

# Influenza in Infants Born to Women Vaccinated During Pregnancy

Julie H. Shakib, DO, MS, MPH,<sup>a</sup> Kent Korgenski, MS, MT,<sup>b</sup> Angela P. Presson, PhD,<sup>a</sup> Xiaoming Sheng, PhD,<sup>a</sup> Michael W. Varner, MD,<sup>c</sup> Andrew T. Pavia, MD,<sup>a</sup> Carrie L. Byington, MD<sup>a</sup>

abstract

**BACKGROUND:** Infants <6 months old with influenza are at risk for adverse outcomes. Our objective was to compare influenza outcomes in infants <6 months old born to women who did and did not report influenza vaccine during pregnancy.

**METHODS:** The study included all women who delivered from 12/2005 to 3/2014 at Intermountain facilities and their infants. Influenza outcomes included infant influenza-like illness (ILI), laboratory-confirmed influenza, and influenza hospitalizations.

**RESULTS:** The cohort included 245 386 women and 249 387 infants. Overall, 23 383 (10%) pregnant women reported influenza immunization. This number increased from 2.2% before the H1N1 pandemic to 21% postpandemic ( $P < .001$ ). A total of 866 infants <6 months old had  $\geq 1$  ILI encounter: 32 (1.34/1000) infants born to women reporting immunization and 834 (3.70/1000) born to women who did not report immunization (relative risk [RR] 0.36; 95% confidence interval [CI], 0.26–0.52;  $P < .001$ ). A total of 658 infants had laboratory-confirmed influenza: 20 (0.84/1000) born to women reporting immunization and 638 (2.83/1000) born to unimmunized women (RR 0.30; 95% CI, 0.19–0.46;  $P < .001$ ). A total of 151 infants with laboratory-confirmed influenza were hospitalized: 3 (0.13/1000) born to women reporting immunization and 148 (0.66/1000) born to unimmunized women (RR 0.19; 95% CI, 0.06–0.60;  $P = .005$ ).

**CONCLUSIONS:** Self-reported influenza immunization during pregnancy was low but increased after the H1N1 pandemic. Infants born to women reporting influenza immunization during pregnancy had risk reductions of 64% for ILI, 70% for laboratory-confirmed influenza, and 81% for influenza hospitalizations in their first 6 months. Maternal influenza immunization during pregnancy is a public health priority.



Departments of <sup>a</sup>Pediatrics, and <sup>c</sup>Obstetrics and Gynecology, University of Utah, Salt Lake City, Utah; and <sup>b</sup>Intermountain Healthcare, Salt Lake City, Utah

Dr Shakib conceptualized and designed the study, performed the statistical analyses, and drafted the initial manuscript; Mr Korgenski conducted the database query and reviewed and revised the manuscript; Drs Presson and Sheng performed the statistical analyses and reviewed and revised the manuscript; Drs Varner, Pavia, and Byington collaborated in conceptualizing and designing the study and revised the initial manuscript; and all authors approved the final manuscript as submitted.

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Address correspondence to Julie H. Shakib, DO, MS, MPH, PO Box 581289, Salt Lake City, UT 84158.  
E-mail: julie.shakib@hsc.utah.edu

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**WHAT'S KNOWN ON THIS SUBJECT:** Infants <6 months old with influenza are at risk for adverse outcomes. Current guidelines recommend immunizing pregnant women to protect young infants against influenza. Few studies have evaluated the effect of maternal immunization during pregnancy on infant influenza outcomes.

**WHAT THIS STUDY ADDS:** Infants born to women reporting influenza immunization during pregnancy had risk reductions in laboratory-confirmed influenza and influenza hospitalizations in their first 6 months. Maternal influenza immunization during pregnancy to protect young infants against influenza is a public health priority.

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Influenza is a common vaccine-preventable illness responsible for substantial morbidity and mortality in children.<sup>1,2</sup> The burden of influenza disease is particularly high in infants <6 months old.<sup>3,4</sup> Attempts to protect infants from influenza during their first 6 months through direct immunization have been unsuccessful because of an insufficient infant immune response.<sup>5-7</sup> Providing passive protection of the infant through maternal immunization is an alternative to direct immunization.

The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices, American Academy of Pediatrics, and American Congress of Obstetricians and Gynecologists (ACOG) have endorsed the importance of immunizing pregnant women to protect young infants against influenza.<sup>8-11</sup> The most recent ACOG committee opinion on influenza immunization during pregnancy states that “maternal immunity is the only effective strategy in newborns.”<sup>9</sup>

Several prospective studies have demonstrated a reduction in both influenza-related illness and laboratory-confirmed influenza in infants born to women receiving influenza vaccine during pregnancy. A 2008 randomized trial in Bangladesh demonstrated a 63% reduction in laboratory-confirmed influenza and a 29% reduction in the incidence of febrile respiratory illness in infants born to mothers who received third trimester influenza vaccine.<sup>12</sup> A 2010 US observational cohort study demonstrated a reduced risk for clinical or laboratory-confirmed influenza infection in the infants for up to 6 months after maternal immunization during pregnancy.<sup>13</sup> A population-based surveillance study conducted in children hospitalized with fever or respiratory symptoms during the 2002 to 2009 influenza seasons found a 45% to 48% reduction in laboratory-confirmed

influenza hospitalizations among infants whose mothers reported influenza immunization during pregnancy.<sup>14</sup> Most recently, a randomized placebo-controlled trial of HIV-negative pregnant women and their infants in South Africa demonstrated vaccine efficacy rates in infants of 48.8% (95% confidence interval [CI], 11.6–70.4) after maternal immunization.<sup>15</sup> In contrast, published results from large retrospective studies of maternal immunization during pregnancy have not supported the reduction in infant influenza-related outcomes demonstrated in prospective studies.<sup>16,17</sup>

Intermountain Healthcare, the largest vertically integrated system of health care facilities in the Intermountain West, has a postpartum immunization policy and queries women about influenza vaccine status on admission for delivery. We recognized the opportunity to use the electronic medical records of Intermountain Healthcare to identify the proportion of delivering women reporting influenza vaccine in pregnancy and compare influenza outcomes in the first 6 months in infants born to women who did and did not report influenza vaccine in pregnancy.

## METHODS

### Protection of Human Subjects

Approval to conduct this study was granted by the institutional review boards of the University of Utah and Intermountain Healthcare in Salt Lake City, Utah. A waiver of informed consent was granted by both institutions.

### Identification of Pregnant Women and Their Infants and Reported Maternal Influenza Vaccine Status From the Intermountain Enterprise Data Warehouse

More than 30 000 deliveries occur at Intermountain facilities each year. Intermountain facilities are

categorized into 4 geographic regions of Utah and Idaho: Urban Central: Salt Lake County (population 1.08 million); Urban North: Weber, Cache, Box Elder, and Cassia counties (population 378 759); Urban South: Utah, Millard, Sanpete, and Sevier counties (population 1.73 million); and Southwest: Washington, Garfield, and Iron counties (population 46 780). All Intermountain facilities share a single electronic medical record database that captures clinical and administrative data. Data are stored in the Intermountain Enterprise Data Warehouse. To retrospectively identify reported influenza vaccine administration during pregnancies occurring over 9 influenza seasons from December 1, 2005 through March 31, 2014, we created a pregnancy episode table that included all women who had at least  $\geq 1$  International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code associated with pregnancy.

All Intermountain facilities administer an intake survey for women as they enter the labor and delivery unit that includes a question about influenza immunization during the current pregnancy. The data are recorded in the electronic medical record. We used this information to define maternal influenza immunization status for the pregnancy. The electronic medical records for infants born during the study period and discharged from the hospital after the delivery encounter were identified and linked to maternal records.

### Infant Influenza Outcomes

We ascertained the following infant influenza-related outcomes in the first 6 months after delivery at an Intermountain facility: proportion of infants with ICD-9-CM codes consistent with  $\geq 1$  episode of influenza-like illness (ILI); laboratory-confirmed influenza by culture, polymerase chain

reaction (PCR), or direct fluorescent antibody (DFA); and laboratory-confirmed influenza hospitalizations. Laboratory-confirmed respiratory syncytial virus (RSV) infection was also ascertained in infants born to women who did and did not report influenza immunization to evaluate the specificity of maternal influenza immunization on infant outcomes.

Although outpatient testing is at the discretion of the clinician at Intermountain facilities, viral respiratory testing is recommended for all children hospitalized with acute respiratory illnesses and for febrile infants <90 days old. From 2005 to 2008, DFA-negative specimens were submitted for viral culture. From 2009 to 2011, DFA-negative specimens were tested by PCR (Luminex xTAG Respiratory Virus Panel; Luminex Diagnostics, Austin, TX). Beginning in 2011, respiratory specimens were initially tested by multiplex PCR (FilmArray Respiratory Panel; BioFire Diagnostics, Salt Lake City, UT).

### Statistical Analysis

Data were analyzed with Stata (version 13.1; Stata Corp, College Station, TX). Descriptive statistics were used to characterize the proportion of women who reported receiving influenza vaccine during pregnancy and the maternal–infant record linkage. Maternal age was compared by *t* test, and the  $\chi^2$  test was used to compare maternal insurance type, maternal residence location (urban versus rural or frontier), and delivery hospital region by reported maternal influenza immunization status. Maternal comorbidities were compared in women who did and did not report influenza immunization via the Elixhauser index, a comorbidity index comprising a comprehensive set of 30 comorbidities defined with ICD-9-CM codes from administrative data.<sup>18</sup> Relative risk (RR) and 95% CI were used to compare immunized and unimmunized mothers across the

primary infant outcomes of interest: presence of ILI, laboratory-confirmed influenza, and hospitalization with laboratory-confirmed influenza.

A multivariable Poisson regression model with robust error variance was used to compare the RR of infant influenza-related outcomes based on maternal influenza vaccine status, adjusted for maternal characteristics including age, birth month, insurance type, residence location, and hospital region.<sup>19</sup> We assessed effect modification by testing interaction terms for each of the maternal characteristics with immunization status.

## RESULTS

### Study Subjects and Maternal–Infant Record Linkage

There were 262 364 deliveries resulting in 263 347 live births during the study period. Maternal and infant records were successfully linked for 249 387 (95%) live births in which the infant was discharged from the hospital after the delivery encounter, and this became the cohort for all analyses. This maternal–infant cohort included 23 847 infants born to 23 383 women who reported receiving influenza vaccine during the current pregnancy episode and 225 540 infants born to 222 003 women who did not report influenza vaccine at time of admission for delivery.

### Self-Reported Influenza Immunization During Pregnancy

In the cohort, 23 383 women (10%) reported receiving influenza vaccine during the current pregnancy episode at time of admission for delivery. Mean maternal age was statistically but not clinically different for women reporting receiving influenza vaccine compared with women who did not report receiving the vaccine (28.1 years [SD 5.2] vs 27.6 years [SD 5.1]; *P* < .001). Pregnant women who had government insurance

or no insurance, resided in a rural or frontier location, or delivered at hospitals in the Urban South or Southwest regions were less likely to report immunization during pregnancy (*P* < .001) (Table 1). In the maternal cohort, 58 282 pregnant women had comorbidities by ICD-9-CM diagnosis: 6317 (26.5%) women who reported influenza immunization compared with 51 965 (23.0%) who did not report immunization (RR = 1.15; 95% CI, 1.12–1.18; *P* < .001). The rate of prematurity was not different between the groups (1.6% in infants born to women reporting influenza immunization vs 1.7% in infants born to mothers not reporting immunization; *P* = .051). Birth weight was also not statistically or clinically different between infants born to women who did and did not report receiving influenza vaccine, with a difference of 7 g (3303 vs 3296 g, respectively; *P* = .068).

The study period encompassed both waves of the H1N1 pandemic (April 2009–August 2010). The proportion of pregnant women reporting influenza vaccine at time of delivery increased significantly during and after the H1N1 pandemic, fell slightly during the seasons that followed, and increased markedly beginning in 2013, with >50% reporting influenza vaccine in the most recent influenza season (Fig 1). The proportion of women reporting influenza vaccine during pregnancy in the cohort increased from 2.2% (range 1.7%–2.8%) over the 4 influenza seasons before the H1N1 pandemic to 21% (range 5.6%–52%) over the 5 seasons including and after the pandemic (*P* < .001).

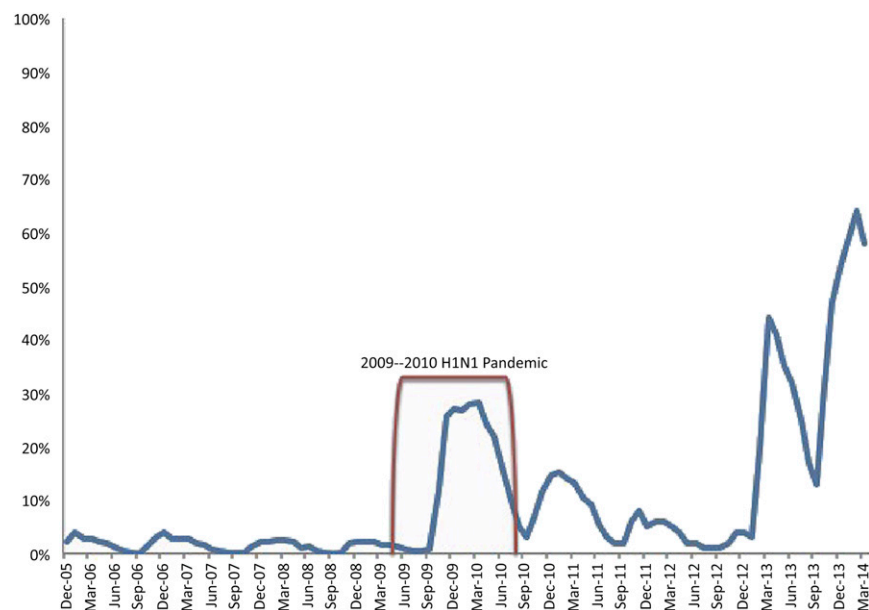
### ILI in Infants

A total of 866 infants had  $\geq 1$  ILI encounters in the first 6 months after delivery: 32 (1.34/1000) infants born to women reporting influenza immunization during a pregnancy episode at time of delivery and 834 (3.70/1000) born to women who did

**TABLE 1** Demographic Characteristics of Maternal Subjects by Reported Maternal Immunization Status

Maternal Influenza Vaccine Status		Reported Vaccine, N = 23 383	No Reported Vaccine, N = 222 003
Insurance type, %	Private	74	69
	Government*	24	28
	Uninsured*	2	3
Residence location, %	Rural/frontier*	9	10
	Urban	91	90
Hospital region, %	Urban central	41	35
	Urban north	36	23
	Urban south*	17	31
	Southwest*	6	11

\* Proportion differed by maternal immunization status at Bonferroni-adjusted significance levels (all  $P$ s < .001).



**FIGURE 1** Proportion of pregnant women reporting influenza vaccine during pregnancy at time of delivery.

not report influenza immunization (RR 0.36; 95% CI, 0.26–0.52;  $P < .001$ ).

There were 241 infants in the cohort with  $\geq 1$  ILI encounter associated with hospitalization. In the hospitalized cohort, 4 (0.17/1000) infants were born to women reporting influenza immunization during pregnancy, compared with 237 (1.05/1000) born to women who did not report influenza immunization during pregnancy (RR 0.16; 95% CI, 0.06–0.43;  $P < .001$ ).

### Laboratory-Confirmed Influenza in Infants

We identified 658 infants with laboratory-confirmed influenza in

the first 6 months after delivery: 20 (0.84/1000) born to immunized women and 638 (2.83/1000) born to women who did not report influenza immunization (RR 0.30; 95% CI, 0.19–0.46;  $P < .001$ ). There were 16 infants (0.67/1000) in the cohort with laboratory-confirmed influenza A born to pregnant women who reported receiving influenza vaccine, compared with 524 (2.32/1000) in infants born to mothers who did not report receiving the vaccine (RR 0.29; 95% CI, 0.18–0.47;  $P < .001$ ). Similarly, 4 (0.17/1000) infants with laboratory-confirmed influenza B in the infant cohort were born to pregnant women who reported influenza immunization versus 116

(0.51/1000) infants born to women who did not report immunization (RR 0.33; 95% CI, 0.12–0.88;  $P = .028$ ).

Of the 658 infants with laboratory-confirmed influenza, 151 (23%) were hospitalized. In the hospitalized cohort, 3 (0.13/1000) infants were born to women reporting immunization and 148 (0.66/1000) born to women who did not report immunization (RR 0.19; 95% CI, 0.06–0.60;  $P = .005$ ). Although there were 136 documented infant deaths in the first 6 months after delivery in this retrospective cohort, no infant death was associated with any influenza-related diagnosis.

In contrast to influenza outcomes, we identified no differences in RSV infection in infants born to women who received influenza vaccine. We identified 5439 infants with laboratory-confirmed RSV in the cohort: 504 (2.1%) infants born to mothers who reported immunization during pregnancy and 4935 (2.2%) infants born to women who did not report receiving the vaccine (RR 0.97; 95% CI, 0.88–1.06;  $P = .453$ ).

With respect to the infant outcomes of interest, in multivariable Poisson regression with robust error variance adjusting for age, birth month, insurance type, residence location, and hospital region, the protective effect of influenza immunization remained significant, and the magnitude of RR changed little from the univariate analysis (Table 2). None of these maternal variables were found to be effect modifiers on infant outcomes of interest including infant ILI, hospitalized ILI, laboratory-confirmed influenza, or hospitalized laboratory-confirmed influenza.

### DISCUSSION

This study reports infant influenza outcomes in a large cohort of infants born to women self-reporting influenza immunization during pregnancy before and after the H1N1 pandemic. The overall proportion

**TABLE 2** RR of Influenza-Related Outcomes in Infants Born to Women Reporting Influenza Vaccine During Pregnancy

Infant Outcome	Unadjusted RR (95% CI)	Adjusted RR <sup>a</sup> (95% CI)
ILI*	0.36 (0.26–0.52)	0.34 (0.24–0.49)
Hospitalized ILI*	0.16 (0.06–0.43)	0.16 (0.06–0.43)
Laboratory-confirmed influenza*	0.30 (0.19–0.46)	0.33 (0.21–0.52)
Hospitalized laboratory-confirmed influenza*	0.19 (0.06–0.60)	0.17 (0.05–0.55)

<sup>a</sup> Adjusted for age, birth month, insurance type, residence location, and hospital region.

\* All results significant ( $P < .005$ ).

of pregnant women reporting influenza immunization was low but increased significantly after the H1N1 pandemic. Infants born to pregnant women who reported receiving influenza vaccine during pregnancy were significantly less likely to have documented health care encounters associated with ILI (64% reduction), and they had a 70% reduction in laboratory-confirmed influenza and an 81% reduction in hospitalization with laboratory-confirmed influenza. Furthermore, in this mother–infant cohort, 97% of all laboratory-confirmed influenza cases occurred in infants born to women who did not report receiving influenza vaccine during pregnancy.

Only 10% of women in this cohort spanning 9 influenza seasons reported influenza immunization, but the proportion of pregnant women reporting influenza immunization increased significantly after the H1N1 pandemic, with a more pronounced recent increase, reaching a high of 52% in the 2013 to 2014 influenza season. Nationally, prepandemic H1N1 National Health Interview Survey seasonal influenza coverage estimates for 2008 to 2009 were only 11%.<sup>20</sup> During the 2009 to 2010 flu season, reported seasonal influenza immunization coverage among pregnant women increased to 32.1% as measured by the National 2009 H1N1 Flu Survey and 47.1% as measured by the Pregnancy Risk Assessment Monitoring System.<sup>16,17</sup> National vaccination coverage of pregnant women has remained relatively stable since the 2010 to 2011 season, with reported immunization coverage during

pregnancy of 34.6% during the 2013 to 2014 influenza season.<sup>18,19</sup> We observed a similar pattern. The higher rates in recent seasons may be associated with efforts by ACOG and CDC to improve influenza coverage in pregnant women. However maternal influenza immunization rates during pregnancy remain suboptimal.

In our cohort we also found that demographic characteristics differed between pregnant women who did and did not report receiving the influenza vaccine. Uninsured pregnant women and those with government insurance were less likely to report receiving influenza immunization during pregnancy. A recent Massachusetts Pregnancy Risk Assessment Monitoring System survey demonstrated that pregnant women who received Medicaid or whose household income was at or below the federal poverty level were significantly less likely to report receiving the seasonal influenza vaccine.<sup>21</sup> Pregnant women living in areas classified as rural or frontier or who received their care in the Urban South or Southwest Intermountain regions were also significantly less likely to report immunization. The Intermountain Urban South region includes Utah County, 1 of 30 US counties with the largest estimated numbers of unvaccinated children from 1995–2001 CDC National Immunization Surveys (NIS) data.<sup>22</sup> It is possible that factors leading to parental vaccine hesitancy in children may similarly affect pregnant women considering maternal immunization during pregnancy. We also documented that women with underlying medical conditions

were more likely to receive influenza immunization. These women may have been recognized as having high risk for influenza complications by their providers and therefore been encouraged to receive influenza vaccine. Interventions that target both healthy pregnant women and those with chronic conditions are needed to increase vaccine uptake.

Infants born to women who reported receiving the influenza vaccine during pregnancy in our cohort were significantly less likely to have a diagnosis of or be hospitalized with ILI or laboratory-confirmed influenza. Several previous retrospective studies have not successfully demonstrated protection against influenza disease in infants. A retrospective study over 5 influenza seasons (1997–2002) concluded that infants born to women who received influenza immunization during pregnancy had an equal risk for influenza or pneumonia admissions and ILI compared with infants born to unimmunized women.<sup>16</sup> Another retrospective cohort study conducted from 1995 to 2001 by the CDC Vaccine Safety Datalink found no reduction in medical visits for respiratory illness among infants of women receiving influenza immunization during pregnancy compared with infants born to unimmunized women.<sup>2,17</sup> These previous studies were performed in smaller cohorts over fewer influenza seasons and did not examine laboratory-confirmed influenza diagnoses in infants. Earlier studies have also demonstrated that ILI can be an insensitive predictor of laboratory-confirmed influenza infection, particularly in young children, leading to misclassification bias.<sup>23</sup> ILI at Intermountain facilities is reported with an influenza-specific ICD-9-CM diagnostic code algorithm that correlates well with laboratory-confirmed influenza, which may reduce misclassification in our study.<sup>24</sup> More importantly, the

widespread use of respiratory viral diagnostic testing in young infants for many years at Intermountain outpatient facilities allowed us to examine the impact of maternal influenza immunization status on infant laboratory-confirmed influenza and hospitalization for laboratory-confirmed influenza. Strikingly, the receipt of influenza vaccine had no effect on RSV outcomes, increasing confidence that the administration of influenza vaccine during pregnancy resulted in specific benefits for infant health outcomes related to influenza.

The results of this large retrospective study support the conclusions of prospective studies regarding the protective benefit of maternal influenza immunization during pregnancy. The morbidity and mortality associated with influenza in infants have been well described.<sup>25,26</sup> Our study strengthens the evidence that maternal immunization provides passive protection against influenza to infants during the vulnerable period before they are old enough to receive active immunization.

One of the strengths of our study is our ability to systematically identify self-reported influenza vaccine in a large retrospective cohort of pregnant women presenting for delivery. It is possible that self-reported influenza immunization at time of delivery is limited by recall bias. We believe that maternal recall of receipt of influenza vaccine is likely to be accurate. In an earlier study conducted in Intermountain facilities, we demonstrated that maternal recollection of receiving intrapartum antibiotics was 85% accurate and that the 15% of women whose recall differed from the medical record were as likely to overreport as underreport receiving treatment.<sup>27</sup> In our study of influenza vaccine, if women who did or did not receive the vaccine were misclassified, the results would have been biased toward the null hypothesis.

Another strength of our study was the success of the maternal–infant record linkage. Our ability to link most of the maternal–infant pairs in our cohort allowed us to capture infant influenza-related outcomes through 6 months by using ICD-9-CM codes. The widespread use of viral diagnostic testing in the Intermountain system is another strength of our study and allowed accurate classification of infants with influenza.

Our study has several limitations. Maternal influenza immunization was self-reported and overall low during the study period compared with current immunization rates in pregnant women. Because maternal immunization status could be confirmed only by self-report at time of delivery, we do not know the exact timing of immunization, which limited our ability to accurately predict the exact timing and duration of protection afforded to the infant by influenza season or year of maternal immunization. Furthermore, we did not know the specific influenza strains women were vaccinated against in our cohort and were therefore unable to match the maternal vaccine strain with the influenza strain observed in the infants, as is typically done in prospective vaccine trials designed to measure vaccine efficacy. However, despite low maternal immunization rates and the inherent limitations of retrospective self-reported immunization data, ours was 1 of the largest retrospective maternal–infant cohorts to date.

Finally, many potential unmeasured factors may have influenced the magnitude of the risk of influenza infection in the infants. It is possible that some of the benefits to the infant attributed to maternal immunization may have resulted from the benefit of cocooning from household contacts immunized against influenza or from disease prevention and care-seeking behaviors in women who did and did not report immunization. Health care provider decision-making regarding testing infants for influenza may also

have been influenced by the provider's awareness of maternal immunization status. Variations in vaccine effectiveness over time may also have influenced the risk of influenza infection in infants. Despite these limitations, the significant decrease in the burden of influenza illness in infants born to women who reported receiving influenza immunization during pregnancy is reassuring. Our results also support the need to incentivize system-level efforts to improve influenza immunization coverage rates in pregnant women, particularly in those with government insurance or no insurance.

## CONCLUSIONS

Self-reported influenza immunization during pregnancy was low but increased after the H1N1 pandemic. Despite low maternal immunization rates, infants born to women reporting influenza immunization during pregnancy had a reduction in risk of 64% for ILI, 70% for laboratory-confirmed influenza, and 81% for influenza hospitalizations in their first 6 months. Protecting young infants from influenza through maternal immunization during pregnancy is a public health priority.

## ABBREVIATIONS

ACOG: American Congress of Obstetricians and Gynecologists

CDC: Centers for Disease Control and Prevention

CI: confidence interval

DFA: direct fluorescent antibody

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

ILI: influenza-like illness

PCR: polymerase chain reaction

RR: relative risk

RSV: respiratory syncytial virus

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