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Impact of Maternal Immunization on Influenza Hospitalizations in Infants

Katherine A. POEHLING, MD, MPH[1,2], **Peter G. SZILAGYI, MD, MPH**[3], **Mary A. STAAT, MD, MPH**[4], **Beverly M. SNIVELY, PhD**[5], **Daniel C. PAYNE, PhD, MSPH**[6], **Carolyn B. BRIDGES, MD**[6], **Susan Y. CHU, PhD, MSPH**[7], **Laney S. LIGHT, MS**[5], **Mila M. PRILL, MSPH**[6], **Lyn FINELLI, DrPH**[6], **Marie R. GRIFFIN, MD, MPH**[8,9], and **Kathryn M. EDWARDS, MD**[10] **for the New Vaccine Surveillance Network**

[1] Department of Pediatrics, Wake Forest University School of Medicine, Winston-Salem, North Carolina

[2] Department of Epidemiology and Prevention, Wake Forest University School of Medicine, Winston-Salem, North Carolina

[5] Department of Biostatistical Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina

[3] Department of Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, New York

[4] Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

[6] National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

[7] Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia

[8] Department of Internal Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

[9] Department of Preventive Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

[10] Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee

Abstract

Objective—To determine whether maternal vaccination during pregnancy was associated with a reduced risk of laboratory-confirmed influenza hospitalizations in infants <6 months old.

Study Design—Active population-based, laboratory-confirmed influenza surveillance was conducted in children hospitalized with fever and/or respiratory symptoms in 3 U.S. counties from November-April during the 2002–2009 influenza seasons. The exposure, influenza vaccination during pregnancy, and the outcome, positive/negative influenza testing among their hospitalized infants, were compared using logistic regression analyses.

Corresponding author: Katherine A. Poehling, MD MPH, Department of Pediatrics, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157, kpoehlin@wfubmc.edu, phone: 336.716.9661, fax: 336.716.7100.

Results—Among 1510 hospitalized infants <6 months old, 151 (10%) had laboratory-confirmed influenza and 294 (19%) mothers reported receiving influenza vaccine during pregnancy. Eighteen (12%) mothers of influenza-positive infants and 276 (20%) mothers of influenza-negative infants were vaccinated (unadjusted OR= 0.53, 95%CI 0.32–0.88 and adjusted OR=0.52, 95%0.30–0.91).

Conclusion—Infants of vaccinated mothers were 45%–48% less likely to have influenza hospitalizations than infants of unvaccinated mothers. Our results support the current influenza vaccination recommendation for pregnant women.

Keywords

infants; influenza hospitalization; influenza vaccine; maternal vaccination; vaccine effectiveness

Introduction

In the United States, influenza vaccination is universally recommended for all children 6 months through 18 years of age due to the large burden of influenza hospitalizations and outpatient visits in this age group.1 Infants <6 months of age have the highest rates of pediatric influenza hospitalizations,2¯6 but none of the influenza vaccines are licensed for this age group.7¯9 Hence, influenza vaccine is recommended for all close contacts of infants to reduce the likelihood of transmission.10 It is also recommended for pregnant women since they have an increased risk of influenza-related complications and hospitalizations, with the highest risk during the third trimester.11¯16 National data indicate that the proportion of pregnant women who received influenza vaccine has increased from a low of 9% in 2002–2003 to a high of 51% in 2009–2010 during the H1N1 influenza pandemic.1,17,18

Influenza vaccination during pregnancy is primarily recommended to protect pregnant women themselves. However, a recent randomized controlled trial from Bangladesh and an observational study among Native American populations reported benefits of influenza vaccine both for mothers and their young infants.19,20 Influenza antibodies are efficiently transferred across the placenta and have been observed to provide indirect protection to infants for the first 2 to 3 months of life, when infants are too young to receive influenza vaccine.20,21 We sought to determine whether maternal vaccination during pregnancy was associated with a reduced risk of laboratory-confirmed influenza hospitalizations in infants <6 months of age living in 3 geographically diverse U.S. counties over seven consecutive influenza seasons. We focused on influenza hospitalizations because they are associated with the highest costs and because most childhood deaths occur among hospitalized patients.22,23

Materials and Methods

The New Vaccine Surveillance Network, funded by the Centers for Disease Control and Prevention, conducted active, population-based, laboratory-confirmed influenza surveillance among children hospitalized with influenza in 3 U.S. counties; Davidson County, Tennessee (Nashville), Hamilton County, Ohio (Cincinnati) or Monroe County, New York (Rochester).2 Children were eligible for enrollment if they were hospitalized with fever and/or acute respiratory symptoms during the winter from November through April and resided within these three counties. Seven consecutive influenza seasons were included; 2002–2003 through 2008–2009 in Nashville and Rochester, and 2003–2004 through 2008–2009 in Cincinnati. In 2008–2009, the seasonal influenza season ended in April 2009, which was prior to the detection of H1N1 in this network.

All enrolled children had nasal and throat swabs obtained for viral culture and/or reverse transcription polymerase chain reaction for influenza A or B as previously described.24 Parents of enrolled children had a standardized questionnaire administered to ascertain presenting symptoms and their duration, birth and past medical history, history of maternal influenza vaccination during pregnancy with the enrolled child, and social history. The medical record was reviewed after discharge.

The study population comprised inpatients <6 months of age enrolled through hospital surveillance with fever and/or acute respiratory symptoms during one of the seven consecutive influenza seasons. Most infants were enrolled as inpatients though some were enrolled as outpatients and subsequently hospitalized. For infants with multiple hospitalizations during an influenza season, only the first hospitalization during the study period was included. Each influenza season was defined as the period spanning the first to last influenza-positive nasal/throat swab among all study infants. Since the opportunity for the mother to receive the influenza vaccine varied by birth month, we divided each influenza season into early, middle and late season tertiles, based on the day of enrollment of influenza-positive infants. A control group of hospitalized infants without laboratory-confirmed influenza were assigned to early, middle and late tertiles by comparing their dates of enrollment with the influenza-positive cases.

The primary exposure variable was maternal influenza vaccination status during pregnancy, and the primary outcome variable was the presence or absence of laboratory-confirmed influenza among their hospitalized infants. Categorical variables that can influence hospitalizations in general and thus could potentially influence influenza-related hospitalizations in infants were compared by chi-square analysis. For adjusted analyses, we created three multivariate logistic regression model analyses *a priori* based on demographic, medical and social risk factors previously shown to be associated with increased risk of influenza or respiratory hospitalizations.2،3،5،25¯29 The core demographic model included the following covariates: age, gender, race/ethnicity, site, study year, and tertile of the influenza season. The second model evaluated the core demographic model and two medical covariates: prematurity and presence of any high-risk medical conditions in the infant for which influenza vaccine was recommended in persons ≥6 months of age.16 The third model included the core demographic model and five additional variables; smoke exposure at home, number of siblings (0 to 3+), daycare attendance, insurance status (public/private/none), and whether the infant was ever breastfed. All model covariates were treated as categorical variables. Confidence intervals were calculated at the 95% level; p-values ≥0.05 were considered statistically significant. All analyses were computed using STATA software 10.0 (Stata Corporation, College Station, TX).

From 2005–2006 through 2008–2009, we asked mothers of young infants if they had an influenza-like illness during pregnancy because an influenza illness during pregnancy could lead to the development of protective antibodies for that influenza serotype in the infant. Hence, we performed a sub-analysis of the unadjusted and the three adjusted models described above to determine the protective effect of either maternal vaccination for all years or influenza-like illness during pregnancy from the last four years of the study period.

Human and Nonhuman Experimentation

The study was approved with informed consent from the parent or guardian by the Institutional Review Boards at each site and the Centers for Disease Control and Prevention.

Results

Over seven influenza seasons, 2122 hospitalized infants were eligible for enrollment in the three NVSN sites and 1423 (67%) of the eligible infants were included from the inpatient setting (Figure 1). Reasons for exclusion were 307 (44%) protocol deviation at Cincinnati, 132 (19%) parental refusal, 130 (19%) parents missed or not available, 89 (13%) lack of language translator, 38 (5%) discharged prior to being approached, and 3 (<1%) physician refusal. Of these 1423 hospitalized and enrolled infants, 57 (4%) had unknown or missing maternal influenza vaccination status, 3 (0.2%) had indeterminate influenza status (i.e., negative RNA control), 3 (0.2%) had unknown race/ethnicity, and 23 (2%) represented a second study hospitalization during the influenza season and were excluded from analysis. The overall study population comprised these 1337 eligible infants enrolled solely from the inpatient setting and an additional 173 eligible infants who were hospitalized following enrollment in the emergency department and fulfilled all inpatient enrollment criteria. Among these 1510 infants hospitalized with fever and/or respiratory symptoms during the influenza season (Table 1), 151 (10%) had laboratory-confirmed influenza —with 136 (90%) influenza A and 15 (10%) influenza B. Among all hospitalized infants, a higher proportion of infants <2 months than those 2–<6 months of age were influenza-positive. The proportion of infants who were influenza-positive varied significantly across study years, ranging from 3% in 2006–2007 to 15% in 2003–2004.

A total of 294 (19%) mothers reported that they had received the influenza vaccine during that pregnancy (Table 2). This proportion varied by influenza season, ranging from 10% in 2003–2004 to 38% in 2008–2009, and by age of the infant at the time of enrollment during the influenza season, ranging from 24% for neonates younger than 1 month to 9% for infants 4–5 months of age. The proportion of infants whose mothers were vaccinated varied from only 13–15% at the Cincinnati and Nashville sites up to 33% at the Rochester site. The proportion of infants whose mothers were vaccinated was 15% for blacks, 21% for whites, and 22% for Hispanics, respectively. Infants with private insurance were more likely to have a vaccinated mother than those with public or no insurance. Breastfed infants were more likely to have mothers who reported being vaccinated than infants of mothers who never breastfed. Non-smoking households had a higher proportion of infants whose mothers were vaccinated than households with a smoker.

Among influenza-positive infants during all study years, 12% of their mothers reported influenza vaccination during pregnancy, while among influenza-negative infants, 20% of their mothers reported influenza vaccination, yielding an unadjusted odds ratio of 0.53 (95% confidence interval, CI, 0.32–0.88). Similar results were obtained in the three multivariate models shown in Figure 2. Since a significant proportion of data from Cincinnati was excluded for protocol violations, a sensitivity analysis that included only Rochester and Nashville data was performed and yielded similar results to the combined data. In the core demographic model, adjusting for age, gender, race/ethnicity, site, study year, and early, middle or late influenza season, the odds ratio for having an influenza-positive, hospitalized infant among vaccinated mothers was 0.55 (95% CI 0.32–0.95). Model 2 included the core demographic model plus prematurity and high-risk conditions and had an odds ratio of 0.55 (95%CI 0.32–0.94). These medical covariates did not impact the estimate and were not included in the third model. Model 3 included the core demographic model, exposure to smoke, siblings, daycare, insurance and presence of breastfeeding and had an odds ratio of 0.52 (95% CI 0.30–0.91). As shown, adjustments for covariates did not affect the results substantially. Overall, results of the multivariate modeling suggest that maternal vaccination reduced the risk of influenza by 45%–48%.

A total of 110 mothers from 2005–2006 through 2008–2009 reported a history of influenza-like illness during pregnancy, of which 81 (74%) had not received the influenza vaccine during that pregnancy. In a sub-analysis combining both maternal influenza vaccination for all seven years and a history of an influenza-like illness during pregnancy for four years, we found that the unadjusted and adjusted estimates were similar with a 45%–49% reduced risk of influenza in the infant.

Comment

Our results indicate that hospitalized infants whose mothers received influenza vaccine during pregnancy were 45% to 48% less likely to have laboratory-confirmed influenza during their first influenza season compared with infants of unvaccinated mothers. Adding history of influenza-like illness during pregnancy to the analyses had little impact on the odds ratio for having an influenza-positive, hospitalized infant. Given that infants <6 months of age have the highest hospitalization rate among all children2¯6 and that the vaccine is not licensed for that age group,16 these data support that infants born to vaccinated mothers benefit from the transfer of maternally derived antibodies.

Four previously published studies support our conclusions. First, a prospective, observational study among Native Americans from 2002–2005 found that infants of vaccinated mothers had a 41% reduction of the risk of laboratory-confirmed influenza infection in the inpatient and outpatient settings as determined by viral culture or antibody titers (relative risk 0.59, 95% CI 0.37–0.93).20 A second study, a randomized controlled trial of maternal influenza vaccination during pregnancy, was conducted in Bangladesh in 2004–2005. In this tropical country with year-round influenza circulation, investigators reported fewer rapid test-confirmed influenza cases among infants of mothers who received influenza vaccine compared with infants of unvaccinated mothers (6 infants versus 16 infants, respectively) for a vaccine effectiveness estimate of 63% (95% CI 5%–85%). Among 110 infants in the influenza vaccine group and 153 infants in the control group, vaccine effectiveness against unspecified respiratory illness with fever was 29% (95% CI 7%–46%).19 Third, a matched case-control study compared hospitalized infants with physician-ordered direct fluorescent antibody for seasonal influenza from 2000 through 2009. Cases with a positive influenza test and controls with a negative test were matched by date of birth and date of hospitalization. Maternal vaccinations were included only if they were confirmed and given at least 14 days prior to delivery. Effectiveness of maternal vaccination among infants <6 months of age was reported to be 91.5% (95% CI 62%–98%). 30 Fourth, a Northern California Kaiser Permanente database study over 5 influenza seasons (1997–2002), found that maternal vaccination was associated with a decreased risk of pneumonia or influenza hospitalization in their infants with an adjusted hazard ratio of 0.63 (95%CI 0.30–1.29), translating into 37% protection.31 Our 95% confidence intervals for protection of maternal vaccination from influenza hospitalizations among infants <6 months of age overlap those from each of these studies.

Our study differs from the previously published studies in several ways. First, we included seven consecutive influenza seasons and used prospective, population-based and laboratory-confirmed surveillance to identify eligible infants. By systematically testing all eligible infants using culture and molecular methods to define influenza infections, we utilized sensitive and specific methods and avoided the biases associated with physician-ordered testing; the study utilizing physician-ordered testing to identify eligible infants had a much higher proportion of infants with high-risk conditions than our study population. Second, we focused on hospitalizations whereas two previous studies included more outpatient visits than hospitalizations. Third, we included three diverse geographic regions of the U.S whereas all previous studies reported data from one geographic region.

Our study has several limitations. Although we enrolled a large proportion of eligible infants a number of them had to be excluded because of protocol violations, and infants who were and were not included in the study population could have systematically differed. Neither confirmed influenza vaccination status nor documented influenza disease status was available from mothers, and serologic assays were not performed on either infants or mothers. Since the study focused on hospitalized infants and not those seen only in the outpatient clinic or emergency departments, the generalizability of these results to outpatient settings is unknown. However, admission criteria for infants with fever and respiratory symptoms change over the first few weeks of life, so limiting the study population to solely inpatients allowed us to focus on severe outcomes.

Our estimates of maternal vaccination are consistent with national estimates,17 and lower than estimates from one health care system that implemented interventions to increase their maternal vaccination rates.33 We have previously reported higher influenza vaccine coverage among children 6–59 months of age in Rochester than that in Nashville or Cincinnati.34 Because of this consistent pattern, these differences seem to reflect geographical differences in influenza vaccination patterns. We found higher rates of maternal vaccination when the infant had private insurance compared with public or no insurance. This differs from the seasonal influenza vaccine coverage reported the Rhode Island Pregnancy Risk Assessment Monitoring System (PRAMS), which found similar coverage between women with public and private insurance. Given that obstetrician-gynecologists have consistently identified financial costs as a major barrier to influenza vaccination of pregnant women,35–37 it is possible that differences in vaccine coverage between public and private insurance vary geographically.

Maternal vaccination during pregnancy is recommended since pregnant women have an increased risk of influenza-associated morbidity and mortality.11–15 However, despite this recommendation, pregnant women have traditionally had the lowest influenza vaccine coverage of any group for whom influenza vaccine is specifically recommended.17 Although most (84.5%) obstetricians support influenza vaccination of all pregnant women, 35 few mothers (20%) actually report being offered influenza vaccination during pregnancy. 38 Obstetricians play a critical role in the influenza vaccination coverage of pregnant women. For first pregnancies, obstetricians are often the only medical professional seeing the pregnant women; for subsequent pregnancies, pregnant women may see the pediatrician, however pediatricians do not tend to vaccinate pregnant women since they are not their patients. Half of all pregnant women who received the monovalent H1N1 vaccine in 2009–2010 reported receiving it in the obstetrician/gynecologist office and none reported receiving it in a pediatric office.18

Because numerous studies have demonstrated comparable or increased influenza antibody titers in the cord blood when compared with maternal levels,3,39–44 maternal vaccination should afford some protection of newborn infants against influenza and is supported by our study. Similar to other studies, we found between 45% and 48% protection against laboratory-confirmed influenza hospitalizations among infants whose mothers reported receiving influenza vaccine during pregnancy. Using data from our earlier studies of 4.5 influenza-attributable hospitalizations among 1000 infants <6 months of age2 and census data of 4,251,095 live-births in the U.S. in 2008,45 we project that there are an average of 19,130 influenza-attributable hospitalizations among infants <6 months of age per year. A 45% to 48% reduction in this burden would yield an estimated 8600 to 9200 fewer influenza-attributable hospitalizations among young infants each year. Thus, our findings suggest that influenza vaccination of pregnant women may reduce the risk of influenza-attributable hospitalization among infants in the first 5 months of life, further supporting the current influenza vaccination recommendations for pregnant women.

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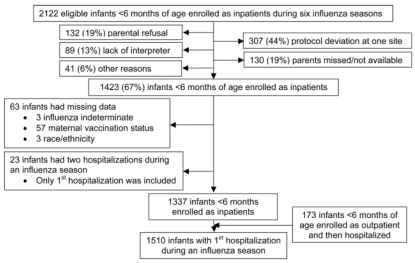

Figure 1.
Study population

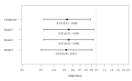

Figure 2.

The odds ratio and 95% confidence interval for the protection provided by influenza vaccination during pregnancy on laboratory-confirmed influenza hospitalizations among infants for unadjusted and adjusted models.

Model 1 includes study year, site, race and ethnicity, gender, age group and timing in influenza season.

Model 2 includes model 1, prematurity and high-risk medical conditions.

Model 3 includes model 1, smoke exposure, daycare, any breast feeding, siblings and insurance status.

Table 1

Characteristics of infants <6 months of age hospitalized with and without laboratory-confirmed influenza.

Characteristic		Total	Influenza +	Influenza −	p-value
			(row %)		
		N=1510	N=151	N=1359	
Maternal Influenza Vaccine	No	1216	133 (11%)	1083 (89%)	0.01
	Yes	294	18 (6%)	276 (94%)	
Influenza Season	Early	572	51 (9%)	521 (91%)	0.51
	Middle	485	50 (10%)	435 (89%)	
	Late	453	50 (11%)	403 (89%)	
Age Group	0 months	399	49 (12%)	350 (87%)	<0.001
	1 month	507	66 (13%)	441 (87%)	
	2–3 months	411	24 (6%)	387 (94%)	
	4–5 months	193	12 (6%)	181 (94%)	
Gender	Female	664	68 (10%)	596 (90%)	0.78
	Male	846	83 (10%)	763 (90%)	
Study Site	Nashville	554	60 (11%)	494 (89%)	0.53
	Rochester	425	44 (10%)	381 (90%)	
	Cincinnati	531	47 (9%)	484 (91%)	
Study Year	2002–2003	99	9 (9%)	90 (91%)	<0.001
	2003–2004	251	38 (15%)	213 (84%)	
	2004–2005	322	40 (12%)	282 (88%)	
	2005–2006	176	16 (9%)	160 (91%)	
	2006–2007	230	8 (3%)	222 (97%)	
	2007–2008	232	29 (13%)	203 (88%)	
	2008–2009	200	11 (6%)	189 (95%)	
Race-ethnicity	White	706	59 (8%)	647 (92%)	0.11
	Black	439	53 (12%)	386 (88%)	
	Hispanic	365	39 (11%)	326 (89%)	
Medical covariates					

Characteristic		Total	Influenza +	Influenza −	p-value
			(row %)		
		N=1510	N=151	N=1359	
Premature	Yes	178	13 (7%)	165 (93%)	0.20
	No	1325	138 (10%)	1187 (90%)	
High Risk Condition	Yes	119	7 (6%)	112 (94%)	0.12
	No	1391	144 (10%)	1247 (90%)	
Social covariates					
Exposed to Smoke	Yes	613	62 (10%)	551 (90%)	0.85
	No	896	88 (10%)	808 (90%)	
# of Siblings	0	341	33 (10%)	308 (90%)	0.10
	1	539	42 (8%)	497 (92%)	
	2	341	43 (13%)	298 (87%)	
	3+	289	33 (11%)	256 (89%)	
Daycare	Yes	152	7 (5%)	145 (95%)	0.02
	No	1356	144 (11%)	1212 (89%)	
Insurance	Public	891	94 (11%)	797 (89%)	0.67
	Private	507	46 (9%)	461 (91%)	
	None	105	10 (10%)	95 (90%)	
Ever Breastfed	Yes	916	97 (11%)	819 (89%)	0.34
	No	594	54 (9%)	540 (91%)	

Percentages may not sum to 100% due to rounding.

Table 2

Characteristics of hospitalized infants < 6 months of age by maternal influenza vaccination status.

Characteristic		Total	Vaccinated	Not Vaccinated	p-value
			(row %)		
		N=1510	N=294	N=1216	
Influenza-positive	No	1359	276 (20%)	1083 (80%)	0.01
	Yes	151	18 (12%)	133 (88%)	
Influenza Season	Early	572	98 (17%)	474 (83%)	0.06
	Middle	485	92 (19%)	393 (81%)	
	Late	453	104 (23%)	349 (77%)	
Age Group	0 months	399	96 (24%)	303 (76%)	<0.001
	1 month	507	92 (18%)	415 (82%)	
	2–3 months	411	88 (21%)	323 (79%)	
	4–5 months	193	18 (9%)	175 (91%)	
Gender	Female	664	123 (19%)	541 (81%)	0.41
	Male	846	171 (20%)	675 (80%)	
Study Site	Nashville	554	84 (15%)	470 (85%)	<0.001
	Rochester	425	142 (33%)	283 (67%)	
	Cincinnati	531	68 (13%)	463 (87%)	
Study Year	2002–2003	99	18 (18%)	81 (82%)	<0.001
	2003–2004	251	25 (10%)	226 (90%)	
	2004–2005	322	43 (13%)	279 (87%)	
	2005–2006	176	31 (18%)	145 (82%)	
	2006–2007	230	45 (20%)	185 (80%)	
	2007–2008	232	57 (25%)	175 (75%)	
	2008–2009	200	75 (38%)	125 (63%)	
Race-ethnicity	White	698	147 (21%)	551 (79%)	0.005
	Black	430	63 (15%)	367 (85%)	
	Hispanic	363	80 (22%)	283 (78%)	
Medical covariates					

Characteristic		Total	Vaccinated	Not Vaccinated	p-value
			(row %)		
		N=1510	N=294	N=1216	
Premature	Yes	178	33 (19%)	145 (81%)	0.73
	No	1325	260 (20%)	1065 (80%)	
High Risk Condition	Yes	119	22 (18%)	97 (82%)	0.78
	No	1391	272 (20%)	1119 (80%)	
Social covariates					
Exposed to Smoke	Yes	613	83 (14%)	530 (86%)	<0.001
	No	896	211 (24%)	685 (76%)	
# of Siblings	0	341	75 (22%)	266 (78%)	0.32
	1	539	108 (20%)	431 (80%)	
	2	341	64 (19%)	277(81%)	
	3+	289	47 (16%)	242 (84%)	
Daycare	Yes	152	29 (19%)	123 (81%)	0.89
	No	1356	265 (20%)	1091 (80%)	
Insurance	Public	891	146 (16%)	745 (84%)	<0.001
	Private	507	137 (27%)	370 (73%)	
	None	105	8 (8%)	97 (92%)	
Ever Breastfed	Yes	916	207 (22%)	709 (77%)	<0.001
	No	594	87 (15%)	507 (85%)	

Percentages may not sum to 100% due to rounding.