Influenza-Associated Morbidity and Mortality in Young and Middle-Aged Women

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In the United States each year, influenza accounts for an estimated 10,000 to 40,000 deaths, nearly 200,000 hospitalizations, and millions of days lost from work. The annual economic costs associated with influenza epidemics exceed $12 billion. Although 60% to 90% of persons who die during influenza season are aged 65 years or older, 45% to 77% of pneumonia- and influenza-associated hospitalizations occur in those younger than 65 years. The high morbidity in adults is due in part to high attack rates—on average, close to 10% of adults have a symptomatic influenza illness each year.

A major strategy for reducing influenza morbidity in the United States is annual administration of influenza vaccine to persons at increased risk for influenza-related complications or persons who can transmit influenza to such high-risk persons. Influenza vaccination levels among persons aged 65 years or older increased substantially from 1985 to 1997, from 23% to approximately 66%, surpassing the national health objective target for the year 2000 of 60%. There has been no parallel improvement in younger high-risk patients, in whom vaccination levels remain less than 30%. Few data exist on rates of influenza-associated serious morbidity among adults with more common high-risk conditions (eg, cardiac or pulmonary disease, diabetes), and no data are available for those with less common high-risk conditions, such as renal failure, malignancy, or human immunodeficiency virus (HIV) infection. Such data should allow health care professionals and their patients to make more informed decisions about annual influenza immunization.

Expanding the universal influenza immunization recommendation to adults younger than 65 years may improve immunization rates and decrease the burden of influenza-associated disease among adults. However, advantages and disadvantages of such a strategy have not been well defined. More information is needed to estimate the risk of serious influenza-related morbidity among young (15-44 years) and middle-aged (45-64 years).
years) adults with and without identified medical risk factors.

We performed a retrospective cohort study to determine the incidence of serious influenza-associated morbidity and mortality for women aged 15 to 44 and 45 to 64 years. We assessed influenza-associated serious morbidity among women with specific chronic medical conditions, for whom annual influenza immunization is recommended4; among women with HIV infection, for whom the benefit of immunization is debated4; and among women with any known high-risk conditions.

### METHODS

#### Overview

We performed a retrospective cohort study among nonpregnant women aged 15 to 64 years enrolled in the Tennessee Medicaid program to identify all hospitalizations for and deaths due to pneumonia, influenza, and other selected acute cardiopulmonary conditions. We chose to study only women because relatively few men in this age group are covered by the Medicaid program. We estimated rates of cardiopulmonary events during 19 consecutive years. Rates of these events during winter months, when influenza was not circulating, were used to estimate the baseline occurrence of study events in the absence of influenza virus. Influenza-attributable serious morbidity and mortality were estimated for women with and without selected chronic medical conditions.

#### Sources of Data

**Computerized Tennessee Medical Files and Tennessee Vital Records.** Tennessee Medicaid data files from 1973 through 1993 include enrollment dates, demographic characteristics, and medical services billed to the program, including hospital and outpatient dates of service, associated diagnoses and procedures, and detailed information on prescriptions filled. Medicaid files have been linked to birth certificates, from which timing of pregnancy is determined, and death certificates, which include date and coded underlying cause of death.34,35

**Vanderbilt University Viral Surveillance.** Influenza season was defined each year as the period from November 1 through April 30 that included the dates of the first and last influenza virus isolation in middle Tennessee as determined by surveillance at Vanderbilt University, Nashville, Tenn.16

#### Risk Groups

All person-time and study outcomes were classified into 1 of 4 risk strata (high risk, recent hospitalization, blind/disabled, or low risk) on the basis of information present in the computerized Medicaid files. Because women may qualify for Medicaid on the basis of disability or medical illness as well as income, the Medicaid population has an overrepresentation of persons with disabilities and chronic medical conditions. We attempted to exclude from our low-risk group women who had traditional high-risk conditions for influenza as well as those who had other chronic medical conditions. Thus, our group of low-risk women included primarily otherwise healthy women in low-income families with dependent children.

The high-risk stratum included women with any of 6 medical conditions for whom annual influenza immunization is currently recommended4 as well as those with HIV infection. All person-time and events in the 180 days following a medical encounter associated with selected diagnostic or procedure codes or selected filled prescriptions were classified into the following 7 categories (not mutually exclusive): (1) chronic lung disease (outpatient International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 277.0, 491-496, 500-506, 515-517, and 519.9 or prescriptions filled for β-agonists, theophylline, inhaled steroids, ipratropium, or cromolyn sodium); (2) diabetes (outpatient ICD-9-CM codes 250 and 648.0 or prescriptions filled for insulin or oral hypoglycemic agents); (3) chronic heart disease (outpatient ICD-9-CM codes 093, 393-398, 402-404, 414, 416, 424, 425, 428, 429, 440, 745, and 746 or digoxin use); (4) malignancy (outpatient ICD-9-CM codes 140-199, except 173, or prescriptions filled for chemotherapeutic agents); (5) long-term corticosteroid use (prescriptions filled for ≥60 days of oral corticosteroids); (6) chronic renal disease (outpatient ICD-9-CM codes 581-583, 585, and 587 or procedure codes indicating dialysis); and (7) HIV infection (inpatient or outpatient ICD-9-CM codes 042-044 and 136.3 or prescriptions filled for zidovudine, didanosine, or zalcitabine).

The recent hospitalization strata included person-time and events not classified as high risk but occurring in the 180 days fol-
lowing a hospitalization for any reason. The blind/disabled stratum included women not in either of the 2 risk groups defined herein who were enrolled in the Medicaid program based on blindness or another disability. The low-risk stratum included all other person-time and events.

Study Outcomes
Study outcomes included acute cardiopulmonary hospitalizations and deaths for pneumonia (International Classification of Diseases, Eighth Revision [ICD-8; 1975-1979] and ICD-9-CM [1980-1992] codes 480-486) and influenza (ICD-8 codes 470-474 and ICD-9-CM code 487) and for a broader range of acute cardiopulmonary conditions, including other acute respiratory conditions (ICD-8 and ICD-9-CM codes 460-466), other respiratory conditions (ICD-8 and ICD-9-CM codes 490-519), and heart failure or myocarditis (ICD-8 codes 422 and 428 and ICD-9-CM codes 422, 427, and 428).

Statistical Analysis
The incidence of study hospitalizations and deaths during influenza and peri-influenza seasons were calculated separately for each risk stratum by dividing the number of hospitalizations and deaths per selected period by the person-time during that period. These crude rates were calculated for each year of the study and for all years combined. In addition, rates during influenza and summer seasons for all years combined were standardized to the comparable risk group during peri-influenza season for age (10-year groups), residence, and, within the high-risk stratum, for the 7 risk groups defined herein.10

The influenza-attributable risk—the number of excess events during influenza season—was calculated by subtracting the rates during the peri-influenza season from adjusted rates during the influenza season. Differences of adjusted rates are thus a weighted average of differences of rates in the stratified categories. A normal approximation was used to generate confidence intervals (CIs).20

RESULTS
Nonpregnant women younger than 65 years enrolled in Medicaid accrued 20,708,544 person-months of follow-up during the 19 study years, of which 18% occurred during influenza season, 31% during peri-influenza season, and 51% during summer season. Demographic characteristics reflected the Medicaid population, with 70% aged 15 to 44 years and 30% aged 45 to 64 years; 47% were African American and 53% were white. Forty-eight percent lived in a major metropolitan area. Eighteen percent had at least 1 indicator of a high-risk medical condition. Chronic lung disease (7.8%), diabetes (6.5%), and chronic heart disease (6.3%) were the most prevalent high-risk medical conditions. Relatively few women had indicators of cancer (1.3%), long-term steroid use (0.8%), chronic renal disease (0.4%), or HIV infection (0.02%). An additional 31% of women were without any of these high-risk conditions but had relatively high rates of cardiorespiratory events. These included women with a recent hospitalization (6%) and those enrolled in the Medicaid program on the basis of blindness or disability (26%). The remaining low-risk women (51%) included primarily otherwise healthy women in low-income families with dependent children.

The incidence rates and influenza-attributable risks of all acute cardiopulmonary events (hospitalizations and deaths) are summarized in Table 1. We identified 53,607 hospitalizations for or deaths due to acute cardiopulmonary conditions during these 19 years, of which 24% occurred when influenza was circulating in the community.

Women in the high-risk group constituted only 18% of the person-time in this cohort but accounted for 75% of total study events. For both age groups, event rates were statistically higher during influenza season compared with peri-influenza or summer seasons. Under the assumption that the rate of events during peri-influenza season represents baseline, events attributable to influenza can be calculated by subtracting the peri-influenza event rate from the influenza event rate. In high-risk women aged 15 to 44 years and 45 to 64 years, respectively, an estimated 10.3 (95% CI, 5.9-14.7) and 26.4 (95% CI, 22.0-30.7) events per 10,000 person-months can be attributed to influenza viral infection. These rates translate into approximately 23 and 58 hospitalizations and deaths (events) annually per 10,000 high-risk women aged 15 to 44 years and 45 to 64 years, respectively, based on an average influenza season of 2.2 months. These estimates would increase by as much as 74% if rates during summer season were used to represent baseline rates.

Within the high-risk group, women aged 15 to 64 years with HIV infection, long-term steroid use, and chronic lung disease had the highest cardiopulmonary event rates during influenza season, followed by women with chronic heart disease, chronic renal disease, malignancy, and diabetes (Table 2). Although event rates varied among women with these medical conditions, the rate of events attributable to influenza were similar in most strata. Women with HIV infection, chronic lung disease, chronic heart disease, chronic renal disease, malignancy, and diabetes experienced significantly more acute cardiopulmonary events during influenza season compared with peri-influenza season. Women with HIV infection had the highest influenza-attributable risk; however, the CI around this estimate was wide (151.6 events per 10,000 person-months [95% CI, 33.5-269.8]). Women receiving long-term steroid therapy had higher event rates during influenza season, although the increase over peri-influenza season was not statistically significant.

For low-risk women, rates of study events during influenza seasons were much lower than for women with high-risk conditions (Table 1). However, event rates were 30% to 50% higher than during peri-influenza season and resulted in estimated influenza-attributable incidence rates of 2.0 (95% CI, 1.6-2.4) and 2.9 (95% CI, 0.58-5.2) events per 10,000 person-months, respectively, for women aged 15 to 44 and 45 to 64 years. These influenza-attributable rates translate into approximately 4 and 6 hospitalizations and deaths (events) per 10,000 young and middle-aged women, respectively, per year, based on an average influenza season of 2.2 months. Women in the recent hospital-

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ization and blind/disabled strata had event rates and influenza-attributable risks that were intermediate between the comparable estimates for women in the low- and high-risk strata (Table 1).

We identified 2045 deaths due to selected cardiopulmonary causes during the 19 study years; 488 deaths (24%) occurred during influenza season and 657 deaths (32%) during peri-influenza season (data not shown). High-risk women accounted for 386 deaths (79%) during influenza season, and among high-risk women, the mortality rate from selected cardiopulmonary causes during influenza season rose 20% over the rate during peri-influenza season. The influenza-attributable mortality rate for high-risk women was 1.1 deaths per 10 000 person-months (95% CI, 0.4-1.7). High-risk women aged 45 to 64 years accounted for 89% of these deaths, and the influenza-attributable mortality rate for this subset was 1.8 deaths per 10 000 person-months (95% CI, 0.8-2.7). These influenza-attributable mortality rates translate into 2.4 excess deaths annually per 10 000 high-risk women overall and 4.0 annual excess deaths per 10 000 among those aged 45 to 64 years. Among low-risk women, deaths due to cardiorespiratory causes were rare and the rate attributable to influenza of 0.02 (95% CI, −0.01 to 0.05) per 10 000 person-months was not statistically significant.

The predominant viral strain and excess cardiopulmonary event rate by influenza season for low- and high-risk women are shown in the Figure. Excess event rates varied markedly from season to season, from a low of 0 to a high of 54 excess events per 10 000 person-months among high-risk women and a low of 0 to a high of 5 excess events per 10 000 person-months among low-risk women.

Table 1. Seasonal Incidence Rates and Influenza-Attributable Risk of Acute Cardiopulmonary Hospitalizations and Deaths and Estimated Annual Excess of Such Events by Age and Risk Group in Women Enrolled in the Tennessee Medicaid Program, 1974-1993

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Influenza Season*</th>
<th>Peri-influenza Season*</th>
<th>Summer Season*</th>
<th>Influenza-Attributable Risk (95% Confidence Interval)†</th>
<th>Estimated No. of Annual Excess Events‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women Aged 15-44 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>Rate</td>
<td>91.7</td>
<td>81.4</td>
<td>73.8</td>
<td>10.3 (5.9-14.7)</td>
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<td>Events, No.</td>
<td>2497</td>
<td>3615</td>
<td>5266</td>
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<td></td>
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<tr>
<td>Person-months, No.</td>
<td>271 276</td>
<td>443 849</td>
<td>713 426</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent hospitalization</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>34.2</td>
<td>24.8</td>
<td>19.2</td>
<td>9.4 (5.6-13.2)</td>
<td>21</td>
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<tr>
<td>Events, No.</td>
<td>486</td>
<td>616</td>
<td>776</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-months, No.</td>
<td>143 069</td>
<td>248 462</td>
<td>407 350</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blind/disabled</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>9.9</td>
<td>7.2</td>
<td>5.4</td>
<td>2.7 (1.7-3.8)</td>
<td>6</td>
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<tr>
<td>Events, No.</td>
<td>478</td>
<td>579</td>
<td>696</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-months, No.</td>
<td>480 508</td>
<td>802 575</td>
<td>1 298 877</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>6.0</td>
<td>4.0</td>
<td>3.1</td>
<td>2.0 (1.6-2.4)</td>
<td>4</td>
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<tr>
<td>Events, No.</td>
<td>1049</td>
<td>1188</td>
<td>1520</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-months, No.</td>
<td>1 753 928</td>
<td>3 001 460</td>
<td>4 924 907</td>
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<td></td>
</tr>
<tr>
<td>Women Aged 45-64 y</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>Rate</td>
<td>152.7</td>
<td>126.3</td>
<td>108.9</td>
<td>26.4 (22.0-30.7)</td>
</tr>
<tr>
<td>Events, No.</td>
<td>6691</td>
<td>9339</td>
<td>13 007</td>
<td></td>
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</tr>
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<td>Person-months, No.</td>
<td>437 693</td>
<td>739 402</td>
<td>1 193 468</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rate</td>
<td>56.1</td>
<td>41.8</td>
<td>29.5</td>
<td>14.3 (9.0-19.6)</td>
<td>31</td>
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<td>Events, No.</td>
<td>351</td>
<td>452</td>
<td>530</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-months, No.</td>
<td>60 759</td>
<td>108 192</td>
<td>174 538</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blind/disabled</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>19.1</td>
<td>14.9</td>
<td>11.1</td>
<td>4.2 (2.8-5.6)</td>
<td>9</td>
</tr>
<tr>
<td>Events, No.</td>
<td>1006</td>
<td>1368</td>
<td>1619</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-months, No.</td>
<td>526 401</td>
<td>916 497</td>
<td>1 456 557</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>11.4</td>
<td>8.52</td>
<td>6.3</td>
<td>2.9 (0.58-5.2)</td>
<td>6</td>
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<tr>
<td>Events, No.</td>
<td>120</td>
<td>164</td>
<td>194</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-months, No.</td>
<td>105 358</td>
<td>192 550</td>
<td>307 440</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Rates are per 10 000 person-months and were standardized within risk groups to peri-influenza season stratified for age, residence, and, within the high-risk group, specific risk condition (human immunodeficiency virus infection, long-term steroid use, chronic lung disease, chronic heart disease, chronic renal disease, malignancy, or diabetes).
† Rates during the peri-influenza season were used as the baseline rates for calculation of the influenza-attributable risk.
‡ Estimates are per 10 000 women and based on average influenza season of 2.2 months.
women. It is noteworthy that the highest influenza-attributable morbidity occurred during seasons in which the influenza A(H3N2) virus was circulating, as would be expected.

**COMMENT**

In this large cohort of nonelderly women with and without high-risk medical conditions, we found that excess hospitalizations and deaths occurred during the periods when influenza was circulating in the community between 1974 and 1993. This effect was most pronounced in women with defined high-risk medical conditions. For every 10,000 such high-risk women aged 15 to 44 years, approximately 58 cardio pulmonary hospitalizations and 4 deaths were related to influenza each year. Event rates greatly exceeded this average for women with certain high-risk conditions and during severe influenza seasons. While lower rates of hospitalization might be expected among enrollees of prepaid health plans, our findings are similar to the results generated from an adult population in a large prepaid group practice during 2 influenza epidemics. In that population, the rates of excess hospitalizations for diagnoses of only pneumonia and influenza during the 2 study years, respectively, were 5.6 and 11.0 per 10,000 high-risk persons aged 15 to 44 years and 39.0 and 63.0 per 10,000 high-risk persons aged 45 to 64 years.

To our knowledge, our study is the first to report rates of excess cardiopulmonary events during influenza season by well-defined high-risk groups. Our results support studies that document excess hospitalization and mortality rates during influenza epidemics for selected cohorts of patients with chronic lung disease, chronic heart disease, or diabetes.

For each year, the predominant viral strain is indicated as H1N1 or H3N2 for influenza A isolates and B for influenza B isolates. Years 1978-1979 and 1979-1980 had no defined influenza season.

To our knowledge, our study is the first to report rates of excess cardiopulmonary events during influenza season by well-defined high-risk groups. Our results support studies that document excess hospitalization and mortality rates during influenza epidemics for selected cohorts of patients with chronic lung disease, chronic heart disease, or diabetes. In our cohort, as expected, acute cardiopulmonary event rates during influenza season for women with chronic lung or heart disease were higher than event rates for women with diabetes, malignancy, or chronic renal disease. However, after subtracting the peri-influenza baseline, the influenza-attributable risks in patients with diabetes, malignancy, and chronic renal disease were comparable with the risks in patients with chronic lung or heart disease. Furthermore, the rates of excess acute cardiopulmonary events in these groups are comparable with previously reported rates in adults older than 65 years without high-risk conditions.
middle-aged individuals with a variety of chronic diseases and support national guidelines to immunize patients with diabetes, malignancy, or chronic heart, lung, or renal disease with influenza vaccine.4

Although patients infected with HIV might be expected to have more severe illness due to influenza virus infection than uninfected individuals, the course of influenza in such persons has not been well delineated. Several case reports and a small case series suggest that influenza A may cause prolonged illness with occasional severe complications in HIV-infected individuals.22-23 We provide the first population-based evidence that these patients experience excess cardiopulmonary morbidity during influenza season. Women with HIV infection had the highest influenza-attributable risk among the women we studied. Our data suggest that for every 10,000 HIV-infected women, 300 would be hospitalized for influenza-related cardiopulmonary causes each season. In a recent outbreak of influenza A among HIV-infected persons in a residential care facility, influenza immunization lessened duration of clinical influenza illness.26 Early reports of detrimental effects of influenza immunization on viral load measurements have not been substantiated.27-29 Taken together, these data provide justification for more widespread use of influenza vaccine for women with HIV infection. More data are needed to determine if the effect of influenza observed in this study would be similar in the more diverse and predominantly male HIV-infected patients in the general population.

Even among women without traditional high-risk medical conditions associated with increased influenza morbidity, acute cardiopulmonary hospitalizations increased significantly during influenza season (Table 1). While hospitalization and mortality rates in our cohort of low-risk individuals were relatively low, the public health impact of extrapolating these rates to the large low-risk population of young and middle-aged US women would be substantial. In contrast with high-risk women, influenza-attributable excess events did not differ markedly with age among low-risk women. This finding is similar to data from enrollees in a prepaid health plan, in whom influenza-associated excess events increased with age among high-risk but not low-risk individuals.21 Women in this cohort without traditional high-risk medical conditions for increased influenza-associated morbidity but who were blind, disabled, or recently hospitalized had intermediate rates of influenza-attributable excess events. This suggests that a variety of other medical conditions could potentially increase the risk of influenza morbidity.

The prevalence of women with low income and chronic medical conditions is greater in the Tennessee Medicaid population compared with women of similar age in the US population, potentially limiting the generalizability of our study.30 We attempted to minimize this limitation by stringently defining our low- and high-risk groups. The low-risk group included primarily healthy women in low-income families with dependent children, while the high-risk group included women with well-defined high-risk medical conditions who had low household incomes. Our data cannot be generalized to pregnant women or postpartum women, who were excluded from this study. We have previously reported that otherwise low-risk women aged 15 to 44 years in the first trimester of pregnancy or first 6 months postpartum have a risk of influenza-related hospitalization that is similar to the risk in nonpregnant women. However, otherwise low-risk women in the second and third trimester of pregnancy experience approximately 14 and 23 excess events per 10,000 women, respectively, in an average influenza season,18 justifying their inclusion as a high-risk group for influenza-related morbidity.4

We used local surveillance data to define influenza seasons. Such surveillance may not reflect influenza activity throughout the state. However, it is clear from the Figure that circulation of the influenza A (H3N2) virus locally was a fairly reliable predictor of seasons associated with high excess morbidity among high-risk persons. In addition, the 4 seasons between 1974 and 1992 that were estimated to have the highest number of influenza-attributable deaths in the United States were 1975-1976, 1980-1981, 1989-1990, and 1991-1992.17 These 4 seasons were also associated with high influenza-attributable event rates among women with high-risk conditions in our study population (Figure).

Our attributable risk calculations assume that other environmental or microbial factors that affect cardiopulmonary hospitalizations and deaths were just as likely to cause serious morbidity during peri-influenza season as during influenza season.31-33 If other factors, such as other viruses or seasonal allergens, were more likely to circulate during the influenza period than during the peri-influenza period, the risk attributed to influenza would be exaggerated. However, if other causes of cardiopulmonary illness were more likely to occur at times when influenza was not circulating,6,11,12,32,33 the effect due to influenza would be underestimated. Using the summer season as baseline would increase the influenza-associated excess event estimates by as much as 74% (Table 1).

This study of excess hospitalizations and deaths quantifies a major impact of influenza on nonelderly women with and without high-risk medical conditions and highlights the variable severity of influenza epidemics. The majority of the influenza-associated morbidity and mortality in our cohort occurred in women with identified chronic medical conditions. At the very minimum, targeted efforts to improve influenza prevention among high-risk young and middle-aged adults are warranted. Furthermore, these data may be useful in determining the cost-benefit ratio of universal influenza immunization.

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**REFERENCES**


The joviality of friends is the best antidote for the venom of the world and the fatigues of life. In the words of the old song: “He loves me who makes me laugh.” —Santiago Ramón y Cajal (1852-1934)