ORIGINAL INVESTIGATION

Excess Mortality Due to Pneumonia or Influenza During Influenza Seasons Among Persons With Acquired Immunodeficiency Syndrome

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Background: Anecdotal reports suggest that influenza-related morbidity may be high among persons with acquired immunodeficiency syndrome (AIDS), but little information is available concerning the population-level impact of influenza on mortality in persons with AIDS.

Methods: Using the Multiple Cause-of-Death data files, which contain information on all deaths occurring in the United States each year, we calculated the numbers of excess deaths and rates of excess death due to pneumonia or influenza among persons with AIDS aged 13 years and older during the influenza seasons 1991-1992 through 1993-1994. For comparison, numbers of excess deaths and excess death rates were also calculated for several other groups including the general US population aged 13 years and older and the general US population aged 65 years and older.

Results: During the 1991-1992, 1992-1993, and 1993-1994 influenza seasons, there were 261, 254, and 191 excess deaths due to pneumonia or influenza in persons with AIDS and excess death rates of 19.74, 15.38, and 10.17 deaths per 10 000 persons, respectively, compared with a summer baseline period. For the same seasons, we observed excess death rates of 1.40, 1.62, and 1.48 for the general US population aged 13 years and older and 8.10, 9.28, and 8.54 for the general US population aged 65 years and older. Thus, persons with AIDS had excess death rates substantially higher than the general US population and similar to, if not somewhat higher than, the general US population aged 65 years and older, a group that is already targeted for annual vaccination. The findings were similar when we compared the preinfluenza season with the influenza season.

Conclusions: Persons with AIDS have significant excess mortality due to pneumonia or influenza during influenza seasons and should be considered a high-risk group that is targeted for the prevention of influenza.

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INFLUENZA CAUSES significant morbidity and mortality in various high-risk groups, including persons with chronic cardiopulmonary disease, diabetes mellitus, and advanced age and those residing in long-term care facilities. However, there is limited information concerning the impact of influenza on morbidity and mortality in persons with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS). Previous reports[1,2] suggested that influenza may severely compromise respiratory function and cause prolonged duration of illness in patients with HIV infection, but, until recently, information regarding the impact of influenza on this patient population has been largely anecdotal.[1-5] Because of potential for substantial benefit, the Advisory Committee on Immunization Practices since 1987 has recommended that HIV-infected individuals receive routine vaccination against influenza.[6,7] However, this policy has been somewhat controversial,[8] and its implementation in clinical settings has not been widespread, as demonstrated by low vaccination rates.[9] Barriers to successful vaccination efforts may include uncertainties regarding immunogenicity of the vaccine in patients with HIV infection[10-15] and implications of possible transient increases in HIV viral load following vaccination.[13-21] Perhaps one of the largest influences on the poor rates of immunization has been the persistent uncertainties concerning the magnitude of risk posed by influenza among persons with AIDS or HIV infection. For this reason, we conducted this study to assess influenza-related excess mortality in persons with AIDS.

METHODS

DATA SOURCE

The Multiple Cause-of-Death data files[22-23] are released annually by the National Center for Health Statistics and contain detailed information for each of the approximately 2.2 million deaths occurring every year in the 50 United States and the District of Columbia. Information in the database is derived from US certificates of death and includes demographic variables, such as age, race, sex, and geographic area, as well as cause-of-death information. Coding of the underlying cause and contributing causes of death for the data files is accomplished using rules established by the World Health Organization that are applied to the information obtained from the death certificates. This coding is increasingly automated, thus reducing or eliminating intercoder variation. Use of information regarding not only the single underlying cause of death, but also the contributing causes of death, can be particularly valuable in achieving a more accurate portrayal of mortality. In some cases, deaths are attributable to a number of concurrent disease processes for which a single underlying cause of death insufficiently accounts for the interactions between chronic or coexisting conditions and the immediate cause of death. Previous publications[22-27] have described the details, potential uses, and limitations of the data files.

From the Multiple Cause-of-Death data file for 1991-1994, we calculated the number of deaths due to pneumonia or influenza each month for adolescents and adults (ie, persons aged 13 years and older) with AIDS. Deaths were classified as being due to pneumonia or influenza (*ICD-9-CM* [*International Classification of Disease, Ninth Revision, Clinical Modification*][28] codes 480-487) if pneumonia or influenza was listed either as an underlying or contributing cause of death in the file. Persons were classified as having AIDS if the *ICD-9-CM* codes consistent with AIDS surveillance case definitions also appeared in the data file for each death. For 1991-1992, we used the 1987 case definition of AIDS[29] (*ICD-9-CM* code 042 [AIDS] or codes 043 [AIDS-related complex] to 044 [other HIV disease], with mention of 1 or more of the AIDS clinical indicator diseases identified by the Centers for Disease Control and Prevention [CDC]). For the 1992-1993 and 1993-1994 influenza seasons and corresponding baseline periods, the 1993 expanded surveillance case definition of AIDS was used. (For the 1993 case definition, the CDC added pulmonary tuberculosis, recurrent pneumonia, and invasive cervical cancer to the list of indicator clinical conditions.[30])

For comparison, we tabulated the number of deaths due to pneumonia or influenza (*ICD-9-CM* codes 480-497) by month for all adults and adolescents in the general US population. We also tabulated these data for 2 additional comparison groups: the general US population 65 years and older (a high-risk group currently targeted for annual influenza vaccination) and the general US population aged 25 to 54 years (more than 90% of AIDS deaths occur in this age group).

INFLUENZA SEASONS

Influenza seasons were defined using national influenza surveillance data collected by the World Health Organization collaborating laboratories in the United States.[31-33] For each month from October to May for the years included in this study, we identified all months for which the total number of influenza isolates was 5% or more of the season's total influenza isolates. All these months constituted the influenza period for each study year.

BASELINE PERIODS

We used 2 baseline periods for establishing baseline pneumonia or influenza death rates. One, the *preinfluenza baseline period*, was defined as the 2 months immediately preceding the influenza season for each study season. The other, the *summer baseline period*, was defined as the June through September immediately preceding each influenza season. Because national influenza surveillance spans October through May, data for the number of influenza isolates were not available for the summer months. However, influenza activity is assumed to be minimal during the summer.

CALCULATION OF EXCESS DEATHS AND DEATH RATES

We calculated excess deaths attributable to pneumonia or influenza during each influenza season by taking the difference between those deaths occurring each month in the influenza season and the monthly average of the preceding baseline period. The total excess deaths for each influenza period were calculated as the sum of the excess deaths for each month during the influenza period. We calculated the excess deaths rates per 10 000 by dividing the total excess deaths for each influenza season by the estimated number of living persons according to population estimates derived from the 1990 US census[34] for the general population and from estimates from the CDC[35] for persons with AIDS aged 13 years or older in the 50 United States and the District of Columbia. We assumed that the distribution of deaths followed a binomial distribution, and we calculated 95% confidence intervals for the death rates, as recommended by the National Center for Health Statistics.[23]

RESULTS

The characteristics of adults and adolescents who died of AIDS during the study period are shown in **Table 1**. Of the persons who died, 85% to 89% were male and more than 90% were between 25 and 54 years of age. In about 15% of the persons, pneumonia or influenza was listed as the underlying or one of the contributing causes of death.

The influenza seasons extended from November through February for the 1991-1992 season, December through April for the 1992-1993 season, and December through February for the 1993-1994 season. Deaths due to pneumonia or influenza among adults and adolescents with AIDS followed a seasonal pattern, with peaks generally occurring during the months of December and January. This pattern paralleled the seasonal variability seen for deaths due to pneumonia or influenza among adults and adolescents in the general US population and also followed the seasonal pattern for positive influenza isolates in the United States (data not shown).

Table 1. Deaths in Persons With AIDS Aged 13 Years and Older*

Characteristics	No. of Persons			
	1991	1992	1993	1994
AIDS listed as the underlying or contributing cause of death	31 061	35 112	39 054	44 029
Males	27 518	30 792	33 809	37 393
By age, y				
13-24	651	616	658	693
25-34	9955	10 901	11 797	12 607
35-44	13 063	14 987	16 862	19 290
45-54	5032	5950	6938	8177
55-64	1674	1896	1996	2391
≥65	686	762	803	871

**Data are from the Multiple Cause-of-Death files[22,23] for the years listed. Death from AIDS (acquired immunodeficiency syndrome) was identified if any of the diagnostic codes listed in the underlying or contributing cause-of-death fields in the data file fulfilled the case definitions for AIDS (see the "Methods" section for additional information on the case definitions used).*

During the 1991-1992, 1992-1993, and 1993-1994 influenza seasons, there were 261, 254, and 191 excess deaths attributable to pneumonia or influenza in persons with AIDS, respectively, compared with the summer baseline period (**Table 2**). These excess deaths corresponded to excess death rates of 19.74, 15.38, and 10.17 deaths per 10 000 adults and adolescents with AIDS. These excess death rates were 6.9 to 14.1 times higher than the excess death rates due to pneumonia or influenza observed among adults and adolescents in the general US population and were even somewhat higher than, although of similar magnitude to, those seen for persons 65 years and older in the general US population (Table 2).

During the same influenza seasons, there were 166, 242, and 176 excess deaths attributable to pneumonia or influenza in persons with AIDS, compared with the preinfluenza baseline periods (Table 2, **Figure**). These excess deaths corresponded to excess death rates of 12.56, 14.65, and 9.37 deaths per 10 000 adults and adolescents with AIDS. These excess death rates were 8.5 to 10.3 times higher than the excess death rates due to pneumonia or influenza observed in adults and adolescents in the general US population. Similar to the comparison to the summer baseline period, these rates were even somewhat higher than those seen for the general US population 65 years and older (Table 2).

The general US population aged 25 to 54 years was selected as an additional comparison group as more than 90% of AIDS deaths in our study occurred in this age group. We found that the excess death rate from pneumonia or influenza was 81 to 155 times higher among adults and adolescents with AIDS than for the general US population aged 25 to 54 years compared with the summer baseline period. Similarly, when using the preinfluenza period as the baseline, we found that the excess death rate for adults and adolescents with AIDS was 106 to 161 times higher than that of the general US population aged 25 to 54 years (Table 2).

COMMENT

We have shown that adults and adolescents with AIDS have substantial excess mortality due to pneumonia or influenza during influenza seasons. The excess death rates from influenza or pneumonia per 10 000 persons are comparable to if not greater than those for the general US population 65 years and older, a high-risk group that is already targeted for routine annual influenza vaccination.

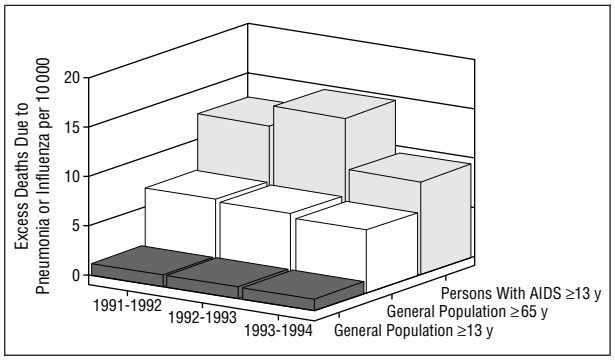
Previous studies have attempted to define the impact of influenza or influenza-related illnesses on morbidity and mortality in persons with HIV infection. In one case report[2] of a child with HIV infection and one case series[1] describing 6 HIV-infected patients from whom influenza virus was isolated, the authors suggested that patients with HIV infection may experience more severe respiratory complications and prolonged duration of illness. In one study[36] that examined hospital use for patients with AIDS in the state of New York, the authors noted that the length of hospital stay was 2.8, 1.1, and 2.4 days longer in January (typically when influenza-related morbidity and mortality peaks nationwide) compared with June during 3 consecutive years, but they made no comment concerning the frequency of hospitalization, reasons for admission, or rates of death. Recently, Neuzil et al[37] demonstrated increased hospitalization rates for cardiopulmonary causes during influenza season in women with HIV infection. This retrospective population-based cohort study of women enrolled in the Medicaid program for the state of Tennessee demonstrated influenza-related excess morbidity in patients with HIV infection. Of all women with high-risk chronic conditions, the risk attributable to influenza was shown to be highest among those with HIV infection. This study estimated the hospitalization rate for influenza-related illnesses to be 300 per 10 000 women with HIV infection. According to their estimates, women with HIV infection were 50 to 75 times more likely to be hospitalized for influenza-related morbidity compared with women aged 15 to 64 years who were without high-risk chronic conditions. Our study augments these findings by defining influenza-associated excess mortality for the entire US adolescent and adult population with AIDS.

Other investigators have used several different types of baseline periods to estimate excess outcome rates associated with influenza. These periods have included summer months,[37-41] peri-influenza periods,[37] and nonepidemic influenza seasons with low rates of influenza activity as defined by relatively flat curves for mortality due to

Table 2. Excess Deaths and Death Rates Due to Pneumonia or Influenza During Influenza Seasons*

	1991-1992		1992-1993		1993-1994	
	Compared With Summer	Compared With Preinfluenza Period	Compared With Summer	Compared With Preinfluenza Period	Compared With Summer	Compared With Preinfluenza Period
Persons with AIDS ≥13 y						
Estimated living population	132 200	132 200	165 200	165 200	187 850	187 850
Excess deaths due to P/I during influenza seasons	261	166	254	242	191	176
Excess death rate per 10 000 (95% CI)	19.74 (17.35-22.14)	12.56 (10.65-14.47)	15.38 (13.48-17.27)	14.65 (12.80-16.50)	10.17 (8.73-11.61)	9.37 (7.99-10.75)
General population by age, y						
≥13						
Estimated living population	205 125 000	205 125 000	207 299 000	207 299 000	209 582 000	209 582 000
Excess deaths due to P/I during influenza seasons	28 759	24 914	33 540	24 671	30 929	22 981
Excess death rate per 10 000 (95% CI)	1.40 (1.38-1.42)	1.21 (1.20-1.23)	1.62 (1.60-1.64)	1.19 (1.18-1.20)	1.48 (1.46-1.49)	1.10 (1.08-1.11)
25-54						
Estimated living population	108 821 000	108 821 000	110 500 000	110 500 000	112 042 000	112 042 000
Excess deaths due to P/I during influenza seasons	1385	1079	1491	1003	1399	993
Excess death rate per 10 000 (95% CI)	0.13 (0.12-0.13)	0.10 (0.09-0.10)	0.13 (0.13-0.14)	0.09 (0.09-0.10)	0.12 (0.12-0.13)	0.09 (0.08-0.09)
≥65						
Estimated living population	31 940 000	31 940 000	32 461 000	32 461 000	32 921 000	32 921 000
Excess deaths due to P/I during influenza seasons	25 869	22 456	30 119	22 151	28 112	20 897
Excess death rate per 10 000 (95% CI)	8.10 (8.00-8.20)	7.03 (6.94-7.12)	9.28 (9.17-9.38)	6.82 (6.73-6.91)	8.54 (8.44-8.64)	6.35 (6.26-6.43)

*AIDS indicates acquired immunodeficiency syndrome; P/I, pneumonia or influenza; CI, confidence interval. Excess deaths were calculated as described in the "Methods" section. Persons in the general population aged 25 to 54 years were included for comparison because 90% or more of the AIDS deaths occurred in this group.



Excess death rates due to pneumonia or influenza during influenza seasons compared with preinfluenza baseline periods. Shown are the excess death rates per 10 000 for the 1991-1992, 1992-1993, and 1993-1994 influenza seasons for the general US population 13 years and older and 65 years and older and for persons with acquired immunodeficiency syndrome (AIDS) aged 13 years and older.

pneumonia and influenza.[42,43] Because the choice of baseline period can influence the calculated rates of excess events, we adapted methods from several previous studies and used 2 different baseline periods in our study. As expected, the use of 2 different baseline periods resulted in somewhat differing point estimates for excess mortality rates but identical conclusions regarding the substantially increased risk among persons with AIDS compared with the general US population.

We used both underlying and contributing causes of death to estimate the total number of deaths due to pneumonia or influenza. According to Barker and Mullooly,[44] up to one half or more of pneumonia-associated deaths may be attributed to underlying chronic medical conditions on death certificates. Consistent with these findings, our estimated number of excess death due to pneumonia or influenza based on both underlying and contributing causes of death are approximately twice those obtained if only deaths with pneumonia or influenza as the underlying cause were included (data not shown). The resulting excess mortality rates of 1.1 to 1.6 deaths per 10 000 that we calculated for adults and adolescents in the general US population are similar to those reported by other investigators. For example, Kavet,[45] in assessing the impact of 3 influenza epidemics during the 1960s, estimated mortality rates of 1.0 to 2.5 per 10 000 persons in the general population. He estimated that in 21% to 37% of these deaths the underlying cause of death was pneumonia or influenza. Barker and Mullooly[46] reported 1.2 excess deaths due to pneumonia or influenza per 10 000 members of the Kaiser Permanente health maintenance or-

ganization in Portland, Ore, for the 1968-1969 and 1972-1973 influenza epidemics. During the 1977-1978 influenza epidemic in Houston, Tex, Glezen[47] reported a mortality rate due to acute respiratory disease among persons aged 20 years and older of 2.26 per 10000.

The Multiple Cause-of-Death data files are derived from death certificates. The use of these and other files based on death certificate data is standard for tracking national mortality trends,[48] including influenza-associated excess mortality.[49,50] It is believed that more than 99% of deaths occurring in the United States are registered.[23] However, several limitations of death certificate data deserve comment and necessitate interpreting our study results with some caution. Previous studies[51,52] have suggested that 9% to 12% of death certificates fail to mention AIDS as the underlying or contributing cause of death among persons with known AIDS. Therefore, it is possible that we underestimated the number of deaths occurring among persons with AIDS. This possible underestimation may explain why our estimates of the total number of deaths due to AIDS were on average 11.5% lower than those estimated by the CDC.[35] Such an underestimation of deaths would most likely have resulted in an underestimation of the excess death rates due to pneumonia and influenza that we reported. In addition, death certificates may not list pneumonia or influenza even when they were a cause of death. In one study,[44] 16% of death certificates for persons who died of pneumonia or influenza did not mention pneumonia or influenza. If it occurred, underreporting pneumonia and influenza on death certificates during the years of this study would probably also have resulted in underestimation of excess death rates. The presence of an AIDS diagnosis, especially among persons with pulmonary opportunistic infections, may also have contributed to a detection bias leading to more frequent listing of pulmonary infections, such as bacterial pneumonias, on the death certificate than might be seen in the general population. However, if present, such a bias was probably most relevant in establishing the baseline rate of death due to pneumonia or influenza. We found no evidence of seasonal variability in the listing of pulmonary opportunistic infections as underlying or contributing causes of death among persons with AIDS (data not shown). Thus, our use of excess death rates above the baseline rate likely minimized the impact of any detection bias.

Another limitation of the present study is that it encompasses years that predate the advent of highly active antiretroviral therapy, which was not widely used to treat persons with HIV infection in the United States until 1996. Since the introduction of highly active antiretroviral therapy, morbidity and mortality from HIV disease and various associated opportunistic infections have decreased significantly.[53] Therefore, it is unclear whether the magnitude of risk that we identified in this study will be present in future years.

Our findings suggest that the magnitude of influenza-related excess mortality in persons with AIDS is comparable to, if not greater than, that seen among the general US population aged 65 years and older, a high-risk group targeted for annual influenza vaccination. Although various reports[13-21] have provided conflicting results of whether influenza vaccination transiently increases HIV viral load after immunization, the clinical relevance of this short-lived phenomenon is unclear. To our knowledge, no detriment in clinical outcome has ever been shown to be associated with this transient viremia.

Questions also persist concerning the efficacy of vaccination in a patient population characterized by defects in cellular and humoral immunity. However, until recently assessments of vaccine efficacy[10-15] have been based on laboratory measurements of antibody response, as opposed to clinical measurements of the protection that vaccination provides. One double-blind, placebo-controlled trial[54] in patients with AIDS and HIV infection showed that influenza vaccination was associated with a 93% efficacy against laboratory-confirmed infection and a 100% efficacy against symptomatic illness. Even in the subgroups of participants with CD4 counts less than 200/μL, 20% of those who received the vaccine vs 50% of those who received placebo experienced respiratory symptoms.

CONCLUSIONS

In this study, adults and adolescents with AIDS had substantial excess mortality due to pneumonia or influenza during influenza seasons. The mortality risk attributable to influenza in this population was comparable to that of the general US population 65 years or older. In the absence of any clear evidence to suggest that influenza vaccination is clinically harmful to persons with HIV infection and AIDS and in light of new information demonstrating protective efficacy provided by vaccination, our findings support recommendations for annual vaccination of persons with AIDS.

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