 (35,000)	7.0 (12,000)	28:1	26
1967–1968	H2N2	[18]	11 (22,000)	113 (21,000)	0.6 (1000)	203:1	4

NOTE. In addition to 4 seasons shown, excess mortality was also detected for 1958–1959, 1961–1962, 1964–1965, and 1965–1966 [7]. However, no age-specific mortality rates for those seasons are available in literature. Pandemic is in bold. During these years, no other influenza A strain types circulated and caused epidemics.

* Because these estimates [18] are all-cause excess mortality, they are not comparable with excess pneumonia and influenza (P&I) mortality estimates in tables 1 and 3. Excess P&I mortality is subset of ~25% of all-cause mortality on average [3].

† No. of excess deaths is given.

‡ These percentages were calculated by using sum of excess deaths in age groups as denominator.

Table 3. Age-specific excess mortality related to influenza A (H3N2), United States.

Season	Influenza subtype	Type of data, source*	Excess mortality rate/100,000 for			Risk ratio ≥65:<65	Proportion (%)‡ of excess deaths in persons <65 years old
			All ages†	Persons ≥65 years old	Persons <65 years old		
1968–1969	**H3N2**	P&I	8.1 (16,400)	44 (8600)	4.3 (7800)	10:1	48
		P&I [19]	7.4 (14,800)	45 (8700)	3.4 (6100)	13:1	41
		All-cause [18]	14 (28,100)	85 (16,500)	6.4 (11,600)	13:1	41
1969–1970	H3N2	P&I	3.3 (6600)	16 (3100)	1.9 (3500)	8:1	53
		P&I [19]	2.4 (4800)	12 (2400)	1.3 (2400)	9:1	50
		All-cause [18]	9.1 (18,400)	51 (10,100)	4.6 (8400)	11:1	45
1970–1971	H3N2	P&I	0.7 (1300)	2.8 (600)	0.4 (800)	7:1	57
1971–1972	H3N2	P&I	4.2 (8700)	29 (5800)	1.5 (2900)	19:1	33
		P&I [19]	0.6 (1200)	4.9 (1000)	0.1 (200)	44:1	17
1972–1973	H3N2	P&I	3.8 (7900)	21 (4500)	1.4 (2600)	15:1	37
		P&I [19]	4.3 (9100)	31 (6500)	1.4 (2600)	23:1	28
		P&I [4]	2.3 (4800)	19 (3800)	0.5 (1000)	34:1	20
1974–1975	H3N2	P&I	3.0 (6500)	19 (4200)	0.8 (1600)	23:1	27
		P&I [19]	3.3 (7100)	26 (5600)	0.8 (1500)	34:1	21
		P&I [4]	1.8 (3800)	15 (3000)	0.4 (800)	34:1	20
1975–1976	H3N2	P&I	5.5 (11,800)	42 (9600)	0.8 (1500)	55:1	13
		P&I [19]	6.3 (13,600)	53 (12,100)	0.8 (1600)	66:1	11
		P&I [4]	4.6 (9800)	40 (8500)	0.7 (1300)	56:1	13
1977–1978	H3N2, H1N1	P&I	3.8 (8300)	30 (7100)	0.6 (1200)	50:1	14
		P&I [19]	3.7 (8200)	31 (7400)	0.4 (800)	79:1	9
		P&I [4]	3.3 (7300)	26 (6300)	0.5 (1000)	50:1	14
1980–1981	H3N2	P&I	5.2 (11,700)	41 (10,400)	0.6 (1200)	67:1	10
		P&I [19]	2.7 (6200)	21 (5300)	0.4 (900)	48:1	14
		P&I [4]	3.9 (8600)	31 (7700)	0.5 (1000)	63:1	11
1982–1983	H3N2	P&I	2.0 (4700)	19 (5000)	0 (0)	Infinite	0
		P&I [19]	1.3 (3100)	11 (3100)	0 (0)	Infinite	0
1984–1985	H3N2	P&I	3.4 (8100)	29 (8000)	0.1 (300)	226:1	3
1987–1988	H3N2	P&I	3.1 (7400)	24 (7000)	0.1 (200)	281:1	2
1989–1990	H3N2	P&I	4.1 (10,100)	30 (9100)	0.3 (600)	116:1	6
1991–1992	H3N2	P&I	2.6 (6600)	19 (6000)	0.2 (400)	99:1	7
1992–1993	H3N2	P&I	2.4 (6200)	16 (5300)	0.2 (500)	73:1	9
1993–1994	H3N2	P&I	3.9 (9950)	29 (9000)	0.3 (600)	97:1	6
1994–1995	H3N2	P&I	2.0 (5200)	15 (4600)	0.1 (200)	150:1	4

NOTE. For 1977–1978, excess mortality may not be attributable to A (H3N2) viruses alone (see footnote to table 1).

* Entries without [source] are estimates for this study and [3]. Because our pneumonia and influenza (P&I) definition was identical to that of Lui and Kendal [4] and Stroup et al. [19], all P&I excess mortality estimates in this table are comparable. However, all-cause excess mortality estimates for 1968–1969 and 1969–1970 seasons [18] are not comparable with P&I estimates.

† Our estimates for 1972–1995 were generated by applying cyclical regression model to weekly vital statistics data [3] and for 1968–1972 by using alternative approach for monthly data.

‡ These percents were calculated by using sum of excess deaths in age groups as denominator.

1981 season) and a 17-fold decrease in risk after 2 decades (by the 1989–1990 season) of circulation of this virus. Among persons ≥65 years of age, there was no reduction in risk of influenza-related mortality after 1 decade and less than a 2-fold reduction in risk after 2 decades.

Factors that may explain the observed mortality pattern. We explored factors that might help explain the observed decrease in mortality among persons <65 years of age following pandemics by developing a model based on the 1968–1969 A (H3N2) pandemic and subsequent A (H3N2) influenza epidemics. In the base model, which assumed that persons of any age who survived their first A (H3N2) infection would gain full protection against fatal disease from A (H3N2) viruses in future seasons, the proportion of excess P&I deaths among persons <65 years old declined slowly. This pattern was substantially different from the observed pattern (regardless of how pandemic and epidemic infection rates were varied).

In subsequent models, we continued to assume full protection against fatal disease for persons <65 years of age but varied the proportion of elderly who acquired full protection. To produce a declining absolute number of influenza-related deaths among persons ≥65 years of age in epidemics following the pandemic, the model indicated that at least 15% of this age group needed to acquire protection against fatal illness

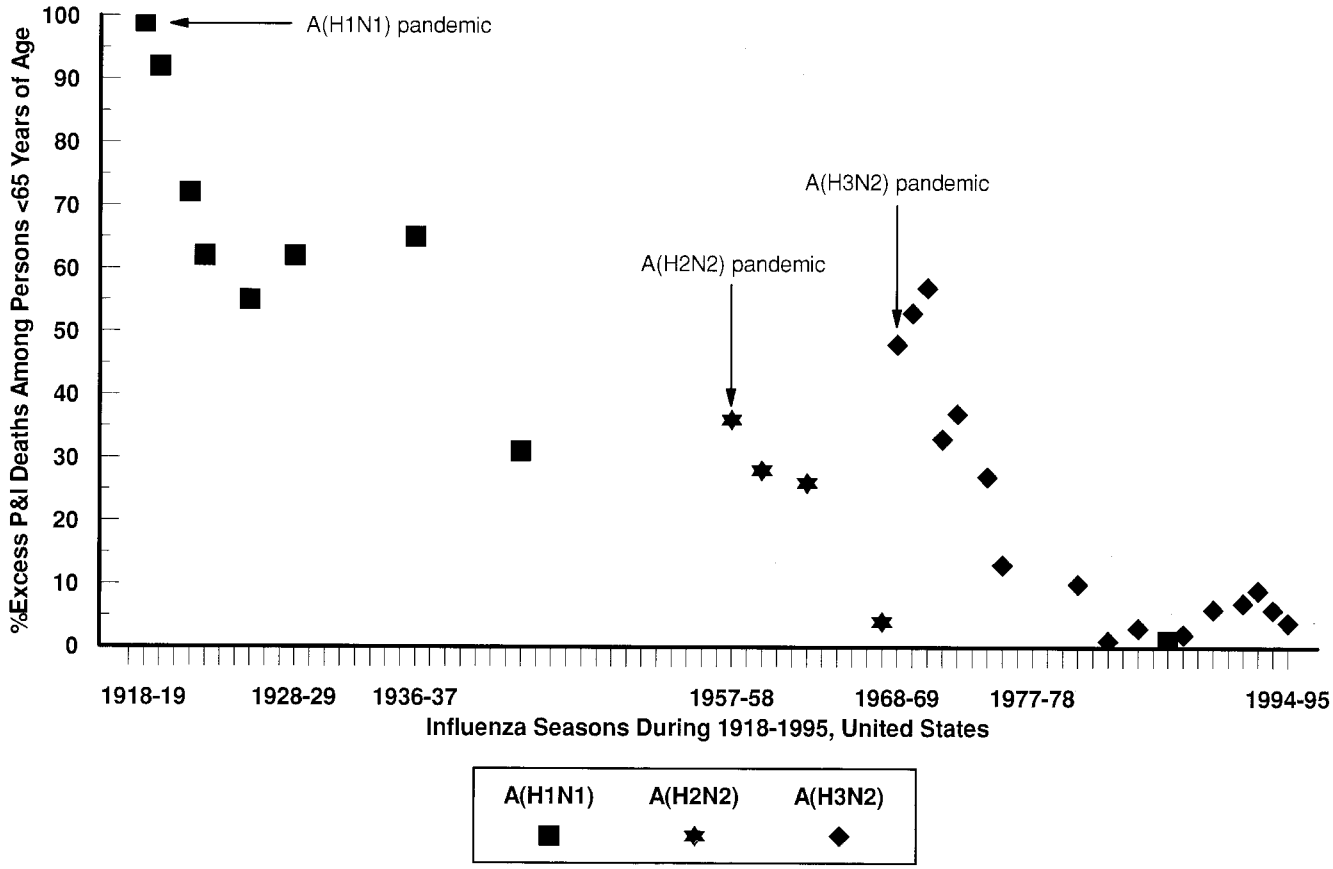

Figure 1. Age distribution of deaths associated with 3 influenza A pandemics and interpandemic seasons in United States, 1918–1995. Data from tables 1–3 are plotted graphically for influenza A (H1N1), A (H2N2), and A (H3N2). For influenza A (H1N1) seasons, only data point for 1986–1987 season was included, which was the only season when excess mortality was attributed solely to A (H1N1) viruses. Data points since 1968 are based on our analysis of pneumonia and influenza (P&I) mortality data.

following a survived infection. Using a realistic range of infection rates, this model yielded an age distribution of influenza-related deaths that was in good agreement with the observed data (figure 2). The slope of the line was most sensitive to the epidemic infection rate.

Discussion

During the 20th century, there has been a consistent age-specific mortality pattern associated with pandemic and epidemic influenza in the United States: Persons <65 years of age initially accounted for a high proportion of influenza-related deaths during each of three influenza A pandemics in this century and then a rapidly declining proportion of deaths during the decades following each pandemic. This decline in the proportion of deaths accounted for by younger persons was more striking and consistent than the decline in the absolute risk of dying from influenza. After each pandemic, the absolute risk of influenza-associated mortality among persons <65 years old fell 7-fold to 28-fold over the following decade during severe influenza epidemics. By contrast, the corresponding reduction in risk among those ⩾65 years old was 2- to 3-fold or less.

We observed a very similar pandemic-epidemic, age-specific mortality pattern when we analyzed data from a study of influenza-related deaths in England [21, 22] (figure 3), suggesting that this pattern also may be characteristic of influenza epidemiology in countries other than the United states. For influenza A (H2N2) seasons in England and Wales during 1964–1968 for example, the proportion of deaths among persons <65 years of age declined from 57% to 9%. Subsequently, 65% of influenza-related deaths during the 1968–1969 A (H3N2) pandemic occurred among persons <65 years old and then declined to 10% during the next decade [21]. Historical records of age-specific influenza-related P&I mortality in London during 1890–1919 also showed a similar pattern. The percentage of P&I deaths accounted for by the 20–40 year age group declined from 20% during the 1890 pandemic to about 10% after 1 decade. This percentage increased to 36% during the 1918–1919 pandemic [22].

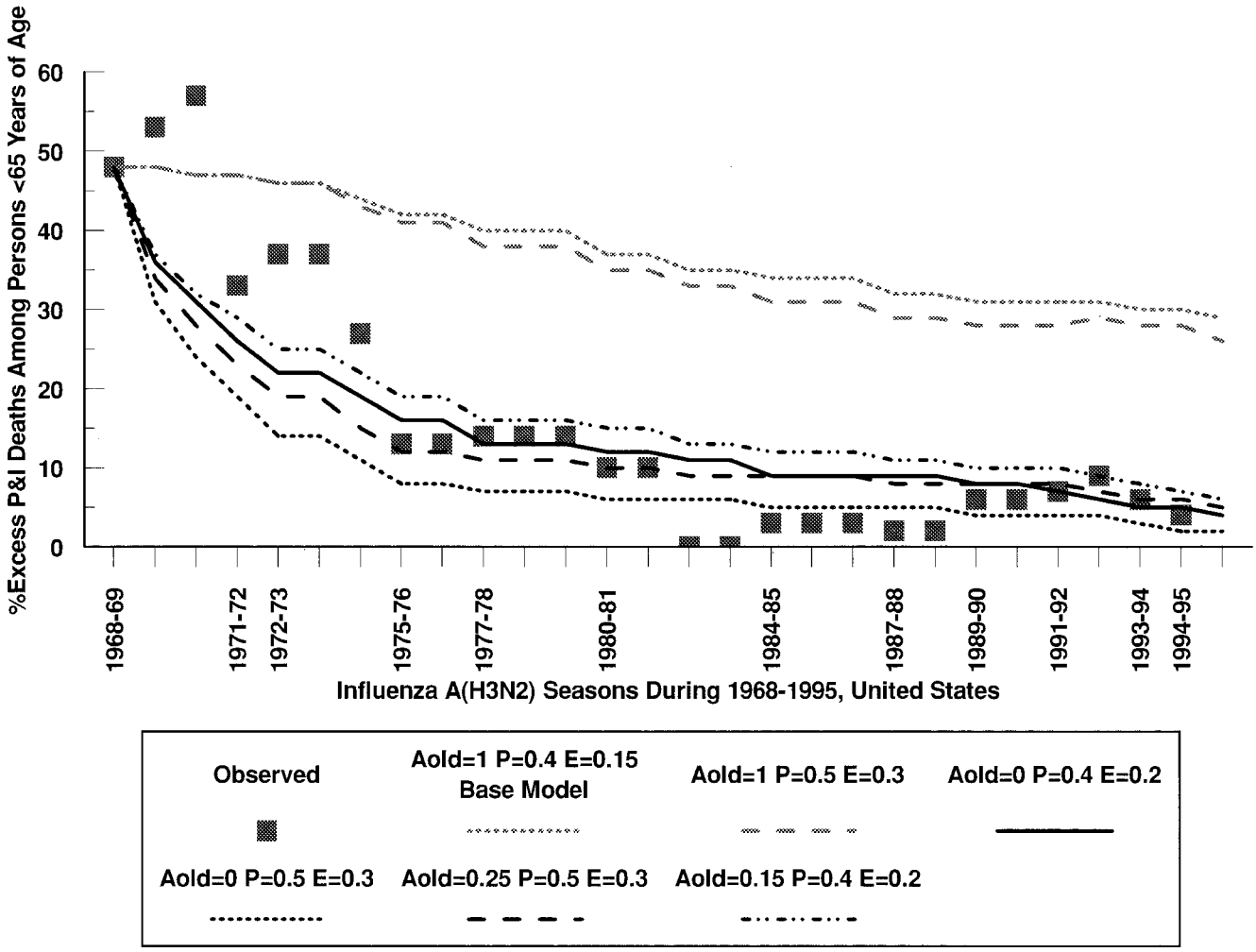

Figure 2. Simulated and observed age distribution of excess mortality during influenza A (H3N2) pandemic and following A (H3N2) epidemics, 1968–1995. Results of computer models testing effect of various factors on age distribution of influenza deaths (lines) against observed age distribution of these deaths (boxes). P&I = pneumonia and influenza.

Comparing the impact of influenza on mortality in different years is complicated by the large variability in the number of influenza-related deaths among different seasons. This variability occurs as a result of a complex interaction between influenza viruses and the human population, including intrinsic differences in virulence and transmissibility of strains and differences in the susceptibility of the general population to influenza infection due to previous exposure to antigenically similar strains and aging of the human population. In addition, comparison of excess mortality estimates among seasons is further complicated by the fact that influenza-related deaths are difficult to ascertain completely [19], and different investigators have used various statistical methods and different mortality data. Nonetheless, analyzing the proportion of excess influenza-related deaths among younger persons, rather than the absolute numbers or rates of such deaths, made it possible to identify a consistent age-related pandemic-epidemic mortality pattern in the data.

During the 1918–1919 pandemic, persons <65 years old accounted for a much higher proportion of the total mortality than that observed during the later two pandemics. In part, this difference may be explained by the aging of the population; the percentage of the US population that is ≥65 years of age increased from 4.5% to 12% from 1920 to 1990 [23, 24]. In addition, the increasing proportion of elderly persons who are ≥85 years old may also contribute to the pattern. Influenza-related mortality rates for persons ≥85 years old are dramatically higher than among persons 65–74 years of age. This pattern has not decreased significantly since the last pandemic [25]. However, the W-shaped age-specific mortality curve for the 1918–1919 pandemic is unlike those for all other recorded pandemics and epidemics of influenza for reasons that have not been adequately explained [5].

The reemergence of influenza A (H1N1) viruses in the 1977–1978 season, after a 20-year absence, was not associated with a mortality pattern similar to that of the three true pandemics.

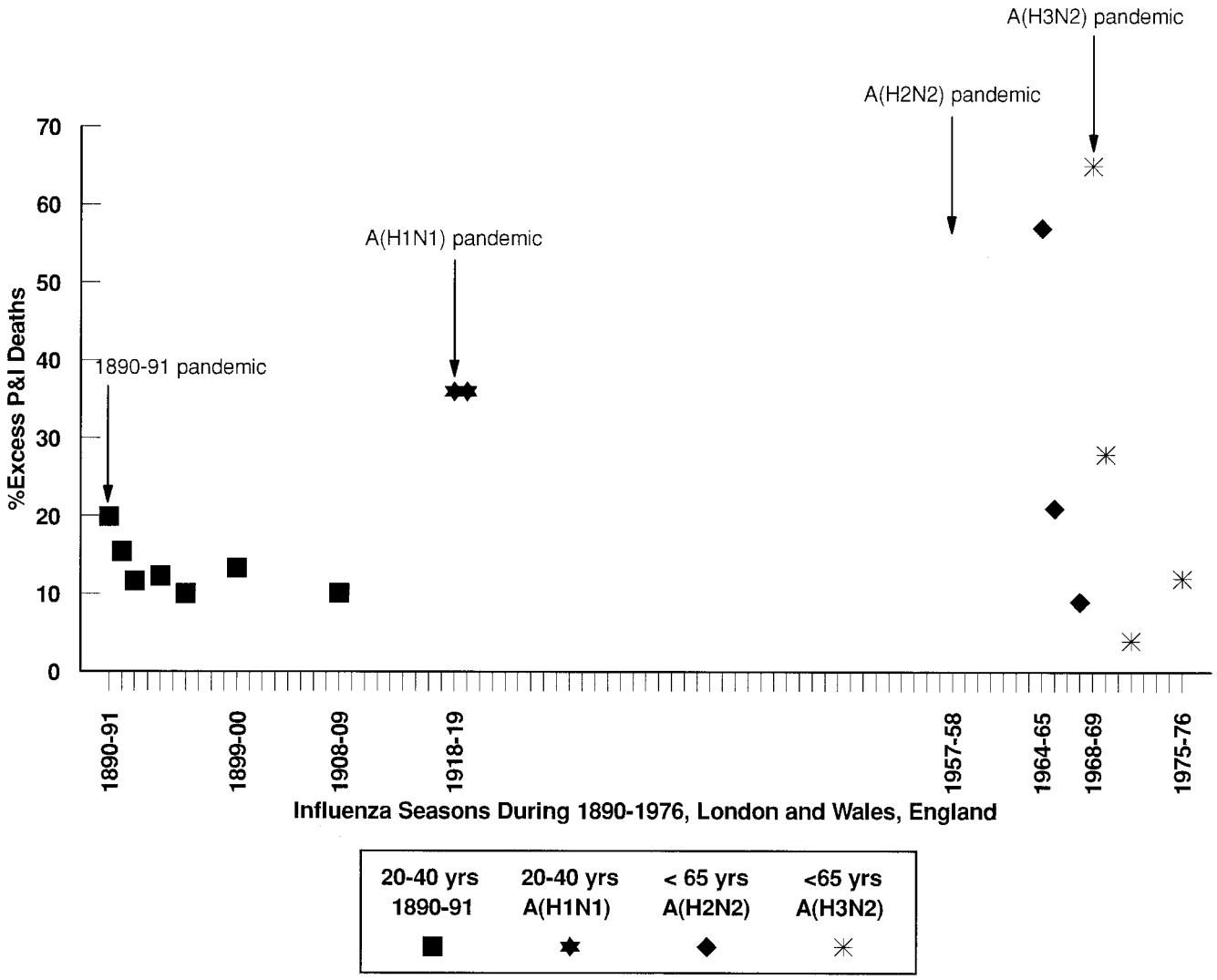

Figure 3. Age distribution of deaths related to influenza pandemics and epidemics in England, 1890–1976. Data on proportional impact of influenza on pneumonia and influenza (P&I) mortality for 20- to 40-year-old age group in London following 1890 pandemic and through 1918–1919 pandemic [21]. For England and Wales, proportion of influenza-related all-cause deaths was calculated for <65-year-old age group [22].

While the picture was complicated by the widespread cocirculation of A (H3N2) viruses, the low proportion of influenza-related deaths observed among younger persons was consistent with the fact that the majority of persons who were 20–65 years of age in 1977 probably had been infected with A (H1N1) viruses before 1957 and were protected by previously acquired antibody [1]. The lack of P&I excess mortality in the 1977–1978 season among children and teenagers who had never been exposed to A (H1N1) viruses (data not shown) suggests that influenza A (H1N1) viruses were relatively avirulent after their reemergence.

Our model suggested that the development of long-term protection against fatal outcomes among persons <65 years old who survived infection with a new influenza A virus subtype could explain the decline in influenza-related mortality in their group during subsequent epidemics of the same virus. These results suggest that younger persons may retain long-lasting immunity better than older persons after exposure to a new influenza virus subtype. This hypothesis requires testing. Other potential factors, such as radically changing attack rates or virulence of the virus among the younger age group (relative to the elderly) during the first decade following a pandemic, were not considered in our model. We consider such possibilities unlikely.

Our study suggests that in the next pandemic, about half of the associated deaths might initially occur among persons <65 years of age. During the 1957–1958 and 1968–1969 pandemics, persons 45–64 years of age accounted for about two-thirds

of all influenza-related deaths in the <65 years of age group [4, 19]. Only 45% of 45- to 64-year-old persons dying from influenza during the 1968–1969 pandemic had a high-risk condition listed on their death certificates. This suggests that about one-sixth of all influenza-related deaths in the 1968–1969 pandemic occurred among persons 45–64 years of age who did not have a high-risk chronic health condition. It would be prudent to consider targeting all persons 45–64 years of age for influenza vaccination during future pandemics and possibly during the following decade.

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