Original Contribution

Community Influenza Activity and Risk of Acute Influenza-like Illness Episodes among Healthy Unvaccinated Pregnant and Postpartum Women

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This study investigated the relation between weekly levels of influenza activity and the risk of acute influenza-like illness episodes among 8,323 healthy pregnant and postpartum women enrolled in a Puget Sound region, Washington, health maintenance organization, Group Health Cooperative, between June 1991 and December 1997. The authors classified weeks between October and May for isolate activity level based on surveillance data for influenza, respiratory syncytial virus, parainfluenza, and adenovirus infection. Influenza-like illness episodes were identified from medical encounters assigned a diagnostic code consistent with a symptomatic influenza infection. The authors compared the occurrence of influenza-like illness episodes within each pregnancy stage for periods with varying levels of influenza isolate detection in the community. Repeated-measures logistic regression methods accounted for time-dependent factors. The adjusted strength of association between influenza exposure and influenza-like illness episodes increased as the pregnancy stage progressed (first trimester odds ratio = 1.12, 95% confidence interval: 0.79, 1.59; second trimester odds ratio = 1.30, 95% confidence interval: 0.97, 1.73; third trimester odds ratio = 1.84, 95% confidence interval: 1.31, 2.59; postpartum period odds ratio = 2.28, 95% confidence interval: 1.42, 3.68). Pregnancy stage modified the association between influenza activity and influenza-like illness episodes. Findings estimate that 20–43 pregnant/postpartum women would need to be vaccinated with an 80% effective vaccine to prevent one influenza-like illness episode.

cohort studies; immunization; influenza, human; postpartum period; pregnancy; regression analysis; respiratory tract infections; sentinel surveillance

Abbreviation: ACIP, Advisory Committee on Immunization Practices.

The US Advisory Committee on Immunization Practices (ACIP) currently recommends that women who will be pregnant during influenza season receive inactivated influenza vaccine (1). This recommendation has resulted from reports of excess maternal mortality during influenza pandemics, physiologic changes during pregnancy that may increase the morbidity of influenza infections, and epidemiologic reports of an increased risk of cardiopulmonary hospitalizations among pregnant women during influenza season (2–18). Despite vaccine recommendations by the...
ACIP and the American College of Obstetricians and Gynecologists (1, 19), immunization coverage among pregnant women remains low compared with that among other groups at high risk of severe influenza morbidity or mortality, specifically 12.8 percent among pregnant women compared with 24.2–65.5 percent across the other high-risk categories (20–26).

This study was designed to estimate the risk of acute clinical illness consistent with influenza among healthy pregnant and postpartum women during influenza seasons that could possibly be prevented by complying with current vaccine recommendations. We compared the risk of acute influenza-like illness episodes during periods of varying levels of influenza activity among members of Group Health Cooperative during pregnancy and postpartum weeks occurring during periods of heightened influenza isolate activity with those occurring during periods without such activity. We classified influenza and other respiratory isolate activity during the influenza season on a week-by-week basis and examined the confounding influence of other seasonal viral respiratory isolates that circulate along with influenza on the relation between influenza activity and influenza-like illness episodes.

We used the data obtained to estimate the number of women who needed to be vaccinated to prevent an influenza-like illness episode.

MATERIALS AND METHODS

Study population

Women were initially eligible for inclusion in the study population if they were members of the Puget Sound region of Group Health Cooperative (a managed care organization that is an affiliate of Kaiser Permanente and serves approximately 395,000 members) and if their administrative records could be linked to at least one livebirth certificate with a delivery date between June 1, 1992, and December 31, 1997. We required women to be continuously enrolled for 365 days or more prior to their first study delivery.

Automated administrative Group Health Cooperative records from June 1, 1991, through December 31, 1997, that contained enrollment, pharmacy, vaccination, outpatient, and emergency and inpatient data were obtained. Diagnostic and procedural codes were based on the International Classification of Diseases, Ninth Edition, and current procedural terminology (27, 28).

We excluded pregnancies if one of the following conditions was present: 1) the woman’s primary care clinic was not a Group Health Cooperative medical facility; 2) the matched maternal administrative record and livebirth certificate did not have exactly the same delivery/birth date and either an exact or last name match with the child or exact name match to the subscriber and first name match to the child; or 3) the first day of the last menstrual period and the clinically estimated gestational age were both missing on the birth certificate, or the last menstrual period resulted in an estimate of a pregnancy duration of greater than 48 weeks and the clinical estimate of gestational age was missing.

We obtained institutional review board approval for this study from Group Health Cooperative, the Washington State Department of Health, and the University of North Carolina at Chapel Hill.

Pregnancy status

We identified pregnancy initiation and delivery dates for women with livebirths that occurred between June 1, 1992, and December 31, 1997, from data recorded on birth certificates and either the date corresponding to the last menstrual period or the clinically estimated gestational age at birth.

Women were excluded after a diagnosis of a chronic condition that would target the woman for an influenza vaccination regardless of her pregnancy status, such as chronic pulmonary and cardiovascular, metabolic, renal, hemoglobinopathy, and immunosuppressive conditions as per ACIP recommendations (1). We excluded women with chronic inherited conditions and limited person-time on the basis of the first date of a predesignated International Classification of Diseases, Ninth Revision, diagnostic code. Each condition was required to have at least two entries on separate days for a specific code to reduce the chance that diagnoses were recorded and subsequently ruled out; however, we did not require two or more entries for cancer diagnoses or procedural codes. Person-time was omitted following postpartum death. We eliminated person-time between June 1st and September 30th because of limited influenza circulation and lack of surveillance data. We omitted vaccinated persons from 2 weeks postvaccination during the same influenza season through the end of the influenza season for influenza vaccinations identified through the automated administrative records. The vaccination date was identified through electronic administrative records for immunizations provided by the Group Health Cooperative. Previous managed care-based studies, including those of Group Health Cooperative, have considered such records to be relatively complete. However, we did not directly assess the completeness of the automated records (29, 30).

We included only pregnancies of greater than 20 weeks’ gestation to reduce the potential for misclassification of pregnancy status for unrecognized early pregnancy loss. The first day of the last menstrual period and the clinical estimate of gestational age at birth were used to determine the pregnancy initiation date. This date was based on the last menstrual period date and was verified by a clinical estimate of gestational age within 14 days of the last menstrual period. However, if the last menstrual period date was missing, then we based the pregnancy initiation date on the clinical estimate of gestational age. If either of these methods resulted in a pregnancy duration of less than 20 or greater than 45 weeks, pregnancy initiation was determined by use of percentile “standards” for gestational age by birth weight from information recorded on the state’s 1990–1999 singleton livebirth certificates stratified by race, parity, and gender. We compared the derived last menstrual period and estimated gestational age dates on the basis of the less extreme placement of the neonate’s birth weight on the percentile standards.

Trimester dates were calculated for each pregnancy week and the 3-month postpartum period. The first trimester was categorized as the initiation date through week 12, the
second trimester as weeks 13–26, and the third trimester as week 27 to delivery; the postpartum period was categorized as the first 13 weeks after delivery. We subsequently eliminated the first two weeks of the first trimester, since these weeks typically represent preconception time, and the delivery week to reduce the potential for heightened reporting due to health-care contact.

**Respiratory isolate data**

The Public Health—Seattle & King County Laboratory (hereafter referred to as “county”) and the University of Washington Clinical Virology Laboratory based out of the Children’s Hospital and Regional Medical Center (hereafter referred to as “pediatric university hospital”) provided weekly respiratory isolate surveillance data for the weeks between October 1st and May 31st. We recorded the number of respiratory specimens tested and the numbers positive for influenza viruses, respiratory syncytial virus, parainfluenza virus, and adenovirus. The county data were based on a sentinel physician network, and their respiratory specimens contributed to the National Respiratory and Enteric Virus Surveillance System. The network consisted of approximately nine public health clinics and 13 private physician offices. The throat and nasopharyngeal specimens were collected within 3 days of symptom onset from patients who met a standard case definition for an influenza-like infection. The pediatric university hospital specimens were obtained for inpatient, emergency, and outpatient diagnostic purposes.

The levels of weekly influenza virus activity were indexed by classifying the weeks between October 1st and May 31st according to the combined county and pediatric university hospital surveillance data. “Active” influenza weeks were defined as weeks when influenza isolates were detected for 2 or more consecutive weeks. We considered the active influenza weeks, as well as the 2 weeks before and after the active weeks, as “exposed,” since detection was considered to represent the tip of the iceberg of isolate activity in the community. We considered a week to be “unexposed” if it was not active or within 2 weeks of an active week.

The “intensity” of influenza isolate activity was based on the number of influenza isolates detected during a given week by use of the total county and pediatric university hospital data. The classifications included the following: 1) no influenza isolates detected, 2) low intensity (1–2 isolates), 3) moderate intensity (3–8 isolates), and 4) high intensity (≥9 isolates). The combined intensity level of other respiratory isolates (e.g., respiratory syncytial virus, parainfluenza, and adenovirus) was also classified for weeks by use of the tertiles of detected isolates as 1) no isolates detected, 2) low intensity (1–4 isolates), 3) moderate intensity (5–18 isolates), and 4) high intensity (≥19 isolates) for the combined isolates.

**Acute influenza-like illness episodes**

Table 1 lists the diagnostic codes considered to be consistent with a symptomatic acute influenza-like illness. In addition to the specified diagnostic codes, prescriptions for the antiviral amantadine or rimantadine were indicative of a symptomatic acute influenza-like illness. Diagnoses considered indicative of a chronic undetected condition were avoided. Illness episodes were identified to minimize variability in health care-seeking behavior and repetitive diagnostic codes during the course of a single acute illness. A separate illness episode was recorded when a medical contact had at least one targeted diagnostic code or prescription and was separated from other contacts by 4 weeks or longer. The onset of an influenza-like illness episode was the date of an outpatient visit or hospital admission when such a diagnosis or prescription was made.

**Statistical analyses**

Specific rates and rate differences for influenza-like illness episodes were estimated for each pregnancy stage and compared with the level of influenza isolate detection in the community. A survey sample approach with a one-stage cluster sample of variance estimates from the Taylor series methods within SUDAAN, version 8.0, software (Research Triangle Institute, Research Triangle Park, North Carolina) was used in a manner similar to those of previous studies that assessed event rate comparisons for correlated data (31, 32).

Repeated-measures logistic regression models estimated the log odds of an influenza-like illness episode on a week-by-week basis for the 8,321 women (301,767 total weeks). A single model with all the pregnancy weeks and separate
models for each pregnancy trimester and the postpartum period were calculated (not shown). A comparison of odds ratios for influenza-exposed and unexposed periods was completed, with adjustment for the activity level of other seasonal respiratory isolates. Given the rarity of the events, we interpreted the odds ratios as risk ratios. The logistic regression models were analyzed by use of SAS, version 8.02, software (SAS Institute, Inc., Cary, North Carolina), and generalized estimating equation methods produced standard errors that accounted for multiple pregnancy events and postpartum weeks entered for each woman (33, 34). In this regard, the study subjects had a clustered data structure according to the number of pregnancy and postpartum weeks included in the study. An independent covariance structure was used, since we obtained negligible correlation estimates from the exchangeable \((r = -0.0021)\) and autoregressive \((r = -0.0009)\) covariance structures. The least biased model was identified by fitting a full model and dropping terms based on chi-square values and their corresponding \(p\) values by use of type three generalized estimating equation analyses. If the interaction terms produced homogeneous stratum-specific odds ratios (change: \(\leq 50\) percent) or \(p\) values associated with the score statistic chi square of greater than 0.20, they were considered for elimination. To identify whether the observed risk deviated from the predicted risk under additive and multiplicative assumptions, we constructed interactive tables (35). The potentially confounding effect of noninfluenza seasonal respiratory activity was evaluated by identifying variables with the largest \(p\) values (i.e., \(p > 0.05\)), removing them from the model, and determining if there was greater than a 10 percent change in the odds ratio.

**RESULTS**

There were 9,222 livebirths (including multiple deliveries) that occurred among the 8,323 women included in the study population, which represented 70.9 percent (9,222/13,003) of the initially eligible pregnancies. The excluded categories were health-care visits in a non-Group Health Cooperative medical facility \((n = 2,714 (20.9\%))\), inadequate birth certificate linkage \((n = 157 (1.2\%))\), lack of pregnancy-dating information \((n = 50 (0.4\%))\), underlying chronic disease \((n = 275 (2.1\%))\), and inability to calculate person-time \((n = 585 (3.5\%))\). Final analyses included 301,778 person-weeks that contributed to influenza surveillance weeks.

Influenza vaccination was rare, with 3.6 percent of the women having one or more vaccine-protected pregnancy or postpartum weeks. The percentage of vaccine-protected weeks declined as the pregnancy stage progressed, with 2.6 percent, 1.6 percent, and 0.6 percent in the first, second, and third trimesters, and with 0.7 percent in the postpartum weeks, respectively, or 1.3 percent overall.

There was an average of 21.3 weeks (range: 14–31) between the first and last influenza isolate detected in each of...
the 1991/1992–1996/1997 influenza seasons. The average number of influenza isolates detected per season was 132.8 (range: 53–276). Although during the study period both the county and pediatric university hospital identified on average four influenza isolates each week, the number of isolates tested each week was on average 5.5 times greater at the county and pediatric university hospital, mainly because of a disproportionately large number of respiratory syncytial virus cases. Figure 1 depicts the number of isolates identified as influenza type A virus or type B virus and the number of parainfluenza, adenovirus, or respiratory syncytial virus isolates based on the combined county and pediatric university hospital data. Respiratory isolate surveillance data were available for 222 weeks.

Table 2 characterizes the weekly classification of respiratory isolate activity. Influenza type A was dominant for all seasons except the 1992/1993 season, when type B accounted for 83 percent of the county isolates. On the basis of the county’s available influenza type A subtyping data, it appeared that the distribution of subtypes detected in the study area reflected national data. In every season except 1995/1996, the predominant subtype was H3N2, while H1N1 was detected in approximately 60 percent of influenza type A isolates from 1995/1996.

We detected 686 influenza-like illness episodes, representing 771 separate health-care contacts. Approximately 8.3 percent of pregnant and postpartum women experienced a symptomatic influenza-like illness episode. A minority of influenza-like illness episodes (5.4 percent of episodes) were considered as severe because of a diagnostic code for pneumonia, acute respiratory failure, or pulmonary collapse; an emergency room visit; or a hospitalization. Specifically, the proportion of severe episodes increased according to pregnancy stage (3.1 percent, 4.0 percent, and 6.2 percent of influenza-like illness episodes for the first trimester, second trimester, and third trimester and 10.9 percent for the postpartum period, respectively). Influenza diagnoses made up only 2.2 percent of the total set of influenza-related codes used to identify influenza-like illness episodes. The majority of influenza-like illness diagnoses were upper respiratory infections (65.7 percent), followed by acute bronchitis and bronchiolitis (22.8 percent), unspecified pneumonia (4.8 percent), unspecified bronchitis (3.6 percent), acute laryngitis and tracheitis (0.7 percent), pulmonary collapse (0.1 percent), and amantadine prescription (0.1 percent).

A general decrease in the unadjusted rates of influenza-like illness episodes after the second trimester was detected, with the lowest rates occurring during the postpartum period (figure 2). Influenza virus activity, pregnancy stage, and the combined intensity of the other seasonal respiratory isolates were all positively associated with the odds of an influenza-like illness episode, but we did not detect a relation between maternal age and the odds of an influenza-like illness episode. Table 3 shows increasingly strong associations between influenza exposure and the odds of an influenza-like illness episode as gestation increases. In the third trimester and the 3-month postpartum period, the odds of a woman’s experiencing an influenza-like illness episode were approximately twofold higher during influenza-exposed periods compared with influenza-unexposed periods. The relation between the level of other seasonal respiratory isolates and the odds of an influenza-like illness episode was at least as strong as that detected for influenza exposure during the first and second trimesters. Other seasonal respiratory viral isolate activity moderately overestimated the association between influenza exposure and influenza-like illness episodes (data not shown).

A general positive trend was detected between the intensity of influenza isolate activity and the odds of an influenza-like illness episode within each pregnancy stage (table 4). The highest level of influenza isolate detection compared with the absence of detection produced consistently significant associations with the odds of influenza-like illness episodes within all pregnancy stages. Low and moderate influenza isolate detections had similar, but nonsignificantly elevated, associations with the odds of an influenza-like illness episode.

We found that pregnancy stage modified the relation between influenza exposure and the odds of an influenza-like illness episode greater than expected for the combined effects of pregnancy stage and influenza exposure on both the additive and multiplicative scales. Although the actual rate of events decreased as the pregnancy stage increased, the relative effect of pregnancy stage on the risk of an influenza-like illness episode increased among the first, second, and third trimesters and the postpartum period. We did not find
this relation between the intensity of the other combined seasonal respiratory isolates and pregnancy stage, showing that these findings were not due to artifacts of the analytical methods.

DISCUSSION

In this study, approximately 8 percent of healthy pregnant and postpartum women experienced influenza-like illness episodes that resulted in health-care utilization. The incidence of influenza-like illness during influenza-exposed periods was approximately 28, 33, 28, and 18 per 10,000 women-weeks for women in the first, second, and third trimesters and postpartum period. Findings from this study are believed to uniquely account for correlated repeated data inherent to studies of influenza during pregnancy and to control for possible biases that could be found when comparing women in different pregnancy stages.

These findings confirm the current belief that influenza activity in the community is associated with an increased risk of acute influenza-like illness during pregnancy. This study demonstrated that the magnitude of the association between heightened influenza activity and risk of influenza-like illness episodes increases from the first trimester to the postpartum period. Women in their third trimester are at increased risk of an influenza-like illness episode. Similar to the findings from other studies of managed care members, the present findings show that the bulk of influenza-like illness episodes is based on diagnostic codes suggestive of mild/moderate acute illness (17, 36). It is possible that the study missed influenza-like illness episodes that resulted in fetal loss because of the inclusion of only those pregnancies that resulted in livebirth. This was done to avoid misclassification of pregnancy status due to early uncaptured fetal loss.

This study demonstrates a heightened association between community influenza viral activity and influenza-like illness episodes during the postpartum period that differs notably from previously reported data identifying the 6-month postpartum period as the period with the lowest relative risk of acute cardiopulmonary hospitalization during the influenza season (18). This discrepancy may be due to

FIGURE 2. Acute influenza-like illness episodes for weeks with and without influenza exposure (refer to the “acute influenza-like illness episodes” and “respiratory isolate data” sections within Materials and Methods for more information), with unadjusted rates and 95% confidence intervals by trimester and postpartum in an unvaccinated maternity cohort, Puget Sound region, Washington, 1992–1997 (n = 301,778 person-weeks).
differences in the two study populations, managed care and Medicaid, which would be expected to have different levels of consistent postpartum health care (37). The postpartum findings in this study may reflect an increased period of risk, perhaps due to heightened exposure to circulating virus from increased contacts following birth, nosocomial transmission, or possible lowered immunity during the postpartum period. The increasingly strong association between community influenza activity and acute influenza-like illness episodes according to pregnancy stage supports the theory that underlying physiologic, and perhaps immunologic, changes that occur during pregnancy may be responsible for increased influenza-like morbidity. It is assumed that physiologic changes related to pulmonary function during late-stage pregnancy would resolve fully during the 3-month postpartum period and would be expected to have a very limited influence on the observed postpartum findings.

The concomitant activity of other seasonal respiratory viral isolates moderately confounded the association between influenza exposure and risk of an influenza-like illness episode. The strength of confounding decreased as the stage of pregnancy progressed and was more noticeable when influenza activity was defined in broad contiguous periods (e.g., influenza-exposed weeks compared with weeks with high influenza virus intensity), since these antigens cocirculate with influenza, produce similar clinical symptoms, and can cause dual respiratory infections (38–43). The nonspecificity of respiratory symptoms resulting from influenza and other seasonal respiratory infections adversely impacts influenza-like illness studies, as well as vaccine efficacy studies, and may result in an over- or underestimation of the potential benefit of influenza vaccination (36, 44).

The advantages of this study design minimized possible biases by comparing women within the same pregnancy stage who received similar health care during pregnancy. The design accounted for time-based analyses and possible correlations in the weekly data, and it enhanced specificity compared with previous studies in both the classification of community influenza activity and identification of influenza-related morbidity (17, 18, 21, 45–49). Although a relatively strict definition of community influenza activity as a surrogate for individual-level influenza infection data was used, the availability of rapid influenza tests would vastly improve the specificity of studies (50). As in all studies that have used influenza isolate activity as a surrogate for individual exposure, diagnostic practices that potentially impact findings include the quality of the surveillance system, the virulence and transmission of influenza in the community, individual susceptibility, and health care-seeking behavior. To enhance the specificity of influenza-related diagnoses, we focused on acute influenza-like illness diagnoses and avoided chronic diagnoses, such as asthma or cardiac conditions, which would place women at high risk of influenza-related morbidity regardless of their pregnancy.

**Table 3. Risk of acute influenza-like illness episodes* in relation to influenza exposure† by pregnancy stage, with odds ratios adjusted for the intensity of community respiratory syncytial virus, parainfluenza, and adenovirus circulation in an unvaccinated maternity cohort, Puget Sound region, Washington, 1992–1997**

<table>
<thead>
<tr>
<th>Respiratory isolate activity</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>Chi square</th>
<th>p value</th>
</tr>
</thead>
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<tr>
<td>Influenza exposure†</td>
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<td></td>
</tr>
<tr>
<td>First trimester</td>
<td>1.12</td>
<td>0.79, 1.59</td>
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<td>0.97, 1.73</td>
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<td>Respiratory syncytial virus, parainfluenza, and adenovirus intensity‡</td>
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<tr>
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* An illness episode was defined as a health-care contact with at least one target code separated from other such encounters by 4 or more weeks. The onset date for an acute influenza-like illness episode was the date when a target diagnosis was made during an outpatient visit, prescription date, or the admission date for hospitalization.† Influenza-exposed weeks = weeks when influenza isolates were detected for 2 or more consecutive weeks (“active week”) or a week fell within 2 weeks of an active week. Influenza-unexposed weeks = weeks that occurred while influenza surveillance was conducted and the week was not exposed. Viral isolate data were obtained from the Public Health—Seattle & King County Laboratory and the University of Washington Clinical Virology Laboratory.‡ Respiratory syncytial virus, parainfluenza, and adenovirus intensity = weeks without any isolates detected, weeks with low intensity (1–4 isolates), weeks with moderate intensity (5–18 isolates), and weeks with high intensity (≥19 isolates). Viral isolate data were obtained from the Public Health—Seattle & King County Laboratory and the University of Washington Clinical Virology Laboratory.

§ Odds ratios for an influenza-like illness episode in relation to influenza exposure according to high, moderate, and low respiratory virus isolate levels combined across all pregnancy stages.
To assess the potential role of influenza vaccination in preventing influenza-like illness episodes, we estimated the adjusted risk difference for influenza-like illness episodes by pregnancy stage, comparing influenza-exposed and -unexposed weeks. On the basis of the periods of influenza exposure, we multiplied the trimester- and postpartum-specific risk differences by the number of weeks in each stage and determined that an estimated 264 additional events occurred among the 9,222 study pregnancies and postpartum periods, yielding an incremental risk of approximately 0.03 influenza-like illness episodes per pregnancy/postpartum period. We also compared weeks having high influenza intensity with weeks having no intensity, resulting in an incremental risk of 0.06 influenza-like illness episodes per pregnancy/postpartum period (572 additional events occurring among 9,222 pregnancies). We determined that between 2.9 and 6.2 influenza-like illness episodes occurred per 100 pregnant/postpartum women. Translating these risk differences into “number needed to vaccinate” and assuming a vaccine effectiveness of 80 percent suggest that vaccination of between 20 and 43 women who expect to be pregnant or postpartum during periods of high influenza intensity or influenza-exposed periods would lead to the prevention of one influenza-like illness episode. Previous findings have

### TABLE 4. Risk of acute influenza-like illness episodes* in relation to influenza intensity † by pregnancy stage, with odds ratios adjusted for the intensity of community respiratory syncytial virus, parainfluenza, and adenovirus circulation in an unvaccinated maternity cohort, Puget Sound region, Washington, 1992–1997

<table>
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<tr>
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<th>95% confidence interval</th>
<th>Chi square</th>
<th>p value</th>
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<tr>
<td><strong>Influenza intensity†</strong></td>
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<td>First trimester</td>
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<td>0.76, 1.57</td>
<td>0.25</td>
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</table>

* An illness episode was defined as a health-care contact with at least one target code separated from other such encounters by 4 or more weeks. The onset date for an acute influenza-like illness episode was the date when a target diagnosis was made during an outpatient visit, the admission date for hospital stays, or the prescription date.

† Influenza intensity = weeks without any influenza isolates detected, weeks with low intensity (1–2 isolates), weeks with moderate intensity (3–8 isolates), and weeks with high intensity (>9 isolates). Viral isolate data were obtained from the Public Health—Seattle & King County Laboratory and the University of Washington Clinical Virology Laboratory.

‡ Respiratory syncytial virus, parainfluenza, and adenovirus intensity = weeks without any isolates detected, weeks with low intensity (1–4 isolates), weeks with moderate intensity (5–18 isolates), and weeks with high intensity (>19 isolates). Viral isolate data were obtained from the Public Health—Seattle & King County Laboratory and the University of Washington Clinical Virology Laboratory.

§ Odds ratios for an influenza-like illness episode in relation to influenza intensity according to high, moderate, and low respiratory virus isolate levels combined across all pregnancy stages.
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Conflict of interest: Dr. Lisa Lindsay was employed by GlaxoSmithKline (GSK) Biologicals, the makers of vaccines, and was conducting research projects related to human papillomavirus vaccine. She has never conducted research on influenza vaccines for GSK. This project was not funded by GSK. Dr. Lisa Jackson is currently conducting research for ID Biomedical Corporation and Chiron Vaccines, serves as a consultant to Chiron Vaccines, and is on the speakers’ bureau for Sanofi Pasteur, Inc.

REFERENCES


estimated that 500 women would need to be vaccinated to prevent an acute cardiopulmonary hospitalization among women in the third trimester, assuming the same level of vaccine effectiveness (18). The level of influenza vaccine effectiveness during pregnancy has recently been reported to be very low for reducing respiratory outpatient visits (36). However, factors that may have minimized apparent vaccine effectiveness included very low vaccine coverage within the healthy study population, low specificity in the definition of influenza seasons, influenza-related morbidity, and lack of control for other seasonal respiratory viruses and other time-related factors. Effectiveness studies based on individual-level influenza infections in pregnant women and their infants would provide improved evidence of the impact of influenza vaccination on mothers and their babies. Current vaccine recommendations target pregnant women. Our findings, however, suggest that maternal benefits could also be gained from vaccine protection during the postpartum period.

Vaccine coverage among healthy pregnant women may improve when the apparent avoidance of vaccination during pregnancy and concerns regarding vaccine effectiveness during pregnancy are addressed. Although the vaccination rate was very low in this study population compared with the self-reported national estimates (3.6 percent vs. 12.8 percent), the finding was comparable to that of another recent study (3.5 percent) (26, 51). It is unclear whether the discrepancy between vaccination rates in the two managed care populations compared with the national estimates is due to underestimates in the administrative databases, overestimates in national self-reported rates, or potentially real differences. There is currently no evidence of risk associated with maternal influenza immunization using the inactivated vaccine based on assessment of maternal adverse reactions and fetal and newborn well-being; an added benefit to the newborn may also be present through passive, transplacentally acquired immunity gained through maternal vaccination (51–62). Additional safety considerations, such as those pertaining to the administration of thimerosal-containing vaccines during pregnancy, have been raised; even though there is no scientific evidence of an association with serious adverse events among vaccine recipients, the availability of thimerosal-free vaccines is increasing and may help to increase influenza vaccine coverage rates in pregnant women (1, 22).

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