American Journal of Epidemiology

Vol. 148, No. 11
Printed in U.S.A.

Impact of Influenza on Acute Cardiopulmonary Hospitalizations in Pregnant Women

Kathleen Maletic Neuzil,[1,3] George W. Reed,[2] Edward F. Mitchel,[2] Lone Simonsen,[4] and Marie R. Griffin[1,2]

This study sought to quantify influenza-related serious morbidity in pregnant women, as measured by hospitalizations for or death from selected acute cardiopulmonary conditions during predefined influenza seasons. The study population included women aged 15–44 years who were enrolled in the Tennessee Medicaid program for at least 180 days between 1974 and 1993. In a nested case-control study, 4,369 women with a first study event during influenza season were compared with 21,845 population controls. The odds ratios associated with study events increased from 1.44 (95% confidence interval (CI) 0.97–2.15) for women at 14–20 weeks' gestation to 4.67 (95% CI 3.42–6.39) for those at 37–42 weeks in comparison with postpartum women. A retrospective cohort analysis, which controlled for risk factors identified in the case-control study, identified 22,824 study events during 1,393,166 women-years of follow-up. Women in their third trimester without other identified risk factors for influenza morbidity had an event rate of 21.7 per 10,000 women-months during influenza season. Approximately half of this morbidity, 10.5 (95% CI 6.7–14.3) events per 10,000 women-months, was attributable to influenza. Influenza-attributable risks in comparable nonpregnant and postpartum women were 1.91 (95% CI 1.51–2.31) and 1.16 (95% CI −0.09 to 2.42) per 10,000 women-months, respectively. The data suggest that, out of every 10,000 women in their third trimester without other identified risk factors who experience an average influenza season of 2.5 months, 25 will be hospitalized with influenza-related morbidity. *Am J Epidemiol* 1998;148:1094–102.

hospitalization; influenza; influenza vaccine; pregnancy

The routine use of influenza vaccine in pregnant women is controversial. While the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices encourages influenza immunization for pregnant women (1), warnings from the manufacturers caution against routine use of the vaccine during pregnancy (2). A barrier to resolving this controversy is the lack of information regarding the risk of influenza-related complications among pregnant women. While influenza-associated excess mortality among pregnant women was documented during the 1918–1919 and 1957–1958 pandemics, it has not been documented during interpandemic periods (3–7). Case reports and papers on small case series published since that time have described women in the third trimester and early puerperium who died from influenza-related complications, but have not quantified risk (7–10). Mortality statistics underestimate the overall health impact of influenza on other known high risk groups, and acute respiratory disease hospitalizations may be a more accurate measure of serious influenza-related morbidity (11). These incidence data are not available for pregnant women.

With this study, we have attempted to quantify the risk of influenza-related complications among women of childbearing age. Such information should enable pregnant women, their health care practitioners, and public policy officials to make more informed choices regarding influenza immunization. We utilized a database developed for studying outcomes of pregnancy which included women aged 15–44 years who were enrolled in the Tennessee Medicaid program between 1974 and 1993. We first performed a nested case-control study of influenza-related hospitalizations to determine the relative risk of influenza morbidity associated with each stage of pregnancy in comparison with postpartum and nonpregnant states, and to iden-

Received for publication November 26, 1997, and accepted for publication April 14, 1998.

Abbreviations: CI, confidence interval; ICD-8, *International Classification of Diseases*, Eighth Revision; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*.

[1] Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN.
[2] Department of Preventive Medicine, Vanderbilt University School of Medicine, Nashville, TN.
[3] Department of Veterans Affairs Medical Center, Nashville, TN.
[4] Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA.

Reprint requests to Dr. Marie R. Griffin, Department of Preventive Medicine, Vanderbilt University School of Medicine, A-1124 Medical Center North, Nashville, TN 37232–2637.

tify other important risk factors for influenza-related serious morbidity. We then performed a retrospective cohort study to determine the incidence of influenza-associated morbidity and mortality for women of childbearing age.

MATERIALS AND METHODS

Database

Data were obtained from linked research files developed for studying outcomes of pregnancy among women enrolled in the Tennessee Medicaid program (12). Medicaid data files included information on demographic characteristics, dates of enrollment, hospital and outpatient diagnoses, prescriptions filled, and all other services billed to Medicaid. For women aged 15–44 years, these Medicaid files were linked to birth certificates and fetal death certificates to identify women with deliveries. The infant birth certificates included the date of the last maternal menstrual period, which permitted an estimate of stage of pregnancy. Medicaid files have also been linked to death certificates, which identify the date of death and the coded underlying cause of death (13).

Population

All women aged 15–44 years of African-American or white ethnicity with at least 180 days of enrollment in the Tennessee Medicaid program were included in the study. Childbearing women outside this age range and of other ethnicities were too few to study. Women entered the study on the first day after June 30, 1974, that they met entry criteria, and they were followed until loss of enrollment, death, or June 30, 1993. The 180-day enrollment period was selected to optimize the availability of preexisting medical and drug records while allowing inclusion of women who enroll in Medicaid on the basis of a current pregnancy.

Definition of influenza seasons

The influenza season was defined each year by the dates of the first and last isolation of influenza virus in middle Tennessee, as determined by ongoing surveillance at Vanderbilt University (14). Comparison of these seasons with the timing of excess pneumonia and influenza deaths estimated for 11 cities in Tennessee and surrounding states that participate in the Centers for Disease Control and Prevention's 121-City Surveillance System yielded good face validity (15). Two of the 19 years studied (1978–1979 and 1979–1980) were defined as having no influenza season because of low influenza activity (less than five viral isolates). The mean duration of the remaining 17 seasons was 10.6 weeks (range, 6–23.2 weeks). Peri-influenza season was defined as each period from November 1 through April 30 in which there was no influenza activity. The influenza and peri-influenza seasons were compared with the dates of first and last isolation of respiratory syncytial virus, as determined by ongoing surveillance at Vanderbilt University, to determine the likelihood of cocirculation of this common winter virus with the influenza virus (14). Non-influenza season was defined as May 1 through October 31.

Study outcomes

Study outcomes included hospitalizations for pneumonia (*International Classification of Diseases,* Eighth Revision (ICD-8) (16), and *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) (17), codes 480–486) and influenza (ICD-8 codes 470–474 and ICD-9-CM code 487), as well as hospitalizations 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). Women who died with a similarly coded underlying cause of death were identified by death certificate. The results of analyses using hospitalization for pneumonia and influenza only and of those using all study events combined were similar; therefore, only the latter findings are presented here.

Ascertainment of pregnancy status

The major exposure of interest was pregnancy. Using the linked birth certificates, we characterized all eligible women by pregnancy status, as follows: 1) by week, in weeks 1–42 of pregnancy, 2) 1–30 days postpartum, 3) 31–180 days postpartum, and 4) no pregnancy in the past 180 days (includes never pregnant women). The date of the last menstrual period was available on the child's birth certificate for approximately 85 percent of the women. For the remainder, the last menstrual period was assigned such that the child's gestational age in weeks fit the median for children of the same race, weight, and birth year.

Ascertainment of other characteristics

We obtained information on the following additional characteristics from the database: age; enrollment category (recipient of Aid to Families with Dependent Children, pregnant, medically needy, or blind/disabled); residence (defined as urban (one of Tennessee's four largest cities), other Standard Met-

ropolitan Statistical Area, or rural (non-Standard Metropolitan Statistical Area)); hospitalization for any condition in the previous 180 days, as an indicator of underlying health; and receipt of influenza vaccine during that season. In addition, high risk medical conditions were categorized into six broad categories based on diagnoses and procedures associated with medical encounters and medications filled in the 180 days prior to the index date. These categories are shown in table 1.

Case-control study

The case-control study was designed to identify risk factors for the selected study events (see above) during the predefined influenza seasons only. A woman qualified as having a case of influenza-associated illness on the day (index date) of her first study-defined hospital admission (or date of death) during influenza season; subsequent events were not analyzed. To construct a sampling frame for control selection, we used the index date for all cases during each influenza season, and we randomly selected controls who met all of the eligibility criteria for cases and were alive and not hospitalized on the index date. We selected controls to achieve five times the number of controls as cases.

Retrospective cohort study

The cohort study was designed to identify all study events (pneumonia, influenza, and other selected acute cardiopulmonary conditions) occurring throughout the year and to estimate rates of such events during influenza seasons and other times of the year. In these analyses, events occurring during peri-influenza season were used to estimate the occurrence of study events due to other causes, including other winter viruses, in the absence of influenza virus. We thus identified all hospitalizations or deaths from a study condition throughout the year among all eligible women in the study cohort. All eligible person-time was characterized by the major exposure of interest, pregnancy, and the covariates defined above.

Statistical analysis

For the case-control study, the relative risk for first eligible hospitalization during influenza season was estimated from odds ratios calculated with a multiple logistic regression model using SAS Proc Logistic (SAS Institute, Cary, North Carolina). We considered all combinations of variables using tests of significance of coefficients and deviance reduction as criteria for inclusion. More attention was paid to those variables that influenced the risk estimates for pregnancy status variables. Receipt of influenza vaccine, being in the blind/disabled enrollment category, and age did not affect these risk estimates, so these variables were excluded from the cohort analysis. For comparisons of pregnancy status, postpartum women were used as the reference group.

For the retrospective cohort study, person-time and

TABLE 1. Indicators of high risk medical conditions for women aged 15–44 years enrolled in the Tennessee Medicaid program, 1974–1993

High risk group	Inpatient or outpatient ICD-9-CM* code(s)	Medication indicators of high risk condition
Chronic cardiac disease	093, 393–398, 402–404, 410–414, 416, 424–425, 428–429, 440, and 745–746	Digoxin
Chronic pulmonary disease	277.0, 491–496, 500–506, 515–517, and 519.9	Beta agonists, theophylline, inhaled steroids, ipratropium, cromolyn sodium
Diabetes mellitus	250 and 648.0	Insulin, oral hypoglycemic agents
Chronic renal disease	581–583, 585, and 587, and procedure codes indicating dialysis	
Malignancy	140–199 (except 173) and 200–208	Chemotherapeutic agents
Immunosuppressive disorders (including human immunodeficiency virus infection)	042–044 and 136.3	Zidovudine, didanosine, zalcitabine, azathioprine, cyclosporin, filgrastim, sargramostim, ≥60 days of oral corticosteroids

* *International Classification of Diseases, Ninth Revision, Clinical Modification* (17).

events were defined as high risk if they occurred in the 6 months following a hospitalization or involved any of the six medical conditions defined above. All other person-time and events were defined as low risk. The incidence of all study hospitalizations and deaths combined was calculated separately for high and low risk women for the influenza, peri-influenza, and non-influenza seasons by dividing the number of hospitalizations and deaths per selected time period by the women-time in that time period. Analyses were conducted using women-years, but results were translated to women-months for ease of interpretation. Pregnant women were categorized as being in the first (weeks 1–13), second (weeks 14–26), or third (weeks 27–42) trimester. Adjusted rates were computed using direct standardization (18). Adjusted rates were also computed with a multivariate Poisson regression model using SAS Proc GENMOD, and the rates were consistent with the direct standardized rates. For these analyses, postpartum women in the peri-influenza season were the reference group; factors in the final model included ethnicity, residence category, and length of influenza season. Influenza-attributable risk was calculated by subtracting the adjusted rates during the peri-influenza season from adjusted rates during the influenza season. The direct standardized rates are sums of Poisson parameters, and a normal approximation was used to generate 95 percent confidence intervals (19).

RESULTS

Case-control analysis

We identified 4,369 women of childbearing age enrolled in the Tennessee Medicaid program between 1974 and 1993 who had a first hospitalization or death from any study condition. We selected 21,845 controls randomly from the same population (table 2). There was a relatively high prevalence of pregnancy in this population, with 15 percent of controls being pregnant or in the first 6 months postpartum. This was a young population: 46 percent of controls were aged 18–24 years, 35 percent were aged 25–34 years, and 19 percent were aged 35–44 years. African Americans comprised more than half of the study group, and over half lived in urban areas. Most of the women (80 percent) were enrolled in the program on the basis of pregnancy or under the Aid to Families with Dependent Children provision. Approximately 6.7 percent of controls had been hospitalized within the previous 6 months, and 9 percent had at least one defined high risk condition, including 4.6 percent with lung disease, 1.7 percent with heart disease, 2.1 percent with diabetes mellitus, 0.2 percent with renal disease, 0.7 percent with cancer, and 0.4 percent with indicators of an immunosuppressed state, predominantly prolonged use of oral corticosteroids (table 3).

TABLE 2. Odds ratio* for any cardiopulmonary event occurring during influenza season among women aged 15–44 years enrolled in the Tennessee Medicaid program, by pregnancy status, 1974–1993

Pregnancy status	Prevalence (%)		OR†	95% CI†
	Cases (n = 4,369)	Controls (n = 21,845)		
Postpartum	4.4	7.7	1.0‡	
Nonpregnant	86.6	85.3	1.11	0.94–1.32
Week 1–7	0.7	1.1	1.06	0.68–1.67
Week 8–13	0.7	1.0	1.23	0.79–1.93
Week 14–20	0.9	1.2	1.44	0.97–2.15
Week 21–26	1.2	0.9	2.52	1.74–3.65
Week 27–31	1.3	0.9	2.62	1.82–3.76
Week 32–36	2.0	1.0	3.21	2.32–4.44
Week 37–42	2.2	0.9	4.67	3.42–6.39

* Odds ratios were adjusted for all factors listed in table 3.
† OR, odds ratio; CI, confidence interval.
‡ Referent.

Controlling for demographic factors and high risk medical conditions, the estimated relative risk of hospital admission for study outcomes increased with increasing length of pregnancy (table 2). The associated odds ratios increased from 1.44 (95 percent confidence interval (CI) 0.97–2.15) during weeks 14–20 of pregnancy to 4.67 (95 percent CI 3.42–6.39) during weeks 37–42, as compared with the postpartum period. Exclusion of hospitalizations that resulted in a delivery did not change the results for weeks 1–31, but it decreased the estimated risks for the last two time periods, to an odds ratio of 2.85 (95 percent CI 2.04–3.99) for weeks 32–36 and an odds ratio of 1.25 (95 percent CI 0.79–1.96) for weeks 37–42. There was no increase in risk associated with the early puerperium (the first month postpartum), so all postpartum women were included in a single group for the final analyses. The relative risk for nonpregnant women was similar to the risk for postpartum women.

White ethnicity, residence in a non-urban area, and being in the blind/disabled enrollment category were demographic factors associated with an increased risk of hospitalization. Increasing age was a modest risk factor for study hospitalizations, with an average 2 percent increase in risk per year (table 3). Having any hospitalization in the past 6 months was an independent risk factor for hospital admission for study events (table 3), as was each of the other previously recognized high risk medical conditions.

Documentation of influenza vaccination in this population was rare. Approximately 26 women per 1,000 with high risk medical conditions, 5 women per 1,000 without identified high risk conditions, and less than 1

TABLE 3. Odds ratio* for any cardiopulmonary event occurring during influenza season among women aged 15–44 years enrolled in the Tennessee Medicaid program, by baseline medical conditions and demographic factors, 1974–1993

Characteristic	Prevalence (%)		OR†	95% CI†
	Cases (n = 4,369)	Controls (n = 21,845)		
Any recent hospitalization‡	31.1	6.7	3.41	3.09–3.76
Chronic pulmonary disease‡	36.0	4.6	8.19	7.44–9.02
Chronic cardiac disease‡	9.8	1.7	3.37	2.83–4.01
Diabetes mellitus‡	6.0	2.1	1.65	1.37–1.99
Chronic renal disease‡	1.2	0.2	2.01	1.28–3.17
Malignancy‡	2.4	0.7	1.92	1.42–2.58
Immunosuppressive disorders‡	2.9	0.4	3.38	2.43–4.72
Receipt of influenza vaccine in previous 6 months	2.2	0.7	1.20	0.87–1.65
Age			1.02	1.01–1.02
White ethnicity§	68.2	46.4	1.34	1.22–1.46
Other SMSA† residence¶	19.6	18.0	1.45	1.30–1.63
Rural residence¶	50.2	28.2	2.15	1.95–2.36
Blind/disabled enrollment category#	35.4	19.8	1.37	1.26–1.50

* Odds ratios were adjusted for all factors listed in tables 2 and 3.
† OR, odds ratio; CI, confidence interval; SMSA, Standard Metropolitan Statistical Area.
‡ Reference category: those without the condition.
§ Reference category: African-American ethnicity.
¶ Reference category: urban residence.
# Reference category: Aid to Families with Dependent Children/pregnant enrollment category.

pregnant woman per 1,000 had a record of receiving influenza vaccine. Receipt of influenza vaccine was not associated with the study outcomes (table 3).

Cohort analysis

During the 19 study years, there were 1,393,166 women-years of follow-up, of which 19 percent were in influenza season, 30 percent were in peri-influenza season, and 50 percent were in non-influenza season. Respiratory syncytial virus season overlapped with influenza season 43 percent of the time, and it occurred exclusively during peri-influenza season 57 percent of the time. There were 7,688 hospitalizations or deaths from pneumonia or influenza during the entire study period and 22,824 total study events.

Ninety-one percent of women in this population had had no hospitalization or defined medical condition in the preceding 6 months. We examined the rate of hospitalization for study events among these low risk women. The incidence of study events was consistently higher during influenza season than during either the peri-influenza season (the period from November through April surrounding each influenza season) or the non-influenza season (table 4). For women in their third trimester, hospitalization rates were 21.74 per 10,000 women-months during influenza season as compared with 11.26 and 7.49 during the peri-influenza and non-influenza seasons, respectively, adjusting for ethnicity, residence category, and influenza season. The hospitalization rate among these low risk women increased with increasing length of pregnancy in all seasons, but most remarkably during influenza season, from 6.46 hospitalizations per 10,000 women-months for women in their first trimester to 21.74 for women in their third trimester.

Similar patterns of higher hospitalization rates during influenza season and increasing rates with increasing duration of pregnancy were observed for both low risk and high risk women (figure 1). However, high risk women, defined as those who had had a hospitalization or high risk condition in the previous 180 days (lower half of figure), had higher hospitalization rates than did their low risk counterparts (upper half of figure), regardless of pregnancy status. Rates during influenza season ranged from a low of 30.94 per 10,000 women-months among high risk postpartum women to a high of 110.44 per 10,000 women-months among high risk women in their third trimester.

To determine the number of study events attributable to influenza in this cohort, we calculated attributable risk by subtracting rates of hospitalization during peri-influenza season from rates during influenza season (table 4). This assumes that the rate during peri-influenza season is the background winter rate—that which would have occurred in the absence of influenza. Among low risk women, the influenza-attributable risk increased with increasing stage of pregnancy. Event rates due to influenza were close to 2 per 10,000 women-months in nonpregnant women

TABLE 4. Adjusted incidence rates* of acute cardiopulmonary events and influenza-attributable risk per 10,000 women-months, by season, among women aged 15–44 years enrolled in the Tennessee Medicaid program, 1974–1993

Pregnancy status	Influenza season			Peri-influenza season			Non-influenza season			IAR†,‡	95% CI†
	Rate/10,000 WM†	No. of events	WM of observation	Rate/10,000 WM	No. of events	WM of observation	Rate/10,000 WM†	No. of events	WM of observation		
Nonpregnant	6.37	1,545	2,246,495	4.46	1,784	3,816,750	3.38	2,231	6,154,809	1.91	1.51–2.31
First trimester	6.46	27	57,874	3.40	29	95,691	2.33	29	142,913	3.06	0.44–5.68
Second trimester	12.58	54	57,813	6.26	49	94,751	4.39	64	154,046	6.32	2.90–9.74
Third trimester	21.74	143	70,800	11.26	133	118,286	7.49	157	202,191	10.48	6.70–14.26
Postpartum	5.62	113	196,452	4.45	145	325,596	3.39	164	507,722	1.16	−0.09 to 2.42

* Rates were adjusted for race, residence, and influenza season. Reference category for adjustment: postpartum women during the peri-influenza season.
† IAR, influenza-attributable risk; CI, confidence interval; WM, women-months.
‡ Rates during the peri-influenza season were used as the background baseline rates for calculation of the influenza-attributable risk.

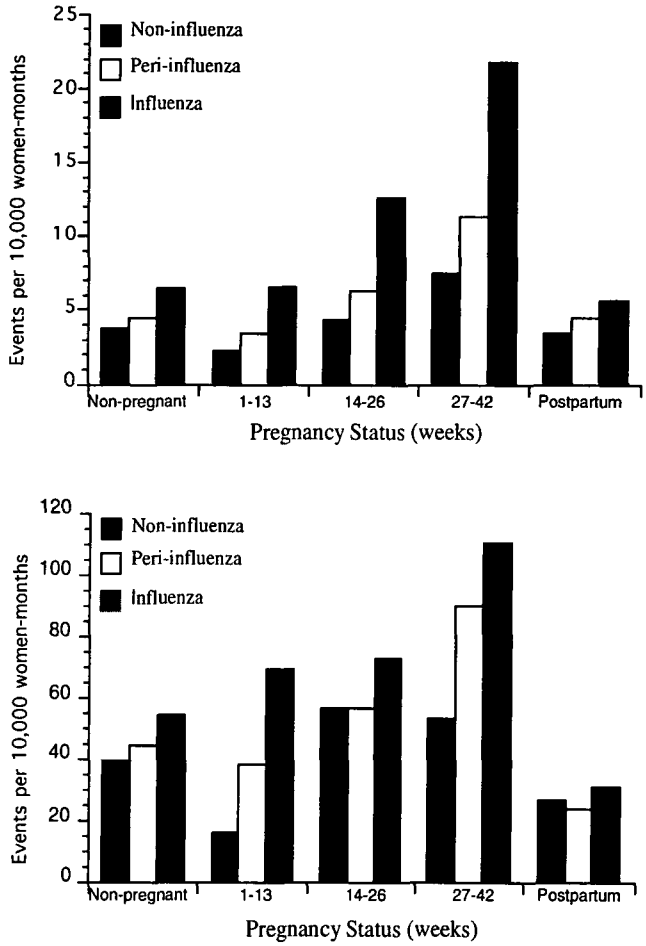

FIGURE 1. Adjusted incidence rates of acute cardiopulmonary events per 10,000 women-months of observation, by medical risk and pregnancy status, among women aged 15–44 years in the Tennessee Medicaid program, 1974–1993. Rates during the three study seasons (influenza, peri-influenza, and non-influenza) are shown for each category of pregnancy status among women with no identified medical risk factors for influenza (low risk women—top) and women with at least one medical risk factor for influenza (high risk women—bottom). Rates were adjusted for residence category, race, and influenza season. (Note the difference in scale between graphs for low risk and high risk women.)

as compared with approximately 3, 6, and 10 per 10,000 women-months among women in their first, second, and third trimesters, respectively. Among high risk women, the women-months of observation were fewer, and confidence intervals around these attributable rates were wide. However, influenza-attributable risks were high for all of these women, ranging from 7 and 10 per 10,000 women-months in postpartum and nonpregnant women to 31, 16, and 21 attributable events among high risk women in their first, second, and third trimesters, respectively.

During the study period, there were 356 women whose study event was associated with death; 164 deaths occurred during non-influenza season, 104 dur-

ing peri-influenza season, and 88 during influenza season. No pregnant women died from cardiopulmonary causes during influenza season.

DISCUSSION

This study identified being in a late stage of pregnancy as an independent risk factor for hospitalizations for influenza and pneumonia, as well as a broader range of acute cardiopulmonary conditions. Women aged 15–44 years in their third trimester of pregnancy were 3–4 times more likely than their postpartum counterparts to be hospitalized for an acute cardiopulmonary illness during influenza season. This increased risk of hospitalization puts women in their third trimester of pregnancy at a level of risk equal to or higher than that of persons identified in this and other populations as having high risk medical conditions, including chronic cardiac and renal disease, diabetes mellitus, and immunosuppression, for whom annual influenza vaccination is recommended (20, 21).

In this population, the incidence of acute cardiorespiratory hospitalizations during influenza season increased with increasing length of pregnancy. The highest incidence rates for study hospitalizations occurred among women in their third trimester of pregnancy with high risk medical conditions. The event rates attributable to influenza were greater than 10 per 10,000 women-months at all stages of pregnancy among these women with identified medical risk factors. Influenza immunization has been routinely recommended by the Advisory Committee on Immunization Practices for all of these medically high risk women, regardless of pregnancy status (22). Our data support this recommendation.

The decision to immunize a pregnant woman without a high risk medical condition is a more challenging one. To better define the number of hospitalizations in this group that were attributable to influenza and thus were potentially preventable by influenza vaccine, we calculated the excess rate of study events occurring during influenza season. The attributable risk was determined by subtracting background incidence rates of acute cardiopulmonary hospitalization from rates during influenza season. The influenza-attributable risk in this study increased with increasing trimester of pregnancy among low risk women. Women in the third trimester of pregnancy had 10.5 excess study events per 10,000 women-months during influenza season. Thus, approximately 1.0 hospitalization per 1,000 women-months was attributable to influenza in this subgroup. Since the average potential exposure time to influenza virus in the 17 seasons included in this study was 2.5 months, we estimate that 2.5 hospitalizations per 1,000 third trimester women can be attributed to influenza. Assuming a vaccine efficacy rate of 80 percent in this population (22, 23), two hospitalizations per 1,000 are potentially preventable. Thus, immunizing 500 women would prevent at least one hospitalization among women who experience an average influenza season (2.5 months) during the third trimester of pregnancy. Using the same method, we estimate that immunizing 833 women would prevent at least one influenza-related hospitalization among similarly exposed women in the second trimester of pregnancy.

Our data suggest that postpartum women are not a group at high risk for cardiopulmonary hospitalization during influenza season. The rate of such hospitalizations returned quickly to baseline in the first month postpartum (data not shown) and remained similar throughout the 6-month postpartum period. Immunization of women who will be in the early postpartum period during influenza season has been considered as a possible means of protecting infants from influenza-related complications through the transfer of maternal antibody; however, there are insufficient data to support this practice to date (24).

Influenza seasons may vary greatly from region to region; therefore, we used local surveillance data to define our influenza seasons. Such data have been used in other observational studies to define the influenza season (11, 25, 26). Our definition of influenza season corresponded well to peak numbers of pneumonia and influenza deaths observed in 11 nearby cities (15). Other investigators have shown that the peak occurrence of acute adult respiratory illnesses, hospitalizations, and deaths coincides with influenza virus activity in the community (11, 21, 27) and that these measurements alone may be used to define influenza season (15, 28). We considered using peak morbidity to define influenza season in this population but preferred to define the season independently of the outcome measure.

We chose postpartum women as the reference group for all analyses, since these women are most similar to pregnant women demographically and healthwise. It is likely that our definition of comorbidity did not adequately control for all serious medical illness, and that among high risk women, those who were able to become pregnant were healthier than their nonpregnant counterparts, who included women too ill to become pregnant. Among women with high risk medical conditions, postpartum women had lower rates of acute cardiopulmonary events than did their nonpregnant counterparts (figure 1). In addition, postpartum women may avoid exposure to sources of respiratory viruses in an effort to protect their newborn infants. However, differences between rates of illness in postpartum and nonpregnant women among low risk

women were small, and use of nonpregnant women or women in their first trimester as the reference group would have yielded similar results for this group.

It is unlikely that these findings are due to chance, given the strong duration effect with pregnancy, which is biologically plausible, and the consistent increase in risk among both low and high risk women. The physiologic changes accompanying pregnancy support the concern about increased risk of serious disease with any respiratory illness. With advancing stage of pregnancy, the functional residual capacity of the lungs decreases and baseline oxygen consumption increases (29, 30). It is possible that pregnant women were hospitalized more readily or with less serious morbidity than their nonpregnant counterparts. This potential bias could have a duration-of-pregnancy effect. However, it is clear that during influenza season these types of hospitalizations are much more common, and that use of the experience of pregnant women during peri-influenza season as the comparison controls for this possible bias. In addition, while preferential hospitalization of pregnant women may overestimate the influenza-associated morbidity in pregnant women, it does not overestimate the cost and inconvenience of these hospitalizations in our cohort.

In each year of the study, influenza season comprised about 2.5 months; the remainder of the 6-month period of November through April was classified as peri-influenza season. The choice of this baseline did not influence the relative risk estimates, but it was important in quantifying attributable risk. Our calculation assumed that other respiratory viruses were just as likely to cause serious cardiorespiratory morbidity during peri-influenza season as during influenza season. The Vanderbilt pediatric surveillance data indicate that respiratory syncytial virus season overlapped with influenza season approximately 43 percent of the time from November 1 through April 30 during the years of this study, supporting this assumption (14). If other respiratory viruses were more likely to circulate during the influenza period than during the peri-influenza period, the risk attributed to influenza would be exaggerated. On the other hand, if these other causes of cardiorespiratory illness were more likely to be present at times when influenza virus was not circulating, the effect due to influenza would be masked.

The recognition of late stage pregnancy as a risk factor for influenza-related complications is one of many elements that must be considered before recommending that immunization be routinely administered to pregnant women. Other important factors include the effect of influenza on the fetus, vaccine safety and efficacy, and cost. Pregnant women in their second or third trimester have no major reactions to influenza vaccine, and they achieve antibody levels comparable to those of their age-matched controls (31–33). As part of the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke, 650 children whose mothers received influenza immunization during pregnancy were followed until age 7. Exposed and unexposed children did not differ with regard to the major outcomes of the study—congenital malformations, stillbirths, and selected intelligence and psychomotor variables (34). A smaller study of influenza vaccination included 176 women at all stages of pregnancy. The immunized and non-immunized groups did not differ in terms of pregnancy outcome or infant development through postpartum week 8 (31). While these results are reassuring, larger studies that address these maternal and fetal health and safety issues are needed.

The strengths of our study included the use of both case-control and cohort designs, the large numbers of pregnant women in our database, and the inclusion of 17 influenza seasons. These factors, along with our narrow and broad outcome measurements (data for pneumonia and influenza alone are not shown) and comparisons of peri-influenza and non-influenza seasons, allowed a comprehensive assessment of the impact of influenza on the health of the women in our cohort.

One limitation of our study was the inability to assess the role of acute influenza-related disease in hospitalizations that resulted in delivery. While the risk for these hospitalizations increased with increasing stage of pregnancy, the inclusion of delivery hospitalizations in which a study outcome was also identified may overestimate the health impact of influenza on pregnant women. Alternatively, fever or severe cardiopulmonary illness may cause fetal or maternal distress and precipitate delivery. More research is needed to define the morbidity and costs associated with such hospitalizations and whether these events are detrimental to the fetus.

In this study population, less than 1 percent of all women and less than 3 percent of medically high risk women received influenza immunization. Whether this is due to underreporting or underutilization of influenza immunization in this cohort cannot be determined. The true protective efficacy of vaccination may have been masked in this population, since the highly select group of women who received influenza vaccine may have had markedly different risk factors for our study outcomes. The low numbers of women vaccinated, as well as the differences between groups, may explain the lack of a protective effect of influenza immunization in our analysis.

In summary, women beyond the first trimester of pregnancy have increased numbers of acute cardiopulmonary hospitalizations during influenza season. By the third trimester, the influenza-attributable risk for such hospitalizations is similar to the risk in nonpregnant, medically high risk women for whom vaccination is currently recommended. These data should allow pregnant women and their health care providers to make more informed choices regarding influenza immunization.

ACKNOWLEDGMENTS

This study was supported by grants from the American Teachers of Preventive Medicine (U50-CCU300760–11) and the Food and Drug Administration (FD-U-000073).

REFERENCES

1. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 1997;46:1–25.
2. Arky R. Physician's desk reference. 51st ed. Montvale, NJ: Med Econ, 1997:1610, 2843.
3. Harris JW. Influenza occurring in pregnant women. JAMA 1919;14:978–80.
4. Woolston WJ, Conley DO. Epidemic pneumonia (Spanish influenza) in pregnancy. JAMA 1918;71:1898–9.
5. Greenberg M, Jacobziner H, Pakter J, et al. Maternal mortality in the epidemic of Asian influenza, New York City, 1957. Am J Obstet Gynecol 1958;76:897–902.
6. Freeman DW, Barno A. Deaths from Asian influenza associated with pregnancy. Am J Obstet Gynecol 1959;78:1172–5.
7. Schoenbaum SC, Weinstein L. Respiratory infection in pregnancy. Clin Obstet Gynecol 1979;22:293–300.
8. Ramphal R, Donnelly WH, Small PA. Fatal influenzal pneumonia in pregnancy: failure to demonstrate transplacental transmission of influenza virus. Am J Obstet Gynecol 1980; 138:347–8.
9. Kort BA, Cefalo RC, Baker VV. Fatal influenza A pneumonia in pregnancy. Am J Perinatol 1986;3:179–82.
10. McKinney WP, Volkert P, Kaufman J. Fatal swine influenza pneumonia during late pregnancy. Arch Intern Med 1990;150: 213–15.
11. Perrotta DM, Decker M, Glezen WP. Acute respiratory disease hospitalizations as a measure of impact of epidemic influenza. Am J Epidemiol 1985;122:468–76.
12. Piper JM, Mitchel EF Jr. Prenatal exposure to prescribed drugs in Tennessee Medicaid, 1983–1988. Paediatr Perinat Epidemiol 1991;5:402–9.
13. Ray WA, Griffin MR. Use of Medicaid data for pharmacoepidemiology. Am J Epidemiol 1989;129:837–49.
14. Fisher RG, Gruber WC, Edwards KM, et al. Twenty years of outpatient respiratory syncytial virus infection: a framework for vaccine efficacy trials. Pediatrics 1997 (http://www.pediatrics.org.99/2/e7:1–5).
15. Simonsen L, Clarke MJ, Stroup DF, et al. A method for timely assessment of influenza-associated mortality in the United States. Epidemiology 1997;8:390–5.
16. World Health Organization. International classification of diseases. Eighth Revision. Geneva, Switzerland: World Health Organization, 1967.
17. Commission on Professional and Hospital Activities, Health Care Financing Administration. International classification of diseases, ninth revision, clinical modification. 2nd ed. Washington, DC: US GPO, 1980. (DHHS publication no. 80–1260).
18. Bishop Y, Fienberg S, Holland P. Discrete multivariate analysis. Cambridge, MA: MIT Press, 1975.
19. Dobson AJ, Kuulasmaa K, Eberle E, et al. Confidence intervals for weighted sums of Poisson parameters. Stat Med 1991;10:457–62.
20. Glezen WP, Frank AL, Taber LH, et al. Influenza in childhood. Pediatr Res 1983;17(12):1029–32. [Conference proceedings].
21. Glezen WP, Decker M, Perrotta DM. Survey of underlying conditions of persons hospitalized with acute respiratory disease during influenza epidemics in Houston, 1978–1981. Am Rev Respir Dis 1987;136:550–5.
22. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 1996;45:1–24.
23. La Montagne JR, Noble GR, Quinnan GV, et al. Summary of clinical trials of inactivated influenza vaccine—1978. Rev Infect Dis 1983;5:723–36.
24. Puck JM, Glezen WP, Frank AL, et al. Protection of infants from infection with influenza A virus by transplacentally acquired antibody. J Infect Dis 1980;142:844–9.
25. Nichol KL, Margolis KL, Wuorenma J, et al. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. N Engl J Med 1994; 331:778–84.
26. Fedson DS, Wajda A, Nichol JP, et al. Clinical effectiveness of influenza vaccination in Manitoba. JAMA 1993;270: 1956–61.
27. Glezen WP, Payne AA, Snyder DN, et al. Mortality and influenza. J Infect Dis 1982;146:313–21.
28. Ahmed AE, Nicholson KG, Nguyen-Van-Tam JS. Reduction in mortality associated with influenza vaccine during 1989–90 epidemic. Lancet 1995;346:591–5.
29. Shahab SZ, Glezen WP. Influenza virus. In: Gonik B, ed. Viral diseases in pregnancy. New York, NY: Springer-Verlag, 1994:215–23.
30. Rodrigues J, Niederman MS. Pneumonia complicating pregnancy. Clin Chest Med 1992;13:679–91.
31. Deinard AS, Ogburn P Jr. A/NJ/8/76 influenza vaccination program: effects on maternal health and pregnancy outcome. Am J Obstet Gynecol 1981;140:240–5.
32. Sumaya CV, Gibbs RS. Immunization of pregnant women with influenza A/New Jersey/76 virus vaccine: reactogenicity and immunogenicity in mother and infant. J Infect Dis 1979; 140:141–6.
33. Englund JA, Mbawuike IN, Hammill H, et al. Maternal immunization with influenza or tetanus toxoid vaccine for passive antibody protection in young infants. J Infect Dis 1993; 168:647–56.
34. Heininen OP, Slone D, Shapiro S. Immunizing agents. In: Birth defects and drugs in pregnancy. Littleton, MA: Publishing Sciences Group, Inc, 1977:314–21.