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Outcomes of infants born to women with influenza A(H1N1)pdm09

Kim Newsome[1], **C. J. Alverson**[1], **Jennifer Williams**[1], **Anne F. McIntyre**[1], **Anne D. Fine**[2], **Cathy Wasserman**[3], **Kathryn H. Lofy**[3], **Meileen Acosta**[4], **Janice K. Louie**[4], **Kathleen Jones-Vessey**[5], **Valoree Stanfield**[6], **Alice Yeung**[2], **Sonja A. Rasmussen**[1]

[1]Centers for Disease Control and Prevention, Atlanta, Georgia

[2]New York City Department of Health and Mental Hygiene, Queens, New York

[3]Washington State Department of Health, Olympia, Washington

[4]California Health and Human Services Agency, Sacramento, California

[5]North Carolina Department of Health and Human Services, Raleigh, North Carolina

[6]Utah Department of Health, Salt Lake City, Utah

Abstract

Background: Pregnant women with influenza are more likely to have complications, but information on infant outcomes is limited.

Methods: Five state/local health departments collected data on outcomes of infants born to pregnant women with 2009 H1N1 influenza reported to the Centers for Disease Control and Prevention from April to December 2009. Collaborating sites linked information on pregnant women with confirmed 2009 H1N1 influenza, many who were severely ill, to their infants' birth certificates. Collaborators also collected birth certificate data from two comparison groups that were matched with H1N1-affected pregnancies on month of conception, sex, and county of residence.

Correspondence: Kim Newsome, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 4770 Buford Highway NE, MS E-86, Atlanta, GA 30341-3717. kan3@cdc.gov.

Present address

Meileen Acosta, Solano County Department of Health and Social Services, 275 Beck Ave, MS 5-240, Fairfield, CA 94533.

Janice K. Louie, San Francisco Department of Public Health, Zuckerberg San Francisco General Hospital, 1001 Potrero Avenue, Ward 94 San Francisco, CA 94110.

Valoree Stanfield, Intermountain Healthcare, Central Office, 36 South State Street, 17th floor Salt Lake City, UT 84111.

Sonja A. Rasmussen, Departments of Pediatrics and Epidemiology, University of Florida College of Medicine and College of Public Health and Health Professions, 1600 SW Archer Road, PO Box 100296 Gainesville, FL 32610.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

Results: 490 pregnant women with influenza, 1,451 women without reported influenza with pregnancies in the same year, and 1,446 pregnant women without reported influenza with prior year pregnancies were included. Women with 2009 H1N1 influenza admitted to an intensive care unit (ICU; $n = 64$) were more likely to deliver preterm infants (<37 weeks), low birth weight infants, and infants with Apgar scores <=6 at 5 min than women in comparison groups (adjusted relative risk, aRR = 3.9 [2.7, 5.6], aRR = 4.6 [2.9, 7.5], and aRR = 8.7 [3.6, 21.2], for same year comparisons, respectively). Women with influenza who were not hospitalized and hospitalized women not admitted to the ICU did not have significantly elevated risks for adverse infant outcomes.

Conclusions: Severely ill women with 2009 H1N1 influenza during pregnancy were more likely to have adverse birth outcomes than women without influenza, providing more support for influenza vaccination during pregnancy.

Keywords

pregnancy; 2009; H1N1; infant; outcomes

1 | INTRODUCTION

After the 2009 influenza A(H1N1)pdm09 (2009 H1N1) pandemic, several studies demonstrated that pregnant women with pandemic influenza were at increased risk for severe outcomes, including hospitalization, intensive care unit (ICU) admission, and death (Mosby, Rasmussen, & Jamieson, 2011; Rasmussen, Jamieson, & Uyeki, 2012). These studies were consistent with observations from previous influenza pandemics and annual epidemics that suggested pregnant women are at increased risk for influenza-associated complications (Beigi, 2007; Rasmussen, Jamieson, & Bresee, 2008; Rasmussen, Jamieson, MacFarlane, et al., 2009). However, before the 2009 H1N1 pandemic, information on pregnancy outcomes among women with influenza was limited. Some studies suggested that pregnant women with influenza might be at increased risk for adverse pregnancy outcomes including spontaneous abortions, pre-term delivery, low birth weight (LBW), and birth defects, among others (Acs, Banhidy, Puho, & Czeizel, 2005, 2006; Beigi, 2007; Hardy, Azarowicz, Mannini, Medearis Jr., & Cooke, 1961; Nuzum, Pilot, Stangl, & Bonar, 1918; Wool-ston & Conley, 1918).

Studies during the 2009 H1N1 pandemic showed that infants born to women with severe 2009 H1N1 influenza, especially those who were ill enough to be admitted to an ICU, were more likely to have poor neonatal outcomes, including LBW, preterm birth, small for gestational age (SGA), low Apgar scores, and increased likelihood of admission to a neonatal ICU (CDC, 2011; Doyle, Goodin, & Hamilton, 2013; Naresh et al., 2013; Pierce, Kurinczuk, Spark, Brocklehurst, & Knight, 2011; Yates et al., 2010). Outcomes for infants born to women with less severe 2009 H1N1 influenza illness were more attenuated, with some studies showing no increased risk (Hansen et al., 2012; Naresh et al., 2013). In addition, some studies showed that pregnant women with 2009 H1N1 influenza might be more likely to have factors that could independently affect the risk for adverse outcomes, like young age at delivery, minority race, and comorbid conditions such as obesity, than

women without 2009 H1N1 (Doyle et al., 2013; Hansen et al., 2012; Naresh et al., 2013; Yates et al., 2010).

To better understand the effects of influenza during pregnancy on infants, we linked data on pregnant women with confirmed or probable 2009 H1N1 influenza identified through public health surveillance efforts in five states during the 2009 H1N1 pandemic to information on their infants available from vital records, and compared these infant outcomes to those of infants born to matched comparison groups of women without 2009 H1N1.

2 | METHODS

This project was a collaboration between the Centers for Disease Control and Prevention (CDC) and health departments in California, New York City, North Carolina, Utah, and Washington. These health departments were selected based on their demographic and regional diversity as well as on the numbers of pregnant women with 2009 H1N1 reported to CDC. These sites made up one-third of the total number of United States cases of 2009 H1N1 influenza among pregnant women who were reported to CDC with illness onset from April to December of 2009.

From April 1 to August 21, 2009, as part of the 2009 H1N1 public health emergency response, CDC requested health department reporting of pregnant women with confirmed or probable H1N1 infection. During this time, a confirmed case was defined as “an individual reported with acute respiratory illness and laboratory-confirmed influenza A (H1N1) by real time reverse transcriptase polymerase chain reaction (rRT-PCR) or viral culture. A probable case was defined as an individual with an acute febrile respiratory illness, a positive test for influenza A, and a negative influenza rRT-PCR test result for seasonal H1and H3” (Siston et al., 2010). From August 21 to December 31, 2009, CDC requested reports for all pregnant women who were admitted to an ICU or who died with confirmed influenza diagnosed by a positive rapid test, rRT-PCR positive test, direct or indirect fluorescent antibody assay, or viral culture. For the purposes of this data linkage study, women with confirmed influenza B were not retained in the study group.

Data collected on women with confirmed or probable 2009 H1N1 influenza included the woman’s date of birth, date of onset of 2009 H1N1 influenza symptoms (or date of diagnosis if onset was not available), gestational age in weeks during pregnancy at symptom onset, type and timing of antiviral medication treatment received, type of care received (hospitalization, ICU admission), type of delivery, conditions that were reported in medical records that increase the risk for influenza-associated complications (e.g., obesity and diabetes), and estimated/actual dates of delivery.

For this study, state/local health department staff performed a data linkage between women with confirmed or probable H1N1 influenza and birth certificates for births to these women in calendar years 2009 and 2010. Health departments used matching software that was available locally; two centers used SAS and three used LinkPlus. Linkages to infants were based on maternal name and maternal date of birth. Possible matches were reviewed manually using other available variables, such as gestational age and location, to confirm

matches. CDC provided technical assistance to the state/local health departments with data linkage as needed. The data linkage process was discussed during periodic conference calls to ensure the linkage was done consistently across sites. Matching rates ranged from 78% to 95% among states that reported rates (CA = 78%, NC = 95%, NYC = 92%, UT = 79%, WA = 94%). For infants of women with confirmed or probable H1N1 during pregnancy, birth certificate data were collected up to 1 year after the latest date of onset of maternal symptoms.

We utilized a matched retrospective cohort design for this study. Infants born to mothers with confirmed 2009 H1N1 influenza constituted our exposed group, and we selected two unexposed groups (i.e., infants born to mothers without reported 2009 H1N1 influenza). For the comparison groups, each state randomly selected three comparison-infants for each exposed infant from birth certificates; infants included in the unexposed comparison groups were matched on month and year of conception (conception date was estimated, based on gestational age and date of birth/delivery), sex, and county of residence. We did not match on maternal age so that we might determine if age was an independent predictor of the outcome. We did include age in the model for the adjusted estimates we present in Table 2.

Because of the concern that mothers of some unexposed infants in the comparison group might have had 2009 H1N1 influenza that was not reported to the state/local health department, we identified a second unexposed comparison group by selecting three infants for each exposed infant from 1 year earlier (same matching criteria was utilized including sex, county of residence, and month of conception, but year of conception was 1 year earlier). This pre-pandemic time-period selection provided a comparison group of infants born to women who were not infected with 2009 H1N1 influenza during pregnancy (although some of these women may have had seasonal influenza).

The following dates were calculated: (a) maternal age at delivery using day, month, and year of maternal birth and of delivery (in two sites) or using month and year of maternal birth and delivery (in three sites); (b) gestational age at infant birth using available data from birth certificates (either calculated from date last normal menses began and date of infant birth or by using obstetric estimate of gestation, if the previous estimate could not be calculated or was implausible); and (c) gestational age at symptom onset by subtracting the time between date of onset of 2009 H1N1 influenza symptoms and date of birth. Delivery during influenza infection was defined as before influenza discharge for hospitalized pregnant women or delivery 2 weeks or less after influenza symptom onset for nonhospitalized women. For one state, delivery during influenza virus infection was estimated by comparing delivery to influenza onset dates. For other states, delivery during influenza virus infection was estimated by comparing the estimated gestational age at delivery and estimated gestational age at onset of influenza when these data were available. Maternal characteristics reported in Table 1, including conditions that increase the risk for influenza-associated complications (i.e., obesity and diabetes), were obtained from the infants' birth certificates; two states were not able to provide data on these maternal medical conditions.

Infant outcomes were defined as follows: LBW as <2,500 g at birth, preterm birth (PTB) as <37 weeks gestation at birth, SGA as <10th percentile as defined by the 2005 natality file (available at NVSS—birth data), and low Apgar as Apgar scores <=6 at 5 min.

Analyses were restricted to singleton infants. Differences were considered to be statistically significant at $p < .05$. Unadjusted and adjusted risk ratios (RRs) and 95% confidence intervals (CIs) were calculated to compare four outcomes (LBW, preterm birth, SGA, and low Apgar scores) between exposed infants (born to women with 2009 H1N1 influenza) and two groups of unexposed (comparison group) infants. Conditional logistic regression models were developed to estimate RR and 95% CI of adverse outcomes of exposed infants born to women with 2009 H1N1 influenza adjusting for maternal age and race/ethnicity (those with missing data on these variables were excluded in adjusted analysis). On occasion, the log binomial model approach did not converge; in these instances we fit log Poisson models as an alternative (Spiegelman & Hertzmark, 2005). In a sensitivity analysis, we also adjusted for BMI and diabetes in the subset of states that provided information on these covariates. Analysis was performed in SAS version 9.3 (SAS Institute Inc., Cary, NC). Data from all state/local health departments were securely transmitted to CDC and merged into a single dataset for analysis. Data were entered into a secure, restricted access database.

3 | RESULTS

A total of 531 liveborn infants (490 singletons) born to women with 2009 H1N1 influenza were identified (131 from California, 53 from North Carolina, 98 from New York City, 77 from Utah, and 131 from Washington among singletons). A total of 16 multiples and 25 infants with unknown multiple gestation were excluded from the analysis. The comparison groups consisted of 1,451 singletons matched on month and year of conception, sex, and county of residence, and 1,446 singletons matched on the same criteria, but using the previous year of conception.

Among the 490 singleton infants born to a mother with confirmed or probable 2009 H1N1 influenza, the following defects were noted on the birth certificate: one case each with omphalocele, cyanotic congenital heart disease, and renal agenesis. Among the comparison groups, the following birth defects were noted on birth certificates: one case each with diaphragmatic hernia, omphalocele, limb reduction defect, undefined circulatory defect, and anencephaly; two cases of undefined muscular defect; and three cases with congenital heart defects.

We compared the distribution of maternal demographic characteristics for women in the year prior ($n = 1,446$) and same year comparison ($n = 1,451$) sets, and maternal age was the only maternal demographic variable with differences between the two comparison groups ($p = .04$; Table 1). When the prior and same year comparison groups were combined and compared to women with 2009 H1N1 influenza, women with 2009 H1N1 influenza were three times more likely than women in the comparison groups to be 18 years of age or younger, compared to greater than or equal to 35 years of age (Unadjusted RR = 3.5 [2.2, 5.5]) and they were more than twice as likely to be black/non-Hispanic race/ethnicity or Hispanic ethnicity compared to white/non-Hispanic race/ethnicity (Unadjusted RR = 2.2

[1.6, 3.0] and 2.4 [1.9, 3.0], respectively; data not shown). In addition, women from comparison groups were more likely to deliver vaginally compared to women with 2009 H1N1 influenza.

Before conducting adjusted comparisons of infant outcomes, we compared the distribution of the infant outcomes for the year prior and same year comparison groups. We observed statistical differences when the two comparison groups were compared to each other; generally poorer infant outcomes were noted among the prior year comparison group than among the same year comparison group (Table 1). Because of the differences in the infant outcomes for the two comparison groups, we retained the separation for the groups for all further infant outcome analyses.

Compared to infants in the comparison groups, those born to women with 2009 H1N1 influenza were more likely to be preterm (aRR = 1.4 [1.1, 1.9] for prior year comparisons; 1.7 [1.3, 2.2] for same year comparisons), and to have low Apgar scores (aRR = 2.3 [1.3, 3.9] for prior year comparisons; 4.0 [2.1, 7.6] for same year comparisons). Infants born to women with 2009 H1N1 influenza were no more likely to be SGA than infants born to comparison women (Table 2).

Women with severe 2009 H1N1 influenza illness (e.g., admitted to the ICU or died, $n = 82$) were more likely to have poor infant outcomes than women with less severe illness (e.g., who were admitted to the hospital but not ICU, $n = 338$, or not admitted to the hospital, $n = 70$). Women with 2009 H1N1 influenza who were admitted to the ICU were more likely to deliver preterm infants, infants with LBW, and infants with Apgar scores <=6 at 5 min than women in comparison groups (aRR = 3.9 [2.7, 5.6], aRR =4.6 [2.9, 7.5] and aRR = 8.7 [3.6, 21.2], for same year comparisons, respectively). In fact, no statistical differences in infant outcomes were found among women in the comparison groups and women with 2009 H1N1 influenza who were admitted to the hospital but not ICU or not admitted to the hospital (Tables 1 and 2).

To further examine the risks for poor infant outcomes, we estimated whether the infant was delivered during or after influenza illness. Infants we estimated to be delivered during maternal influenza illness were more likely to have poor infant outcomes (lower Apgar scores, more preterm birth, and lower birth weight using unadjusted RR) than women in the comparison groups (Table 2). When we examined infants we estimated to be born after their mothers had recovered from influenza, with one exception, the infants were no more likely to have poorer infant outcomes than infants of women in both comparison groups; the exception was that low Apgar scores were more common among women with influenza who delivered after influenza recovery compared to women in the same year comparison group (aRR = 2.6 [1.1, 6.0]). Restricting our analysis to women who delivered after recovery from influenza illness, we also examined the impact of trimester of infection on the developing fetus. Among women estimated to have delivered after influenza recovery, although small numbers limit interpretability, those who were diagnosed with 2009 H1N1 influenza during the first trimester had higher risks than women in the same year comparison group for preterm birth (aRR = 3.0 [1.3, 6.9]). Influenza illness in later trimesters among women

estimated to have delivered after influenza recovery was not associated with higher risk of adverse infant outcomes.

4 | DISCUSSION

In our study, infants born to women with 2009 H1N1 influenza were more likely to be preterm and to have low Apgar scores at 5 min than women without 2009 H1N1. Women with 2009 H1N1 influenza who were admitted to the ICU were more likely to deliver preterm, LBW infants, and infants with Apgar scores <=6 at 5 min than women in comparison groups. No statistically significant differences were noted when comparing outcomes for infants born to women with 2009 H1N1 who were not severely ill (no hospitalization, without ICU-admission or death) to those born to women without 2009 H1N1 (in prior or same year comparison groups).

These results are consistent with previous findings of poor infant outcomes among pregnant women who were severely ill with 2009 H1N1 influenza virus infection (CDC, 2011; Doyle et al., 2013; Naresh et al., 2013; Pierce et al., 2011; Yates et al., 2010) including a Florida study that found infants born to a cohort of mostly severely ill pregnant women with 2009 H1N1 were approximately two times more likely to be of LBW and born preterm (RR =1.8, [1.1,2.8] and 2.2, [1.5, 3.3], respectively) than infants born to noninfected pregnant women (Doyle et al., 2013).

Our findings of no increased adverse infant outcomes among women with less severe flu illness is also consistent with previous studies. A population-based cohort study found no association between 2009 H1N1 illness during pregnancy and preterm birth (Fell et al., 2018). Similarly, a large population-based study of mostly nonhospitalized pregnant women with 2009 H1N1 did not find statistical differences for preterm birth, LBW or SGA among infants born to women with and without reported 2009 H1N1 (Hansen et al., 2012). We observe some results that differ slightly with previous findings. Although other studies have noted increased risk for SGA infants among women with 2009 H1N1 (CDC, 2011; Naresh et al., 2013) and seasonal maternal influenza (Hansen et al., 2012), we did not observe any differences in SGA infants born to women with 2009 H1N1 compared to women from prior or same year comparison groups.

Although small numbers and multiple comparisons limit interpretation, the generally higher number of poor birth outcomes among women who delivered after recovery from 2009 H1N1 influenza infection that was diagnosed in the first trimester compared to later trimesters deserves further investigation.

A strength of these analyses is the multi-site design: the five collaborating sites made up one-third of the total number of United States cases of 2009 H1N1 influenza among pregnant women who were reported to CDC during the first months of the pandemic. In addition, this study is among the first to use a matched retrospective cohort design and the only study to match infants born to women with 2009 H1N1 in pregnancy to infants born in the previous year to women without known 2009 H1N1 influenza. The matched retrospective cohort design utilizing two matched comparison groups was selected in

response to two potential risks for exposure misclassification bias: (a) less frequent influenza testing and less health department reporting in the year prior to the 2009 H1N1 pandemic and (b) more common influenza infection during the same year of the 2009 H1N1 pandemic. Our study observed attenuated risk differences among the prior year comparison group compared to the same year comparison group suggesting that there are important differences among comparison groups selected in different years.

One limitation for this analysis is that the conditional logistic model included maternal age and race/ethnicity, but did not include other potentially confounding maternal characteristics like maternal education and comorbid conditions. We did not include maternal education in the adjusted model because of evidence of collinearity with age. We did not include maternal obesity and diabetes because two states were missing these variables in our study group and thus, these variables could not be included in the adjusted analysis for five states. In a sensitivity analysis, we added obesity and diabetes to the adjusted model (which included for maternal age and race/ethnicity) in the subset of states with those data, and the effect estimates did not change appreciably.

Although not within the scope of this analysis, future analyses of infant outcomes related to maternal influenza virus infection would benefit from comparisons of ICU admissions during pregnancy among women with and without influenza infection. In addition, if women are hospitalized for illness there is potential for bias in the observer recording of the Apgar score. Finally, it is important to note that some of the hospitalized women who were not admitted to the ICU in this surveillance population may have been hospitalized for delivery, and influenza illness was discovered at the same time.

In summary, this study uses a novel research design and provides more evidence that severely ill women with 2009 H1N1 influenza during pregnancy are more likely to have adverse birth outcomes than women without influenza. As noted previously (Mosby et al., 2011; Rasmussen et al., 2012) pregnant women are more likely to become severely ill when infected with 2009 H191 influenza than nonpregnant women. Together, these findings support the importance of influenza vaccination among pregnant women and the importance of antiviral treatment as early as possible for pregnant women to avert severe illness as previous data suggest women treated early with antivirals are less likely to progress to severe illness (Rasmussen, Kissin, Yeung, et al., 2011). More research is needed to further understand the nuances of infant risks among pregnancies with seasonal influenza virus infection, but these current findings provide important additional evidence of influenza risk during pregnancy.

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TABLE 1

Characteristics of women with 2009 H1N1 influenza during pregnancy and infants born to them and matched controls

	Any maternal flu (*n* = 490)		**Maternal flu, not Severe[a] (*n* = 408)**		**Controls from prior year (*n* = 1,446)**		**Controls from same year (*n* = 1,451)**	
	n	**(%)**	***n***	**(%)**	***n***	**(%)**	***n***	**(%)**
Maternal characteristic								
Age in years[b–f]								
<=18	43	(8.8)	41	(10.0)	85	(5.9)	63	(4.3)
19–34	403	(82.2)	333	(81.6)	1,135	(78.5)	1,123	(77.4)
> = 35	40	(8.2)	32	(7.8)	218	(15.1)	258	(17.8)
Missing	4	(0.8)	2	(0.5)	8	(0.6)	7	(0.5)
Race/ethnicity[b–e]								
White non-Hispanic	135	(27.6)	113	(27.7)	643	(44.5)	675	(46.5)
Black non-Hispanic	67	(13.7)	53	(13.0)	150	(10.4)	149	(10.3)
Hispanic	218	(44.5)	185	(45.3)	449	(31.1)	446	(30.7)
Other	64	(13.1)	54	(13.2)	191	(13.2)	169	(11.6)
Missing	6	(1.2)	3	(0.7)	13	(0.9)	12	(0.8)
Pre-existing conditions[g]								
Obesity[b,d]	108	(22.0)	87	(21.3)	231	(16.0)	272	(18.7)
No obesity	295	(60.2)	250	(61.3)	993	(68.7)	967	(66.6)
Missing	87	(17.8)	71	(17.4)	222	(15.4)	212	(14.6)
Diabetes[b–d]	15	(3.0)	12	(2.9)	13	(0.9)	23	(1.6)
No diabetes	336	(68.6)	303	(74.2)	1,008	(69.7)	1,014	(69.9)
Missing	139	(28.4)	93	(22.8)	425	(29.4)	414	(28.5)
Education[b–e]								
<High school	153	(31.2)	129	(31.6)	309	(21.4)	286	(19.7)
High school graduate; some college	269	(54.9)	230	(56.4)	720	(49.8)	714	(49.2)
College graduate or more	43	(8.8)	35	(8.6)	364	(25.2)	400	(27.6)
Missing	25	(5.1)	14	(3.4)	53	(3.7)	51	(3.5)
Method of delivery[b,c]								
C-section	176	(35.9)	127	(31.1)	411	(28.4)	401	(27.6)

	Any maternal flu (*n* = 490)		Maternal flu, not Severe[a] (*n* = 408)		Controls from prior year (*n* = 1,446)		Controls from same year (*n* = 1,451)	
	n	**(%)**	***n***	**(%)**	***n***	**(%)**	***n***	**(%)**
Vaginal	314	(64.1)	281	(68.9)	1,033	(71.4)	1,049	(72.3)
Missing	0		0		2	(0.1)	1	(0.1)
Infant characteristic								
Gestational age[b,c]								
Preterm (<37 weeks at delivery)	75	(15.3)	39	(9.6)	146	(10.1)	118	(8.1)
Term (> = 37 weeks at delivery)	414	(84.5)	369	(90.4)	1,299	(89.8)	1,332	(91.8)
Missing	1	(0.2)	0		1	(0.1)	1	(0.1)
Gestational weight[c,f]								
Low birthweight (<2,500 g)	51	(10.4)	22	(5.4)	109	(7.5)	75	(5.2)
Normal birthweight (> = 2,500 g)	439	(89.6)	386	(94.6)	1,336	(92.4)	1,376	(94.8)
Missing	0		0		1	(0.1)	0	
Small-for-gestational-age								
<10th centile	43	(8.8)	33	(8.1)	113	(7.8)	119	(8.2)
> = 10th centile	445	(90.8)	374	(91.7)	1,329	(91.9)	1,330	(91.7)
Missing	2	(0.4)	1	(0.2)	4	(0.3)	2	(0.1)
5-min Apgar[b,c,f]								
Low (<=6)	24	(4.9)	9	(2.2)	32	(2.2)	18	(1.2)
Normal (>6)	463	(94.5)	397	(97.3)	1,405	(97.2)	1,424	(98.1)
Missing	3	(0.6)	2	(0.5)	9	(0.6)	9	(0.6)

[a] Maternal Flu (not severe) = Not hospitalized for influenza treatment or admitted to hospital but not to the intensive care unit (ICU) for influenza treatment.

[b] Prior-year controls compared to any maternal flu $p < .01$; X2 test for Heterogeneity (excluding missing).

[c] Same-year controls compared to any maternal flu $p < .05$; X2 test for Heterogeneity (excluding missing).

[d] Prior-year controls compared to nonsevere maternal flu $p < .01$; X2 test for Heterogeneity (excluding missing).

[e] Same-year controls compared to nonsevere maternal flu $p < .01$; X2 test for Heterogeneity (excluding missing).

[f] Prior-year controls compared to same-year controls $p < .05$; X2 test for Heterogeneity (excluding missing).

[g] One state did not collect information on maternal obesity, and another state did not collect information on maternal diabetes; these states were excluded from the respective analyses.

TABLE 2

Risk ratios and adjusted risk ratios: Maternal influenza exposures and infant outcomes

	Infant outcomes															
	PTB (Prior year comparison)		PTB (Same year comparison)		LBW (Prior year comparison)		LBW (Same year comparison)		SGA (Prior year comparison)		SGA (Same year comparison)		Low Apgar[a] (Prior year comparison)		Low Apgar[a] (Same year comparison)	
	CrudeRR[b] (95%CI)[c]	aRR[d] (95%CI)[c]	CrudeRR[b] (95%CI)[c]	aRR[d] (95%CI)[c]	CrudeRR[b] (95%CI)[c]	aRR[d] (95%CI)[c]	CrudeRR[b] (95%CI)[c]	aRR[d] (95%CI)[c]	CrudeRR[b] (95%CI)[c]	aRR[d] (95%CI)[c]	CrudeRR[b] (95%CI)[c]	aRR[d] (95%CI)[c]	CrudeRR[b] (95%CI)[c]	aRR[d] (95%CI)[c]	CrudeRR[b] (95%CI)[c]	aRR[d] (95%CI)[c]
Any maternal flu (*n* = 490)	**1.5 (1.2, 2.0)**	**1.4 (1.1, 1.9)**	**1.9 (1.4, 2.5)**	**1.7 (1.3, 2.2)**	1.4 (1.0, 1.9)	1.2 (0.9, 1.7)	**2.0 (1.4, 2.8)**	**1.8 (1.2, 2.6)**	1.1 (0.8, 1.6)	1.0 (0.7, 1.4)	1.1 (0.8, 1.5)	0.9 (0.6, 1.2)	**2.2 (1.3, 3.7)**	**2.3 (1.3, 3.9)**	**3.9 (2.2, 7.2)**	**4.0 (2.1, 7.6)**
Flu severity groups																
No hospital (hosp; *n* = 70)	1.0 (0.5, 2.0)	1.0 (0.5, 2.0)	1.2 (0.6, 2.5)	1.2 (0.6, 2.4)	0.8 (0.3, 2.0)	0.6 (0.2, 1.7)	1.1 (0.4, 2.9)	0.8 (0.3, 2.6)	1.5 (0.7, 2.9)	1.1 (0.5, 2.4)	1.4 (0.7, 2.7)	1.0 (0.5, 2.3)	1.3 (0.3, 5.2)	1.4 (0.3, 5.7)	2.3 (0.5, 9.7)	2.6 (0.6, 11.1)
Hosp/no-ICU admission (*n* = 338)	0.9 (0.7, 1.3)	0.9 (0.6, 1.3)	1.2 (0.8, 1.7)	1.1 (0.7, 1.5)	0.7 (0.4, 1.1)	0.7 (0.4, 1.1)	1.0 (0.6, 1.7)	1.0 (0.6, 1.6)	0.9 (0.6, 1.4)	0.9 (0.6, 1.3)	0.9 (0.6, 1.4)	0.8 (0.5, 1.2)	0.9 (0.4, 2.1)	1.0 (0.4, 2.2)	1.7 (0.7, 4.0)	1.6 (0.7, 4.0)
Hosp-ICU admission (*n* = 64)	**3.7 (2.6, 5.3)**	**3.6 (2.4, 5.2)**	**4.6 (3.2, 6.6)**	**3.9 (2.7, 5.6)**	**3.9 (2.6, 6.0)**	**3.6 (2.2, 5.7)**	**5.7 (3.7, 8.9)**	**4.6 (2.9, 7.5)**	1.4 (0.7, 2.9)	1.2 (0.5, 2.6)	1.3 (0.6, 2.7)	1.1 (0.5 2.5)	**5.0 (2.3, 10.9)**	**5.4 (2.3, 12.5)**	**8.9 (3.9, 20.5)**	**8.7 (3.6, 21.2)**
Death (*n* = 18)	**7.0 (5.0, 9.8)**	**8.1 (5.5, 11.9)**	**8.7 (6.1, 12.3)**	**7.9 (5.1, 12.4)**	**7.4 (4.7, 11.6)**	**8.9 (5.3, 15.0)**	**10.7 (6.7, 17.2)**	**9.2 (5.3, 16.1)**	2.3 (0.8, 6.4)	1.4 (0.4, 5.0)	2.1 (0.8, 6.1)	1.2 (0.3, 4.6)	**20.0 (10.7, 37.1)**	**26.6 (13.7, 51.4)**	**35.6 (17.8, 71.1)**	**NC**
Influenza timing																
Delivery during flu (*n* = 110)	**3.1 (2.2, 4.2)**	**3.0 (2.1, 4.2)**	**3.8 (2.7, 5.3)**	**3.6 (2.6, 5.0)**	**3.4 (2.3, 4.9)**	**3.2 (2.2, 4.7)**	**4.9 (3.3, 7.3)**	**4.8 (3.2, 7.1)**	1.2 (0.6, 2.2)	1.2 (0.7 2.3)	1.1 (0.6, 2.0)	1.1 (0.6, 2.0)	**4.1 (2.1, 8.2)**	**4.6 (2.3, 9.2)**	**7.3 (3.5, 15.5)**	**NC**
Delivery after flu (all trimesters; *n* = 259)	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)	1.1 (0.7, 1.7)	1.0 (0.7, 1.6)	0.6 (0.3, 1.1)	0.6 (0.3, 1.1)	0.9 (0.5, 1.6)	0.9 (0.5, 1.6)	0.9 (0.6, 1.5)	0.8 (0.5, 1.3)	0.9 (0.6, 1.4)	0.7 (0.4, 1.2)	1.4 (0.7, 3.0)	1.4 (0.7, 3.1)	**2.5 (1.1, 5.7)**	**2.6 (1.1, 6.0)**
Delivery after flu (first trimester infection; *n* = 17)	2.3 (1.0, 5.6)	2.3 (1.0, 5.2)	**2.9 (1.2, 6.9)**	**3.0 (1.3, 6.9)**	1.6 (0.4, 5.8)	1.7 (0.5, 6.2)	2.3 (0.6, 8.5)	2.5 (0.7, 9.3)	1.5 (0.4, 5.6)	0.7 (0.1, 4.6)	1.4 (0.4, 5.3)	0.6 (0.1, 4.1)	2.6 (0.4, 18.2)	3.1 (0.5, 21.1)	4.7 (0.7, 33.3)	5.0 (0.7, 35.4)
Delivery after flu (second trimester infection; *n* = 98)	1.0 (0.6, 1.9)	1.0 (0.5, 1.8)	1.3 (0.7, 2.3)	1.1 (0.6, 2.1)	0.5 (0.2, 1.4)	0.5 (0.2, 1.4)	0.8 (0.3, 2.1)	0.7 (0.3, 2.0)	0.9 (0.4, 1.9)	0.9 (0.4, 1.8)	0.9 (0.4, 1.8)	0.8 (0.4, 1.6)	1.4 (0.4, 4.5)	1.6 (0.5, 5.0)	2.5 (0.7, 8.3)	2.7 (0.8, 9.1)
Delivery after flu (third tri infection; *n* = 142)	0.6 (0.3, 1.2)	0.6 (0.3, 1.2)	0.8 (0.4, 1.5)	0.7 (0.4, 1.4)	0.6 (0.3, 1.3)	0.5 (0.2, 1.2)	0.8 (0.4, 1.8)	0.8 (0.4, 1.8)	0.9 (0.5, 1.7)	0.8 (0.4, 1.6)	0.9 (0.5, 1.6)	0.7 (0.4, 1.4)	1.3 (0.5, 3.6)	1.3 (0.5, 3.5)	2.3 (0.8, 6.6)	2.4 (0.8, 7.1)

Bold = statistical significance at $p = .05$; ICU = intensive care unit; LBW = Low birth weight, <2,500 g; NC = not calculated because of insufficient cell size; PTB = preterm birth, <37 weeks at delivery; SGA = small for gestational age, weight <10th centile for gestational age.

[a] Low Apgar = 5-min Apgar <=6.

[b] Crude RR = crude relative risk.

[c] 95% CI = 95% confidence interval.

[d] aRR = adjusted RR = relative risk adjusted for maternal race/ethnicity and age.