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Infant Hospitalizations and Mortality After Maternal Vaccination

Lakshmi Sukumaran, MD, MPH[a], **Natalie L. McCarthy, MPH**[a], **Elyse O. Kharbanda, MD, MPH**[b], **Gabriela Vazquez-Benitez, Ph D**[b], **Heather S. Lipkind, MD, MS**[c], **Lisa Jackson, MD, MPH**[d], **Nicola P. Klein, MD, PhD**[e], **Allison L. Naleway, PhD**[f], **David L. McClure, PhD**[g], **Rulin C. Hechter, MD, PhD**[h], **Alison T. Kawai, ScD**[i], **Jason M. Glanz, PhD**[j], and **Eric S. Weintraub, MPH**[a]

[a]Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, Georgia

[b]HealthPartners Institute, Minneapolis, Minnesota

[c]Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale School of Medicine, Yale University, New Haven, Connecticut

[d]Kaiser Permanente Washington Health Research Institute, Seattle, Washington

[e]Division of Research, Kaiser Permanente of Northern California, Oakland, California

[f]Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon

[g]Marshfield Clinic Research Institute, Marshfield, Wisconsin

[h]Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, California

[l] Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts;

[j]Institute for Health Research, Kaiser Permanente Colorado, Denver, Colorado.

Abstract

BACKGROUND: The Advisory Committee on Immunization Practices currently recommends pregnant women receive influenza and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccines. There are limited studies of the long-term safety in infants for vaccines administered during pregnancy. We evaluate whether maternal receipt of influenza and Tdap vaccines increases the risk of infant hospitalization or death in the first 6 months of life.

METHODS: We included singleton, live birth pregnancies in the Vaccine Safety Datalink between 2004 and 2014. Outcomes were infant hospitalizations and mortality in the first 6 months of life. We performed a case-control study matching case patients and controls 1:1 and used

Address correspondence to Lakshmi Sukumaran, MD, MPH, Immunization Safety Office, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS D-26, Atlanta, GA 30333. sukumaran@cdc.gov.

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conditional logistic regression to estimate odds ratios for maternal exposure to influenza and/or Tdap vaccines in pregnancy.

RESULTS: There were 413 034 live births in our population. Of these, 25 222 infants had hospitalizations and 157 infants died in the first 6 months of life. We found no association between infant hospitalization and maternal influenza (adjusted odds ratio: 1.00; 95% confidence interval [CI]: 0.96–1.04) or Tdap (adjusted odds ratio: 0.94; 95% CI: 0.88–1.01) vaccinations. We found no association between infant mortality and maternal influenza (adjusted odds ratio: 0.96; 95% CI: 0.54–1.69) or Tdap (adjusted odds ratio: 0.44; 95% CI: 0.17–1.13) vaccinations.

CONCLUSIONS: We found no association between vaccination during pregnancy and risk of infant hospitalization or death in the first 6 months of life. These findings support the safety of current recommendations for influenza and Tdap vaccination during pregnancy.

The Advisory Committee on Immunization Practices currently recommends 2 vaccines to be given during each pregnancy; influenza vaccine has been recommended at any time during pregnancy since 2004 to prevent maternal influenza disease and complications[1] and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine has been recommended during each pregnancy since 2012, with a preference for administration between 27 and 36 weeks' gestation, to protect infants from pertussis disease.[2] Given the relative proximity of an immunization administered during pregnancy to a potential infant hospitalization or death, an observed temporal association with maternal influenza or Tdap vaccine during pregnancy and infant death or hospitalization may raise concerns about a possible causal relationship.

Both pertussis and influenza infections are associated with hospitalizations and fatalities in infants, and severity is highest before infants are eligible for the respective vaccines. Approximately half of infants <4 months of age with pertussis require hospitalization, and the majority of deaths from pertussis occur in these infants.[3] In 2014, the US pertussis case rate in infants <6 months of age was 169 per 100 000 infants.[4] Furthermore, there were 8 deaths in infants <3 months of age and 1 death in infants 3 to 11 months of age out of 13 total deaths from pertussis in all age groups in 2014. Similarly, infants are at high risk of hospitalization and death from influenza. The US influenza hospitalization rate ranges from 1.8 to 7.2 per 1000 in infants <6 months of age.[5] For the 2013–2014 influenza season, there were 96 laboratory-confirmed, influenza-associated pediatric deaths, 18 of which occurred in children aged <6 months.[6] Maternal immunization with influenza and Tdap vaccines allows for passive antibody transfer and protection to infants for the respective diseases when they are most vulnerable.[1,2,7]

In 2015, the infant (≤12 months) mortality rate in the United States was 589.5 per 100 000 live births,[8] and the leading causes of infant deaths were (1) congenital malformations, deformations, and chromosomal abnormalities; (2) disorders related to low birth weight and short gestation; and (3) sudden infant death syndrome. In 2010, the leading causes of hospitalizations in infants ≤12 months were (1) acute bronchitis (238 per 10 000 population), (2) jaundice (104 per 10 000 population), and (3) pneumonia (56 per 10 000 population).[9] Although there have been reassuring safety data for influenza and Tdap vaccines in which maternal acute events, pregnancy complications, and birth outcomes were

evaluated,[10–19] there have been limited safety studies beyond the immediate neonatal period.[20–24] Vaccine safety continues to be a primary reason why providers and patients choose not to vaccinate during pregnancy.[25–27] Although the biologic plausibility is unclear for the association of maternal vaccination and infant hospitalization or death, there may be concerns of long-term effects on infants after any pregnancy exposure. In this study, we evaluate whether maternal receipt of influenza and Tdap vaccines increases the risk of hospitalization or death in US infants in the first 6 months of life.

METHODS

Study Population

The Vaccine Safety Datalink (VSD) is a collaboration between the Centers for Disease Control and Prevention and 8 integrated health care systems (sites) and includes vaccination and health care data on ~10 million persons per year.[28] In addition, the VSD includes data on ~ 125 000 pregnant women annually.

We used data on pregnant women from 5 VSD sites with available data that comprise over 90% of the VSD population: Kaiser Permanente Northern California (Oakland, CA), Kaiser Permanente Southern California (Pasadena, CA), Kaiser Permanente Colorado (Denver, CO), Marshfield Clinic Research Foundation (Marshfield, WI), and Kaiser Permanente Northwest (Portland, OR).

We used the validated VSD Pregnancy Episode Algorithm to identify pregnant women.[29] The Pregnancy Episode Algorithm uses comprehensive electronic medical record and administrative databases (including diagnosis and procedure codes, laboratory tests, pharmacy records, and imaging procedures) to identify pregnancies, pregnancy outcomes, and pregnancy start and end dates, and it is able to link pregnant women to their infants. We included women from the VSD with pregnancies ending in a live birth between January 1, 2004, and June 30, 2014. We required pregnant women to be enrolled at a VSD site for the duration of the pregnancy episode and to have at least 1 prenatal care visit. To increase completeness of data, infants of these pregnant women were required to have a birth record and to have VSD site enrollment until 6 months of life or until the time of death. We excluded pregnancies in which a live vaccine was administered because live vaccines are contraindicated in pregnancy. We also excluded infants of multiple gestation pregnancies, infants born before 34 weeks' gestation, and infants with major birth defects because these infants are at a higher risk of hospitalization and death. Furthermore, we excluded all infants who died during their delivery hospitalization because cause of death in these infants is often a perinatal complication (such as placental abruption) that would likely be unrelated to maternal vaccination. Additionally, infants who die during the birth hospitalization may be less likely to be enrolled in the VSD and captured in our data. We also excluded infants with external causes of death (*International Classification of Diseases, 10th Revision* [ICD-10] codes S00-T98 and V00-Y98) and infants with external causes of hospitalizations (*International Classification of Diseases, Ninth Revision* [ICD-9] codes 800–999, E800-E999) due to injury and poisonings because these are unlikely to result from a maternal vaccination. ICD-10 coding was not available for hospitalization diagnoses in the United States during the time of this study.

Case-Control Matching

Among infants meeting inclusion criteria, those infants with hospitalizations or deaths within the first 6 months of life were included in this analysis. Respiratory hospitalization case patients were a subset of hospitalization case patients defined by any respiratory ICD-9 code (033, 460–488, 491–496, 510–519) associated with a hospitalization in the first 6 months of life. For infants with >1 hospitalization, the first hospitalization was selected for each category (ie, first all-cause hospitalization, first respiratory hospitalization). Furthermore, an infant could be included as a death case patient and hospitalization case patient if the infant was hospitalized and later died. In the VSD, deaths are identified from state death records, electronic medical records, and administrative sources, and there is approximately a 1-year lag from the time of death to the availability of state death records. Because of lag time in the death data, we evaluated deaths occurring from January 1, 2004, to December 31, 2013, and hospitalizations from January 1, 2004, to December 31, 2014. Matched controls for the infant mortality analysis were selected among infants in the study who survived the first 6 months of life. Matched controls for the infant hospitalization and respiratory hospitalization analyses were selected from infants without death or hospitalization in the first 6 months of life. All infant controls were required to have at least 1 diphtheria-tetanus-acellular pertussis (DTaP) vaccine recorded between 6 weeks and 6 months of age to ensure infants were accessing the health care system. We matched case patients and controls 1:1 using optimal matching.[30] Case patients and controls were matched on the basis of VSD site, birth month and year (within 1 month), and gestational age groups of late preterm (34–36 weeks), term (37–41 weeks), and postterm (42–44 weeks). With our optimal matching, we successfully found controls for 100% of our case patients by using these parameters.

Vaccinations

The exposure of interest was maternal vaccination with any influenza and/or Tdap vaccines during pregnancy. A vaccine during pregnancy was defined as one given from 7 days after the pregnancy start date to 7 days before the pregnancy end date. These time windows were chosen to avoid including exposures to vaccinations given before or immediately after pregnancy. We stratified vaccine exposures as any influenza vaccine (with or without Tdap), any Tdap vaccine (with or without influenza), and both influenza and Tdap vaccines in the same pregnancy. In our evaluation of maternal influenza vaccine, we also repeated our analysis limiting outcomes to events occurring during the influenza season (October through May), to ascertain any protective findings that may be more evident when influenza virus is circulating. We also did a sensitivity analysis stratifying our exposure by influenza vaccine only and Tdap vaccine only to see if our results would differ by limiting our exposure groups.

Statistical Analysis

We measured rates of influenza and Tdap maternal vaccination in our study cohort from 2004 to 2013. We also measured trends of infant deaths and hospitalizations during this same time period to look for any ecological associations between maternal vaccination and our infant outcomes. For our main analysis, we performed a conditional logistic regression

analysis to estimate the odds of maternal vaccination in matched case patients and controls. In our analysis, we determined a priori to include the following potential confounders from electronic VSD data sources[28]: Kotelchuck Adequacy of Prenatal Care Index,[31] race and ethnicity (non-Hispanic African American or American Indian versus other races and ethnicities), maternal age, pregnancy complications and maternal comorbidities (hemorrhage, hypertensive disorders, renal disease, diabetes, thyroid disease, cardiovascular disease, epilepsy), smoking during pregnancy (yes, no, or unknown), infant DTaP exposure before outcome (or index date in matched controls), duration of birth hospitalization in days, and gestational age at delivery in weeks.

We also reviewed medical records of infants with respiratory related deaths (ICD-10 codes: A37, J00–J99). We reviewed clinical information relating to a potential influenza- or pertussis-related cause of death and laboratory data in the 2-week period preceding death. For influenza laboratory data, we looked for positive influenza A or B rapid antigen, polymerase chain reaction (PCR), viral culture, and direct fluorescent antibody test results in all respiratory death case patients. For pertussis, we looked for positive *Bordetella pertussis* PCR and culture test results for any death case patient with the ICD-10 code A37 (whooping cough).

We determined a priori that with an expected average exposure rate of 15% for both vaccines throughout the study period,[32–34] we would need at least 840 case patients to have 80% power to detect an odds ratio of 1.5. The protocol for this study was approved by the Centers for Disease Control and Prevention Institutional Review Board and institutional review boards at each of the participating VSD sites. All analyses were conducted by using SAS version 9.3 (SAS Institute, Inc, Cary, NC).

RESULTS

During our study period, we identified 500 447 pregnancies ending in a live birth that met enrollment criteria. We excluded 87 413 (17.5%) because of maternal or infant factors (Fig 1). Of the remaining 413 034 infants, 25 222 infants had 1 or more hospitalizations and 157 infants died. Of the hospitalized infants, 4644 (18.4%) had a respiratory cause for their hospitalization; 105 (2.2%) of these infants had an influenza ICD-9 code (487, 488), and 137 (3%) had a pertussis ICD-9 code (033.0, 033.9). Of the deaths, 14 (9%) had a respiratory cause of death; however, none of these deaths were considered to have been caused by influenza or pertussis infections on the basis of our laboratory and medical record review. Of the 157 infants that died, the age at death ranged from 1 to 180 days with a mean of 61 days and a median of 51 days. The most common causes of death were unknown causes (32%), sudden infant death syndrome (21%), and certain conditions originating in the perinatal period (17%).

We analyzed overall trends of influenza and/or pertussis vaccination in pregnancy and trends of infant hospitalization and mortality in our study population from 2004 to 2013 (Fig 2). From 2004, there was an increase in maternal influenza vaccination, which became more dramatic in 2009 after the H1N1 influenza pandemic. Maternal Tdap vaccination increased starting in 2010 when California recommended pregnant women to receive Tdap in

pregnancy in response to the 2010 statewide pertussis epidemic.[35] There was another increase in Tdap vaccination in 2012 after the most recent Advisory Committee on Immunization Practices recommendation to administer Tdap vaccination in every pregnancy.[2] We observed no increase in the infant hospitalization rate or infant mortality rate during the same time period.

We matched case patients with eligible controls and compared characteristics between these groups (Table 1, Supplemental Table 3). Infants who were hospitalized were more likely to have mothers with pregnancy complications, less likely to be delivered by cesarean delivery, and less likely to be of African American non-Hispanic or American Indian race. Mean maternal age, gestational age at delivery, and length of birth hospitalization were statistically significantly different between the groups but not clinically different. Infants who died were similar to matched controls.

In our adjusted analysis, we found no significant association between infant hospitalization or death in the first 6 months of life and receipt of maternal influenza and/ or Tdap vaccines and no significant association between infant hospitalization from respiratory causes and maternal influenza vaccine (Table 2). However, the odds of maternal Tdap vaccination was significantly lower among infants with hospitalizations because of respiratory causes (adjusted odds ratio: 0.79; 95% confidence interval [CI]: 0.67–0.94; $P = .007$) compared with controls without hospitalization. Furthermore, when evaluating infant hospitalizations and death occurring during periods of influenza virus circulation (October through May) and peak influenza virus circulation (November through February), we found no association with maternal influenza vaccine exposure (data not shown). When limiting our exposure groups to women receiving influenza vaccine without Tdap vaccine and Tdap vaccine without influenza vaccine, our results were similar to our main analysis (Supplemental Table 4).

DiSCUSSiON

In our study of maternal influenza and Tdap vaccines, we found no increased risk of infant all-cause hospitalizations, hospitalizations from respiratory causes, or all-cause mortality in the first 6 months of life. Our study helps strengthen the growing evidence of long-term safety of vaccination in pregnancy for infants.

Our findings are similar to other studies that have evaluated infant mortality and morbidity after maternal vaccination in pregnancy, most of which have evaluated the safety of adjuvanted H1N1 influenza-containing vaccines. Studies of short-term infant mortality in the first 7 days of life,[20] growth and development and health care visits for infections in the first year of life,[23] early neonatal or childhood death,[22] and childhood hospitalization rates,[21] have not found an increased risk of these outcomes in children of women who received adjuvanted H1N1 influenza–containing vaccines in pregnancy. Unlike these previous studies, however, our study included women who received any type of influenza vaccine, none of which contain adjuvants in the United States, and we found similar results.

Our findings are also consistent with studies in which researchers have evaluated infant mortality and morbidity after Tdap vaccination in pregnancy. These researchers have

evaluated neonatal mortality,[10,36] NICU admissions,[37] length of hospitalization, ventilation requirement, intraventricular hemorrhage, transient tachypnea of the newborn, neonatal sepsis, pneumonia, respiratory distress syndrome, and convulsions.[36,38] There were no differences in outcomes between infants of Tdap-vaccinated and unvaccinated mothers in these studies. Our study included a longer follow-up period than these previous studies and still showed no increased risk of infant mortality or hospitalization after maternal Tdap vaccination.

Other long-term outcomes that have previously been studied after maternal Tdap vaccination include childhood development scores at 13 months of life,[13] infant growth up to 5 to 7 months of age,[24] and complex chronic conditions at 12 months of age.[17] The researchers for these studies did not find an increased risk of these infant outcomes after maternal Tdap vaccination during pregnancy. Our study managed a larger number of infants and had similar findings to these studies, further demonstrating long-term safety in infants of Tdap vaccine exposure in pregnancy.

We did find a protective association between maternal Tdap during pregnancy and infant respiratory hospitalizations, which is consistent with results of other published studies that have looked at infant pertussis as an outcome.[7,39–42] However, only 3% of infants hospitalized for respiratory causes had a pertussis ICD-9 code. This could indicate that infants with pertussis are not being appropriately diagnosed and tested.[43] It is also possible that other factors (eg, the healthy adherer effect[44] and other differences in people who choose vaccination and those who do not) are contributing to this finding.

This study does have some limitations. The VSD captures data on an insured population, which could translate to better health outcomes than the general population. Additionally, VSD has a high rate of women with adequate prenatal care on the basis of the Kotelchuck index, which can translate to better infant outcomes.[31] A recent study has revealed that despite being a fully insured population, the VSD is comparable to the total US population on many important demographic factors.[45] Moreover, the VSD population size is large, and even groups that typically comprise a smaller proportion of insured populations (ie, lower income populations) still have a substantial (>2 million individuals) presence in the VSD. There may have been bias related to requiring controls to have a DTaP vaccine record to be included in the study. We did this to ensure we had access to health care utilization data to avoid misclassifying case patients as controls. To look for bias, we repeated our analysis of hospitalizations requiring case patients to have a DTaP vaccine (98.0% of case patients) and found similar results to our main findings. We looked at broad safety outcomes (hospitalizations, respiratory hospitalizations, and deaths) and may not capture true increases in a specific outcome, if such an association was present. We relied on vaccination data from our VSD electronic data files and may not have captured vaccines in pregnancy occurring outside the health care system. However, previous internal work looking at influenza vaccination in pregnancy revealed that the VSD vaccine files are over 98% complete in capturing these data (J. Donahue, DVM, PhD, unpublished observations). We did not evaluate the risks of infant hospitalizations and mortality in multiple gestation infants, very preterm infants, and those with major birth defects because these infants are at a much higher risk of the outcomes we studied; therefore, our results are not generalizable to these

populations. Finally, we were sufficiently powered for our outcomes of hospitalizations and hospitalizations from respiratory causes but underpowered for the outcome of death.

This is the first study in which infant hospitalizations and mortality in the first 6 months of life after maternal influenza vaccine and Tdap vaccines are evaluated. In this large case-control study, we found no increased risk of infant hospitalization and death after vaccination in pregnancy.

Our findings support the safety of influenza and pertussis vaccinations during pregnancy for infants of vaccinated mothers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

CI	confidence interval
DTaP	diphtheria-tetanus-acellular pertussis
ICD-9	*International Classification of Diseases, Ninth Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
PCR	polymerase chain reaction
Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis
VSD	Vaccine Safety Datalink

Biography

Dr Sukumaran conceptualized and designed the study, participated in data collection, conducted the analysis, drafted the initial manuscript, and reviewed and revised the manuscript; Ms McCarthy participated in the conceptualization and design of the study, designed the data collection instruments, collected data, participated in the analysis, and reviewed and revised the manuscript; Mr Weintraub participated in the conceptualization and design of the study, participated in the analysis, and critically reviewed the manuscript; Drs Kharbanda, Vazquez-Benitez, Lipkind, Jackson, Klein, Naleway, McClure, Hechter, Kawai, and Glanz contributed to the acquisition and interpretation of data and reviewed and revised the manuscript; all authors critically reviewed the final manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT:

Influenza and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines are recommended in pregnancy. Although there is evidence that these vaccines are safe in pregnant women, there are limited long-term data on infants born to mothers vaccinated during pregnancy.

WHAT THIS STUDY ADDS:

Influenza and tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnancy are not associated with an increased risk of hospitalization or death in infants. Our findings contribute to the knowledge of the long-term safety of vaccination during pregnancy.

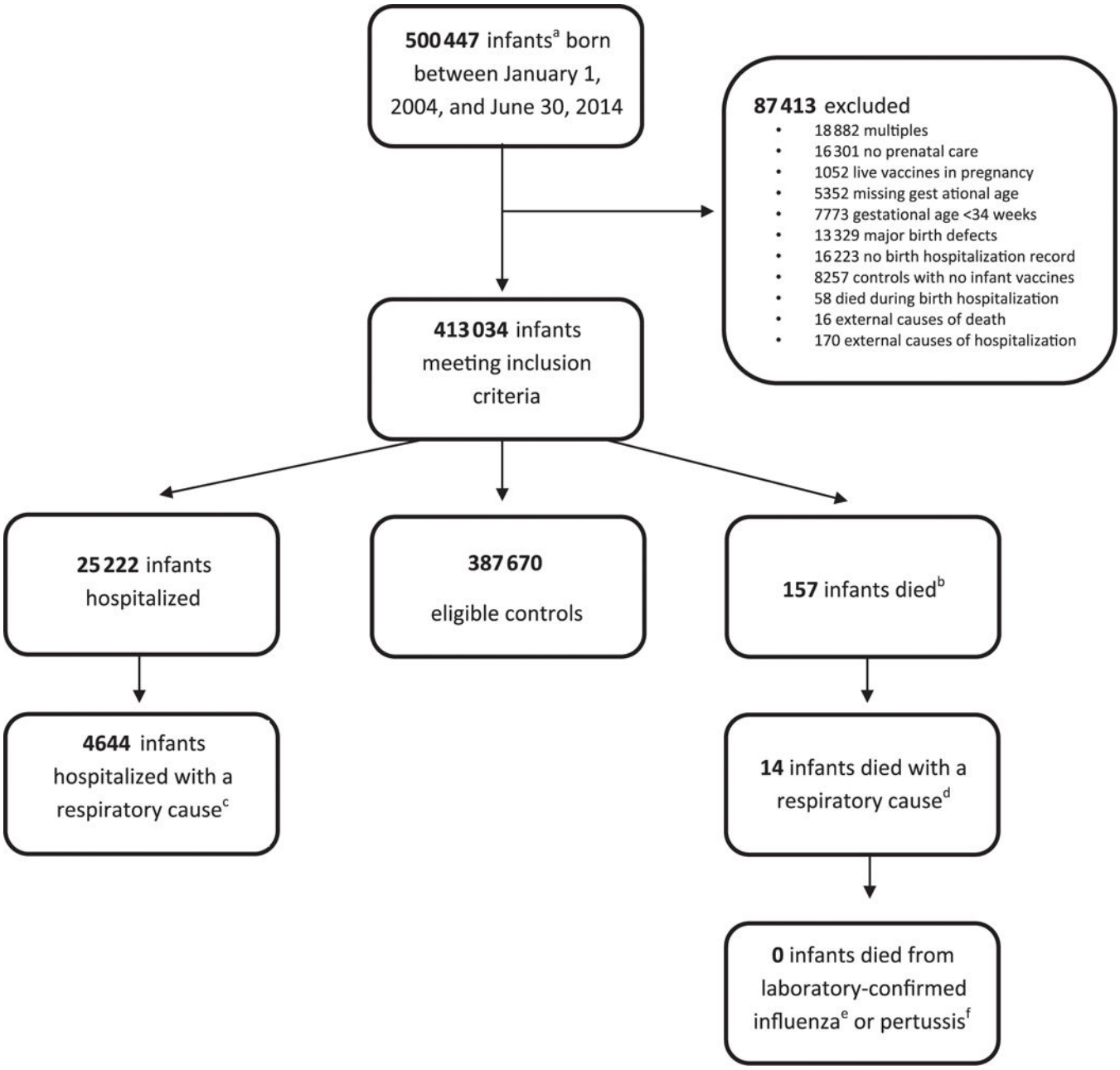

FIGURE 1.

Study population of infants with hospitalization or death in the first 6 months of life in the VSD, 2004–2014. [a] Infants with continuous enrollment in the VSD until 6 months of age or until the time of death whose mothers were enrolled for the duration of their pregnancy. [b] Fifteen infants were hospitalization and death case patients. [c] Defined as ICD-9 codes: 033, 460–488, 491–496, 510–519. [d] Defined as ICD-10 codes: A37, J00–J99. [e] Positive influenza A or B antigen, viral culture, PCR, or direct fluorescent antibody test results within 14 days of hospitalization. [f] Positive *B pertussis* PCR or culture test results within 14 days of hospitalization.

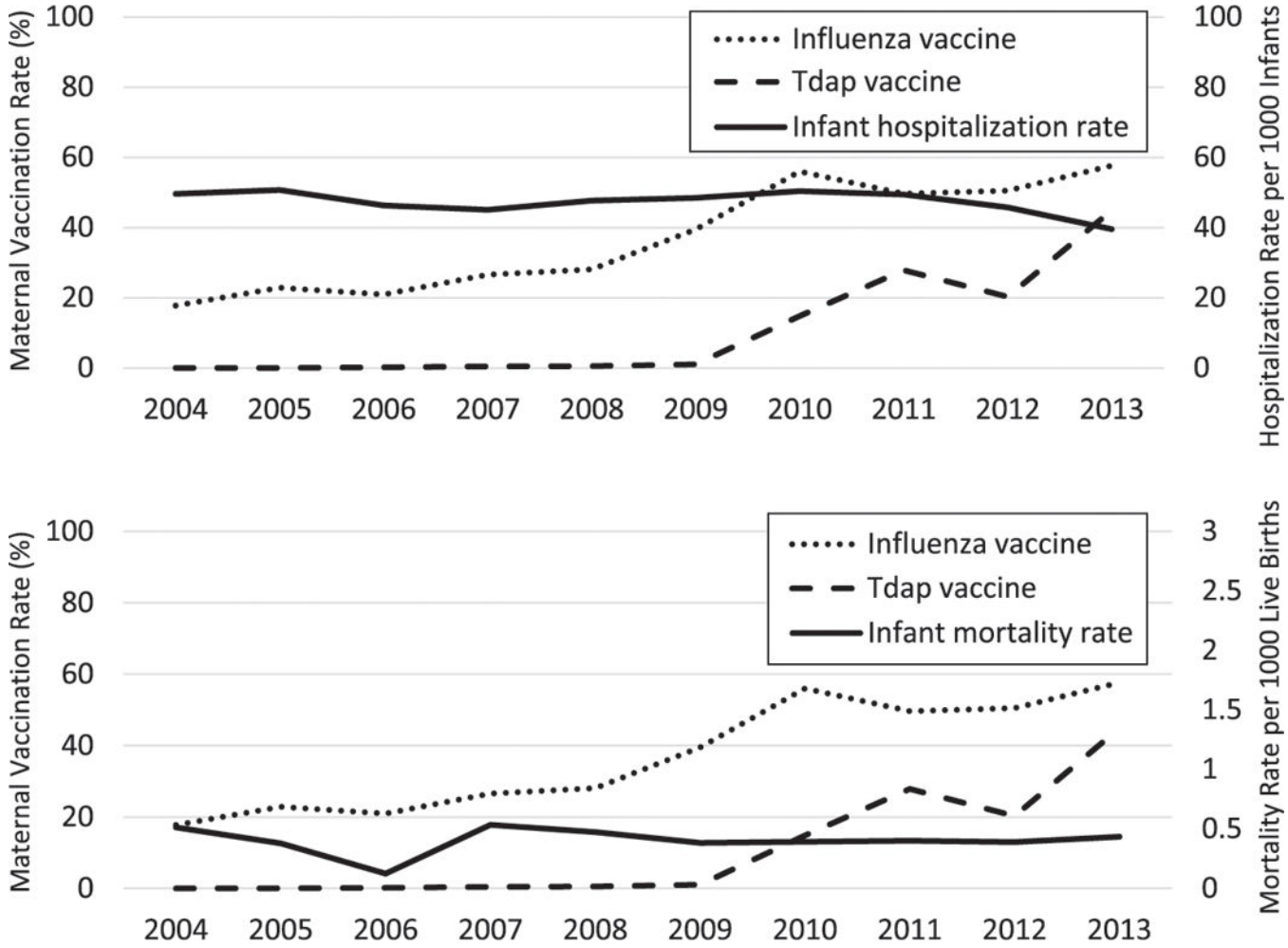

FIGURE 2.

Rates of maternal influenza and Tdap vaccination, infant hospitalization, and infant mortality in the VSD, 2004–2013.

TABLE 1

Characteristics of Matched Case Patients and Controls for Infant Hospitalizations and Mortality in the First 6 Months of Life in the VSD, 2004–2014

	Hospitalization Case Patients (*n* = 25 222)	Matched Controls (*n* = 25 222)	*P*[a]	Death Case Patients (*n* = 157)	Matched Controls (*n* = 157)	*P*
Mean age at event in d (range)	36 (1–183)	—	—	61 (1–180)	—	—
Mean gestational age at delivery in wk (range)	39 (34–43)	39 (34–43)	<.0001	39 (34–41)	39 (34–41)	.88
Mean maternal age in y (range)	31 (13–54)	31 (13–55)	.0005	30 (15–41)	30 (16–41)	.23
Mean length of delivery hospitalization in d (range)	2.2 (0–103)	2.2 (0–110)	<.0001	3.5 (0–41)	2.2 (0–18)	.43
Smoking during pregnancy, %	8.9	9.2	.39	15	10	.35
Pregnancy complications, %[b]	31.0	28.7	<.0001	34	27	.14
Cesarean delivery, %	23.6	27.9	<.0001	36	31	.52
Adequate prenatal care by Kotelchuck index, %[31]	94.2	93.9	.30	92	92	.92
African American non-Hispanic or American Indian race, %	5.9	7.2	<.0001	10	6	.14

—, not applicable.

[a] *P* values calculated by χ^2 tests for categorical variables and Wilcoxon median 2-sample tests for continuous variables.

[b] Pregnancy complications include hemorrhage, hypertensive disorders, renal disease, diabetes, thyroid disease, cardiovascular disease, and epilepsy.

TABLE 2

Matched Case-Control Analysis of Infant Hospitalizations and Death in the First 6 Months of Life in the VSD After Maternal Vaccination, 2004–2014

	1:1 Matched Analysis of Hospitalizations (*n* = 50 444)			1:1 Matched Analysis of Respiratory Hospitalizations (*n* = 9288)			1:1 Matched Analysis of Deaths (*n* = 314)		
Vaccine in pregnancy	Influenza[a]	Tdap[b]	Both[c]	Influenza	Tdap	Both	Influenza	Tdap	Both
Case patients exposed, %	38.7	12.8	8.6	38.4	9.9	7.1	32	6	3
Controls exposed, %	39.3	13.4	9.0	38.1	11.4	7.4	37	12	8
Crude OR (95% CI)	0.97 (0.93–1.01)	0.91 (0.85–0.97)	0.94 (0.87–1.01)	1.02 (0.93–1.12)	0.79 (0.67–0.93)	0.93 (0.78–1.13)	0.81 (0.49–1.31)	0.41 (0.17–0.99)	0.25 (0.07–0.89)
aOR[d] (95% CI)	1.00 (0.96–1.04)	0.94 (0.88–1.01)	0.97 (0.90–1.05)	1.08 (0.97–1.19)	0.79 (0.67–0.94)	0.97 (0.80–1.17)	0.96 (0.54–1.69)	0.44 (0.17–1.13)	0.32 (0.08–1.24)
P[e]	.93	.09	.44	.15	.007	.73	.87	.09	.10

aOR, adjusted odds ratio; OR odds ratio.

[a] Influenza vaccine in pregnancy given with or without Tdap vaccine.

[b] Tdap vaccine in pregnancy given with or without influenza vaccine.

[c] Both influenza and Tdap vaccines given in the same pregnancy.

[d] Adjusting for pregnancy complications, adequacy of prenatal care, smoking during pregnancy, race, maternal age, infant DTaP receipt before event, length of birth hospitalization in days, and gestational age at delivery in weeks.

[e] *P* values correspond to the aOR.