MAJOR ARTICLE

Influenza Vaccine Given to Pregnant Women Reduces Hospitalization Due to Influenza in Their Infants

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Background. Infants aged <12 months are at high risk of hospitalization for influenza. Influenza vaccine is recommended for pregnant women and for most children; however, no vaccine is approved for infants aged <6 months. Effective approaches are needed to protect this vulnerable population. Vaccination of women during pregnancy may protect the infant through transfer of antibodies from the mother. Few studies have examined the effectiveness of this strategy, and those studies produced mixed results.

Methods. In a matched case-control study, case patients were infants aged <12 months admitted to a large urban hospital in the northeastern United States because of laboratory-confirmed influenza from 2000 to 2009. For each case, we enrolled 1 or 2 control subjects who were infants who tested negative for influenza and matched cases by date of birth and date of hospitalization (within 4 weeks). Vaccine effectiveness was calculated on the basis of matched odds ratios and was adjusted for confounding.

Results. The mothers of 2 (2.2%) of 91 case subjects and 31 (19.9%) of 156 control subjects aged <6 months, and 1 (4.6%) of 22 case subjects and 2 (5.6%) of 36 control subjects aged ⩾6 months, had received influenza vaccine during pregnancy. The effectiveness of influenza vaccine given to mothers during pregnancy in preventing hospitalization among their infants, adjusted for potential confounders, was 91.5% (95% confidence interval [CI], 61.7%–98.1%; $P = .001$) for infants aged <6 months. The unadjusted effectiveness was 90.7% (95% CI, 59.9%–97.8%; $P = .001$).

Conclusions. Influenza vaccine given to pregnant women is 91.5% effective in preventing hospitalization of their infants for influenza in the first 6 months of life.

Influenza is the leading cause of vaccine-preventable death in the United States [1], responsible for 200,000 hospitalizations and 36,000 deaths per year [2]. The highest burden of disease is among infants, pregnant women, elderly persons, and people with certain chronic medical conditions. In children, the highest incidence of hospitalization attributable to influenza is among infants aged <1 year, with those aged <6 months at highest risk [3]. Rates of hospitalization of healthy infants for influenza are similar to those of high-risk adults, and rates are even higher among infants with underlying chronic medical problems, particularly respiratory conditions [3].

Inactivated influenza vaccine is recommended by the Centers for Disease Control and Prevention (CDC) for all pregnant women and children, except for infants aged <6 months (for whom the vaccine is poorly immunogenic) and for persons with a serious allergy to egg protein [4, 5]. Strategies for protecting these groups have included only washing hands, avoiding contact with persons infected with influenza, and vaccinating close contacts [4], but the effectiveness of these strategies is unknown.

One potential approach to protecting young infants against influenza infection is to vaccinate their mothers during pregnancy [6, 7]. Both animal and human studies support the possibility of protecting the offspring against influenza by immunization of the mother. Antibodies (immunoglobulin G) cross the placenta via active transport from the mother to the fetus, particularly in the final weeks of pregnancy [8–11]. Additional antibodies (immunoglobulin A) are transferred from the mother to the infant via breastmilk [12].

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One study showed that an infant's concentration of influenza antibodies at birth correlated with that of the mother. Although the study failed to find a protective effect, infants with higher concentrations of influenza antibodies had delayed onset and decreased severity of influenza infection [13]. The same protection could be achieved via influenza vaccination of pregnant women [13–16]. Another study showed influenza vaccination during pregnancy resulted in influenza-specific antibody concentrations in the infants at birth that were higher than those in their mothers, suggesting active transport from mother to infant [14]. The presence of maternally derived antibodies in infancy does not inhibit development of natural immunity later in life from vaccination or natural infection [16, 17].

Two previous studies of hospitalized infants have compared rates of influenza-like illness or medically attended acute respiratory infections between infants whose mothers had received influenza vaccine during pregnancy and infants whose mothers had not received this vaccine; however, neither study found a protective effect [18, 19]. Recently, a clinical trial evaluated women who received inactivated influenza vaccine during their third trimester of pregnancy in Bangladesh, where influenza circulates year-round, and followed up their infants for up to 24 weeks after birth. Researchers in that study found a 63% decrease in the number of laboratory-confirmed influenza infections in those infants, compared with infants of women in a control group who received a conjugate pneumococcal vaccine during pregnancy. However, the study did not assess the vaccine's effectiveness for either hospitalization or severity of illness in the infants [20].

We conducted a matched case-control study of infants at Yale–New Haven Children's Hospital, a large urban hospital in the northeastern United States, to assess the effectiveness of influenza vaccine given to pregnant women in decreasing the number of hospitalizations for laboratory-documented influenza among their infants.

METHODS

Eligibility requirements. Subjects were infants aged <12 months who were hospitalized for laboratory-confirmed influenza between October 2000 and April 2009 (prior to the arrival of the 2009 pandemic influenza in this region).

We excluded infants who were adopted at birth, infants whose mothers had a contraindication to inactivated influenza vaccine or were unable to consent to participate (eg, were deceased or had unknown whereabouts), infants who were hospitalized for reasons unrelated to respiratory infection (as determined by review of medical records), infants whose parents could not complete the interview in English or Spanish, and infants with influenza infection acquired when the patient was already in the hospital (ie, nosocomial). Infants who received influenza vaccine at least 2 weeks prior to admission to the hospital were excluded from the analyses, because it would be impossible to separate the effect of vaccination of the mother from that of vaccination of the infant.

Identification of potential cases. Cases were infants hospitalized for influenza with documentation of either a nasal swab or aspirate sample that was positive for influenza by direct fluorescent antibody (DFA) test. Case subjects were identified from the list of all patients who had a nasal swab or aspirate sample submitted to the hospital's clinical virology laboratory for the DFA test (Light Diagnostics). This test has been shown to be 96.2% sensitive and 99.0% specific for influenza, compared with PCR, in our clinical virology laboratory [21]. Samples deemed inadequate by the laboratory were not included. Data collection started in 2007. Subjects hospitalized between 2000 and early 2007 were identified historically from the clinical virology laboratory list of all tests for influenza and were enrolled by telephone. During the 2007–2008 and 2008–2009 influenza seasons, research staff identified cases prospectively by reviewing clinical virology laboratory lists of all tests for influenza and the daily list of new hospital admissions, to enroll patients in the hospital setting and to collect a nasal aspirate sample.

The nasal samples obtained from the case subjects identified prospectively (2007–2009) were all confirmed to be negative for 2009 pandemic influenza A H1N1. RNA was extracted from the clinical specimens using RNeasy Mini Kit (Qiagen) per the manufacturer's instructions. Reverse transcription and polymerase chain reaction were performed using primers and parameters described by the World Health Organization/CDC protocol [22] and the AccessQuick RT-PCR System (Promega).

Selection of controls. For each case, we enrolled 1 or 2 matched control subjects, who were hospitalized infants with DFA results negative for influenza. Control subjects from the list of all patients who had a DFA test for influenza were matched to cases by date of birth and date of hospitalization. Matching started with the subjects born within 2 weeks (before or after the case date of birth) and who were admitted within 2 weeks (before or after the case date of hospital admission) and then, if necessary, proceeded to those born within 4 weeks and admitted within 2 weeks from the case, then those born within 2 weeks and admitted within 4 weeks, and finally those born within 4 weeks and admitted within 4 weeks. We used lists of random numbers to determine the order in which to contact potential eligible subjects within each case-control group. We used risk-set sampling in our selection of cases and controls [23].

Collection of data and ascertainment of vaccinations. We conducted interviews with the parents of all study subjects for information about demographic characteristics, possible confounders (such as breast-feeding or susceptible individuals in the household), and comorbidities and to identify all possible

locations where vaccination was given. Interviews were conducted in person when a case subject or control subject was identified prior to discharge from the hospital, if possible, or otherwise by phone. All interviews were conducted in English or Spanish.

Information about vaccinations and comorbidities of the infants was obtained by reviewing records of all providers of medical care. We reviewed mothers' medical records from primary medical providers, obstetricians, pharmacies, and anywhere the mother stated that she had received influenza vaccine. We used this information to ascertain whether a woman had received influenza vaccine during pregnancy, whether she had received the vaccine at any time prior to that pregnancy, and whether she had received the vaccine during the same influenza season as the infant's hospital admission. A woman was considered vaccinated if there was written documentation of receipt of influenza vaccine during her pregnancy, excluding vaccinations received within 14 days of delivery.

We also collected clinical data from the hospital medical record, including any abnormal vital signs (highest temperature and respiratory rates and lowest oxygen saturation levels), clinical signs of increased work of breathing, results of chest radiographs, and the need for intubation and/or admission to the intensive care unit (ICU). We classified the severity of each case subject's symptoms on a scale of 0–16 points, based on our modification of a validated scale of severity of respiratory symptoms in infants (Table 1) [24].

Statistical analysis. We calculated a matched odds ratio for vaccination of mothers of case subjects, compared with mothers of matched control subjects. The vaccine's effectiveness was calculated as 1 minus the matched odds ratio, multiplied by 100. Conditional logistic regression was used to adjust for potential confounders, including race, ethnicity, sex, age, day care attendance, prematurity, vaccination of household contacts, breast-feeding, and relevant chronic illness (asthma/reactive airways disease, chronic lung disease, conditions requiring medical equipment to facilitate breathing, heart defects, blood disorders, seizures, metabolic or endocrine disorders, severe gastrointestinal disease, kidney disease, or spinal cord injury).

A stratified analysis was also conducted to assess for effect modification by age of the subject (≥6 months vs <6 months) on the basis of the CDC recommendation to begin influenza vaccination at age 6 months. Whether the subject was identified at the time of hospitalization or historically via billing data was also evaluated as a possible confounder or effect modifier.

We also assessed the significance of the clinical severity of influenza of the cases using Student's *t* test or the Wilcoxon rank-sum test, as appropriate. Analyses were conducted using SAS, version 9.1.3 for Microsoft Windows (SAS Institute).

RESULTS

We identified a total of 220 eligible case subjects (infants aged <12 months who were hospitalized for influenza) between October 2000 and April 2009. Of these, 36 (16%) could not be contacted by researchers (eg, had an incorrect or outdated phone number or had moved with no forwarding information). Of the remaining 184 potential case subjects, parents of 27 (15%) declined to participate, and 157 (85%) were enrolled. Enrollment for this study started in July 2007. Of all case subjects, 33 were hospitalized between January 2008 and April 2009 (identified prospectively via active surveillance of laboratory data and hospital admissions), and 124 were hospitalized between October 2000 and May 2007 (identified historically via laboratory data). Of the case subjects, 130 (82.8%) were infected with influenza A and 27 (17.2%) were infected with influenza B; none were infected with the 2009 pandemic influenza A H1N1. For the case subjects, 430 potentially suitable matched control subjects were identified; of these, 114 (26.5%) could not be contacted. Of those that we were able to reach, 45 (14.2%) declined to participate, and 270 (85.7%) were enrolled. Data are presented on the 113 cases and 192 controls in matched groups, with complete data for the case and at least 1 matched control. Demographic characteristics of subjects identified prospectively and historically differed statistically significantly only for report of sick household members during the month before hospitalization (59.8% vs 23.3%; $P < .001$) and length of hospital stay (5.0 ± 13.2 vs 2.9 ± 3.7 days; $P = .030$).

Table 1. Clinical Severity Scale Used to Assess Severity of Influenza

	Point value		
Parameter	0	1	2
Heart rate, max no. of beats/min			
Age 0–7 days	<130	130–160	>160
Age 1–4 weeks	<135	135–170	>170
Age 1–6 months	<140	140–170	>170
Age ≥6 months	<130	130–160	>160
Respiratory rate, max no. of breaths/min			
Age 0–1 month	<50	50–70	>70
Age 1–6 months	<30	30–50	>50
Age ≥6 months	<20	20–40	>40
Oxygen saturation (by pulse oximeter), %	≥94	…	<94
Wheezing	No	Yes	…
Retractions (intercostal, subcostal, etc)	No	…	Yes
Nasal flaring	No	Yes	…
Required intubation/mechanical ventilation	No	…	Yes
Required ICU care	No	…	Yes
Abnormal chest radiograph	No	…	Yes

NOTE. Value range is 0–16 (mild, 0–3; moderate, 4–5; severe, 6–16). ICU, intensive care unit; max, maximum.

Table 2. Characteristics of Infants Hospitalized with Influenza and Matched Control Subjects

Characteristic	No. (%) of case subjects (n = 113)	No. (%) of control subjects (n = 192)	P
Age, months			.998
0 to <3	40 (35.4)	69 (35.9)	
3 to <6	51 (45.1)	87 (45.3)	
6 to <9	12 (10.6)	19 (9.9)	
9 to <12	10 (8.9)	17 (8.9)	
Mean age ± SD, months	3.2 ± 2.8	3.1 ± 2.9	
Median age, months	2.0	2.0	
Male sex	57 (50.4)	101 (52.6)	.715
Hispanic ethnicity	45 (39.8)	59 (30.7)	.106
Race			.135
White	73 (64.6)	129 (67.2)	
Black	21 (18.6)	21 (10.9)	
Other	19 (16.8)	42 (21.9)	
Ever breast-fed	59 (55.7)	115 (67.3)	.052
Attends day care	11 (9.8)	18 (9.4)	.898
Environmental tobacco smoke exposure	35 (31.0)	56 (29.2)	.739
Premature (gestational age ⩽37 weeks)	13 (11.6)	37 (19.3)	.082
Gestational age <32 weeks	1 (0.9)	10 (3.5)	
Gestational age 32 to ⩽37 weeks	12 (10.7)	27 (14.1)	
Chronic medical conditions[a]	41 (36.3)	74 (38.5)	.695
Respiratory conditions	25 (22.1)	25 (24.5)	.640
Type of residence			.028
Single family home	56 (49.6)	110 (57.3)	
Multifamily home	22 (19.5)	26 (13.5)	
Apartment	31 (27.4)	56 (29.2)	
Other setting[b]	4 (3.5)	0 (0.0)	
No. of people living at home (including subject)			
Mean ± SD	4.9 ± 2.1	4.4 ± 1.3	.015
Median	5.0	4.0	
Household contacts received influenza vaccine			.001
None	64 (56.6)	67 (34.9)	
Some	37 (32.7)	96 (50.0)	
All	12 (10.6)	29 (15.1)	

NOTE. SD, standard deviation.

[a] Includes respiratory conditions (asthma, reactive airways disease, chronic lung disease, and conditions requiring medical equipment to facilitate breathing) as well as heart defects, blood disorders, seizures, metabolic or endocrine problems, severe stomach problems, kidney disease, and spinal cord injuries.

[b] Other settings include dormitories, shelters, and mobile homes.

Case subjects and matched control subjects were comparable for most demographic characteristics and risk factors (Table 2). Of the case subjects, 81% were aged <6 months. Case subjects came from households with a larger number of household members, compared with those of control subjects (4.9 ± 2.0 vs 4.4 ± 1.3 persons; $P = .015$), and they were significantly less likely to live with household members who had received influenza vaccine (32.7% vs 50.0% for any household members vaccinated; 10.6% vs 15.1% for all household members vaccinated; $P = .001$). The mothers of 2 (2.2%) of 91 case subjects and 31 (19.9%) of 156 control subjects aged <6 months and mothers of 1 (4.6%) of 22 case subjects and 2 (5.6%) of 36 control subjects aged ⩾6 months had received influenza vaccine during pregnancy (Table 3).

The unadjusted effectiveness of influenza vaccine given to mothers during pregnancy in preventing hospitalization for influenza among their infants was 90.7% (95% confidence interval [CI], 59.9%–97.8%; $P = .001$) for infants aged <6

Table 3. Receipt of Influenza Vaccine by Subjects' Mothers

Characteristic	No. (%) of case subjects (n = 113)	No. (%) of control subjects (n = 192)	P
Vaccination status during pregnancy			<.001
Not vaccinated	110 (97.4)	159 (82.8)	
Vaccinated	3 (2.7)	33 (17.2)	
During hospitalization season	2 (1.8)	32 (16.7)	
During prior season	1 (0.9)	1 (0.5)	
For those vaccinated during pregnancy, vaccination occurred			.541
First trimester	0 (0.0)	0 (0.0)	
Second trimester	1 (33.3)	7 (21.2)	
Third trimester	2 (66.7)	26 (78.8)	
During influenza season when infant was hospitalized			<.001
Mother was not vaccinated	109 (96.5)	155 (80.7)	
Mother was vaccinated	4 (3.5)	37 (19.3)	

months. In the final adjusted model, immunization of household contacts (ie, persons other than the subject's mother residing in the household at the time of admission) (adjusted odds ratio, 0.420; 95% CI, 0.221–0.798; $P = .008$) and prematurity (adjusted odds ratio, 0.375; 95% CI, 0.153–0.918; $P = .032$) were retained, resulting in an adjusted effectiveness of the vaccine of 91.5% (95% CI, 61.7%–98.1%; $P = .001$) for this age group. The effectiveness of the vaccine for infants aged ⩾6 months was −41.4% (95% CI, −2257.3% to 91.5%; $P = .809$). The effectiveness of the vaccine did not differ significantly when we compared those identified prospectively with those identified historically (for historically identified subjects: effectiveness, 88.9%; 95% CI, 13.1%–98.6%; $P = .036$; for prospectively identified subjects: effectiveness, 92.0%; 95% CI, 37.0–99.0; $P = .016$; for the Breslow Day test for homogeneity of the odds ratios, $P = .767$). Also, exclusion of subjects born before 32 weeks gestational age did not significantly affect the estimate.

There were no significant differences in demographic characteristics between mothers who received influenza vaccine and those who did not (Table 4). Among vaccinated mothers, the 2 groups did not differ significantly in the trimester of pregnancy during which vaccination occurred, with 2 (66.7%) of the case subjects' mothers and 26 (78.8%) of the control subjects' mothers receiving vaccines during the third trimester. A mother's chance of being offered influenza vaccine during pregnancy will vary depending on the time of year when the pregnancy begins, but we expect that this variability did not differ significantly between case and control subjects, because these 2 groups were closely matched by the infants' dates of birth.

The median clinical severity scores of the case subjects enrolled was 4, on a scale of 0–16 (Figure 1). There were 11 case subjects (9.7%) admitted to the ICU. Case subjects aged ⩾6 months at the time of hospitalization had a significantly higher mean severity score than did those aged <6 months (6.3 ± 3.1 vs 4.1 ± 2.7; $P = .001$), and those with chronic medical conditions had higher severity scores than did those without (5.3 ± 2.5 vs 3.5 ± 2.2; $P = .003$). Differences in clinical se-

Table 4. Effectiveness of Influenza Vaccine Given to Mothers During Pregnancy in Preventing Hospitalization for Influenza among Their Infants

Measure	Subjects aged <6 months	Subjects aged ⩾6 months
No. (%) of case infants; no. (%) of control infants		
Mother was vaccinated	2 (2.2); 31 (19.9)	1 (4.6); 2 (5.6)
Mother was not vaccinated	89 (97.8); 125 (80.1)	21 (95.5); 34 (94.4)
Vaccine effectiveness (95% CI), %		
Unadjusted	90.7 (59.9–97.8)[a]	−41.4 (−2257.3 to 91.5)[b]
Adjusted[c]	91.5 (61.7–98.1)[a]	…

NOTE. CI, confidence interval.

[a] $P = .001$.

[b] $P = .809$.

[c] The adjusted model for subjects aged <6 months retained vaccination of household contacts and prematurity.

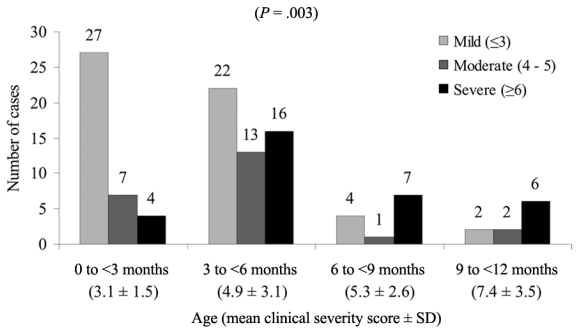

Figure 1. Clinical severity score by age group

verity scores of the case subjects by mother's vaccination status during pregnancy were not statistically significant.

DISCUSSION

Our study shows that inactivated influenza vaccine given to pregnant women is highly effective (91.5%) in preventing hospitalization for laboratory-confirmed influenza among their infants aged <6 months. These results have great clinical relevance, because they provide a strategy to confer protection to young infants at high risk for the disease and for whom no vaccine is currently available. Furthermore, this strategy has important public health implications, because vaccination protects not only young infants but also their mothers, who are in the high-risk category for severe influenza. Our results on the effectiveness of this approach in the United States, where influenza is seasonal, are consistent with findings of a randomized trial of influenza vaccine in Bangladesh, a tropical, developing country where the pattern and transmission of influenza is perennial [20].

Although there was inadequate statistical power to assess the vaccine's effectiveness for infants aged ⩾6 months, an estimate of −41.4% with wide confidence intervals indicates that a null effect in this age group is plausible. This difference in protective effect for infants aged ⩾6 months and infants aged <6 months at hospitalization could be explained by the decrease in the concentration of passively transferred antibodies, which one would expect to have dropped to negligible levels by age 6–9 months. The interpretation of this effect is, however, complicated by small numbers of subjects.

There were several possible limitations to our study. We lacked statistical power to estimate the effectiveness of influenza vaccine for infants aged ⩾6 months. It also was not possible to assess independent effects of second trimester vaccination versus third trimester vaccination, because of small numbers. Furthermore, our study did not have adequate power to assess the vaccine's effectiveness by influenza season, allowing us to assess for year-to-year variability. Future prospective studies are needed to evaluate longer-term effectiveness, in subsequent influenza seasons, of this novel strategy. We did not type strains to determine whether influenza infections were caused by strains included in the vaccine, and further research is needed to evaluate differences in vaccine effectiveness by circulating strain and vaccine strain match. It is possible that recall bias could have influenced the ability of mothers to recall information that could not be verified by the medical record, such as the length of time they breast-fed their infant.

The CDC and the American College of Obstetricians and Gynecologists (ACOG) recommend inactivated influenza vaccination for women who will be pregnant during the influenza season [4], and inactivated influenza vaccine given to pregnant women is safe and immunogenic [25]. Despite data on safety and the potential benefit to both mother and infant, rates of vaccination with influenza vaccine among pregnant women are poor and vary widely for different health care providers and regions [26]. In spite of the ACOG's recommendation of influenza vaccination for pregnant women as a means of protection for women against severe infection, in 2003 only one-third of obstetricians offered this vaccine to their patients during pregnancy [27]. In our sample, only 17.2% of mothers of control subjects received influenza vaccine during pregnancy. It is notable, however, that rates of influenza vaccination during pregnancy have improved steadily in the past few years; 10% control subjects in 2000–2004, 15% of control subjects in 2005–2007, and 35% control subjects in 2008–2009 were born to mothers who had received influenza vaccine during pregnancy, a trend similar to that in national data from these years [4].

The public health implications of our findings are important, because the effective strategy of the protection of the infant through vaccination during pregnancy may also serve as an incentive for pregnant women (who are also at high risk for complications from severe influenza) to accept influenza vaccine and for their care providers to offer it. Hopefully, this evidence could also be used in community and public campaigns to improve the overall vaccination rates in these high-risk groups. Also, this strategy improves on the cost-effectiveness of influenza vaccine in pregnant women [28]. Influenza vaccine given to pregnant women is an effective approach to decreasing the number of hospitalizations for influenza among their infants aged <6 months.

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