

Protective Effect of Maternal Influenza Vaccination on Influenza in Their Infants: A Prospective Cohort Study

Satoko Ohfuji,^{1,2} Masaaki Deguchi,⁴ Daisuke Tachibana,³ Masayasu Koyama,³ Tetsu Takagi,⁵ Takayuki Yoshioka,⁶ Akinori Urae,⁸ Kazuya Ito,^{1,2} Tetsuo Kase,^{1,2} Akiko Maeda,¹ Kyoko Kondo,⁷ Wakaba Fukushima,^{1,2} and Yoshio Hirota,^{1,9,10} for the Osaka Pregnant Women Influenza Study Group^a

¹Department of Public Health, ²Research Center for Infectious Disease Sciences, and ³Department of Obstetrics and Gynecology, Osaka City University Graduate School of Medicine, ⁴Department of Obstetrics and Gynecology, Kishiwada City Hospital, ⁵Takagi Ladies Clinic, ⁶Osaka Branch, Mediscience Planning, and ⁷Osaka City University Hospital, Osaka, ⁸Head Office, Mediscience Planning, Tokyo, and ⁹College of Healthcare Management and ¹⁰Clinical Epidemiology Research Center, SOUSEIKAI Global Clinical Research Center, Fukuoka, Japan.

Background. Infants <6 months of age are too young to receive influenza vaccine, despite being at high risk for severe influenza-related complications.

Methods. To examine the effectiveness of maternal influenza vaccination in preventing influenza in their infants, we conducted a prospective cohort study of 3441 infants born at participating hospitals before the 2013–2014 influenza season. At the time of recruitment, their mothers completed a questionnaire about influenza vaccination status for the 2013–2014 season. A follow-up survey was conducted after the end of the 2013–2014 season to collect information regarding influenza diagnosis and hospitalization among infants.

Results. During the 2013–2014 influenza season, 71 infants (2%) had influenza diagnosed, and 13 infants (0.4%) were hospitalized with influenza. Maternal influenza vaccination (especially prenatal vaccination) decreased the odds of influenza among infants. The effectiveness of prenatal vaccination was 61% (95% confidence interval, 16%–81%), whereas that of postpartum vaccination was 53% (–28%–83%). Although maternal influenza vaccination was also associated with a decreased odds of influenza-related hospitalization among infants, vaccine effectiveness (73%) did not reach statistical significance, owing to the limited number of infants hospitalized because of influenza.

Conclusions. The present findings indicated that pregnant women and postpartum women should receive influenza vaccination to protect their infants.

Keywords. Influenza; infants; maternal vaccination; prospective cohort study; vaccine effectiveness.

Infants <6 months of age are too young to receive the influenza vaccine, despite being at high risk for severe influenza-related complications. In the United States, to protect these infants, influenza vaccination has been recommended for individuals who live with or care for these infants, particularly their mothers [1]. In addition, the World Health Organization issued a position paper recommending that pregnant women be accorded the highest priority for seasonal influenza vaccination, owing to expectations of vaccine effectiveness in preventing influenza in mothers and their infants [2].

However, to our knowledge, only 7 studies have reported the effectiveness of maternal influenza vaccination for influenza in

infants <6 months of age [3–9]. Moreover, these previous studies have reported inconsistent results. Four studies indicated significant vaccine effectiveness in preventing infant influenza and its related hospitalization [3–6], while the remaining 3 studies did not indicate any effectiveness of maternal influenza vaccination [7–9]. We believe there could be several possible reasons for this inconsistency. Since the previous studies focused on the effectiveness of vaccination of pregnant women, they might not have taken the possible effects of vaccination of postpartum women into consideration. Influenza vaccination of postpartum women may prevent influenza among mothers, which may contribute to protecting their infants from influenza. If, however, these postpartum-vaccinated women were classified as unvaccinated women, it would lead to underestimation of the effectiveness of maternal influenza vaccination. In addition, studies that used acute febrile respiratory illness rather than laboratory-confirmed influenza as a study outcome may have included noninfluenza cases, so that the resultant outcome misclassification would make it more difficult to detect vaccine effectiveness.

Thus, in the present prospective cohort study, which investigated the effectiveness of maternal influenza vaccination in preventing infant influenza and its related hospitalization, maternal

Received 28 September 2017; editorial decision 27 November 2017; accepted 30 November 2017; published online December 5, 2017.

^aMembers of the study group are listed at the end of the text.

Correspondence: S. Ohfuji, MD, PhD, Department of Public Health, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka-city, Osaka 545–8585, Japan (satop@med.osaka-cu.ac.jp).

The Journal of Infectious Diseases® 2018;217:878–86

© The Author(s) 2017. Published by Oxford University Press for the Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com DOI: 10.1093/infdis/jix629

influenza vaccination was divided into prenatal vaccination and postpartum vaccination in the detailed analysis, and the effectiveness of vaccination during each period was estimated separately. In addition, although we used pediatrician-diagnosed influenza as the main study outcome, we considered it an appropriate substitute for laboratory-confirmed influenza because the influenza rapid diagnostic test is routinely performed for infants who visit pediatric hospitals and clinics for medical treatment of acute febrile respiratory illnesses during the influenza season in Japan.

METHODS

Participants

This study was conducted with the cooperation of the 117 maternity hospitals and clinics affiliated with the Obstetrical Gynecological Society of Osaka, Japan. To enroll infants born at the collaborating hospitals and clinics before the start of the 2013–2014 influenza season, 10 720 pregnant women (regardless of gestational age) who were attending these hospitals and clinics between September 2013 and December 2013 were recruited to participate in the present study. At that time, 2812 women were in the first trimester, whereas 3585 and 4323 women were in the second and third trimesters, respectively. A total of 3841 infants were delivered by these women before the start of the 2013–2014 influenza season (ie, between October and December 2013) and were identified as study candidates. Mothers of the participating infants received an explanation of the study from their obstetrician and verbally provided informed consent prior to participation.

The study protocol was approved by the Ethics Committees at the Osaka City University Graduate School of Medicine and was performed in accordance with the Declaration of Helsinki.

Information Collection

At the time of recruitment, data on the following maternal characteristics were obtained by means of a self-administered questionnaire completed by each infant's mother: maternal age, height and weight before pregnancy, underlying illnesses, and influenza vaccination status for the 2013–2014 season.

With respect to the follow-up survey conducted after the 2013–2014 influenza season (ie, May 2014), the mothers were asked to fill out a mail-back questionnaire to collect the following information that had become available since the time of recruitment: for infants, the date and gestational week of birth, birth weight, daycare attendance, influenza diagnosis made by a pediatrician, and hospitalization; and for mothers, influenza vaccination history after recruitment and influenza diagnosis. Mothers of infants who had been hospitalized were also asked to provide the name of the disease that led to hospitalization and the name of the hospital. To confirm this self-reported information on hospitalization, we contacted

the pediatricians at the relevant hospitals and asked them to provide the following information from the subject's hospital records: date of admission, date of discharge, name of disease that led to hospitalization, and laboratory data at the time of hospitalization.

In addition, to obtain clinical information about the infants' birth, the obstetrician caring for their mothers was asked to complete a structured questionnaire. The questionnaire gathered information about the infants' date and gestational week of birth, birth weight, presence of congenital malformation, and birth order (ie, the mother's parity status when the infant was delivered).

Statistical Analysis

As an exposure variable, the effect of maternal influenza vaccination was first investigated after categorizing mothers as unvaccinated or receiving vaccination and then after categorizing them as unvaccinated, receiving prenatal vaccination, or receiving postpartum vaccination.

The following 2 outcome measures for infants were used in the present study: pediatrician-diagnosed influenza and hospitalization due to an influenza diagnosis.

With regard to explanatory variables, maternal age was categorized as <29, 30–34, and ≥ 35 years. The following maternal influenza-related underlying conditions, based on a previous report, were included: chronic respiratory disorders (including asthma), cardiovascular disorders (excluding isolated hypertension), kidney disease, liver disease, neurological disorders, blood disorders, metabolic disorders (including diabetes), immunocompromised state (due to factors such as malignant tumors, connective tissue disorders, inflammatory bowel disease, and chronic rheumatism), and obesity (ie, a body mass index [calculated as the weight in kilograms divided by the height in meters squared] of ≥ 25.0) [1]. Data regarding the number of siblings of the infants were based on the mother's parity status recorded during the obstetrician-administered questionnaire.

A logistic regression model was used to calculate the odds ratio (OR) and 95% confidence interval (CI) for the associations between maternal influenza vaccination and the outcome measures. In the multivariate model, we included all variables in the univariate analyses that were related to both maternal vaccination status (ie, the exposure variable) and infant influenza diagnosis (ie, the outcome index) with *P* values of $<.10$. Furthermore, stratified analysis was conducted to examine whether the effectiveness of maternal influenza vaccination against influenza acquisition by their infants varied according to the maternal influenza diagnostic status in the relevant season. The χ^2 and Wilcoxon rank-sum tests were also used where appropriate. All analyses were 2-tailed and were conducted using SAS, version 9.3.

RESULTS

Among 3841 infants, incomplete data on the variables under study caused the exclusion of 400 infants, leaving 3441 infants (89.6%) for analysis. Table 1 shows the characteristics of the study infants and their mothers. Median maternal age was 32 years, and 22% of mothers had influenza-related underlying conditions. A total of 39% of mothers received the influenza vaccine for the 2013–2014 season, and 27% were vaccinated during their pregnancy. A total of 5% of study infants were born prematurely, whereas 9% had a low birth weight. Approximately half the infants had older siblings, and 8% began attending day-care facilities in the 2013–2014 season.

Table 2 shows the association between maternal influenza vaccination and select background characteristics. Unvaccinated mothers were younger than vaccinated mothers. In addition, infants' birth month appeared to affect the timing of maternal vaccination (ie, during the prenatal or postpartum periods).

Table 1. Characteristics of the Study Infants and their Mothers

Characteristic	Study Subjects (n = 3441)
Among mothers	
Age, y	32 (17–49)
Presence of influenza-related underlying condition(s)	758 (22)
Influenza vaccination status for 2013–2014 season	
Unvaccinated	2101 (61)
Vaccinated	1340 (39)
Timing of influenza vaccination	
Prenatal	943 (27)
Postpartum	397 (12)
Receipt of influenza diagnosis during 2013–2014 season	152 (4)
Among infants	
Birth month	
October	886 (26)
November	1227 (36)
December	1328 (38)
Gestational week	
Overall	39.6 (23.1–42.4)
22–36	179 (5)
37–41	3244 (94)
≥42	18 (1)
Birth weight, g	
Overall	3024 (428–4716)
<2500	317 (9)
≥2500	3124 (91)
Congenital malformation	
Present	155 (5)
Older siblings, no.	
Absent	1825 (53)
1	1137 (33)
≥2	479 (14)
Attends daycare	260 (8)

Data are no. (%) of subjects or median value (range).

Preterm birth, low birth weight, and congenital malformations were more often observed in infants delivered by unvaccinated mothers. Vaccinated mothers were likely to be multipara, suggesting that their infants had at least 1 older sibling.

During the 2013–2014 influenza season, 71 infants (2%) had influenza diagnosed (Table 3). Univariate analysis revealed that maternal influenza vaccination had a decreasing effect on the occurrence of pediatrician-diagnosed influenza among infants. The proportion of infants with an influenza diagnosis was also lower among those born in December or with a low birth weight. On the other hand, maternal influenza diagnosis, presence of older siblings, and daycare attendance were associated with a higher risk of influenza among infants. Even after considering the effects of these potential confounding factors, maternal vaccination showed a decreasing OR for an influenza diagnosis among infants (OR, 0.42; 95% CI, .22–.78). In particular, prenatal vaccination was associated with a statistically significantly lower OR of 0.39 (95% CI, .19–.84). Although postpartum vaccination also showed a decreasing OR for influenza among infants, it did not reach statistically significant levels, owing to the limited number of study subjects. Conversely, a diagnosis of maternal influenza elevated the OR for a diagnosis of influenza in infants by 36-fold, implicating influenza in mothers as a strong risk factor for influenza virus infection in infants. In addition, the presence of older siblings or daycare attendance also increased the ORs for influenza among infants by approximately 2–3-fold.

Table 4 shows the association between infant hospitalization due to influenza and background characteristics, including maternal vaccination. In multivariate analysis, maternal vaccination decreased the OR for infant hospitalization due to influenza by approximately one fourth, with marginal statistical significance (OR, 0.27; 95% CI, .06–1.24). The OR of prenatal vaccination was also decreased to 0.33, which, however, was not statistically significant. We could not calculate the OR of postpartum vaccination, since there were no hospitalized cases in this category. On the other hand, maternal influenza was associated with a higher risk of infant hospitalization due to influenza, while a greater number of older siblings was also associated with an elevated OR for infant hospitalization. The ORs for these variables were 13.8 (95% CI, 4.42–42.9) and 6.88 (95% CI, 1.27–37.3), respectively.

The effect of maternal influenza vaccination was examined in terms of the status of maternal influenza diagnosis in the 2013–2014 season (Table 5). Among mothers with a diagnosis of influenza in the 2013–2014 season, the proportion of infants with influenza was 33% for unvaccinated mothers, 16% for those with a prenatal vaccination, and 16% for those with a postpartum vaccination. Among mothers without a diagnosis of influenza, the proportions of infants with influenza were much smaller (1% for unvaccinated mothers, 0.4% for those with a prenatal vaccination, and 0.8% for those with a postpartum vaccination).

Table 2. Association Between Maternal Influenza Vaccination and Select Background Characteristics, by Maternal Vaccination Status

Characteristic	Unvaccinated (n = 2101)	Prenatal Vaccination (n = 943)	Postpartum Vaccination (n = 397)	P
Among mothers				
Age, y	32 (17–49)	33 (19–47)	33 (17–46)	<.01
Presence of influenza-related underlying condition(s)	457 (22)	213 (23)	88 (22)	.87
Receipt of influenza diagnosis during 2013–2014 season	103 (5)	37 (4)	12 (3)	.17
Among infants				
Birth month				
October	567 (27)	53 (6)	266 (67)	<.01
November	765 (36)	345 (37)	117 (29)	
December	769 (37)	545 (58)	14 (4)	
Gestational week				
22–36	123 (6)	41 (4)	15 (4)	.02
37–41	1969 (94)	896 (95)	379 (95)	
≥42	9 (0.4)	6 (1)	3 (1)	
Birth weight, g				
<2500	215 (10)	74 (8)	28 (7)	.01
≥2500	1886 (90)	869 (92)	369 (93)	
Presence of congenital malformation				
Older siblings, no.	114 (5)	24 (3)	17 (4)	<.01
0	1217 (58)	423 (45)	185 (47)	<.01
1	597 (28)	387 (41)	153 (39)	
≥2	287 (14)	133 (14)	59 (15)	
Attends daycare	166 (8)	55 (6)	39 (10)	.03

Data are no. (%) of subjects or median value (range).

However, the ORs of maternal influenza vaccination were quite similar regardless of whether the mothers received a diagnosis of influenza. Regarding infant hospitalization due to influenza, stratified analysis could not provide meaningful results, since the number of infants hospitalized due to influenza was very limited.

DISCUSSION

The findings of the present study demonstrated that maternal influenza vaccination decreases the occurrence of influenza and its related hospitalization in their infants. Among infants, the vaccine effectiveness of maternal influenza vaccination was 58% (95% CI, 22%–78%) for pediatrician-diagnosed influenza and 73% (95% CI, –24%–94%) for influenza-related hospitalization. These results are consistent with those of previous studies conducted in other countries [3–6].

When we examined the effects of maternal vaccination by dividing it into prenatal vaccination and postpartum vaccination, prenatal vaccination seemed to be more effective in preventing influenza infection in infants; the effectiveness of prenatal vaccination for infants' pediatrician-diagnosed influenza was 61% (95% CI, 16%–81%) and that of postpartum vaccination was 53% (95% CI, –28%–83%). However, we did not conclude that postpartum vaccination had no effect on infant influenza, because the effectiveness of postpartum vaccination was 53% (point estimate) and the number of study subjects with postpartum vaccination was really smaller than the number of

those with prenatal vaccination. It is therefore possible that the lack of statistical significance in the effectiveness of postpartum vaccination might have resulted from the lack of statistical power in our study.

There are 2 possible mechanisms for the observed effect of maternal influenza vaccination on decreasing the risk of influenza among infants. The first is through passive immunity, in which maternal antibodies produced in response to prenatal vaccination are transferred to the fetus via the umbilical cord and, thus, protect the infant from contracting influenza. Previous studies have reported this possibility by showing the presence of passive antibodies in umbilical cords and serum samples from infants [10–13]. The second mechanism is that vaccinated mothers have a lower risk of developing influenza, which secondarily results in a reduced risk of influenza among infants. In theory, since prenatal vaccination could have both of these effects and postpartum vaccination only includes the latter mechanism, the difference between the effectiveness of prenatal and postpartum vaccination is probably the effect of passive immunity. From this point of view, the effect of passive immunity could be calculated as only 8%, and the remaining 53% might be explained by the latter mechanism. Hence, prenatal vaccination is expected to be more effective for preventing influenza in infants because it exerts effects through both mechanisms described above. Prenatal vaccination is therefore considered preferable for preventing influenza among infants, although if mothers do not receive influenza vaccination during

Table 3. Association Between Subjects' Background Characteristics, Including Maternal Influenza Vaccination Status, and Pediatrician-Diagnosed Influenza in Infants

Characteristics	Influenza Cases, n/N (%)	Univariate		Multivariate ^a	
		OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Among mothers					
Age, y ^b					
<29	22/1043 (2)	1.07 (.60–1.91)	.81	...	
30–34	25/1269 (2)	1.00		...	
≥35	24/1129 (2)	1.08 (.61–1.90)	.79	...	
Influenza-related underlying conditions					
Absent	59/2683 (2)	1.00		...	
Present	12/758 (2)	0.72 (.38–1.34)	.30	...	
Influenza vaccination during 2013–2014 season					
Absent	56/2101 (3)	1.00		1.00	
Present	15/1340 (1)	0.41 (.23–.73)	<.01	0.42 (.22–.78)	<.01
Timing of influenza vaccination					
Prenatal	10/943 (1)	0.39 (.20–.77)	<.01	0.39 ^c (.19–.84)	.02
Postpartum	5/397 (1)	0.47 (.19–1.17)	.10	0.47 ^c (.17–1.28)	.14
Influenza diagnosis during 2013–2014 season					
Absent	29/3289 (1)	1.00		1.00	
Present	42/152 (28)	42.9 (25.8–71.5)	<.01	36.0 (21.1–61.4)	<.01
Among infants					
Birth month					
October	24/886 (3)	1.00		1.00	
November	31/1227 (3)	0.93 (.54–1.60)	.80	0.99 (.53–1.82)	.96
December	16/1328 (1)	0.44 (.23–.83)	.01	0.50 (.25–1.01)	.05
Birth weight, g					
<2500	2/317 (1)	0.28 (.07–1.15)	.08	0.26 (.06–1.16)	.08
≥2500	69/3124 (2)	1.00		1.00	
Congenital malformation					
Absent	69/3286 (2)	1.00		...	
Present	2/155 (1)	0.61 (.15–2.51)	.49	...	
Older siblings, no. ^d					
0	17/1825 (1)	1.00		1.00	
1	33/1137 (3)	3.18 (1.76–5.73)	<.01	2.02 (1.06–3.85)	.03
≥2	21/479 (4)	4.88 (2.55–9.32)	<.01	3.29 (1.61–6.71)	<.01
Daycare attendance					
Absent	59/3181 (2)	1.00		1.00	
Present	12/260 (5)	2.56 (1.36–4.83)	<.01	2.05 (.98–4.32)	.06

Abbreviations: CI, confidence interval; OR, odds ratio.

^aModel includes variables in this table.^bIn univariate analysis, $P_{\text{trend}} = .46$.^cThe OR was obtained from the model in which maternal influenza vaccination status during the 2013–2014 influenza season (ie, unvaccinated or vaccinated) was replaced by maternal vaccination status that included stratification of vaccination timing (ie, unvaccinated, prenatal vaccination, or postpartum vaccination).^dIn univariate and multivariate analyses, $P_{\text{trend}} = <.01$.

pregnancy, postpartum vaccination would also be useful in protecting their infants from the threat of influenza.

The present study also showed strong associations between an influenza diagnosis among infants and the presence of influenza in their mothers, the presence of older siblings, and attendance at a daycare facility. In particular, the risk of an influenza diagnosis among infants with mothers who had influenza was 36 times the risk among infants without mothers who had influenza. In general, younger infants, especially those aged <6 months, tend to be kept inside the house during winter; therefore, household members are usually the primary source

of influenza virus infection among infants. Mothers in particular tend to have the most contact with infants because they are usually their main caregivers. Hence, if a mother is infected with influenza virus, it is often easily transmitted to their infant. Infants can also be exposed to influenza virus in the daycare setting. Therefore, to protect infants <6 months of age who are too young to be vaccinated, family members living in the same household (particularly mothers) should receive influenza vaccine; the stratified analysis in the present study supported this recommendation by also showing the protective effect of maternal influenza vaccination against influenza among infants

Table 4. Association Between Subjects' Background Characteristics, Including Maternal Influenza Vaccination Status, and Infant Hospitalization Due to an Influenza Diagnosis

Characteristic	Hospitalized Cases, n/N (%)	Univariate		Multivariate ^a	
		OR (95% CI)	P	OR (95% CI)	P
Among mothers					
Age, y ^b					
<29	5/1043 (0.5)	1.52 (.41–5.69)	.53	...	
30–34	4/1269 (0.3)	1.00		...	
≥35	4/1129 (0.4)	1.12 (.28–4.51)	.87	...	
Influenza-related underlying conditions					
Absent	10/2683 (0.4)	1.00		...	
Present	3/758 (0.4)	1.06 (.29–3.87)	.93	...	
Influenza vaccination during 2013–2014 season					
Absent	11/2101 (0.5)	1.00		1.00	
Present	2/1340 (0.1)	0.28 (.06–1.28)	.10	0.27 (.06–1.24)	.09
Timing of influenza vaccination					
Prenatal	2/943 (0.2)	0.40 (.09–1.83)	.24	0.33 ^c (.07–1.56)	.16
Postpartum	0/397 (0)	NA		NA	
Influenza diagnosis during 2013–2014 season					
Absent	7/3289 (0.2)	1.00		1.00	
Present	6/152 (3.9)	19.3 (6.40–58.1)	<.01	13.8 (4.42–42.9)	<.01
Among infants					
Birth month					
October	2/886 (0.2)	1.00		1.00	
November	5/1227 (0.4)	1.81 (.35–9.34)	.48	1.98 (.37–10.5)	.42
December	6/1328 (0.5)	2.01 (.40–9.96)	.40	2.53 (.49–13.0)	.27
Birth weight, g					
<2500	0/317 (0)	NA		NA	
≥2500	13/3124 (0.4)	
Congenital malformation					
Absent	12/3286 (0.4)	1.00		...	
Present	1/155 (0.6)	1.77 (.23–13.7)	.58	...	
Older siblings, no. ^d					
0	2/1825 (0.1)	1.00		1.00	
1	6/1137 (0.5)	4.84 (.97–24.0)	.05	3.96 (.78–20.2)	.098
≥2	5/479 (1.0)	9.62 (1.86–49.7)	<.01	6.88 (1.27–37.3)	.03
Daycare attendance					
Absent	11/3181 (0.3)	1.00		1.00	
Present	2/260 (0.8)	2.23 (.49–10.1)	.30	1.49 (.31–7.27)	.62

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

^aModel includes variables in this table.

^bIn univariate analysis, $P_{\text{trend}} = .93$.

^cThe OR was obtained from the model in which maternal influenza vaccination status during the 2013–2014 influenza season (ie, unvaccinated or vaccinated) was replaced by maternal vaccination status that included stratification of vaccination timing (ie, unvaccinated, prenatal vaccination, or postpartum vaccination).

^dIn univariate analysis, $P_{\text{trend}} < .01$; in multivariate analysis, $P_{\text{trend}} = .02$.

whose mothers received a diagnosis of influenza. And if family members contract influenza, protective measures, such as wearing masks and putting some distance between infected family members and the infant, should be taken to avoid transmission to the infant.

In the present study, infants born in December and those with low a birth weight had a lower risk of influenza. These findings are unexpected but might be explained by the possibility that a decreased opportunity for contact with influenza virus results in a lower odds of contracting influenza. Specifically, during the influenza season, infants born in December are younger than

those born in October and, thus, have a greater likelihood of remaining indoors in the winter. In addition, because infants with a low birth weight are usually treated in incubators until they reach an adequate weight, they may have spent less time at home during the influenza season than those with a normal or higher birth weight. However, we cannot confirm whether this explanation is accurate, since we did not obtain any information on the frequency of leaving home and the date of hospital discharge after birth. In addition, infants born in December had an increased odds of hospitalization, although the association was not statistically significant. Thus, it seems sensible to have

Table 5. Effect of Maternal Influenza Vaccination on Infants' Influenza, by Presence or Absence of Maternal Influenza Diagnosis During the 2013–2014 Season

Characteristic, by Diagnosis Status	Pediatrician-Diagnosed Influenza			Hospitalization Due to influenza		
	Proportion (%)	OR (95% CI) ^a	<i>P</i>	Proportion (%)	OR (95% CI) ^a	<i>P</i>
Present (n = 152)						
Influenza vaccination during 2013–2014 season						
Absent	34/103 (33.0)	1.00		5/103 (4.9)	1.00	
Present	8/49 (16.3)	0.41 (.17–.99)	.048	1/49 (2.0)	0.43 (.05–4.06)	.46
Timing of influenza vaccination						
Prenatal	6/37 (16.2)	0.42 ^b (.15–1.18)	.099	1/37 (2.7)	0.46 ^b (.05–4.45)	.50
Postpartum	2/12 (16.7)	0.36 ^b (.07–1.86)	.22	0/12 (0)	NA	
Absent (n = 3289)						
Influenza vaccination during 2013–2014 season						
Absent	22/1998 (1.1)	1.00		6/1998 (0.3)	1.00	
Present	7/1291 (0.5)	0.42 (.18–1.01)	.051	1/1291 (0.1)	0.23 (.03–1.94)	.18
Timing of influenza vaccination						
Prenatal	4/906 (0.4)	0.40 ^b (.13–1.19)	.098	1/906 (0.1)	0.30 ^b (.04–2.58)	.27
Postpartum	3/385 (0.8)	0.47 ^b (.13–1.65)	.24	0/385 (0)	NA	

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

^aModel includes maternal influenza vaccination status during the 2013–2014 influenza season, birth month, birth weight, older siblings, and daycare attendance.

^bThe OR was obtained from the model in which maternal influenza vaccination status during the 2013–2014 influenza season (ie, unvaccinated or vaccinated) was replaced by maternal vaccination status that included stratification of vaccination timing (ie, unvaccinated, prenatal vaccination, or postpartum vaccination).

reservations about a relationship between birth month and influenza risk among infants.

The present study has the following advantages. First, this is the first study to investigate the effects of maternal vaccination on influenza among infants by using a large cohort of infants (>3000). This enabled us to examine not only the effects of maternal vaccination, but also that of prenatal versus postpartum vaccination, which further helps to elucidate the mechanisms of protective effects of maternal influenza vaccination against influenza among infants. Second, while information on infant hospitalization relied on self-reported data from mothers, the accuracy of the data was ensured by contacting the relevant admitting hospital. Although we were able to obtain information from hospital records for only 54% of infants reported to be hospitalized, almost all information obtained from mothers about the admission date and name of the disease leading to hospitalization was identical to the data from the hospital records. Thus, we believe that the self-reported information about infant hospitalization was reliable. Third, since all study subjects were recruited from within Osaka Prefecture, characteristics of the subjects' exposure to influenza viruses were considered to be similar.

However, this study also had some limitations. First, there may have been some misclassification of infants' influenza diagnoses. However, in Japan, since rapid diagnostic tests are conventionally used in the clinical setting, almost all reports of infant influenza would be expected to be based on the results of rapid tests. On the other hand, the infants' influenza diagnoses would be affected by their mothers' attitudes toward seeking medical attention. For example, febrile infants observed at

home without visiting a medical facility may have been classified as not having influenza even if they had contracted the virus. However, since infants were as young as several months olds, most mothers would have taken their infants to the hospital or clinic if they had a fever. Thus, the number of misclassifications of infants' influenza diagnoses, if any, would be expected to be low, compared with the studies targeting older infants. Second, generally speaking, since vaccinated mothers have a higher level of health consciousness than unvaccinated mothers, they might avoid taking their infants outside in the influenza season. If this behavior was different between vaccinated and unvaccinated mothers, the observed vaccine effectiveness in the present study might be biased toward overestimation. Third, since the infants in the present study were all born at obstetric facilities in Osaka Prefecture before the beginning of the 2013–2014 influenza season, there is some concern about the generalizability of the results. Further investigation in different seasons and regions is desirable to confirm the validity of the findings in the present study.

In conclusion, these results indicate that maternal vaccination could protect infants from contracting influenza. Pregnant women should receive influenza vaccination to protect not only themselves but also their infants. If they do not receive influenza vaccination during pregnancy, postpartum vaccination would also be useful in protecting their infants from the threat of influenza.

MEMBERS OF THE STUDY GROUP

Other members in the Osaka Pregnant Women Influenza Study Group are as follows (in alphabetical order of affiliation):

Shiro Imai (Department of Gynecology and Obstetrics, Aizenbashi Hospital), Eiko Akagaki (Akagaki Ladies Clinic), Mariko Akai (Akai Maternity Clinic), Yoshitsune Azuma (Azuma Ladies Clinic), Shinichi Hamada (Department of Obstetrics and Gynecology, Bell Land General Hospital), Satoru Motoyama (Department of Obstetrics and Gynecology, Chibune General Hospital), Hiroko Chimori (Chimori Medical Clinic), Shoko Nakagawa (Department of Obstetrics and Gynecology, Fuchu Hospital), Takehiko Fukuda (Fukuda Lady's Clinic), Masahisa Hagiwara (Hagiwara Clinic), Hideto Okuda (Hamada Women's Hospital), Takuro Hamanaka (Hamanaka Obstetrics and Gynecology), Seiichi Yamamasu (Obstetrics and Gynecology, Hannan Chuo Hospital), Kenji Hirota (Obstetrics and Gynecology, Hanwasumiyoshi General Hospital), Masataka Oku (Obstetrics and Gynecology, Higashi Osaka City General Hospital), Keizo Hiramatsu (Hiramatsu Obstetrics and Gynecology Clinic), Masanori Hisamatsu (Hisamatsu Maternity Clinic), Yasushi Iijima (Iijima Women's Hospital), Mikio Takehara (Department of Obstetrics and Gynecology, Ikeda City Hospital), Somei Ikeda (Ikeda OB/GYN Clinic), Takeshi Inoue (Inoue Lady's Clinic), Eriko Yamashita (Ishida Hospital), Aisaku Fukuda (The Centre for Reproductive Medicine and Infertility, IVF Osaka Clinic), Itsuko Iwata (Iwata Clinic), Junko Nishio (Department of Obstetrics and Gynecology, Izumiotsu Municipal Hospital), Tateki Tsutsui (Department of Obstetrics and Gynecology, Japan Community Healthcare Organization Osaka Hospital), Kenji Yamaji (Kajimoto Clinic), Takao Kamiya (Kamiya Ladies Clinic), Atsushi Kasamatsu (Department of Obstetrics and Gynecology, Kansai Medical University Hirakata Hospital), Tatsuya Nakajima (Department of Obstetrics and Gynecology, Kansai Medical University Takii Hospital), Kanji Kasahara (Kasahara Clinic), Kenjitsu Kasamatsu (Kasamatsu Obstetrics and Gynecology/Pediatrics), Kawabata Ryoichi (Kawabata Lady's Clinic), Kazume Kawabata (Kawabata Women's Clinic), Kozo Kadowaki (Department of Obstetrics and Gynecology, Kawachi General Hospital), Hiroshi Nomura (Kawashima Ladies Clinic), Tomoyuki Kikuchi (Kikuchi Ladies Clinic), Ayako Suzuki (Department of Obstetrics and Gynecology, Kinki University), Tadayoshi Nagano (Department of Obstetrics and Gynecology, Kitano Hospital), Yoshitsugu Komeda (Komeda Ladies Clinic), Ryouyuke Kondo (Kondo Ladies Clinic), Shinjin Konishi (Konishi Ladies Clinic), Hideo Takemura (Kosaka Women's Hospital), Masako Kasumi (Masako Ladies Clinic), Kazuo Masuhiro (Masuhiro Maternity Clinic), Ryoji Ito (Department of Obstetrics and Gynecology, Matsushita Memorial Hospital), Yoshiki Sakamoto (Department of Obstetrics and Gynecology, Mimihara General Hospital), Kouzo Hirai (Minami-Morimachi Ladies Clinic), Yoshimitsu Yamamoto (Department of Obstetrics and Gynecology, Minoh City Hospital), Yoshitaka Kariya (Minoh Ladies Clinic), Osamu Misaki (Misaki Clinic), Akira

Miyake (Miyake Clinic), Yasuko Osako (Mom Women's Clinic Osako), Masao Mori (Mori Obstetrics and Gynecology Clinic), Keizo Naka (Naka Ladies Clinic), Yasumasa Tokura (Nakai Clinic), Jun Yoshimatsu (Department of Perinatology and Gynecology, National Cerebral and Cardiovascular Center), Keiji Tatsumi (Department of Obstetrics and Gynecology, National Hospital Organization Osaka National Hospital), Takayoshi Kanda (Department of Obstetrics and Gynecology, National Hospital Organization Osaka Minami Medical Center), Masahiro Nishikawa (Nishikawa Ladies Clinic), Sekio Nishimoto (Nishimoto Ladies Clinic), Yoshihiro Nishioka (Nishioka Clinic), Takao Funato (Department of Obstetrics and Gynecology, Nissay Hospital), Kouichi Nozaki (Nozaki Ladies Clinic), Gengo Ohira (Ohira Ladies Clinic), Yoshiyuki Okamura (Okamura Ladies Clinic), Yuzo Oga (Oga Clinic), Osamu Nakamoto (Department of Obstetrics and Gynecology, Osaka City General Hospital), Shinichi Nakata (Department of Obstetrics and Gynecology, Osaka City Juso Hospital), Tetsuo Nakamura (Department of Obstetrics and Gynecology, Osaka City Sumiyoshi Hospital), Masahiko Takemura (Department of Obstetrics and Gynecology, Osaka General Medical Center), Toshiyuki Sadou (Department of Obstetrics and Gynecology, Osaka Gyoumeikan Hospital), Nobuaki Mitsuda (Department of Obstetrics, Osaka Medical Center and Research Institute for Maternal and Child Health), Daisuke Fujita (Department of Obstetrics and Gynecology, Osaka Medical College), Koji Hisamoto (Department of Obstetrics and Gynecology, Osaka Police Hospital), Shinobu Akada (Department of Obstetrics and Gynecology, Osaka Prefectural Medical Center for Respiratory and Allergic Diseases), Takafumi Nonogaki, Chinami Horiuchi (Department of Obstetrics and Gynecology, Osaka Red Cross Hospital), Yasuhiko Shiki (Department of Obstetrics and Gynecology, Osaka Rousai Hospital), Tadashi Kimura (Department of Obstetrics and Gynecology, Osaka University Graduate School of Medicine), Koutaro Kitamura (Obstetrics and Gynecology, PL Hospital), Kazuhide Ogita (Department of Obstetrics and Gynecology, Rinku General Medical Center), Shigeki Matsuo (Saint Barnabas Hospital), Yoshihito Ikeda (Department of Obstetrics and Gynecology, Saiseikai Ibaraki Hospital), Akihiro Moriyama (Department of Obstetrics and Gynecology, Saiseikai Nakatsu Hospital), Yuki-yoshi Ishikawa (Department of Obstetrics and Gynecology, Saiseikai Noe Hospital), Hiroshi Muso (Department of Obstetrics and Gynecology, Saiseikai Senri Hospital), Fuminori Kitada (Department of Obstetrics and Gynecology, Saiseikai Suita Hospital), Toshiya Yamamoto (Department of Obstetrics and Gynecology, Sakai City Hospital), Megumi Takemura (Department of Obstetrics and Gynecology, Sakibana Hospital), Takeshi Sawada (Sawada Ladies Clinic), Kentaro Shimura (Shimura Women's Clinic), Koh Shinyashiki (Shinyashiki Obstetrics and Gynecology), Mitsuhiko Masuda (Department of Obstetrics and Gynecology, Shiseikai

Corporate Juridical Person), Tsuneo Shoda (Shoda Medical Clinic), Takamichi Nishizaki (Department of Obstetrics and Gynecology, Suita Municipal Hospital), Yoshinori Suzuki (Suzuki Clinic), Isao Suzuki (Suzuki Obstetrics and Gynecology), Hiroshi Nanjyo (Department of Obstetrics and Gynecology, Taisho Hospital), Keiko Takabatake (Takabatake Women's Clinic), Kikuya Takase (Takase Ladies Clinic), Satoshi Nakago (Department of Obstetrics and Gynecology, Takatsuki General Hospital), Jun Takeyama (Takeyama Ladies Clinic), Takeshi Taniguchi (Taniguchi Hospital), Keiichi Tasaka (Tasaka Clinic), Toshiaki Tatsumi (Tatsumi Ladies Clinic), Atsushi Tokuhira (Department of Obstetrics and Gynecology, Toyonaka Municipal Hospital), Shogo Tsubokura (Tsubokura Women's Clinic), Kayoko Ueda (Ueda Ladies Clinic), Yukiko Uenae (Uenae Ladies Clinic), Takahiko Unno (Unno Maternity Clinic), Hiroshi Yabuki (Yabuki Maternity Clinic), Tokihiro Yanamoto (Yanamoto Maternity Clinic), Yoshihiko Yamada (Department of Obstetrics and Gynecology, Yao Municipal Hospital), Nobuyuki Maruo (Department of Obstetrics and Gynecology, Yodogawa Christian Hospital), and Yoshitsugu Takada (Department of Obstetrics and Gynecology, Yoshikawa Hospital).

Notes

Financial support. This work was supported by the Ministry of Health, Labor, and Welfare, Japan (Research on Emerging and Reemerging Infectious Diseases, Health, and Labor Sciences research grants H23-SHINKO-IPPAN-017 and H26-SHINKOGYOSEI-SHITEI-003); and JSPS KAKENHI, Japan (grant in aid for scientific research [B] JP25293152).

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

- Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2013–14. *MMWR Recomm Rep* **2013**; 62:1–43.
- World Health Organization. Vaccines against influenza WHO position paper—November 2012. *Weekly Epidemiol Rec* **2012**; 87:461–76.
- Steinhoff MC, Omer SB, Roy E, et al. Neonatal outcomes after influenza immunization during pregnancy: a randomized controlled trial. *CMAJ* **2012**; 184:645–53.
- Benowitz I, Esposito DB, Gracey KD, Shapiro ED, Vázquez M. Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. *Clin Infect Dis* **2010**; 51:1355–61.
- Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med* **2008**; 359:1555–64.
- Black SB, Shinefield HR, France EK, Fireman BH, Platt ST, Shay D; Vaccine Safety Datalink Workgroup. Effectiveness of influenza vaccine during pregnancy in preventing hospitalizations and outpatient visits for respiratory illness in pregnant women and their infants. *Am J Perinatol* **2004**; 21:333–9.
- Reuman PD, Ayoub EM, Small PA. Effect of passive maternal antibody on influenza illness in children: a prospective study of influenza A in mother-infant pairs. *Pediatr Infect Dis J* **1987**; 6:398–403.
- 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.
- Englund JA, Mbawuike IN, Hammill H, Holleman MC, Baxter BD, Glezen WP. Maternal immunization with influenza or tetanus toxoid vaccine for passive antibody protection in young infants. *J Infect Dis* **1993**; 168:647–56.
- Puck JM, Glezen WP, Frank AL, Six HR. Protection of infants from infection with influenza A virus by transplacentally acquired antibody. *J Infect Dis* **1980**; 142:844–9.
- Steinhoff MC, Omer SB, Roy E, et al. Influenza immunization in pregnancy—antibody responses in mothers and infants. *N Engl J Med* **2010**; 362:1644–6.
- France EK, Smith-Ray R, McClure D, et al. Impact of maternal influenza vaccination during pregnancy on the incidence of acute respiratory illness visits among infants. *Arch Pediatr Adolesc Med* **2006**; 160:1277–83.
- Eick AA, Uyeki TM, Klimov A, et al. Maternal influenza vaccination and effect on influenza virus infection in young infants. *Arch Pediatr Adolesc Med* **2011**; 165:104–11.