Title

Pertussis among the youngest infants in California: Evaluating the effectiveness of prenatal Tdap vaccination and identifying infants at greatest risk of disease

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Pertussis among the youngest infants in California: Evaluating the effectiveness of prenatal Tdap vaccination and identifying infants at greatest risk of disease

by

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University of California, Berkeley

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Abstract

Pertussis among the youngest infants in California:
Evaluating the effectiveness of prenatal Tdap vaccination and identifying infants at greatest risk of disease

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Doctor of Philosophy in Epidemiology

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Pertussis (whooping cough) is a respiratory infection caused by the bacterium *Bordetella pertussis* that results in prolonged cough illness often characterized by paroxysms, followed by an inspiratory "whoop". Nearly all severe and fatal cases of pertussis occur in infants younger than three months of age, who are too young to be protected through active immunization. To help protect infants from pertussis during this vulnerable period in their first few weeks of life, women are recommended to receive a pertussis vaccine booster (Tdap) at the start of the third trimester of each pregnancy to optimize transplacental transfer of antibodies to the fetus. This recommendation was made by the Advisory Committee on Immunization Practices in 2013 based on immunogenicity data, and no studies in the United States have yet evaluated the effectiveness of this strategy in reducing pertussis incidence among infants.

The objectives of this research are to evaluate the effectiveness of prenatal Tdap vaccination in both preventing pertussis and reducing severity of illness in infants, characterize infants at greatest risk of pertussis in California, and identify risk factors for pertussis among Hispanic and non-Hispanic infants.

Chapter 1 summarizes the current literature and presents background information for pertussis and pertussis vaccines to provide the context for this research.

Chapter 2 evaluates the impact of prenatal Tdap vaccination on the risk of pertussis in infants within the first few weeks of life among the cohort of women who gave birth in California from January 1, 2013 through December 31, 2014. I demonstrate that Tdap vaccination received during pregnancy is 85% effective at preventing pertussis in infants younger than eight weeks of age compared to Tdap vaccination received postpartum. Additionally, I present data to support the current ACIP recommendation to administer Tdap between 27-36 weeks gestation.

Chapter 3 includes a retrospective evaluation of the cohort of infants in California who were reported with pertussis before three months of age from January 1, 2013 through December 31, 2014. I determine that infants whose mothers received Tdap vaccine during pregnancy had a lower risk of hospitalization or intensive care unit admission and had shorter hospital stays compared to infants born to unvaccinated mothers, indicating an impact of prenatal Tdap vaccination on pertussis severity. Tdap vaccination during pregnancy was determined to be 58% effective at preventing hospitalization among infants with pertussis.

Chapter 4 presents a case-control study in which I describe pertussis cases in infants younger than four months of age and evaluate maternal and infant characteristics associated with pertussis among Hispanic and non-Hispanic infants. Additionally, I evaluate the relationship between maternal parity, a proxy for the number of siblings, and risk of pertussis and determine that infants of all racial/ethnic groups whose mothers are of higher parity are more likely to be reported with pertussis in the first four months of life compared to first-born infants, with the odds of pertussis increasing with higher maternal parity. Case-infants of all racial/ethnic groups were also more likely to have younger mothers who were born in 1997 and later and who likely only ever received DTaP vaccines during childhood. Maternal age and parity largely explain the increased risk of pertussis observed among Hispanic infants.

Finally, chapter 5 summarizes the major findings of each chapter, provides a conclusion and suggests future directions.

The data used in this dissertation are both unique and robust as the dissertation includes matched surveillance, immunization and vital records data from the entire state of California for multiple years, capturing a peak in disease incidence. More pertussis hospitalizations and deaths have occurred in California in recent years than in any other state, so this is an ideal setting in which to evaluate severe cases of pertussis. Ultimately, this research will assist in targeting vaccination policies to prevent severe disease in the most vulnerable populations.

Dedication

I dedicate this dissertation to my partner, Steve, and to our children, Wesley, Perianne and Iris, whose love, support and encouragement have carried me from the beginning to the end of this journey.

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And finally, I would like to acknowledge all of the children and families affected by pertussis in California and hope that this research helps contribute to the end of vaccine-preventable infant deaths from pertussis.

Chapter 1:
Background on pertussis and pertussis vaccines

Epidemiologic features of pertussis

Pertussis, also known as whooping cough, is a disease caused by respiratory infection with the bacterium *Bordetella pertussis*; infection results in a wide spectrum of clinical manifestations depending on the age and immune status of the host. Classic pertussis begins with runny nose and occasional cough for one to two weeks (the catarrhal stage) and then progresses into a prolonged cough illness, often characterized by paroxysms sometimes followed by an inspiratory "whoop" (the paroxysmal stage). The cough often lasts six weeks or more, which is why pertussis is known as the "hundred day cough" in some countries[1]. Pertussis is spread easily, especially within households, via aerosolized droplets; the secondary attack rate among susceptible household contacts is estimated to be 80%[2] and a recent estimate indicates a reproduction number (R_0) of around 5.5 in the post-vaccination era[3].

Pertussis is cyclical, with peaks in incidence occurring every two to five years. Prior to the initiation of routine immunization in the late 1940s, an estimated 115,000-270,000 cases of pertussis and 5,000-10,000 pertussis-related deaths were reported each year in the United States[4]. Since the 1980's, the incidence of pertussis has been increasing nationwide, with each cyclic peak surpassing in magnitude that of prior years. California experienced an epidemic of pertussis in 2010, with over 9,100 reported cases, 808 hospitalizations and ten deaths; all of the deaths were in infants younger than three months of age[5]. More recently, California experienced another epidemic of pertussis in 2014, with over 11,000 reported cases, more than had been reported in a single year in the preceding 70 years[6].

Pertussis remains a major cause of morbidity and mortality globally. The most recently available estimates from the World Health Organization suggest approximately 16 million cases of pertussis occurred worldwide and that nearly 200,000 children died from the disease in 2008[7].

Pertussis in infants

Most severe and fatal cases of pertussis occur in infants younger than three months of age; in these infants, disease onset typically appears mild and cough is not always noticeable but often leads to apnea and hypoxia[8,9]. In the U.S., over 60% of infants less than 12 months of age with pertussis are hospitalized, and nearly all pertussis-related deaths occur in infants younger than four months of age[10,11]. In infants with pertussis who require intensive care, common complications include bacterial pneumonia, extreme leukocytosis and pulmonary hypertension, leading to case fatality proportions as high as 70%[12,13,14].

Routine infant immunization against pertussis is recommended by the Advisory Committee on Immunization Practices (ACIP) of the United States; however, the first

dose of pertussis vaccine is not recommended until two months of age, and infants are not considered fully protected until after receipt of three doses at six months of age.

Risk factors for pertussis and the Hispanic disparity

Prior studies have evaluated risk factors for pertussis and pertussis deaths. In one study of pertussis cases, female sex, birth weight less than 2,500 grams, and maternal education of less than 12 years were independently associated with the risk of pertussis or pertussis death[15]. Previous small studies have assessed pertussis deaths among infants, and several have shown that leukocytosis with lymphocytosis and pneumonia are commonly observed among severe pertussis cases, and are significantly associated with the risk of a fatal outcome [16,17,18,19,20,21]. A recent case-control study in California evaluated characteristics and treatments associated with death among infants with pertussis and found that fatal cases had significantly higher white blood cell counts, younger gestational ages and lower birth weights and were less likely to have received macrolide antibiotics compared to non-fatal cases[22].

Since 1990, higher rates of pertussis, hospitalization for pertussis, and pertussis-related deaths have been reported among Hispanic infants compared to infants of other racial and ethnic groups[23]. During the 2010 pertussis epidemic in California, the rate ratio for pertussis in Hispanic infants less than six months of age compared to white, non-Hispanic infants less than six months of age was 2.3, and the case fatality rate ratio was 4.1[24]. Reasons for the increased risk of pertussis among Hispanic infants are unknown. Undervaccination among Hispanic infants is not a likely cause, as data from the National Immunization Survey indicate that Hispanic children generally are not less likely than children of other racial/ethnic groups to have received pertussis vaccine, and the higher risk of pertussis among Hispanic infants is diminished by 6-12 months of age (CDPH, unpublished data), after infants are protected from the primary series of pertussis vaccination[25].

A leading hypothesis is that the Hispanic overrepresentation among infant pertussis cases may be driven by the larger average household size observed among Hispanic families, as young infants in such settings have greater opportunities for exposure. A recent study in Oregon[26] found that increasing household size was associated with a greater risk of pertussis, providing evidence to support this hypothesis; however, this small study included only 23 Hispanic case-infants, therefore a larger study is needed to further evaluate this association and simultaneously examine other risk factors for pertussis among Hispanic infants.

Pertussis vaccines

The first pertussis vaccine licensed in the United States was a highly effective, inactivated whole-bacterial-cell-derived vaccine that was combined with diphtheria and tetanus toxoids (DTwP); it was administered on a three-dose schedule at two, four and six months of age, with two booster doses at 18 months and four years of age. DTwP successfully reduced the incidence of reported pertussis cases and deaths but was associated with frequent local reactions at the site of injection, as well as perceptions that it caused more severe neurologic side effects, such as febrile seizures[27]. Vaccine

safety concerns eventually led to the development and use of a new, less reactogenic acellular vaccine and suspension of the use of DTwP in the United States and a number of other wealthy countries[28]. Two acellular pertussis (aP) vaccines have replaced DTwP vaccine in the United States. They contain three or five purified antigens: pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN) and fimbrae (FIM) 1 and 3[29]. Acellular pertussis vaccines were first recommended for use in the United States in 1992 for the fourth and fifth booster doses, and then for all five doses in 1997. As a result, persons born in the United States who are now 19-20 years of age or younger have received only acellular pertussis vaccines.

Neither vaccination nor *B. pertussis* infection confers lifelong immunity. Immunity following natural pertussis infection wanes in 4-20 years, while immunity to pertussis following DTwP immunization is estimated to wane over 4-12 years; therefore, even when DTwP vaccine was used, adolescents and adults vaccinated in infancy had waning immunity to the disease although no pertussis vaccine was licensed for use in persons older than six years of age[30]. In 2005, a vaccine containing reduced pertussis antigen combined with tetanus and diphtheria toxoids (Tdap) was licensed and recommended by ACIP for routine use as a single booster dose in adolescents 11-12 years of age, and in place of one tetanus-diphtheria (Td) booster in older adolescents and in adults 19-64 years of age[31].

Immunologic response to acellular pertussis vaccines and waning immunity

Studies indicate that antibody levels and immunity induced by DTaP vaccine are high immediately following vaccination but wane within a few years, faster than expected when the vaccine was licensed and faster than antibodies generated in response to DTwP vaccine[32,33,34]. Additionally, recently published data on the duration of clinical protection induced by Tdap show similar rapid waning of immunity[35,36]. Two studies also suggest that vaccine-induced immunity wanes faster in children and adolescents who are in the cohort born during or after 1997 and have received only acellular pertussis vaccines (DTaP and Tdap)[37,38].

Antibodies to pertussis toxin (PT) are thought to play a major role in protection against pertussis[39,40] but the role of antibodies to the other aP vaccine antigens is less clear. Recently, strains of *B. pertussis* that do not express the antigen pertactin have been identified in the United States and other countries[41,42]. It is unknown to what extent the increase in such strains is contributing to the increased incidence of reported pertussis, the lower vaccine effectiveness, and the faster waning of immunity that have been documented in epidemiologic studies.

Pertussis vaccination of pregnant women

Although older children, adolescents and adults typically do not develop severe disease from pertussis infection, studies have demonstrated that the most common sources of *B. pertussis* infection for most infants are parents and other household contacts, including older siblings and caretakers, with mild or unrecognized pertussis[43,44,45]; the majority of whom had been previously immunized with pertussis vaccine. In 2006, ACIP

recommended the “cocooning” strategy, which includes administering Tdap vaccine to mothers in the immediate postpartum period, as well as other close contacts of infants with the goal of preventing transmission to vulnerable infants before they are protected through primary immunization. However, data to demonstrate the effectiveness of this strategy and determine whether Tdap reduces transmission of *B. pertussis* are lacking.

Very young infants have immature immune systems and do not have the ability to mount a cell-mediated response; as a result, they are reliant on passively-acquired maternal antibodies for protection against pathogens like *B. pertussis*[46]. Antibodies to PT and FHA are actively transported across the placenta, providing the infant with concentrations of antibody comparable to or higher than serum antibody concentrations in the mother[47], suggesting that vaccinating pregnant women with Tdap may confer protection to the infant. Studies that have evaluated the persistence of antibodies after a dose of Tdap indicate that levels peak in the mother during the first month after vaccination and quickly decay by one year post-vaccination[48,49]. Additionally, one study evaluating pertussis antibody concentrations at birth in mother-infant cord blood samples determined that most infants did not have sufficient antibody concentrations to confer protection, despite maternal Tdap vaccination within the prior two years[50]. Therefore, there is a need to revaccinate previously-immunized women with Tdap during each pregnancy in order to achieve sufficiently high maternal antibody concentrations to provide passive protection to the newborn baby.

In October 2011, ACIP recommended that all women receive Tdap vaccine during pregnancy if they had not previously received it, with the primary goal of protecting the infant during the first few weeks of life through the transfer of maternal antibodies across the placenta to the infant[51]. In February 2013, ACIP modified the recommendation to state that all women should receive Tdap vaccine during each pregnancy, preferably between 27 and 36 weeks gestation, regardless of their prior vaccination history[52]. This strategy is now preferred over cocooning because it provides direct protection to the infant.

The uptake of this vaccine recommendation among obstetricians and gynecologists and Tdap vaccine coverage among pregnant women in California is unknown but, until recently, was thought to be relatively low[53]. Among pregnant women enrolled in Northern California Kaiser Permanente, receipt of Tdap was estimated at 15.9%, 30.0% and 19.5% during 2010, 2011 and 2012, respectively[54]. Similarly, in a survey conducted at 100 birthing hospitals in California during October 2013, only 25% of new mothers reported receiving Tdap during pregnancy, whereas an additional 44% received Tdap in the hospital after delivery (CDPH, unpublished data, 2013). However, efforts to increase vaccine coverage have been successful among Northern California Kaiser Permanente patients; starting in the third quarter of 2014, an estimated 84% of pregnant women received Tdap vaccine in their third trimester (T. Flanagan; Northern California Kaiser Permanente; personal communications; November 26, 2014). Studies have shown that offering vaccine to pregnant women on-site during routine prenatal care visits results in the greatest uptake[55]. It is possible that concerns about the safety of administering this vaccine during pregnancy have slowed vaccine uptake; however,

several recent studies have evaluated maternal and infant outcomes among women who received Tdap vaccine during pregnancy and have not identified any significant risk to mothers or their infants[56,57,58].

The prenatal Tdap recommendation by ACIP was made based on immunogenicity data alone and no studies in the U.S. have demonstrated the effectiveness of this strategy in reducing the incidence of pertussis among infants. Recent data indicate that infants born to women who received Tdap either during or after pregnancy had a reduced risk of pertussis in Australia,[59] and that maternal Tdap vaccination during pregnancy was 91% effective at preventing pertussis among infants younger than two months of age in the United Kingdom[60,61]. These data are encouraging and suggest that this vaccination strategy will protect many infants from pertussis in the first weeks of life. However, more data are needed to evaluate the effectiveness of this strategy, especially among women and infants in the United States.

The timing of Tdap administration during pregnancy is likely critical to maximizing protection in the infant. A minimum of two weeks is needed after Tdap vaccination before a substantial immune response is achieved[62], and active transport of IgG antibodies across the placenta takes place primarily after 30 weeks of gestation[63]. Therefore, to ensure sufficient antibody transfer to the fetus prior to delivery, the optimal timing of vaccination is likely to be early in the third trimester.

In a recent study evaluating young infants with pertussis, infants who received even one dose of DTaP vaccine had a lower risk of death[64]. Similarly, it may be the case that among infants born to women who received Tdap vaccination during pregnancy, even those who do not achieve high enough levels of anti-pertussis antibodies to prevent illness with *B. pertussis* may still be protected against severe disease and death. Antibody to PT is the most critical component of the immune response in preventing the extreme leukocytosis that can lead to irreversible pulmonary hypertension and poor outcomes in young infants[65]. Therefore, an important question that has not yet been answered is whether infants with pertussis born to women who received Tdap vaccine during pregnancy have less severe disease and better clinical outcomes, compared to infants born to unvaccinated mothers.

<u>The baboon model for pertussis</u>

A recently described baboon model has been established as an effective mimic of pertussis disease in humans[66]. A major finding using this model is that the host immune response to natural *B. pertussis* infection results in near-sterilizing immunity, preventing re-colonization of the nasopharynx in the convalescent phase[67]. However, while receipt of acellular pertussis vaccine protected against signs of severe clinical disease in baboons, it did not prevent infection with *B. pertussis* and did not prevent transmission to contacts[68]. If these findings are translatable to humans, then infected persons who have received only acellular pertussis vaccine may be able to spread *B. pertussis* and infect others, even if asymptomatic, suggesting that even recently vaccinated household contacts who do not show signs of pertussis could spread *B. pertussis* to vulnerable infants.

Another important finding from the baboon model studies is that maternal vaccination with aP vaccine during the third trimester protected five to six week-old infant baboons from leukocytosis but not colonization with *B. pertussis* following direct challenge with the organism; all vaccinated infant baboons (n=7) were protected from signs of pertussis illness whereas, all control infant baboons (n=3) developed severe or fatal disease[69]. If the same is true for humans, then infants born to women who are vaccinated during pregnancy may, despite becoming infected with *B. pertussis*, be protected from severe disease and death. More needs to be understood about asymptomatic *B. pertussis* infection in human infants and the role of asymptomatic transmission of *B. pertussis* by recipients of acellular pertussis vaccine. However, these findings highlight the critical need to protect infants during the early weeks of life through passively-acquired maternal antibody rather than through cocooning.

Contributions of research

The incidence of pertussis is increasing in the U.S. and in many other countries; therefore, it is critical to understand the reasons for this resurgence and identify strategies to prevent severe disease and death. We expect to see large numbers of pertussis cases in children and adolescents who have received only acellular pertussis vaccine, and this cohort is increasing in size each year, making the risk of transmission of *B. pertussis* to infants an ever-increasing problem. In this era of changing epidemiologic features of pertussis, data are needed to identify populations most at risk of the disease and to formulate strategies that effectively prevent transmission to vulnerable infants.

The objectives of this research are: 1) to evaluate the impact of maternal Tdap vaccination during pregnancy on pertussis illness and severity in infants [Chapters 2 and 3] and 2) to identify infants at greatest risk of pertussis by evaluating risk factors among Hispanic and non-Hispanic infants and evaluating the impact of parity and maternal age on risk of pertussis [Chapter 4]. There are no published data in the United States demonstrating the effectiveness of maternal Tdap vaccination during pregnancy in preventing pertussis or in mitigating severe disease in infants, so the findings from this study will be critically important in evaluating and possibly revising national vaccination policy. Additionally, vaccine advisory committees in other countries, such as Canada, are considering adoption of a prenatal Tdap vaccine recommendation, so these data may help inform vaccination policies globally.

For decades, Hispanic infants have been shown to be at greatest risk of pertussis, although the reasons for this disparity remain unclear. The findings from Chapter 4 will identify risk factors associated with pertussis among Hispanic and non-Hispanic infants and will provide important information in understanding the relationship between maternal parity, a proxy for household size, and risk of pertussis.

California is the ideal location for conducting these studies, as it has a large and diverse population that has recently experienced a pertussis epidemic, and there is widespread awareness of pertussis among the general public and medical providers. Additionally,

the use of multiple data sources and a large birth cohort across several years provides a large and rich dataset with accurate data concerning the exposure, outcome and covariates. Ultimately this research will serve to provide new evidence to help protect vulnerable infants too young to be vaccinated, who are at greatest risk of severe disease and death from pertussis.

Human subjects considerations

These studies were reviewed by the California Department of Public Health Committee for the Protection of Human Subjects and the University of California, Berkeley Committee for the Protection of Human Subjects. All surveillance, medical record and electronic data were maintained on a secure server and/or in locked cabinets within the California Department of Public Health where only authorized personnel have access.

Chapter 2:
Effectiveness of maternal Tdap vaccination in preventing pertussis among young infants: A comparison of prenatal versus postpartum vaccination

ABSTRACT

Background: Most severe and fatal cases of pertussis occur in infants younger than eight weeks of age, before initiation of the primary pertussis vaccine series. To help protect infants from pertussis during this vulnerable period, women are recommended to receive Tdap vaccine at the start of the third trimester of each pregnancy to optimize transplacental transfer of antibodies to the fetus. This recommendation was made by the Advisory Committee on Immunization Practices based on immunogenicity data, and no studies in the United States have yet evaluated the effectiveness of this strategy in reducing pertussis incidence in infants.

Methods: I evaluated a cohort of mothers with documented Tdap vaccination histories in the California Immunization Registry (CAIR) to determine if infants whose mothers received Tdap vaccine between 27 and 36 weeks gestation had a lower risk of pertussis in the first eight weeks of life, compared to infants born to women who received Tdap vaccine postpartum.

Results: Prenatal Tdap vaccination during 27-36 weeks gestation was found to be 85% more effective at preventing pertussis in infants younger than eight weeks of age compared to Tdap vaccination postpartum. Vaccination received during 27-36 weeks gestation was more effective at preventing pertussis in infants than vaccination received prior to 27 weeks or after 36 weeks gestation.

Conclusions: Tdap vaccination during 27-36 weeks gestation was 85% more effective at preventing pertussis in infants younger than eight weeks of age compared to Tdap vaccination postpartum. Efforts should be made by prenatal care providers to provide Tdap vaccine to pregnant women during routine prenatal visits at the earliest opportunity between 27-36 weeks gestation.

INTRODUCTION

Very young infants are at greatest risk of severe disease and death from pertussis. Infants too young to be vaccinated are reliant on passively-acquired maternal antibodies for protection against pertussis[70]. It has been demonstrated that in women who receive Tdap vaccine during pregnancy, antibodies to *B. pertussis* antigens are actively transported across the placenta to the infant, making it possible that giving Tdap to pregnant women may confer direct protection against pertussis to the infant[71].

With the primary goal of protecting infants during the first few weeks of life, the Advisory Committee on Immunization Practices (ACIP) recommends that all women in the United States receive Tdap vaccine during each pregnancy, preferably between 27 and 36 weeks gestation, and regardless of their prior Tdap vaccination history;[72,73]. This strategy is preferred over postpartum vaccination because it provides direct protection to the infant. The timing of Tdap administration during pregnancy is likely critical to maximizing antibody transfer to the infant. Active transport of IgG antibodies across the placenta takes place primarily after 30 weeks of gestation[74] and after Tdap vaccination, a minimum of two weeks is required before a substantial immune response is achieved[75]; antibody concentrations are thought to decline rapidly[76]. One recent study found that women vaccinated between 13 and 25 weeks of pregnancy transferred higher concentrations of anti-pertussis antibodies to their infants compared to women vaccinated after 26 weeks gestation, and suggests that the optimal window of vaccination is likely between 13 and 33 weeks gestation[77].

Recent observational studies evaluating pertussis trends indicate that infants born to women who received Tdap either during or after pregnancy had a reduced risk of pertussis in the United Kingdom[78] and Australia[79]. A case-control study in the United Kingdom also found that maternal Tdap vaccination during pregnancy was 91% effective at preventing pertussis among infants younger than two months of age[80]. However, this study included only 10 case-mothers and 39 control-mothers who had received Tdap vaccine during pregnancy. Results from these studies are encouraging and suggest that this vaccination strategy will protect many infants from pertussis in the first weeks of life. However, more data are needed to demonstrate the effectiveness of this strategy, especially among women and infants in the United States.

I evaluated a cohort of mothers with documented Tdap vaccination histories in the California Immunization Registry to determine if infants whose mothers received Tdap vaccine during pregnancy between 27 and 36 weeks gestation had a lower risk of pertussis in the first weeks of life, compared to infants born to women who received Tdap vaccine postpartum. The goal of this study was to assess whether prenatal Tdap vaccination is more effective than postpartum Tdap vaccination in reducing risk of pertussis in infants.

Data Sources

Pertussis surveillance data: By California statute, laboratories and clinicians in California must report suspected cases of pertussis to local public health departments;

all cases with an acute cough illness meeting the Council of State and Territorial Epidemiologists (CSTE) clinical case definition of pertussis or with laboratory detection of *B. pertussis* by culture or polymerase chain reaction (PCR) are subsequently reported to the California Department of Public Health (CDPH). Local health department investigators complete case report forms containing demographic, clinical, laboratory and epidemiologic data collected through patient and provider interviews and medical record reviews. Additionally, for hospitalized cases occurring in young infants, medical records are requested and reviewed by CDPH staff to ensure accuracy of the surveillance data. Surveillance data for all pertussis cases reported in California are maintained by the CDPH Immunization Branch.

California Immunization Registry (CAIR): The CDPH Immunization Branch, in conjunction with local health jurisdictions, maintains an immunization registry of California residents. Participation in the registry is optional for providers, but many large health systems and pharmacy chains report doses to CAIR either through direct entry or electronic exchange of immunization records from electronic health records. As of the second quarter of 2015, there were approximately ten million patient records in CAIR (S. Nickell, CDPH Immunization Branch, personal communication; October 19, 2015).

Birth certificate data: The CDPH Center for Health Statistics maintains the vital statistics of all live births occurring in California. The annual birth statistical master file contains linked records for all infants born in California during the calendar year and their mothers, including information on demographic characteristics (i.e., race and ethnicity, age, residence) for both parents, as well as pregnancy and delivery characteristics.

METHODS

I used a retrospective cohort study design to evaluate the impact of Tdap vaccine receipt during pregnancy on the risk of pertussis in young infants. To construct the cohort, I obtained all Tdap vaccine doses administered to women 14 to 44 years of age during January 1, 2012 through December 31, 2015 that were recorded in CAIR. These data were linked to birth certificate data for all women with a live birth in California from January 1, 2013 through December 31, 2014 to identify women with a recorded Tdap vaccine dose administered during the pregnancy or within 14 days postpartum, using a matching algorithm consisting of a combination of the following variables: mother's name, mother's date of birth, and mother's address and city of residence. The corresponding infants from this birth cohort were matched to pertussis surveillance data to identify infants born in 2013 or 2014 who were reported to CDPH with pertussis at <12 months of age at the time of disease onset, using a matching algorithm consisting of a combination of the following variables: infant's name, infant's sex, infant's date of birth, city and county of residence, mother's name, and father's name to determine if the infant developed pertussis. All matches were reviewed for accuracy.

The Tdap dose was determined to have occurred during pregnancy if it was administered before the date of birth for the infant and after the date of last menses, as recorded on the birth certificate. Week of gestation for Tdap dose administration was

calculated as the number of weeks between the date of last menses reported on the birth certificate and the date of the recorded Tdap dose in CAIR. When a missing or invalid date of menses was recorded on the birth certificate, gestational age at time of Tdap administration was estimated using the number of weeks from the recorded Tdap dose and the obstetric estimate of gestational age at the infant's birth. Doses were considered to be postpartum if they were administered 0 to 14 days after the birth of the infant.

The primary exposure was coded as a binary variable. Infants were considered exposed if their mother had a record of receiving Tdap vaccine between 27 and 36 weeks gestation during the pregnancy for the infant and unexposed if the mother received Tdap vaccine 0-14 days postpartum. Infants of women who received Tdap vaccine postpartum were used for the comparator group because their mothers were unlikely to have received Tdap during pregnancy and to have been misclassified as unexposed. Infants whose mothers received Tdap vaccine during pregnancy but before 27 weeks or after 36 weeks gestation were excluded from analysis of the primary exposure but were retained in the analysis of the secondary exposure.

The secondary measure of exposure was less restrictive and was also coded as a binary variable. Infants were considered exposed if their mother had a record of receiving Tdap vaccine at any gestational age during the pregnancy for the infant and unexposed if the mother received Tdap vaccine 0 to 14 days postpartum.

The primary outcome of interest was pertussis illness in the infant occurring within the first eight weeks of life. This outcome was determined by the presence of a case report of pertussis for the infant in the CDPH surveillance database. Individual-level explanatory variables were selected based upon the findings of prior studies and the information available in the vital statistics database and included: maternal age, maternal race and ethnicity, number of prior births, payer for prenatal care, and infant sex, birth weight and gestational age.

A secondary outcome was pertussis in the infant occurring $\leq$12 weeks of life. For this analysis, infants were excluded if they were reported to have had pertussis occurring $\geq$13 weeks of age because pertussis in this age group may be attributable to missing or delayed doses of the primary DTaP series, and information concerning infant's DTaP vaccination history was not available for this cohort. Furthermore, infants with pertussis at $\geq$13 weeks of age tend to have better outcomes, require fewer medical interventions and have shorter, or no, hospitalization stays.

Bivariate comparisons of maternal and infant characteristics between mother-infant pairs with Tdap administered during pregnancy to those in whom vaccine was administered postpartum were calculated using Chi-square tests for categorical variables and associated relative risk (RRs) and 95% confidence intervals (CIs) constructed. Two-sided p-values were calculated using analysis of variance for normally distributed continuous data or the Wilcoxon-Mann-Whitney test for non-

normally distributed continuous variables and the Cochrane-Armitage test to evaluate trends.

Multivariate logistic regression was used to calculate the odds ratio (OR) and 95% CI of pertussis among infants whose mothers received Tdap vaccine during pregnancy compared to infants whose mothers received Tdap vaccine postpartum, controlling for potential confounding. Covariates found to be significant at $p<0.05$ level in the bivariate analysis were included in the multivariate models. Four models were constructed to evaluate the primary and secondary exposures and outcomes:

1a. Exposure: Tdap at 27-36 weeks gestation
Outcome: Pertussis <8 weeks of age
1b. Exposure: Tdap at 27-36 weeks gestation
Outcome: Pertussis $\leq$12 weeks of age
2a. Exposure: Tdap any point during pregnancy
Outcome: Pertussis <8 weeks of age
2b. Exposure Tdap any point during pregnancy
Outcome: Pertussis $\leq$12 weeks of age

Vaccine effectiveness (VE) was defined as (1 – OR) x 100%[81]. Logistic regression was used to calculate ORs and 95% CIs of pertussis in infants in each model and unadjusted VE estimates were calculated. VE estimates adjusted for race/ethnicity, number of prenatal visits, mother's country of birth, payer for prenatal care, number of prior births, infant sex, gestational age and birth weight were also calculated.

VE estimates of Tdap vaccination between 27 and 36 weeks gestation and at any point during pregnancy were also calculated for both the primary and secondary endpoints of pertussis occurring <8 weeks of age and $\leq$12 weeks of age.

Among women who received Tdap vaccine during pregnancy and at least 14 days prior to delivery of the infant, I also evaluated the timing of the Tdap dose. Logistic regression was used to construct ORs and 95% CIs for the odds of pertussis among infants whose mothers received Tdap in the second trimester (13-26 weeks gestation) versus the third trimester (27-36 weeks gestation), as well as infants whose mothers received Tdap only during the third trimester, comparing 27-31 weeks gestation versus 32-36 weeks gestation, while controlling for preterm birth, number of prior live births, and age of the mother in all models.

RESULTS

A total of 336,775 women 14-44 years of age had a dose of Tdap vaccine that was administered between January 1, 2012 and December 31, 2015 and recorded in CAIR. Of these, 74,791 women were identified as having had a live birth in 2013 or 2014 in California and a recorded Tdap vaccine dose administered during the pregnancy or within 14 days after delivery. Two hundred eighty-seven mother-infant pairs were

excluded because the baby had a gestational age of less than 27 weeks or a birth weight of less than 500 grams. Among the remaining 74,504 mother-infant pairs retained for analysis, 42,941 (58%) mothers were vaccinated during pregnancy and 31,563 (42%) mothers were vaccinated postpartum.

A total of 1,562 infants reported to CDPH with pertussis within the first year of life were known to have been born in California during 2013-2014 and to have a gestational age of at least 27 weeks and a birth weight of at least 500 grams. Of these, 562 (36%) were ≤12 weeks of age and 321 (21%) were <8 weeks of age at time of their pertussis onset. A total of 994,971 live births occurred in California during 2013-2014 with a gestational age of at least 27 weeks and a birth weight of at least 500 grams. The statewide incidence of pertussis among infants under 12 months of age was 1.6 cases per 1,000 births. My cohort of 74,504 women-infant pairs represented 7.5% of the total eligible birth cohort in California during the study interval.

Differences were observed between the mother-infant pairs in which the mother received Tdap during pregnancy compared to those in which the mother was vaccinated postpartum. Women vaccinated during pregnancy were more likely to be Hispanic, White or Black and less likely to be Asian/Pacific Islander (API) ($p<0.001$) (Table 1). Women vaccinated during pregnancy were also less likely to have been born in the U.S. ($p<0.001$), to be covered by Medicaid ($p<0.001$), and to have had fewer prior births ($p<0.001$). Infants born to women vaccinated during pregnancy were more likely to be female ($p=0.034$) and less likely to be preterm or of low birth weight ($p<0.001$) (Table 1).

One hundred nineteen infants in the cohort were reported to have had pertussis in the first year of life, for an incidence of 1.6 cases per 1,000 births. Of these, 35 (29%) were younger than 13 weeks of age, of whom 25 (21%) were younger than eight weeks of age. Infants born to women who received Tdap during pregnancy were less likely to have been reported with pertussis at less than eight weeks of age ($p=0.010$) or less than 13 weeks of age ($p=0.010$). However, there was no difference in the risk of pertussis among infants less than one year of age ($p=0.111$) born to women who were vaccinated during pregnancy compared to infants born to women who were vaccinated postpartum (Table 1).

Among the 42,218 women vaccinated during pregnancy with known date of last menses, 77% received Tdap during the recommended window of 27-36 weeks gestation, 14% were vaccinated in the first or second trimester and 9% received Tdap after 36 weeks gestation but prior to delivery (Table 2 and Figure 1). Infants whose mothers received Tdap vaccine during the recommended window of 27-36 weeks gestation were less likely to have pertussis before 13 weeks of age compared to infants whose mothers received Tdap earlier or later in gestation (OR 0.22; 95% CI 0.08-0.63; $p=0.005$).

Among the 31,563 women vaccinated after delivery, most received Tdap vaccine within two days of delivery, suggesting they were likely vaccinated prior to hospital discharge (Figure 2).

In the multivariate regression models, receipt of Tdap vaccine between 27-36 weeks gestation was highly protective against the infant developing pertussis at <8 weeks of age [Model 1a] and <13 weeks of age [Model 1b], controlling for covariates (Table 3). Similarly, receipt of Tdap vaccine at any point during the pregnancy remained highly protective against pertussis in the infant with onset <8 weeks of age [Model 2a] and at ≤12 weeks of age [Model 2b], when controlling for covariates (Table 4). The only covariate associated with pertussis in the infant was the number of prior births, which was significantly associated with an increased risk of pertussis at <8 weeks and ≤12 weeks of age in all four models (Tables 3 and 4).

The VE of Tdap vaccination administered during 27-36 weeks gestation was 85% (95% CI 33-98%) against pertussis in infants <8 weeks of age and 72% (95% CI 30-89%) in preventing pertussis in infants ≤12 weeks of age, compared to Tdap vaccination given postpartum and adjusting for maternal and infant covariates (Table 5). The VE of Tdap at any point during the pregnancy was 64% (95% CI 11-85%) in preventing pertussis in infants <8 weeks of age and 53% (95% CI 8-76%) in preventing pertussis in infants ≤12 weeks of age compared to Tdap vaccination received postpartum and adjusting for maternal and infant covariates (Table 5). Unadjusted and adjusted VE estimates were similar, so only adjusted estimates are shown.

Among the 15 case-infants ≤12 weeks of age whose mothers were vaccinated during pregnancy, only six (40%) were vaccinated during the recommended window of 27-36 weeks gestation.

In the sub-analysis of women-infant pairs who received Tdap vaccine during pregnancy and at least 14 days prior to delivery of the infant, infants whose mothers received Tdap vaccine during the second trimester were significantly more likely to have pertussis at <8 weeks (OR 8.1; 95% CI 1.3-49.0) and ≤12 weeks of age (OR 4.6; 95% CI 1.39-15.25), when controlling for age of the mother, number of prior births and preterm birth (Table 6). Additionally, infants whose mothers received Tdap vaccine early in the third trimester between 27-31 weeks gestation had lower odds of pertussis at <8 weeks and ≤12 weeks of age compared to infants whose mothers received Tdap vaccine between 31-36 weeks gestation, although confidence intervals were wide and included the null (Table 7).

DISCUSSION

This is the first known study in the United States demonstrating the effectiveness of prenatal Tdap vaccination against pertussis in young infants. This study found that Tdap vaccination during pregnancy more effectively prevented pertussis in young infants than Tdap vaccine given postpartum. Tdap vaccination received at 27-36 weeks gestation was 85% more effective at preventing pertussis in infants younger than eight weeks of age compared to Tdap vaccination postpartum. Importantly, this study also found that vaccination received during the recommended window of 27-36 weeks gestation in the third trimester was more effective than vaccination received earlier in

pregnancy during the second trimester. Although not statistically significant, the findings from this study also suggest that giving Tdap vaccine at the start of the third trimester, prior to 31 weeks gestation, is more effective at reducing risk of pertussis in infants than giving Tdap after 31 weeks gestation. A prior study found that women vaccinated during the second trimester of pregnancy transferred higher concentrations of anti-pertussis antibodies to their infants compared to women vaccinated during the third trimester; however, in that study, the majority of women that were vaccinated during the second trimester were vaccinated between 17 and 25 weeks gestation (79%) and the majority of women vaccinated in the third trimester were vaccinated between 34 and 41 weeks gestation (79%)[82]. Taken together, these findings are consistent in highlighting the need for prenatal care providers to offer Tdap at the earliest opportunity after 27 weeks gestation.

A strength of this study is that it compares two vaccination strategies for preventing pertussis in infants. A prior data simulation study estimated that Tdap vaccination given during the third trimester of pregnancy was more cost effective and would result in a 13% greater reduction in infant pertussis cases <6 months of age compared to Tdap given postpartum[83]. The results from this observational study show greater effectiveness of Tdap given during pregnancy compared to Tdap given postpartum.

The effectiveness estimates presented here are likely underestimates of the total impact that Tdap vaccination during pregnancy has on infant pertussis because the comparison group is not unvaccinated mothers, but rather mothers who were vaccinated in the postpartum period. It has been shown that infants born to women who received Tdap vaccine postpartum (through cocooning) are thought to already be at lower risk of pertussis compared to infants whose mothers do not receive any doses of Tdap during or after the pregnancy[84,85]. It is likely that maternal Tdap vaccination during pregnancy would be more than 86% effective at preventing pertussis in infants younger than eight weeks of age if compared to non-receipt of Tdap vaccine.

The design of this study minimized the risk of misclassification bias due to use of provider-reported exposure data on Tdap vaccination from the CAIR database. Additionally, the exposure data were collected prior to the outcome of pertussis in the infant; therefore any errors in exposure classification would be irrespective of the outcome (i.e., nondifferential).

Significant differences were observed between mother-infant pairs in which mothers were vaccinated during pregnancy and those vaccinated postpartum, including the payer for prenatal care, race and ethnicity, number of prenatal visits and mother's country of birth. This is expected given that vaccination during pregnancy may be a marker for both access to and quality of prenatal care. Importantly, in the multivariate model, these factors were not associated with the risk of pertussis in the infant, except for the number of prior births. Infants were 1.5 times more likely to have pertussis before eight weeks of age with each prior birth of the mother, suggesting that having older siblings in the house is an important risk factor for pertussis, consistent with a

recent study demonstrating that the most common source of *B. pertussis* for young infants is older siblings[86].

When using all infant pertussis <12 months of age as an endpoint, this study found that prenatal Tdap vaccination showed no impact on risk of pertussis in infants <12 months of age. This is expected given that maternal antibodies to pertussis are unlikely to persist in the infant longer than a few months and also suggests there was a similar baseline risk of pertussis among infants in the vaccinated and unvaccinated population.

A limitation in this study is that use of CAIR is voluntary by providers and uptake is low for adults. It is possible that the population of pregnant women whose Tdap doses are recorded in CAIR is not representative of all women delivering infants in California. However, the incidence of pertussis among infants less than 12 months of age was 1.6 cases per 1,000 births, the same as the incidence in the source population, suggesting that the cohort was representative of the source population with respect to the risk of the outcome.

CONCLUSION

Tdap vaccination administered during 27-36 weeks of gestation was 85% effective at preventing pertussis in infants younger than eight weeks of age, compared to Tdap vaccine given postpartum. Vaccination during the recommended window in the third trimester was more effective than vaccination during the second trimester. All prenatal care providers should adopt the current ACIP prenatal Tdap recommendation, and efforts to provide Tdap vaccine to pregnant women during routine prenatal visits at the earliest opportunity between 27-36 weeks gestation need to be enhanced in order to reduce morbidity and mortality of pertussis among infants.

TABLES AND FIGURES

Table 1: Infant and maternal characteristics of the cohort of women with a live birth in California from 2013-2014 with documentation of receipt of Tdap vaccine during pregnancy or postpartum in the California Immunization Registry

	Prenatal Tdap N=42,941		Postpartum Tdap N=31,563		
	N	(%)	N	(%)	p-value
Maternal Characteristics					
Race/ethnicity					
Hispanic	25789/41269	(62)	18770/30630	(61)	0.001
White, non-Hispanic	6318/41269	(15)	4102/30630	(13)	<0.001
Black, non-Hispanic	2307/41269	(6)	1494/30630	(5)	<0.001
Asian/Pacific Islander	6855/41269	(17)	6264/30630	(20)	<0.001
Maternal age in years (mean [IQR])	28.2 [23-33]		28.3 [24-33]		0.136
Number of prenatal visits* (men [IQR])	12.4 [10-14]		11.8 [10-14]		0.001
Mother's country of birth					
USA	20170/42941	(47)	15438/31563	(49)	<0.001
Payer for prenatal care					
Self pay	392/41382	(1)	2486/30694	(8)	<0.001
Medicaid (Medi-Cal)	25661/41382	(62)	20755/30694	(68)	<0.001
Private	15329/41382	(37)	7453/30694	(24)	<0.001
WIC	28549/42636	(67)	21671/31339	(69)	<0.001
Number of total births (mean [IQR])**	2.0 [1-3]		2.1 [1-3]		<0.001
Infant Characteristics					
Male	21793/42941	(51)	16268/31563	(52)	0.033
Preterm (<37 weeks gestation)	2885/42941	(7)	2966/31563	(9)	<0.001
Low birth weight (<2,500 grams)	2316/42938	(5)	2296/31561	(7)	<0.001
Age at onset of pertussis illness					
<8 weeks of age	8/42908	(0.02)	17/31534	(0.05)	0.010
≤12 weeks of age	15/42912	(0.03)	25/31540	(0.08)	0.010
<12 months of age	60/42941	(0.14)	59/31563	(0.19)	0.111

*restricted to those with <50 visits

**restricted to those with <10 total births

Table 2: Timing of Tdap vaccine administration during pregnancy

	N	(%)
Total with Tdap during pregnancy	42,941	
Gestational age at time of Tdap administration*		
<27 weeks	6,092	(14)
27-36 weeks**	32,445	(77)
>36 weeks	3,681	(9)

*among 42,218 with known gestational age

**834 (3%) of these were administered <14 days prior to delivery

Figure 1. Week of gestation of receipt of Tdap vaccine among women vaccinated during pregnancy

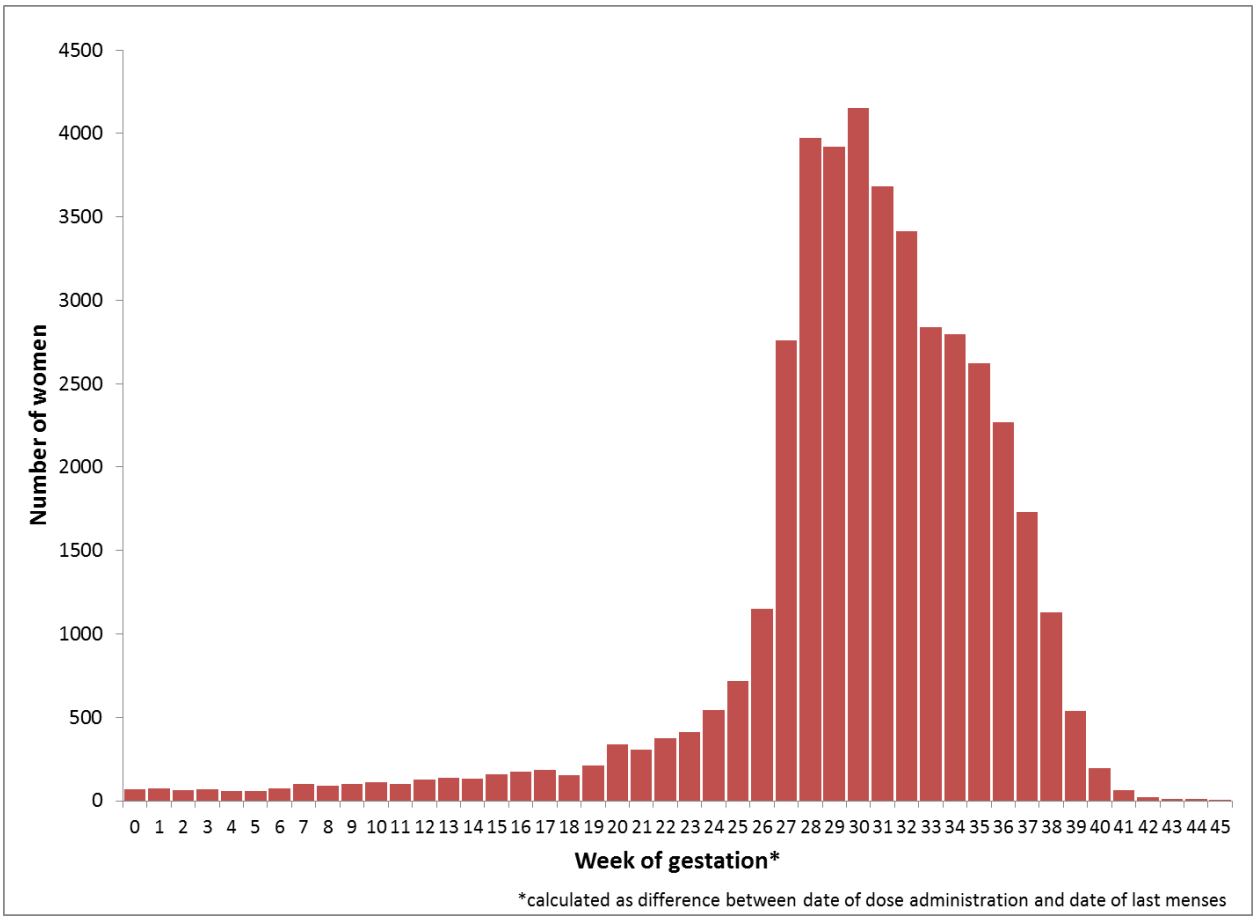

Figure 2. Number of days after delivery of receipt of Tdap vaccine among women vaccinated postpartum

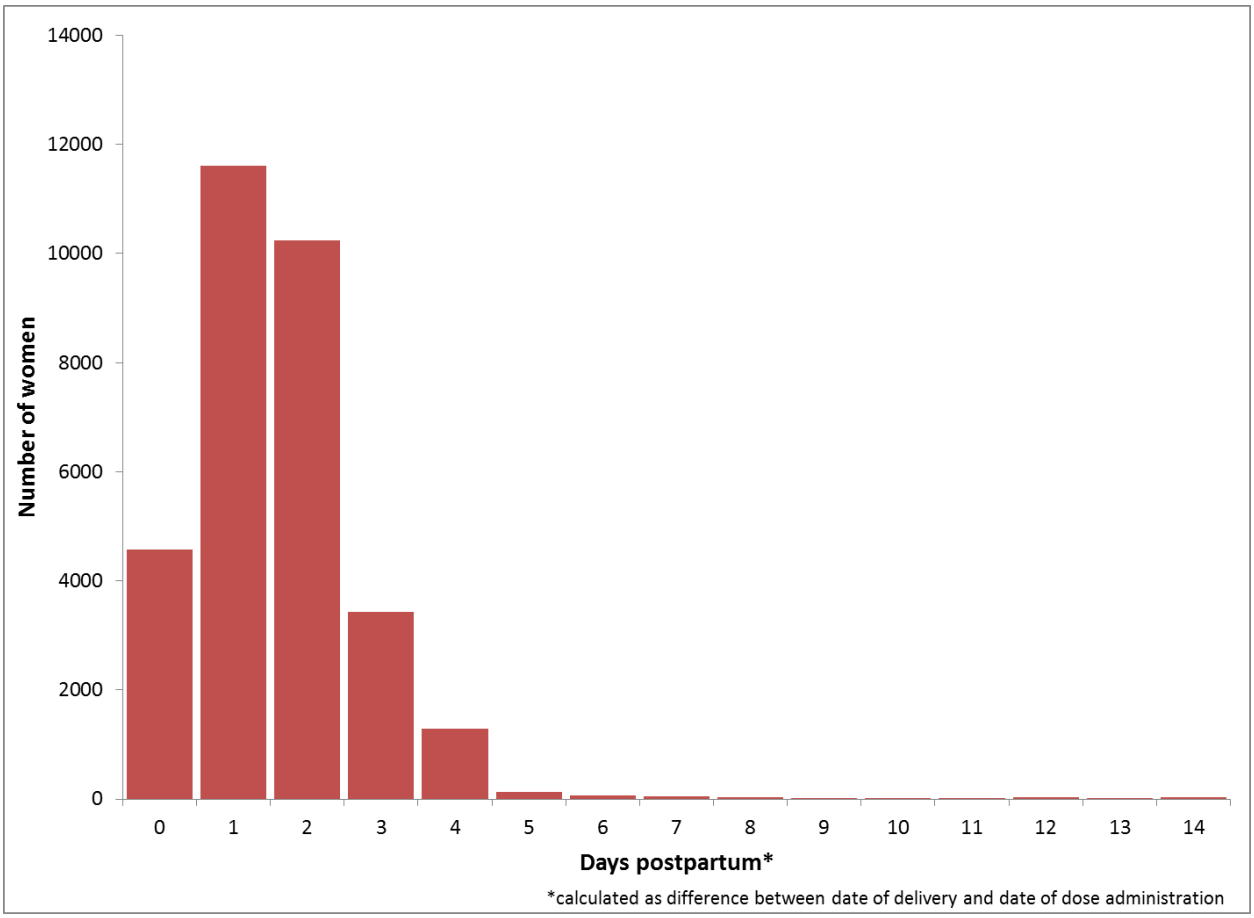

Table 3: Multivariate regression results evaluating receipt of Tdap vaccine between 27-36 weeks gestation and pertussis <8 weeks of age [Model 1a] and ≤12 weeks of age [Model 1b]

	Model 1a: pertussis <8 weeks of age		Model 1b : pertussis ≤12 weeks of age	
Parameter	**OR**	**95% CI**	**OR**	**95% CI**
Maternal Characteristics				
Tdap 27-36 weeks gestation	0.15	0.03-0.65	0.28	0.11-0.70
Ethnicity				
Non-Hispanic		REF		REF
Hispanic	3.21	0.71-14.58	4.28	1.25-14.66
Number of prenatal visits	1.06	0.96-1.16	1.03	0.95-1.12
Total prior births	1.48	1.15-1.91	1.34	1.08-1.67
Payer				
Private or self-pay		REF		REF
Medicaid	2.21	0.48-10.20	1.47	0.53-4.02
Born outside USA	0.58	0.22-1.48	0.57	0.27-1.20
Infant Characteristics				
Male	0.53	0.20-1.42	0.45	0.21-0.99
Preterm*	1.66	0.35-7.93	1.29	0.34-4.86
Low birthweight**	1.22	0.19-7.74	1.39	0.31-6.18

*indicates infants born between 27 and 36 weeks gestation; infants born <27 weeks gestation were excluded

**indicates infants with birth weight of 55-2500 grams; infants with birth weight of <500 grams were excuded

Table 4: Multivariate regression results evaluating receipt of Tdap vaccine at any point during pregnancy and pertussis at less than 8 weeks of age [Model 2a] and less than 13 weeks of age [Model 2b]

	Model 2a : pertussis <8 weeks of age		Model 2b : pertussis ≤12 weeks of age	
Parameter	**OR**	**95% CI**	**OR**	**95% CI**
Maternal Characteristics				
Tdap any week of pregnancy	0.36	0.15-0.89	0.47	0.24-0.92
Ethnicity				
Non-Hispanic		REF		REF
Hispanic	4.35	0.97-19.45	4.16	1.42-12.23
Number of prenatal visits	1.05	0.97-1.13	1.02	0.97-1.10
Total prior births	1.51	1.20-1.90	1.34	1.09-1.63
Payer				
Private or self-pay		REF		REF
Medicaid	1.70	0.48-6.08	1.28	0.54-3.05
Born outside USA	0.73	0.32-1.69	0.72	0.38-1.39
Infant Characteristics				
Male	0.67	0.29-1.56	0.61	0.32-1.18
Preterm*	0.92	0.19-4.41	0.99	0.29-3.34
Low birthweight**	2.32	0.49-11.09	2.34	0.70-7.84

*indicates infants born between 27 and 36 weeks gestation; infants born <27 weeks gestation were excluded

**indicates infants with birth weight of 55-2500 grams; infants with birth weight of <500 grams were excuded

Table 5. Vaccine effectiveness estimates compared to postpartum Tdap administration

	Pertussis <8 weeks of age			Pertussis ≤12 weeks of age		
	Adjusted VE*	95% CI	Number of cases <8w	Adjusted VE*	95% CI	Number of cases ≤12w
Pregnancy Tdap						
27-36 weeks gestation	85.4%	33.0-96.7	18	71.6%	29.6-88.6	30
Any time during pregnancy	63.8%	10.6-85.4	23	53.0%	8.2-75.9	38

*adjusted for mother's ethnicity, number of prenatal visits, prior births, payer, mother's country of birth, infant's birth weight and gestational age

Table 6. Multivariate regression results evaluating timing of Tdap vaccine during the second trimester and third trimester of pregnancy and pertussis at < 8 weeks of age and ≤12 weeks of age

	pertussis <8 weeks of age*		pertussis ≤12 weeks of age**	
Parameter	**OR**	**95% CI**	**OR**	**95% CI**
Maternal Characteristics				
Age in years	0.94	0.79-1.11	0.92	0.82-1.03
Prior births	1.63	0.90-2.97	1.38	0.86-2.24
Tdap timing during pregnancy				
Second trimester [14-26 weeks gestation]	8.06	1.33-48.97	4.60	1.39-15.25
Early third trimester [27-36 weeks gestation]		REF		REF
Infant Characteristics				
Preterm birth	2.84	0.31-25.72	2.78	0.60-13.03

*includes 5 cases and 35,959 controls

**includes 11 cases and 35,959 controls

Table 7. Multivariate regression results evaluating timing of Tdap vaccine during 27-31 weeks and 32-36 weeks gestation of the third trimester of pregnancy and pertussis at <8 weeks of age and ≤12 weeks of age

	pertussis <8 weeks of age*		pertussis ≤12 weeks of age**	
Parameter	**OR**	**95% CI**	**OR**	**95% CI**
Maternal Characteristics				
Age in years	0.96	0.74-1.25	0.92	0.79-1.07
Prior births	1.96	0.90-4.28	1.48	0.80-2.75
Tdap timing during pregnancy				
27-31 weeks gestation	0.43	0.02-7.58	0.62	0.12-3.19
31-36 weeks gestation		REF		REF
Infant Characteristics				
Preterm birth	17.81	0.99-319.68	3.66	0.41-32.99

*includes 2 cases and 31,194 controls

**includes 6 cases and 31,194 controls

Chapter 3:
Effect of prenatal Tdap vaccination on severity of pertussis in infants

ABSTRACT

Background: Passively-acquired maternal antibodies may offer infants protection against pertussis in the first weeks of life. All U.S. women are recommended to receive Tdap vaccine at 27-36 weeks gestation during each pregnancy; limited data show that this strategy reduces the risk of pertussis among young infants. The impact of this strategy on the outcomes of infants with pertussis has not been evaluated.

Methods: I use a retrospective cohort study design to evaluate whether infants with pertussis born in 2013-2014 whose mothers received Tdap vaccine during pregnancy had a lower risk of hospitalization or intensive care unit admission compared to infants of unvaccinated mothers.

Results: Infants with pertussis born to vaccinated mothers were significantly less likely to be hospitalized and had significantly shorter hospital stays compared to infants with pertussis born to unvaccinated mothers after adjustment for chronological and gestational age and receipt of DTaP vaccine by the infant. Unadjusted and adjusted VE for preventing hospitalization among infants with pertussis was 72% and 58%, respectively. No infants born to vaccinated mothers required intubation or died from pertussis.

Conclusion: Among infants with pertussis, prenatal Tdap vaccination was 58% effective in preventing hospitalizations. Infants whose mothers were unvaccinated had a higher risk of hospitalization and ICU admission and longer hospital stays. Tdap vaccination during pregnancy is a critical strategy for reducing morbidity and mortality from pertussis.

INTRODUCTION

Infants too young to receive the first dose of DTaP vaccine are at the greatest risk of severe disease and death from pertussis[87,88,89,90,91,92,93,94,95]. In the United States from 1994 to 2004, 58% of infant deaths due to pertussis occurred in infants less than two months of age[96] and during the 2010 California epidemic, all ten pertussis-related deaths were in infants younger than eight weeks of age[97].

Young infants have immature immune systems and rely on passively-acquired maternal antibodies to protect them in the first few weeks or months of life[98]. In the United States, all women are recommended to receive Tdap vaccine at 27-36 weeks gestation during each pregnancy to protect infants through transplacental transfer of antibodies[99]. Limited data in the United Kingdom show that this strategy reduces the risk of pertussis among infants younger than two months of age[100,101]. However, no studies have evaluated the impact of this strategy on the severity of outcomes among infants who develop pertussis. Studies have shown that infants who receive the first dose of DTaP vaccine at around six to eight weeks of age have a lower risk of hospitalization and death from pertussis compared to unvaccinated infants[102]. A possible mechanism for this protective effect is that after one dose of DTaP vaccine, infants mount a sufficient antibody response to pertussis toxin (PT) to prevent development of severe leukocytosis, which can lead to irreversible pulmonary hypertension and death[103]. A recent study using a baboon model found that baboon infants born to mothers vaccinated against pertussis in the third trimester of pregnancy were protected against leukocytosis following a direct challenge with *B. pertussis*[104]. Similarly, infants born to women who received Tdap vaccine during pregnancy may be born with sufficient antibody to PT to prevent severe disease and death due to pertussis[105,106].

I used a retrospective cohort study design to evaluate whether infants whose mothers received Tdap vaccine during pregnancy had less severe pertussis illness than infants with pertussis whose mothers did not receive Tdap vaccine during pregnancy.

METHODS

I evaluated the cohort of infants reported with pertussis in California with illness onset occurring at less than 63 days of age and born between January 1, 2011 and December 31, 2015. The age cut-off of 63 days was selected because most infants receive the first dose of DTaP vaccine at two months of age and I sought to exclude any potential confounding effects of protection from active immunization.

Birth certificate vital records for the infant and CAIR Tdap immunization records for the mother were linked to the CDPH surveillance reports using a matching algorithm consisting of a combination of the following variables: infant's last name, infant's first name, infant's date of birth, infant's sex, mother's last name, mother's first name, mother's date of birth, father's last name, and city of residence. All matches were reviewed to ensure accuracy.

Signs, clinical course, DTaP vaccination history and outcomes were reported on surveillance forms and verified through hospital medical record review. Maternal Tdap vaccination histories were self-reported or provider-verified through public health case investigations and recorded on surveillance reports. Length of hospital stay was calculated as the number of days between the admission and discharge dates and summed across hospital stays for multiple admissions or transfers. Infant's gestational age and birth weight, maternal age, maternal country of birth, date of last menses and number of prenatal visits were reported in the birth certificate records. CAIR records for mothers of infants with pertussis were reviewed for all Tdap doses occurring during the pregnancy or within two weeks postpartum.

The exposure was coded as a binary variable. Infants were considered exposed if their mother self-reported or had documented receipt of Tdap at any point during the relevant pregnancy. When available, the trimester in which the Tdap dose was received and date of administration were recorded; week of gestation for when the dose was administered was calculated as the number of weeks between the date of last menses reported on the birth certificate and the recorded Tdap dose.

Unexposed infants were those whose mothers had documentation of not receiving Tdap vaccine during pregnancy through self-report or hospital admission records or who had documentation or self-report of Tdap vaccine receipt postpartum within two weeks of delivery. If there was no Tdap vaccine dose recorded on the surveillance report, medical record or CAIR and the mother did not recall Tdap vaccine receipt during or immediately after pregnancy, the exposure was considered unknown.

Bivariate comparisons of demographic variables, symptoms, clinical course and outcomes between exposed and unexposed infants were calculated using chi-square and Fisher's exact tests for categorical variables; associated relative risks (RRs) and 95% confidence intervals (CIs) were constructed. Two-sided p-values were calculated using analysis of variance for normally distributed continuous data or the Wilcoxon-Mann-Whitney test for non-normally distributed continuous variables and the Cochrane-Armitage test to evaluate trends.

Infants were excluded from analyses if their mother's Tdap vaccination status was unknown, so as to avoid misclassification of the exposure. To assess potential bias due to missing data, bivariate comparisons of demographic variables, birth and clinical characteristics of infant pertussis cases with and without known exposure data were evaluated and associated odds ratios (ORs) were calculated. Birth certificate records were unavailable for infants who were born in 2015 or who were born outside of California; these infants were excluded from estimations requiring maternal age, maternal country of birth, number of prenatal visits, gestational age and birth weight.

The primary outcomes of interest were hospitalization for at least 24 hours, length of hospital stay, admission to an intensive care unit (ICU) for any length of time, intubation and death from pertussis. Hospitalization, ICU admission, intubation, and death were coded as dichotomous variables. Using two multivariate logistic regression models I

estimated the independent effect of prenatal Tdap vaccination on risk of the severe outcomes of: 1) hospitalization and 2) ICU admission while simultaneously adjusting for other important covariates, as shown below:

Model 1: Effect on hospitalization

$$\text{Log-odds (Hospitalization=1}|A_i,X_i) = \beta_0 + \beta_1\text{Prenatal Tdap receipt} + \beta_2\text{Infant age} + \beta_3\text{Gestational age} + \beta_4\text{DTaP receipt} + \varepsilon_i$$

Model 2: Effect on ICU admission

$$\text{Log-odds(ICU=1}|A_i,X_i) = \beta_0 + \beta_1\text{Prenatal Tdap receipt} + \beta_2\text{Infant age} + \beta_3\text{Gestational age} + \varepsilon_i$$

Where A_i is the exposure variable indicating maternal Tdap vaccination during pregnancy and covariates controlled for in these models are indicated.

Vaccine effectiveness (VE) of maternal Tdap vaccination during pregnancy in preventing hospitalization in the infants with pertussis was defined as (1 – OR) x 100%[107]. Logistic regression was used to calculate ORs and 95% CIs for hospitalization among infants born to vaccinated and unvaccinated mothers and unadjusted VE estimates were calculated. VE estimates adjusted for chronological and gestational age of the infant and receipt of DTaP were also calculated. Unadjusted and adjusted VE estimates were also calculated for infants whose mothers were known to have received Tdap vaccine during the third trimester.

RESULTS

A total of 752 infants born from January 1, 2011 through December 31, 2015 were reported with pertussis at less than 63 days of age. The most commonly reported clinical sign was paroxysmal cough (83%), followed by cyanosis (65%), apnea (59%) and post-tussive vomiting or emesis (58%) (Table 1). Whoop was reported in fewer than half (47%) of cases. Among infant pertussis cases with complete information, 495 (68%) were hospitalized, with 25% of hospitalized cases requiring intensive care. Forty-four infants required intubation and six infants died. Four (1%) infants received the first dose of DTaP vaccine at least 14 days prior to onset of pertussis (Table 1).

Three infants with pertussis were known to have been born outside of California, either in another country or another U.S. state and 116 infants were born in 2015 and did not have available birth data. Of the remaining 633 infants, 607 (96%) were successfully linked to their birth certificate record. Nearly all (91%) were reported to be full-term ($\geq$37 weeks gestation) and of normal birth weight (Table 1).

A total of 420 (56%) infants had known maternal vaccination status. Comparisons of infants with and without complete data are presented in Table 2. The majority of demographic features and maternal and infant characteristics were similar between cases with and without complete data; however, infants with missing exposure data were more likely to be preterm (p-value=0.04), have apnea (p-value=0.03), be admitted

to the ICU (p-value=0.03), develop seizures (p-value=0.01), or die (p-value=0.04) (Table 2).

Of the mothers of 420 infants with complete exposure data, 49 (12%) had received Tdap vaccine during pregnancy, while the remaining mothers received Tdap vaccination postpartum or not at all (Table 1). Among those vaccinated during pregnancy, 8 (16%) received Tdap during the first or second trimester, 37 (76%) received Tdap during the third trimester and 4 (8%) received Tdap at an unknown point during the pregnancy. Among the 18 mothers who received Tdap vaccine during the third trimester and had documented vaccine administration dates, 14 (78%) received Tdap during the recommended window of 27-36 weeks gestation and 4 (22%) received Tdap after 36 weeks gestation (Table 3).

Infants whose mothers received Tdap vaccine during pregnancy were older (median age 45 days versus 35 days, p-value 0.034) but did not differ with regard to race or ethnicity, sex, gestational age, birth weight, or DTaP vaccination (Table 3). Clinical findings differed between exposed and unexposed infants, and infants whose mothers received Tdap vaccine during pregnancy were less likely to have the classic pertussis signs of paroxysmal cough (RR 0.41; 95% CI 0.25-0.68), apnea (RR 0.66; 95% CI 0.47-0.91), cyanosis (RR 0.53; 95% CI 0.39-0.73) or whoop (RR 0.78; 95% CI 0.62-0.99), although the frequency of post-tussive vomiting was similar (Table 4).

Infants whose mothers received Tdap vaccine during pregnancy had a significantly lower risk of hospitalization (RR 0.5; 95% CI 0.4-0.6) or ICU admission (RR 0.8; 95% CI 0.7-0.9). Among those who were hospitalized, infants whose mothers were vaccinated had shorter hospital stays (median 3 days versus 6 days, p-value 0.019). No infant born to a vaccinated mother developed seizures, required intubation or died (Table 4).

Mothers who received Tdap vaccine during pregnancy were significantly less likely to have had their prenatal care paid for by Medicaid (Medi-Cal) insurance (RR 0.6; 95% CI 0.4-0.9). There was no difference in maternal age, country of mother's birth or number of prenatal visits between exposed and unexposed infants. (Table 4)

In the first multivariate regression model [Model 1] evaluating factors associated with hospitalization, infants whose mothers received Tdap vaccine during pregnancy were significantly less likely to have been hospitalized (OR 0.4; 95% CI 0.2-0.9), after adjusting for infant's chronological and gestational age and receipt of DTaP vaccine (Table 5).

In Model 2, no infants who received DTaP vaccine were admitted to an ICU, so receipt of DTaP vaccine was dropped from the multivariate model to allow for convergence. When adjusting for infant's chronological age and gestational age, maternal Tdap vaccination during pregnancy was associated with a lower odds of ICU admission (OR 0.5, 95% CI 0.2-1.2); however, the CI included the null (Table 6).

The VE for prenatal Tdap in preventing hospitalization among infants with pertussis was 72% (95% CI 49-85%); after adjusting for infant's chronological and gestational age and receipt of DTaP vaccine, it was 58% (95% CI 15-80%) (Table 7). VE estimates remained similar when analyses were restricted to infants whose mothers were known to have received Tdap vaccine during the third trimester.

DISCUSSION

This is the first known study to demonstrate that prenatal Tdap vaccination reduces severity of pertussis in infants. Infants whose mothers were vaccinated with Tdap during pregnancy had a lower risk of hospitalization and of ICU admission and had shorter hospital stays compared to infants whose mothers were not vaccinated. No infants born to vaccinated mothers required intubation or died from pertussis. Prenatal Tdap was 58% effective in preventing hospitalization in infants with pertussis. Classic pertussis signs and clinical findings were observed less frequently among infants born to vaccinated mothers, suggesting they had more mild disease.

Among the women who received Tdap vaccine during pregnancy, at least 24% were vaccinated outside of the recommended window of 27-36 weeks gestation. This may explain why the pertussis illness in the infant was not prevented by prenatal vaccination. As recommended by the ACIP, all pregnant women should be offered Tdap vaccine at the earliest opportunity during routine prenatal visits between 27 and 36 weeks gestation to optimize opportunities for transplacental antibody transfer prior to delivery.

There are several important limitations to this study. Foremost, misclassification of the exposure (i.e., not accurately reporting prenatal Tdap) could have occurred because maternal Tdap vaccination histories were not always verified by the provider and there may have been recall bias if mothers of severely ill infants recalled and reported Tdap vaccination differently than mothers of infants with milder pertussis. Recall bias could have occurred in either direction and would have resulted in a biased VE estimate. While non-differential misclassification of the exposures would not bias the results, it would lead us to a less precise estimation of vaccine effectiveness. However, the use of several data sources, including those with provider verification of maternal vaccination histories, reduced the risk of both recall bias and exposure misclassification.

Complete exposure data were available for only 56% of cases, and some differences were observed between cases with and without complete data. Cases with complete exposure data were more likely to have been admitted to the ICU, develop seizures or die compared to those with missing maternal Tdap data. It is possible that public health communicable disease investigators were more persistent in obtaining maternal vaccination histories for more severe cases. Additionally, hospital admission records were available as an additional data source for more severe cases. There is the possibility of differential data missingness because documentation of non-receipt of vaccine or documentation of vaccinate received postpartum was necessary to determine nonexposure. Therefore, it is possible that more infants of unknown exposure status were born to unvaccinated mothers. However, because infants with

missing exposure data also had less severe outcomes, the problem of missing exposure data is likely to have biased the results towards the null. The distributions of other characteristics between our cases with and without complete exposure data were similar, so it unclear whether exposure data missingness had a meaningful impact on the study results.

The cohort of infants with pertussis in this study is based on surveillance data and includes only provider-diagnosed and reported pertussis cases. However, because pertussis reporting is mandated for both laboratories and clinicians and ill infants in this young age group are virtually always brought to a medical provider, underreporting, particularly of infants hospitalized for pertussis, is unlikely.

Finally, the estimate of VE in this study is only a partial measure of the impact of maternal Tdap vaccination during pregnancy. All of the infants in our cohort had pertussis, so I was unable to estimate the effect of maternal Tdap vaccination on prevention of pertussis illness in infants. Furthermore, many of the unexposed infants had mothers who received Tdap vaccination postpartum, and information on the breastfeeding status of mothers was not collected, so it was not possible to determine if there was any protective effect of antibodies transferred via breast milk. If antibodies transferred via the breast milk do provide some level of protection against severe pertussis, then this would have lowered the VE estimates presented here because the comparison group would include infants who were already protected against hospitalization, ICU admission and death from pertussis.

California has a large and diverse population; therefore, the findings presented here should be generalizable to other populations. Other countries that are experiencing a high incidence of pertussis should consider recommending routine vaccination of pregnant women against pertussis during every pregnancy. These findings should be communicated to both prenatal care providers and pregnant women to encourage uptake of Tdap vaccine during pregnancy.

CONCLUSION

Prenatal Tdap vaccination was found to be 58% effective in preventing hospitalization among infants with pertussis. Infants whose mothers did not receive Tdap during pregnancy had a higher risk of hospitalization and ICU admission and longer hospital stays. No infant born to a vaccinated mother required intubation or died from pertussis. Prenatal Tdap vaccination of mothers is a critical strategy for reducing the morbidity and mortality from pertussis.

TABLES AND FIGURES

Table 1: Infant and maternal demographic features, signs and clinical characteristics among pertussis cases <63 days of age – California, 2011-2015*

	Number	(%)†
Infant characteristics		
Male	375/747	(50)
Race/ethnicity		
Hispanic	476/676	(70)
White, non-Hispanic	128/676	(19)
Black, non-Hispanic	35/676	(5)
Asian/Pacific Islander	32/676	(5)
Other	5/676	(1)
Preterm (<37 weeks gestation)	53/602	(9)
Low birth weight (<2,500 grams)	34/607	(6)
Infant age in days (median [IQR])	37 [23-51]	
DTaP (infant) ≥14 days prior to onset	4/752	(1)
Year of birth		
2011	173/752	(23)
2012	65/752	(9)
2013	114/752	(15)
2014	284/752	(38)
2015*	116/752	(15)
Maternal characteristics		
Maternal age in years (median [IQR])	28 [23-33]	
Number of prenatal visits (median [IQR])	12 [10-14]	
Mother's country of birth		
United States	364/607	(60)
Other	243/607	(40)
Tdap received during pregnancy	49/420	(12)
Payer for prenatal care		
Medicaid (Medi-Cal)	394/606	(65)
Private	167/606	(28)
Other/self	45/606	(7)
Laboratory confirmed by culture or PCR	642/659	(97)
Signs and symptoms of pertussis		
Cough	738/741	(100)
Paroxysms	571/684	(83)
Posttussive vomiting	383/663	(58)
Whoop	289/615	(47)
Apnea	427/723	(59)
Cyanosis	285/436	(65)
Course of pertussis illness		
Hospialized	495/731	(68)
Days hospitalized, median [IQR]	6 [3-13]	
ICU admission	151/613	(25)
Seizure	15/656	(2)
Intubated	44/615	(7)
Died	6/752	(1)

*Reported to CDPH as of 2/2/2016

†Of those with known data

Table 2: Demographic features, signs and clinical characteristics among pertussis cases <63 days of age with and without data concerning maternal Tdap vaccination

	Complete Tdap data N=420		Missing Tdap data N=303		
	Number	(%)†	Number	(%)†	p-value
Infant characteristics					
Race/ethnicity					
Hispanic	279/389	(72)	180/236	(76)	0.37
White, non-Hispanic	72/389	(19)	52/263	(20)	0.69
Black, non-Hispanic	17/389	(4)	16/263	(6)	0.33
Asian/Pacific Islander	18/389	(5)	13/263	(5)	0.85
Male	171/344	(50)	134/263	(51)	0.76
Preterm (<37 weeks gestation)	23/340	(7)	30/262	(11)	0.04
Low birth weight (<2,500 grams)	18/344	(5)	16/263	(6)	0.65
DTaP (infant) ≥14 days prior to onset	9/420	(2)	1/303	(<1)	0.05
Age in days (median [IQR])	12 [10-14]		12 [10-13]		0.109
Year of birth					
2011	56/420	(13)	92/303	(30)	<0.001
2012	40/420	(10)	24/303	(8)	0.45
2013	38/420	(9)	58/303	(19)	<0.001
2014	193/420	(46)	79/303	(26)	<0.001
2015*	93/420	(22)	50/303	(17)	0.06
Maternal characteristics					
Maternal age in years (median [IQR])	28 [24-33]		28 [22-33]		0.34
Number of prenatal visits	12 [10-14]		12 [10-13]		0.109
Mother's country of birth					
USA	193/344	(56)	171/263	(65)	0.03
Payer for prenatal care					
Medicaid (Medi-Cal)	235/344	(68)	159/263	(60)	0.044
Private	90/344	(26)	77/263	(29)	0.395
Laboratory confirmed, culture or PCR					
Signs and symptoms of pertussis					
Cough	417/420	(99)	292/292	(100)	0.15
Paroxysms	328/388	(85)	226/270	(84)	0.77
Posttussive vomiting	223/377	(6)	147/262	(56)	0.44
Whoop	161/358	(45)	117/234	(50)	0.23
Apnea	232/365	(64)	137/249	(55)	0.03
Cyanosis	193/297	(65)	85/126	(67)	0.62
Course of pertussis illness					
Hospialized	292/420	(70)	184/282	(65)	0.23
Days hospitalized, median [IQR]	6 [3-13]		5 [2-11]		0.506
ICU admission	108/391	(28)	39/202	(19)	0.03
Seizure	14/370	(4)	1/250	(<1)	0.01
Intubated	28/390	(7)	13/205	(6)	0.70
Died	6/420	(1)	0/303	(0)	0.04

*Reported to CDPH as of 2/2/2016

†Of those with known data

Table 3. Bivariate analyses comparing demographic features, signs and clinical course between infants <63 days of age with pertussis born to women with and without Tdap vaccination during pregnancy

	Tdap N=49	No Tdap N=371			
	N (%)†	N (%)†	p-value	RR	95% CI
Infant characteristics					
Male	25/48 (52)	185/370 (50)	0.786	1.06	0.74-1.50
Race/ethnicity					
Hispanic	27/43 (63)	252/346 (73)	0.170	0.73	0.48-1.12
White, non-Hispanic	11/43 (26)	61/346 (18)	0.201	1.11	0.92-1.33
Black, non-Hispanic	1/43 (2)	16/346 (5)	0.707	0.98	0.93-1.03
Asian/Pacific Islander	3/43 (7)	15/346 (4)	0.435	1.03	0.94-1.12
Preterm (<37 weeks gestation)	1/38 (3)	22/302 (7)	0.492	0.95	0.90-1.01
Low birth weight (<2,500 grams)	2/38 (5)	16/306 (5)	0.993	1.00	0.92-1.08
Infant age in days (median [IQR])	**45 [31-52]**	35 [22-50]	**0.034**		
DTaP ≥14 days prior to onset	3/49 (6)	6/371 (2)	0.076	1.05	0.97-1.13
Year of birth					
2011	7/49 (14)	58/371 (16)	0.166**		
2012	1/49 (2)	34/371 (9)			
2013	2/49 (4)	42/371 (11)			
2014	28/49 (57)	172/371 (46)			
2015*	11/49 (22)	65/371 (18)			
Maternal characteristics					
Maternal age in years (median [IQR])	28 [24-33]	28 [24-33]	0.912		
Number of prenatal visitis (median [IQR])	12 [10-15]	12 [10-14]	0.284		
Payer					
Medicaid (Medi-Cal)	**20/38 (53)**	215/306 (70)	**0.028**	**0.63**	**0.43-0.92**
Private	16/38 (42)	74/306 (24)	0.018	1.31	0.99-1.73
Laboratory confirmed by culture or PCR	36/37 (97)	324/329 (98)	0.475	0.56	0.07-4.68
Signs and symptoms of pertussis					
Cough	48/49 (98)	369/371 (99)	0.311	0.26	0.02-2.86
Paroxysms	**29/43 (67)**	299/345 (87)	**0.001**	**0.41**	**0.25-0.68**
Posttussive vomiting	22/41 (54)	201/336 (60)	0.440	0.87	0.61-1.24
Whoop	**13/41 (32)**	148/317 (47)	**0.070**	**0.78**	**0.62-0.99**
Apnea	**20/42 (48)**	212/323 (66)	**0.023**	**0.66**	**0.47-0.91**
Cyanosis	**15/37 (41)**	178/260 (68)	**<0.001**	**0.53**	**0.39-0.73**
Course of pertussis illness					
Hospialized	**21/49 (43)**	271/371 (73)	**<0.001**	**0.47**	**0.35-0.63**
Days hospitalized, median [IQR]	**3 [1-6]**	6 [3-14]	**0.019**		
ICU admission	**6/48 (13)**	102/343 (30)	**0.012**	**0.80**	**0.70-0.91**
Seizure	0/34 (0)	14/336 (4)	0.627	0.96	0.94-0.98
Intubated	**0/46 (0)**	28/344 (8)	**0.060**	**0.92**	**0.89-0.95**
Died	0/49 (0)	6/371 (2)	1.000	0.98	0.97-1.00

*Reported to CDPH as of 2/2/2016

†Of those with known data

**p value for trend

Table 4. Timing of Tdap vaccinations received during pregnancy

	N	(%)†
First or second trimester	8	(16)
Third trimester	37	(76)
27-36 weeks*	14	(38)
>36 weeks**	4	(11)
Unknown	19	(51)
Unknown trimester#	4	(8)

*one of these infant was born 11 days after vaccination (37 weeks gestation and was LWB (<2000 g)

**all of these infants were born ≤14 days after vaccination (1, 4, 6, 14)

#at least one of these was born at 33 weeks

Table 5. Results of multivariate logistic regression model predicting hospitalization from pertussis among infants <63 days of age

Parameter	OR	95% CI
Tdap during pregnancy	0.42	0.20-0.85
Age in weeks (infant)	0.81	0.72-0.91
DTaP $\geq$14 days prior to onset	0.32	0.06-1.77
Gestational age (weeks)	0.88	0.78-0.99

Table 6. Results of multivariate logistic regression model predicting ICU admission from pertussis among infants <63 days of age

Parameter	OR	95% CI
Tdap during pregnancy	0.49	0.19-1.23
Age in weeks (infant)	0.80	0.72-0.90
Gestational age (weeks)	0.97	0.91-1.00

Table 7. Maternal Tdap Vaccine effectiveness estimates in preventing hospitalization from pertussis among infants <63 days of age

	Number of vaccinated	Unadjusted VE	95% CI	Total hospitalized	Adjusted* VE	95% CI	Total hospitalized
Maternal Tdap							
Any point in pregnancy	49	72.3%	49.0-85.0	292	58.3%	14.9-79.6	244
3rd trimester only	35	75.4%	49.8-88.0	285	52.1%	-0.16-80.3	237

*adjusted for infants chronological age, gestational age, and receipt of DTaP vaccine

Chapter 4.
Risk factors for pertussis among Hispanic infants: Do maternal age and parity explain the disparity?

ABSTRACT

Background: Hispanic infants are at greatest risk of pertussis compared to infants of other racial and ethnic groups; the reasons for this increased risk are unclear. Studies have shown that the source of *B. pertussis* infection for most infants is household members; therefore, larger household sizes, often associated with Hispanic families, may provide greater opportunities for exposure to pertussis and largely explain this disparity.

Methods: I evaluate data from the California birth cohort using a case-control study design to identify risk factors for pertussis among Hispanic and non-Hispanic infants. Cases were infants born in California during 2013 through 2014 and reported to the California Department of Public Health (CDPH) with pertussis occurring before four months of age. Controls were all other infants from the 2013-2014 California birth cohort who survived to at least four months of age. Bivariate comparisons of maternal and infant characteristics between cases and controls were calculated among Hispanic and non-Hispanic infants. Multivariate logistic regression analysis was used to identify risk factors for pertussis among Hispanic and non-Hispanic infants and to evaluate the impact of maternal parity and maternal age on risk of pertussis.

Results: Increased maternal parity was associated with a greater likelihood of pertussis among Hispanic and non-Hispanic infants, even when adjusting for important covariates. In the stratified models, a dose-response effect was observed, with increased likelihood of pertussis with each additional prior live birth. Additionally, younger mothers of all racial and ethnic groups, particularly mothers born during or after 1997, who likely received only DTaP vaccines and no doses of DTwP vaccine, were more likely to have an infant with pertussis.

Conclusion: Infants of all racial/ethnic groups who have older siblings are at increased risk of pertussis, consistent with a recent study indicating that siblings are now the most common source of *B. pertussis* for young infants. Infants of all racial/ethnic groups born to younger mothers were also more likely to have pertussis. These two risk factors largely account for the increased risk of pertussis among Hispanic infants.

INTRODUCTION

Infants younger than four months of age, who are too young to be fully protected through active immunization with diphtheria, tetanus and acellular pertussis (DTaP) vaccine, are at greatest risk of severe disease and death from pertussis. To mitigate this risk, in the U.S., all pregnant women are recommended to receive Tdap vaccine between 27 and 36 weeks gestation during each pregnancy. Infants of vaccinated women receive transplacentally-acquired antibodies that protect them in the early weeks of life, until they are old enough to be vaccinated themselves. However, uptake of this recommendation has been suboptimal and vaccine coverage among pregnant women is thought to be low. Identifying infants with an increased risk of pertussis can inform strategies to target maternal vaccination efforts in California.

For over a decade, Hispanic infants have been noted to be at increased risk of pertussis compared to infants of other racial and ethnic groups; however, the reasons for this difference are unclear. This disparity is unlikely to be due to lack of infant vaccination, as vaccination coverage among Hispanic infants and children is not lower than that among other racial/ethnic groups[108]. Furthermore, this disparity in the risk of pertussis is largely gone by the time infants reach six months of age and are protected by routine immunization[109]. Studies have shown that the source of *B. pertussis* infection for most infants is a household member[110,111,112], leading to the hypothesis that the larger average household size of Hispanic families may provide greater opportunities for exposure of infants to pertussis[113,114,115]. A recent study in Oregon found that larger household size was a risk factor for pertussis among both Hispanic and non-Hispanic infants younger than six months of age; however, this study was based on only 82 case-infants, only 23 of whom were Hispanic[116].

It is also known that Hispanic mothers in California are younger that mothers of other racial/ethnic groups[117]; therefore, another hypothesis for the Hispanic disparity is that maternal age may be associated with the risk of pertussis in infants. DTaP replaced DTwP in the United States in 1997, and studies have suggested that younger persons who have received only DTaP vaccine have less protection against pertussis. It is possible that younger mothers, born during or after 1997 and who have received only DTaP vaccine, transfer lower levels of antibodies to pertussis antigens to their infants during pregnancy, placing their infants at greater risk of pertussis in the first weeks of life.

I evaluated data from the California birth cohort using a case-control study design to identify risk factors for pertussis among Hispanic and non-Hispanic infants, with the primary hypothesis being that increased maternal parity, a proxy for the number of siblings, is associated with a greater likelihood of pertussis in infancy. In addition to other potential risk factors for pertussis, I evaluated whether infants with pertussis are more likely to have younger mothers who were born during or after 1997, and therefore likely to have received only acellular pertussis (DTaP) vaccines[118]. I evaluated these questions separately among Hispanic and non-Hispanic infants.

METHODS

Cases were identified through surveillance reports for infants born in California from January 1, 2013 through December 31, 2014 and reported to the California Department of Public Health (CDPH) as having pertussis with onset before four months of age. These reports were linked to the infants' birth certificate records using a matching algorithm consisting of a combination of the following variables: infant's last name, infant's first name, infant's date of birth, infant's sex, mother's last name, mother's first name, mother's date of birth, father's last name, and mother's city of residence. All matches were reviewed to ensure accuracy. All cases had an acute cough illness meeting the Council of State and Territorial Epidemiologists (CSTE) clinical case definition for pertussis or had laboratory detection of *B. pertussis* by culture or polymerase chain reaction (PCR) and had illness onset occurring before four months of age.

Controls were all other infants in the 2013-2014 California birth cohort who survived to at least four months of age. Death certificate data were reviewed and all control infants reported to have died before four months of age were excluded.

Cases and controls were excluded if they had a recorded birth weight of less than 500 grams or a gestational age of less than 24 weeks, to avoid possibly invalid or extremely uncommon gestations.

To evaluate parity, the key explanatory variable was the mother's total number of live born babies who were reported in the vital statistics data to be alive at the time of the birth of the case or control infant. This number was used as a proxy for the number of siblings and was evaluated as both a continuous and a categorical variable (0, 1, 2, 3, and 4 or more live births). Similarly, to evaluate maternal age, I examined mother's age in years at the time of the infant's birth as a continuous variable and as a categorical variable, based on whether the mother was born before January 1, 1997 and therefore likely to have received at least one dose of whole-cell (DTwP) pertussis vaccine versus mothers born on or after January 1, 1997, and therefore likely to have received only DTaP vaccine.

Additional individual-level covariates for inclusion in the analysis were selected based upon the findings of prior studies and the information available in the vital statistics database. These variables include: maternal race and ethnicity (non-Hispanic white; non-Hispanic, black; non-Hispanic Asian/Pacific Islander (API); and Hispanic of any race), a detailed Hispanic-ethnicity variable (Mexican, Central or South American, Puerto Rican or other/unknown); mother's nationality (U.S.-born versus foreign-born); anticipated payer for prenatal care (Medicaid versus private); total number of prenatal care visits, as a proxy for access to care; infant sex, birth weight, and gestational age; hospital of birth; and geographic region of residence within California. Twelve geographic regions were used, as further described in Appendix A.

First, bivariate comparisons of maternal and infant characteristics between cases and controls were calculated using Chi-square tests for categorical variables and associated odds ratios (ORs) and 95% confidence intervals (CIs) were constructed; two-sided p-values were calculated using analysis of variance for normally distributed continuous data or the Wilcoxon-Mann-Whitney test for non-normally distributed continuous variables and the Cochran-Armitage test to evaluate trends. Pertussis cases were stratified by birth hospital, and the incidence of pertussis among infants less than four months of age per 1,000 births was calculated for each facility.

Similarly, cases and controls were stratified into Hispanic, of any race, and non-Hispanic, of any race, and maternal and infant characteristics of cases and controls were also compared.

Next, multivariate logistic regression analysis was used to calculate the OR and 95% CI of pertussis among first born infants compared to later born infants, controlling for potential confounding factors. Six multivariate models were constructed: Models 1a and 1b evaluated infants of all racial and ethnic groups including parity as a continuous variable [Model 1a] or a categorical variable [Model 1b]; Models 2a and 2b evaluated characteristics associated with pertussis in Hispanic infants only, including parity as a continuous variable [Model 2a] or a categorical variable [Model 2b]; and Models 3a and 3b evaluated characteristics associated with pertussis in non-Hispanic infants only, including parity as a continuous variable [Model 2a] or a categorical variable [Model 3b].

Covariates that were significant at the $p<0.05$ level in bivariate comparisons were considered for inclusion in the multivariate models; the stratified bivariate comparisons were used for the Hispanic-only and non-Hispanic-only models. Possible interaction terms included maternal age and parity, maternal age and birth before 1997, and maternal race and parity; interaction terms were retained in the model if the p-value on the coefficient was <0.10.

RESULTS

A total of 783 infants born in 2013-2014 who developed pertussis at less than four months of age were reported to CDPH. Of these, five were excluded: four were known to have been born out of state and one had a recorded gestational age of less than 24 weeks. Of the remaining 778 infants, 755 (97%) could be linked with their birth certificate records.

There were 995,267 children born alive in California who survived to at least four months of age and who did not have a reported case of pertussis during their first four months of life. Of these, 1,778 were excluded for having invalid or extremely uncommon gestational ages before 24 weeks or birth weights below 500 grams; therefore, 755 cases and 993,489 controls were included in the final dataset.

All infants:
In the bivariate analysis including all infants, mothers of infants with pertussis were significantly more likely to be Hispanic (OR 2.70, 95% CI 2.30-3.17) and significantly less likely to be Asian/Pacific Islander (API) (OR 0.29, 95% CI 0.21-0.41), Black (OR 0.66, 95% CI 0.45-0.97) or White (OR 0.54, 95% CI 0.44-0.65). Mothers of infants with pertussis were younger on average (median ages 28 versus 29 years, respectively, p=0.002) and were more likely to have been born in 1997 or later (OR 3.69, 95% CI 2.39-5.70) but also had more prior live births compared to mothers of infants without pertussis (mean 1.63 versus 1.08 prior births, p-value <0.001). Mothers of infants with pertussis were more likely to have had Medicaid (Medi-Cal) as the payer for prenatal care (OR 2.53; 95% CI 2.15-2.97)) and less likely to have had private insurance (OR 0.42; 95% CI 0.36-0.50); however, there was no difference in the number of prenatal visits. Infants with pertussis were more likely to have been born preterm (OR 1.38; 95% CI 1.10-1.73) or to have had a birth weight below 2,500 grams (OR 1.32; 95% CI 1.01-1.71); no difference was observed for sex of the infant (Table 1).

Significantly more cases than expected were reported from the Central Valley region (OR 1.99; 95% CI 1.63-2.24) and the San Diego region (OR 1.61; 95% CI 1.32-1.97), and fewer cases were reported from the San Francisco Bay Area region (OR 0.57; 95% CI 0.46-0.72) (Table 1). Two hundred sixty-one hospitals in California had at least 100 live births during 2013 and 2014. Of these hospitals, 184 (70%) had at least one infant reported with pertussis before four months of age, and the median number of cases in each facility was 2 (range 0-31 cases). Eighty-four hospitals had an incidence of $\geq$1 pertussis case younger than four months of age per 1,000 births and the median incidence was 0.5 cases per 1,000 births (range 0-4.6 cases per 1,000 births) (Appendix B).

In the multivariate analyses that included all infants [Models 1a and 1b], infants with pertussis were nearly twice as likely to be Hispanic (OR 1.89; 95% CI 1.51-2.36) and less likely to be Asian or Pacific Islander (OR 0.57; 95% 0.38-0.84), after adjusting for covariates. Mothers of infants with pertussis were more than twice as likely to have been born on or after January 1, 1997 (OR 2.65; 95% CI 1.59-4.41), even after adjusting for mother's age, and also had more prior births, with an increase in the likelihood of pertussis with each additional prior birth (OR for 2 prior births versus 0 prior births 1.39; 95% CI 0.92-2.11; OR for 3 prior births versus 0 prior births 1.82; 95% CI 1.02-3.26) (Tables 2a and 2b). In addition, having been born prematurely remained significantly associated with having pertussis (OR 1.40; 95% CI 1.04-1.87). No interaction terms were retained in the models. In post-hoc analyses, Hispanic ethnicity was associated with both mother's birth on or after January 1, 1997 (OR for Chi-squre test 4.5; 95% CI 4.3-4.8) and increased maternal parity (p-value for two sided Wilcoxon-Mann-Whitney test <0.001).

Hispanic infants:
In the bivariate analyses of Hispanic infants, mothers of infants with pertussis were more likely to be of Mexican origin (OR 2.70; 95% CI 2.30-3.17) and less likely to be of Central or South American (OR 0.54, 95% CI 0.44-0.65) or Puerto Rican (OR 0.66; 95%

CI 0.45-0.97) origin; however, no difference was observed in the risk of pertussis by mother's place of birth being in the U.S. or outside the U.S.. Similar to the trends observed among all infants, Hispanic mothers of infants with pertussis were younger (median age 28 versus 29 years, p-value=0.002) and more likely to have been born on January 1, 1997 or later (OR 3.69; 95% CI 2.39-5.70), but also had more prior live births compared to Hispanic mothers of infants without pertussis (mean 1.69 versus 1.27, p-value <0.001). Hispanic mothers of infants with pertussis were more likely to have had Medicaid (Medi-Cal) as the payer for prenatal care (OR 1.98; 95% CI 1.60-2.47)) and less likely to have had private insurance (OR 0.50; 95% CI 0.40-0.62); there was no difference observed in the number of prenatal visits. Hispanic infants with pertussis were more likely to have been born preterm (OR 1.63; 95% CI 1.02-1.09) or to have been of low birth weight (OR 1.47; 95% CI 1.09-1.99), and no difference was observed for sex of the infant (Table 3). No significant regional differences in the residence of infants with pertussis were observed among Hispanic infants.

In the multivariate analyses that included only Hispanic infants [Models 2a and 2b], only three variables showed an independent association with pertussis: the number of prior live births, mother's birth before 1997, and infant having been born pre-term. Hispanic mothers of infants with pertussis were more likely to have been born in January 1, 1997 or later (OR 2.59; 95% CI 1.50-4.46), even when adjusting for mother's age. However, Hispanic mothers of infants with pertussis were also more likely to have had more prior births, with an increase in likelihood of pertussis for each additional birth (OR for 2 versus 0 prior births 1.67; 95% CI 1.25-2.22; OR for 3 versus 0 prior births 2.22; 95% CI 1.58-3.10 and OR for 4 or more versus 0 prior births 3.12; 95% CI 2.16-4.50) (Tables 4a and 4b). Preterm birth remained significantly associated with pertussis (OR 1.65; 95% CI 1.20-2.27). There were no independent associations with pertussis observed among any of the specific Hispanic national origins or the payer types for prenatal care (Tables 4a and 4b).

Non-Hispanic infants:
In the bivariate analyses of non-Hispanic infants, mothers of infants with pertussis were more likely to be White (OR 1.49; 95% CI 1.10-2.01) and less likely to be Asian or Pacific Islander (OR 0.52; 95% CI 0.34-0.67). Non-Hispanic mothers of infants with pertussis were less likely to be foreign-born (OR 0.48, 95% 0.34-0.67). There was no difference in the age of non-Hispanic mothers with and without pertussis. Similar to trends observed among Hispanic infants, mothers of infants with pertussis were more likely to have been born on January 1, 1997 or later (OR 6.73; 95% CI 2.50-18.11) and to have had more prior live births compared to mothers of infants without pertussis (mean 1.43 versus 0.91, p-value <0.001). Non-Hispanic mothers of infants with pertussis were more likely to have had Medicaid as the payer for prenatal care (OR 1.73; 95% CI 1.27-2.34)) and less likely to have had private insurance (OR 0.69; 95% CI 0.51-0.92). Similarly, there was no difference observed in the number of prenatal visits. Differing from what was observed for Hispanic infants with pertussis, non-Hispanic infants with pertussis were not more likely to have been born preterm or to have been born of low birth weight ,and no difference was observed for infant sex between non-Hispanic infants with and without pertussis (Table 5).

Regional difference were observed in the rate of pertussis among non-Hispanic infants; significantly more cases than expected were reported from the Central Valley and San Diego regions and significantly fewer cases of pertussis from the San Francisco Bay Area and Los Angeles regions (Table 5).

In the multivariate analyses that included only non-Hispanic infants [Models 3a and 3b], similar trends were observed. Mothers of infants with pertussis were more likely to have been born on January 1, 1997 or later (OR 4.35; 95% CI 1.01-18.76) and also more likely to had more prior live births, with a dose-response effect observed for each additional prior birth (OR for 0 versus 1 prior birth, 1.57; OR for 2 versus 0 prior births 2.19; OR for 3 versus 0 prior births 5.01). Regional differences were also observed in the multivariate model, with significantly more infants with pertussis being reported from the San Diego and Central Valley regions than expected (OR 3.06; 95% CI 1.88-5.00 and OR 4.61; 95% CI 3.01-7.05, respectively). There were no differences observed between infants with and without pertussis by maternal age, payer for prenatal care, the number of prenatal visits received, infant's birth weight or infant's gestational age (Tables 6a and 6b).

DISCUSSION

This is the largest epidemiologic investigation of the risk factors for pertussis among Hispanic and non-Hispanic infants younger than four months of age. In our study, increased maternal parity was consistently associated with a greater likelihood of pertussis in all models, even when adjusting for important covariates. In the stratified models, a clear dose-response effect was observed, with increasing likelihood of pertussis with each additional prior live birth. These findings suggest that infants of all race/ethnicities who have older siblings or who reside in larger households are at increased risk of pertussis, consistent with a recent study indicating that siblings are now the most common source of *B. pertussis* for young infants.

Hispanic ethnicity confounds the relationship between maternal parity and pertussis, because differences were identified in the stratified models compared to the crude model that included all infants. In the multivariate models that included all infants, increasing parity and maternal age largely explained the increased odds of pertussis observed among Hispanic infants, because the addition of these covariates in the multivariate model lowered the OR for Hispanic ethnicity. Hispanic ethnicity was associated with both increased maternal parity and mother's birth on or after January1, 1997. However, Hispanic ethnicity remained an independent risk factor for pertussis at a young age, even when adjusting for other covariates.

This study identified another important risk factor for pertussis in early infancy: mothers of infants with pertussis were younger, and having a mother born during or after 1997, who likely received only DTaP vaccines and no doses of DTwP vaccine, was associated with an increased odds of pertussis at a young age. It is possible that infants born to mothers who have received only DTaP receive lower levels of transplcentally-acquired

anti-pertussis antibodies, making them more susceptible to pertussis. To date, studies that have evaluated levels of pertussis antibody transfer from mother to fetus have primarily included women who had received at least one dose of DTwP; similar studies are needed to determine if antibody transfer among women who received Tdap during pregnancy differs in women who were primed with DTwP versus DTaP. The cohort of women who have received only DTaP vaccine will comprise a growing proportion of child-bearing women over time, including during the next cyclic peak of pertussis incidence. As a result, it will be increasingly important to determine the effectiveness of Tdap vaccination during pregnancy in protecting infants and determine if lower titers of antibodies are transferred from DTaP-only mothers.

Although this study found that Medicaid insurance for prenatal care was associated with an increased likelihood of pertussis in the bivariate analyses, there was not an independent association between Medicaid insurance for prenatal care and pertussis in the stratified multivariate analyses evaluating Hispanic and non-Hispanic infants separately. There were also no observed differences between infants with and without pertussis with regard to the number of prenatal visits, suggesting that lack of prenatal care or inability to access care are not major factors influencing the risk of pertussis for young infants.

A major limitation of this study is that data on mother's Tdap vaccination history were unavailable, so I were unable to evaluate how this variable affected the infant's risk for pertussis. Specifically, I was not able to determine if women of higher parity were less likely to have received Tdap vaccination during subsequent pregnancies, which could be a plausible mechanism for an increased risk of pertussis in children of higher birth order. However, this is unlikely to explain the decades-long trend of a higher rate of pertussis among Hispanic infants that has been present since before the prenatal Tdap recommendation was promulgated. Similarly, I was not able to assess whether younger women who were born in or after 1997 were less likely to have received Tdap vaccine during pregnancy. Such women may have received Tdap vaccine in accord with the routine adolescent recommendation, but unless vaccinated during pregnancy would likely not have transfered protective levels of anti-pertussis antibodies to their infants.

Another potential limitation of this study is that surveillance data were used to identify pertussis cases. Surveillance data are reported by laboratories and clinicians to public health officials and some cases may be missed. This may bias these results to be generalizable only to more severe cases, which are more likely to be brought for medical care and be reported to public health. However, because this study was limited to pertussis cases occurring among very young infants, who often develop more severe disease, reporting bias may be less of a concern. Furthermore, the study periods included two years when pertussis was widely reported in the media and there was a high level of awareness among clinicians and the general public.

Several regions of California and birth hospitals stood out as having high numbers of cases and an increased incidence of pertussis cases among infants younger than four months of age. Obstetric providers in these areas should be targeted to encourage

stocking vaccine in the office and providing Tdap vaccine on-site during routine prenatal care visits.

Efforts should be made to encourage all prenatal care providers to recommend strongly that their patients receive Tdap vaccination at the start of the third trimester of each pregnancy at the earliest opportunity, regardless of prior Tdap vaccination history. To minimize barriers to receiving vaccine, Tdap vaccine should be offered on-site during routine prenatal visits. Also, administration of an additional booster dose of pertussis vaccine should be considered for siblings and other household members of young infants who are several years out from receipt of their prior pertussis-containing vaccine.

CONCLUSION

This study adds to the growing body of evidence that the increased incidence of pertussis observed among Hispanic infants is largely driven by larger household size. Infants of all racial/ethnic groups who have older siblings have a greater likelihood of developing pertussis before four months of age.

An important finding from this study is that younger mothers who were born after the switch from DTwP to DTaP vaccine in the United States were more likely to have an infant with pertussis than older mothers, who were likely to have received at least one dose of DTwP vaccine. More studies are needed to determine if the titer of antibodies transferred across the placenta differs between women who have received DTwP and those who have received only DTaP.

Obstetricians should ensure that all pregnant women receive Tdap vaccine during the third trimester of each pregnancy, regardless of prior vaccination history. Administering a pertussis booster to all household contacts who have not been vaccinated in the prior two years should also be considered, particularly if the mother did not receive Tdap during pregnancy.

TABLES AND FIGURES

Table 1: Infant and maternal characteristics* of all infants <4 months of age with and without pertussis who were born in California, 2013-2014

	Case		Control				
	N	(%)	N	(%)	p-value	OR	95% CI
Infant characteristics							
Male	402/755	(53)	508,982/993,485	(51)	0.270	0.92	0.80-1.06
Preterm (<37 weeks gestation)	**85/755**	**(11)**	83,492/993,489	(8)	**0.005**	**1.38**	**1.10-1.73**
Low birth weight (<2,500 grams)	**63/755**	**(8)**	64,093/993,431	(6)	**0.034**	**1.32**	**1.01-1.71**
Maternal characteristics							
Race/ethnicity							
Hispanic	**533/743**	**(72)**	474,451/974,305	(49)	**<0.001**	**2.7**	**2.30-3.17**
White, non-Hispanic	**131/727**	**(18)**	274,970/946,462	(29)	**<0.001**	**0.54**	**0.44-0.65**
Black, non-Hispanic	**26/727**	**(4)**	50,479/946,462	(5)	**0.035**	**0.66**	**0.45-0.97**
Asian/Pacific Islander	**37/727**	**(5)**	146,562/946,462	(15)	**<0.001**	**0.29**	**0.21-0.41**
Foreign-born	273/755	(36)	379,950/993,489	(38)	0.239	0.91	0.79-1.06
Maternal age in years¶ (median [IQR])	**28 [22-33]**		29 [24-33]		**0.002**		
Born after 1997	**21/755**	**(3)**	7,646/993,489	(1)	**<0.001**	**3.69**	**2.39-5.70**
Number of prenatal visits† (median [IQR])	12 [10-14]		12 [10-14]		0.901		
Number of prior births‡ (median [IQR])	1 [1-3]		1 [1-2]		<0.001		
Payer							
Self pay	**15/663**	**(<1)**	38,999/906,176)	(4)	**0.010**	0.51	0.31-0.86
Medicaid (Medi-Cal)	**439/663**	**(66)**	395,796/906,176	(44)	**<0.001**	**2.53**	**2.15-2.97**
Private	**209/663**	**(32)**	471,381/906,176	(52)	**<0.001**	**0.42**	**0.36-0.50**
Region of residence¶¶					0.115**		
Bay Area	83/755	(11)	176,170/993,489	(18)			
Central Coast	30/755	(4)	36,237/993,489	(4)			
Central Valley	115/755	(15)	81,944/993,489	(8)			
Inland Empire	79/756	(10)	104,092/993,489	(10)			
Los Angeles	212/755	(28)	289,357/993,489	(29)			
Northern Coast	7/755	(1)	6,680/993,489	(1)			
Northern Inland	2/755	(<1)	6,6969/993,489	(1)			
Orange	55/755	(7)	81,292/993,489	(8)			
Sacramento/Upper Sierras	34/755	(5)	68,471/993,489	(7)			
San Diego	**113/755**	**(15)**	97,692/993,489	(10)		**1.61**	**1.32-1.97**
Upper Central Valley/Yosemite	25/755	(3)	43,922/993,489	(4)			
Western Basin	0/755	(0)	663/993,489	(<1)			

*Of those with known data

¶Restricted to those aged 14-44 years

†Restrcited to those with less than 50 total prenatal visits

‡†Restrcited to those with less than 11 prior live births

**P value for trend; non-significant p values and ORs not shown

¶¶Counties attributed to each region are listed in Appendix A.

Table 2a: Multivariate regression results evaluating maternal and infant characteristics associated with pertussis among infants younger than four months of age [Model 1a]

Parameter	OR	95% CI
Maternal Characteristics		
Age	1.00	0.99-1.02
Birth in/after 1997	2.65	1.59-4.41
Race/ethnicity		
White	REF	
Hispanic	1.89	1.51-2.36
Black	0.83	0.52-1.34
API	0.57	0.38-0.84
Total prior births	1.03	1.02-1.04
Payer		
Self pay	REF	
Medicaid	1.71	1.01-2.89
Private	0.90	0.53-1.54
Infant Characteristics		
Preterm*	1.39	1.04-1.87
Low birthweight†	1.10	0.78-1.55

*indicates infants born between 27 and 36 weeks gestation; infants born <27 weeks gestation were excluded

†indicates infants with birth weight of 500-2500 grams; infants with birth weight of <500 grams were excuded

Table 2b: Multivariate regression results evaluating maternal and infant characteristics associated with pertussis among infants younger than four months of age of any race/ethnicity [Model 1b]

Parameter	OR	95% CI
Maternal Characteristics		
Age	0.97	0.96-0.99
Birth in/after 1997	2.84	1.69-4.76
Race/ethnicity		
White	REF	
Hispanic	1.69	1.35-2.12
Black	0.74	0.46-1.19
API	0.62	0.42-0.92
Total prior births		
0 (first born)	REF	
1	1.16	0.88-1.53
2	1.39	0.92-2.11
3	1.82	1.02-3.26
4 or more	1.8	0.74-4.36
Payer		
Self pay	REF	
Medicaid	1.46	0.86-2.47
Private	0.96	0.56-1.63
Infant Characteristics		
Preterm*	1.32	0.99-1.76
Low birthweight†	1.14	0.81-1.60

*indicates infants born between 27 and 36 weeks gestation; infants born <27 weeks gestation were excluded

†indicates infants with birth weight of 500-2500 grams; infants with birth weight of <500 grams were excuded

Table 3: Infant and maternal characteristics* of among Hispanic infants <4 months of age with and without pertussis who were born in California, 2013-2014

	Hispanic Cases		Hispanic Non-Cases				
	N	(%)	N	(%)	p-value	OR	95% CI
Infant characteristics							
Male	287/533	(54)	242,164/232,286	(51)	0.195	0.89	0.75-1.06
Preterm (<37 weeks gestation)	**70/533**	**(13)**	40,376/474,451	(9)	**<0.001**	**1.63**	**1.02-1.09**
Low birth weight (<2,500 grams)	**46/533**	**(9)**	28,642/474,421	(6)	**0.012**	**1.47**	**1.09-1.99**
Maternal characteristics							
Hispanic ethnicity							
Mexican	**533/743**	**(72)**	474,451/974,305	(49)	**<0.001**	**2.7**	**2.30-3.17**
Central/South American	**131/727**	**(18)**	274,970/946,462	(29)	**<0.001**	**0.54**	**0.44-0.65**
Puerto Rican	**26/727**	**(4)**	50,479/946,462	(5)	**0.035**	**0.66**	**0.45-0.97**
Other/unknown	**37/727**	**(5)**	146,562/946,462	(15)	**<0.001**	**0.29**	**0.21-0.41**
Foreign-born	232/533	(44)	211,134/474,451	(45)	0.651	0.961	0.81-1.14
Maternal age in years¶ (median [IQR])	**28 [22-33]**		29 [24-33]		**0.002**		
Born after 1997	**21/755**	**(3)**	7,646/993,489	(1)	**<0.001**	**3.69**	**2.39-5.70**
Number of prenatal visits† (median [IQR])	12 [10-14]		12 [10-14]		0.901		
Number of prior births‡ (median [IQR])	**1 [1-3]**		1 [1-2]		**<0.001**		
Payer							
Self pay	9/474	(2)	9,644/431,300	(2)	0.620	0.85	0.44-1.64
Medicaid (Medi-Cal)	**370/474**	**(78)**	276,924/431,300	(64)	**<0.001**	**1.98**	**1.60-2.47**
Private	**95/474**	**(20)**	144,732/431,300	(34)	**<0.001**	**0.50**	**0.40-0.62**
Region of residence¶¶					0.352**		
Bay Area	53/533	(10)	53,379/474,451	(11)			
Central Coast	25/533	(5)	22,648/474,451	(5)			
Central Valley	87/533	(16)	52,439/474,451	(11)			
Inland Empire	57/533	(11)	60,839/474,451	(13)			
Los Angeles	177/533	(33)	161,424/474,451	(34)			
Northern Coast	2/533	(<1)	1,525/474,451	(<1)			
Northern Inland	0/533	(0)	940/474,451	(<1)			
Orange	49/533	(9)	36,169/474,451	(8)			
Sacramento/Upper Sierras	18/533	(3)	18,428/474,451	(4)			
San Diego	47/533	(9)	43,132/474,451	(9)			
Upper Central Valley/Yosemite	18/533	(4)	23,286/474,451	(5)			
Western Basin	0/533	(0)	242/474,451	(1)			

*Of those with known data

¶Restricted to those aged 14-44 years

†Restrcited to those with less than 50 total prenatal visits

‡Restrcited to those with less than 11 prior live births

**P value for trend; non-significant p values and ORs not shown

¶¶Counties attributed to each region are listed in Appendix A.

Table 4a: Multivariate regression results evaluating maternal and infant characteristics associated with pertussis among Hispanic infants younger than four months of age [Model 2a]

Parameter	OR	95% CI
Maternal Characteristics		
Age	1.01	0.99-1.02
Birth in/after 1997	2.59	1.50-4.46
Hispanic ethnicity		
Mexican		REF
Central/South American	0.64	0.45-0.92
Puerto Rican	0.86	0.28-2.68
Other/Unknown	1.25	0.97-1.61
Total prior births	1.03	1.01-1.05
Payer		
Self pay		REF
Medicaid	1.44	0.74-2.80
Private	0.71	0.36-1.41
Infant Characteristics		
Preterm*	1.65	1.20-2.27
Low birthweight†	0.97	0.66-1.45

*indicates infants born between 27 and 36 weeks gestation; infants born <27 weeks gestation were excluded

†indicates infants with birth weight of 500-2500 grams; infants with birth weight of <500 grams were excuded

Table 4b: Multivariate regression results evaluating maternal and infant characteristics associated with pertussis among Hispanic infants younger than four months of age [Model 2b]

Parameter	OR	95% CI
Maternal Characteristics		
Age	0.98	0.96-1.00
Birth after 1997	2.64	1.52-4.60
Hispanic ethnicity		
Mexican		REF
Central/South American	0.69	0.48-0.99
Puerto Rican	0.89	0.29-2.78
Other/Unknown	1.22	0.95-1.58
Total prior births		
0 (first born)		REF
1	1.24	0.95-1.61
2	**1.67**	**1.25-2.22**
3	**2.22**	**1.58-3.10**
4 or more	**3.12**	**2.16-4.50**
Payer		
Self pay		REF
Medicaid	1.28	0.66-2.49
Private	0.75	0.38-1.48
Infant Characteristics		
Preterm*	1.56	1.15-2.17
Low birthweight†	1.01	0.68-1.49

*indicates infants born between 27 and 36 weeks gestation; infants born <27 weeks gestation were excluded

†indicates infants with birth weight of 500-2500 grams; infants with birth weight of <500 grams were excuded

Table 5: Infant and maternal characteristics* of non-Hispanic infants <4 months of age with and without pertussis who were born in California, 2013-2014

	Non-Hispanic Cases		Non-Hispanic Non-Cases				
	N	(%)	N	(%)	p-value	OR	95% CI
Infant characteristics							
Male	103/210	(49)	242,912/499,851	(49)	0.896	1.02	0.78-1.33
Preterm (<37 weeks gestation)	15/210	(7)	40,901/499,854	(8)	0.583	0.86	0.51-1.46
Low birth weight (<2,500 grams)	17/210	(8)	33,618/499,827	(7)	0.428	1.22	0.74-2.01
Maternal characteristics							
Race/ethnicity							
White, non-Hispanic	**131/194**	**(68)**	274,970/471,958	(58)	**0.009**	**1.49**	**1.10-2.01**
Black, non-Hispanic	26/194	(13)	50,426/471,958	(11)	0.221	1.29	0.86-1.96
Asian/Pacific Islander	**37/194**	**(19)**	146,562/471,958	(31)	**<0.001**	**0.52**	**0.37-0.75**
Foreign-born	**39/210**	**(19)**	161,943/499,854	(32)	**<0.001**	**0.48**	**0.34-0.67**
Maternal age in years¶ (median [IQR])	30 [25-34]		31 [27-34]		0.228		
Born after 1997	**4/210**	**(2)**	1,439/499,854	(<1)	**<0.001**	**6.73**	**2.50-18.11**
Number of prenatal visits† (median [IQR])	12 [10-14]		12 [10-14]		0.450		
Number of prior births (median [IQR])‡	**1 [0-2]**		**1 [0-1]**		**<0.001**		
Payer							
Self pay	6/178	(3)	28,628/457,132	(6)	0.111	0.52	0.23-1.18
Medicaid (Medi-Cal)	**65/178**	**(37)**	114,230/457,132	(25)	**<0.001**	**1.73**	**1.27-2.34**
Private	**107/178**	**(60)**	314,274/457,132	(69)	**0.013**	**0.69**	**0.51-0.92**
Region of residence¶¶					**<0.001****		
Bay Area	**27/210**	**(13)**	116,706/499,854	(23)		**0.48**	**0.32-0.73**
Central Coast	5/210	(2)	13,412/499,854	(3)			
Central Valley	**28/210**	**(13)**	29,059/499,854	(6)		**2.49**	**1.67-3.71**
Inland Empire	22/210	(10)	42,674/499,854	(9)			
Los Angeles	**34/210**	**(16)**	124,975/499,854	(25)		**0.58**	**0.40-0.84**
Northern Coast	5/210	(2)	5,100/499,854	(1)			
Northern Inland	2/210	(1)	5,973/499,854	(1)			
Orange	5/210	(2)	43,975/499,854	(9)			
Sacramento/Upper Sierras	16/210	(8)	49,469/499,854	(10)			
San Diego	**59/210**	**(28)**	47,779/499,854	(10)		**3.7**	**2.74-5.00**
Upper Central Valley/Yosemite	7/210	(3)	20,319/499,854	(4)			
Western Basin	0/210	(0)	416/499,854	(<1)			

*Of those with known data

¶Restricted to those aged 14-44 years

†Restrcited to those with less than 50 total prenatal visits

‡Restrcited to those with less than 11 prior live births

**P value for trend; non-significant p values and ORs not shown

¶¶Counties attributed to each region are listed in Appendix A.

Table 6a: Multivariate regression results evaluating maternal and infant characteristics associated with pertussis among non-Hispanic infants younger than four months of age [Model 3a]

Parameter	OR	95% CI
Maternal Characteristics		
Age	1.01	0.98-1.04
Birth in/after 1997	3.53	0.83-15.10
Race/ethnicity		
White	REF	
Black	0.98	0.59-1.59
API	0.92	0.57-1.47
Born outside USA	0.59	036-0.95
Total prior births	**1.03**	**1.01-1.05**
Payer		
Self pay	REF	
Medicaid	1.63	0.68-3.92
Private	0.97	0.41-2.28
Geographic Region*		
Bay Area	0.86	0.51-1.46
Central Valley	**3.31**	**2.03-5.39**
Los Angeles	0.99	0.61-1.59
San Diego	**4.23**	**2.77-6.47**

*Geographic regions listed in Appendix A

Table 6b: Multivariate regression results evaluating maternal and infant characteristics associated with pertussis among non-Hispanic infants younger than four months of age [Model 3b]

Parameter	OR	95% CI
Maternal Characteristics		
Age	0.97	0.94-1.00
Birth in/after 1997	**4.35**	**1.01-18.76**
Race/ethnicity		
White	REF	
Black	0.84	0.51-1.39
API	0.93	0.58-1.49
Born outside USA	0.63	0.39-1.02
Total prior births		
0 (first born)	REF	
1	**1.57**	**1.05-2.36**
2	**2.19**	**1.35-3.56**
3	**5.01**	**2.95-8.52**
4 or more	**4.07**	**2.03-8.14**
Payer		
Self pay	REF	
Medicaid	1.38	0.58-3.03
Private	1.07	0.46-2.50
Geographic Region*		
Bay Area	0.99	0.58-1.68
Central Valley	**3.06**	**1.88-5.00**
Los Angeles	1.13	0.70-1.82
San Diego	**4.61**	**3.01-7.05**

*Geographic regions listed in Appendix A

Chapter 5.
Discussion, Significance and Future Steps

The incidence of pertussis is increasing both in the U.S. and globally, so there is a critical need to evaluate the current vaccination strategies aimed at preventing pertussis in young infants, who are at greatest risk of hospitalization and death from the disease. The findings from these studies provide important evidence in determining the impact of prenatal Tdap vaccination on the risk of pertussis and severe pertussis in young infants.

In Chapter 1, the context for this research was provided through a summary of the literature on pertussis and pertussis-containing vaccines.

Chapter 2 presented the first study in the United States evaluating the effectiveness of maternal Tdap vaccination during pregnancy on preventing pertussis in infants and demonstrated that prenatal Tdap vaccination is more effective than postpartum Tdap vaccination. Additionally, this study provided new evidence that administration of Tdap vaccine between 27 and 36 weeks gestation is more effective than earlier administration during the second trimester. Not all countries that recommend prenatal Tdap do so in the same gestational window; for example, in Mexico, all women are recommended to receive Tdap during pregnancy starting at 20 weeks gestation[119]. The findings from this study also suggest that administration during 27 through 31 weeks gestation is more effective than administration during 32 through 36 weeks gestation; due to the risk of early delivery, all women should receive Tdap at the earliest opportunity during the recommended window.

Chapter 3 presented the first known study to evaluate the impact of prenatal Tdap vaccination on the severity of pertussis in young infants. In this retrospective evaluation, I determined that infants younger than three months of age whose mothers received Tdap vaccine during pregnancy had a lower risk of hospitalization or intensive care unit admission and had shorter hospital stays compared to infants born to unvaccinated mothers, indicating that prenatal Tdap vaccination reduces pertussis severity. Tdap vaccination during pregnancy was determined to be 58% effective at preventing hospitalization among infants with pertussis compared with infants with pertussis who were born to unvaccinated mothers.

In Chapter 4, I presented the results of a case-control study in which I described infant pertussis cases younger than four months of age and evaluated maternal and infant characteristics associated with pertussis among Hispanic and non-Hispanic infants. Identifying hospitals with a high incidence of pertussis allows for more strategic outreach efforts to ensure the prenatal care providers in communities at highest risk of pertussis adopt the ACIP recommendation for routine prenatal Tdap vaccination. Additionally, I identified two new risk factors for pertussis in infants of all racial/ethnic groups. First, infants whose mothers are of higher parity were more likely to be reported with pertussis in the first four months of life, compared to first-born infants, with

the odds of pertussis increasing with increasing maternal parity. The identification of this new risk factor for pertussis is important, as it highlights the need for pregnant women to receive Tdap vaccine during each pregnancy to ensure infants of higher birth order are protected in their first weeks of life. Second, infants with pertussis were more likely to have younger mothers, who were born in 1997 and later and who likely received only DTaP vaccine in childhood. More research is needed to evaluate transplacental antibody transfer by women who have received only acellular pertussis vaccines, to determine if the effectiveness of prenatal Tdap in preventing pertussis in their infants is reduced. These two risk factors, maternal age and parity, largely explained the increased risk of pertussis observed among Hispanic infants.

These studies collectively support the current ACIP recommendation to give Tdap vaccine to all pregnant women during the third trimester of each pregnancy, which is likely to be the most effective strategy in reducing morbidity and mortality of pertussis among young infants in the United States. All prenatal care providers should strongly recommend and offer Tdap vaccine to women at the earliest opportunity between 27-36 weeks of gestation of every pregnancy. Adoption of a similar recommendation in other countries that have noted a resurgence in reported pertussis should be considered.

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Appendix A

California County Regions

Region 1: San Francisco Bay Area
- Alameda
- Contra Costa
- Marin
- Napa
- San Francisco
- San Mateo
- Santa Clara
- Solano
- Sonoma

Region 2: Central Coast
- Monterey
- San Benito
- San Luis Obispo
- Santa Cruz
- Santa Barbara

Region 3: Central Valley
- Fresno
- Kern
- Kings
- Madera
- Tulare

Region 4: Inland Empire
- Riverside
- San Bernardino

Region 5: Los Angeles
- Los Angeles
- Ventura

Region 6: North Coast
- Del Norte
- Humboldt
- Lake
- Mendocino

Region 7: Northern Inland
- Lassen
- Modoc
- Plumas
- Shasta
- Siskiyou
- Tehama
- Trinity

Region 8: Orange
- Orange

Region 9: Sacramento/Upper Sierras
- Butte
- Colusa
- El Dorado
- Glenn
- Nevada
- Placer
- Sacramento
- Sierra
- Sutter
- Yolo
- Yuba

Region 10: San Diego
- Imperial
- San Diego

Region 11: Upper Central Valley/Yosemite
- Alpine
- Amador
- Calaveras
- Mariposa
- Merced
- San Joaquin
- Stanislaus
- Tuolumne

Region 12: Western Basin
- Inyo
- Mono

Appendix B

Rate of pertussis cases <4 months of age by facility of birth

Facility name	Facility City	Non cases	Cases <4 months	Total births*	Rate per 1,000 births
BEST START BIRTH CENTER	SAN DIEGO	433	2	435	4.60
COASTAL COMMUNITIES HOSPITAL	SANTA ANA	1,888	7	1,895	3.69
BELLFLOWER MEDICAL CENTER	BELLFLOWER	270	1	271	3.69
MENDOCINO COAST DISTRICT HOSPITAL	FORT BRAGG	276	1	277	3.61
PALO VERDE HOSPITAL	BLYTHE	294	1	295	3.39
SCRIPPS MEMORIAL HOSPITAL: ENCINITAS	ENCINITAS	3,838	13	3,851	3.38
ST HELENA CLEARLAKE	CLEARLAKE	342	1	343	2.92
DOCTORS HOSPITAL OF MANTECA	MANTECA	1,412	4	1,416	2.82
COMMUNITY REGIONAL MEDICAL CENTER	FRESNO	11,727	31	11,758	2.64
ENLOE MEDICAL CENTER	CHICO	3,086	8	3,094	2.59
MAD RIVER COMMUNITY HOSPITAL	ARCATA	1,158	3	1,161	2.58
SANTA PAULA HOSPITAL	SANTA PAULA	792	2	794	2.52
MADERA COMMUNITY HOSPITAL	MADERA	2,950	7	2,957	2.37
TWIN CITIES COMMUNITY HOSPITAL	TEMPLETON	1,343	3	1,346	2.23
RIDGECREST REGIONAL HOSPITAL	RIDGECREST	899	2	901	2.22
ST. AGNES HOSPITAL	FRESNO	6,355	14	6,369	2.20
WESTERN MEDICAL CTR - ANAHEIM	ANAHEIM	2,361	5	2,366	2.11
KERN MEDICAL CENTER	BAKERSFIELD	5,743	12	5,755	2.09
DOWNEY REGIONAL MEDICAL CENTER	DOWNEY	2,406	5	2,411	2.07
SANTA CLARA VALLEY MEDICAL CENTER	SAN JOSE	6,801	14	6,815	2.05
WESTERN MEDICAL CTR-SANTA ANA	SANTA ANA	4,087	8	4,095	1.95
TRI-CITY MEDICAL CENTER	OCEANSIDE	5,134	10	5,144	1.94
SELMA COMMUNITY HOSPITAL	SELMA	1,052	2	1,054	1.90
PACIFIC ALLIANCE MEDICAL CENTER	LOS ANGELES	4,755	9	4,764	1.89
LOMA LINDA UNIVERSITY MED CENTER	MURRIETA	2,207	4	2,211	1.81
ST. FRANCIS MEDICAL CENTER	LYNWOOD	10,015	18	10,033	1.79
FRENCH HOSPITAL MEDICAL CENTER	SAN LUIS OBISPO	1,123	2	1,125	1.78
CORONA REGIONAL MEDICAL CENTER	CORONA	2,254	4	2,258	1.77
RANCHO SPRINGS MEDICAL CENTER	MURRIETA	6,362	11	6,373	1.73
SCRIPPS MEMORIAL HOSPITAL	LA JOLLA	7,627	13	7,640	1.70
SAN JOAQUIN GENERAL HOSPITAL	FRENCH CAMP	3,590	6	3,596	1.67
PROVIDENCE LCM SAN PEDRO	SAN PEDRO	1,205	2	1,207	1.66
BARTON MEMORIAL HOSPITAL	S. LAKE TAHOE	628	1	629	1.59
NAVAL MEDICAL CENTER (BALBOA)	SAN DIEGO	6,295	10	6,305	1.59
SIERRA VIEW DISTRICT HOSPITAL	PORTERVILLE	3,172	5	3,177	1.57
SHARP CHULA VISTA MEDICAL CENTER	CHULA VISTA	5,314	8	5,322	1.50
POMERADO HOSPITAL	POWAY	2,686	4	2,690	1.49
GROSSMONT HOSPITAL	LA MESA	7,603	11	7,614	1.44
COMMUNITY HOSPITAL OF SAN BERNARDINO	SAN BERNARDINO	4,163	6	4,169	1.44

Facility name	Facility City	Non cases	Cases <4 months	Total births*	Rate per 1,000 births
WOODLAND HEALTH CARE	WOODLAND	1,394	2	1,396	1.43
REDWOOD MEMORIAL HOSPITAL	FORTUNA	705	1	706	1.42
CLOVIS COMMUNITY HOSPITAL	CLOVIS	9,224	13	9,237	1.41
VALLEY PRESBYTERIAN HOSPITAL	VAN NUYS	7,097	10	7,107	1.41
TAHOE FOREST HOSPITAL	TRUCKEE	730	1	731	1.37
LAC HARBOR UCLA MEDICAL CENTER	TORRANCE	1,480	2	1,482	1.35
KAISER HOSPITAL: VALLEJO	VALLEJO	3,731	5	3,736	1.34
SAN FRANCISCO GENERAL HOSPITAL	SAN FRANCISCO	2,259	3	2,262	1.33
ST. MARY MEDICAL CENTER	LONG BEACH	5,279	7	5,286	1.32
SCRIPPS MERCY HOSPITAL	SAN DIEGO	3,800	5	3,805	1.31
PROVIDENCE HOLY CROSS MEDICAL CENTER	MISSION HILLS	6,277	8	6,285	1.27
COMMUNITY HOSPITAL	MONTEREY	2,372	3	2,375	1.26
ST. BERNARDINE MEDICAL CENTER	SAN BERNARDINO	4,008	5	4,013	1.25
CENTRAL VALLEY GENERAL HOSP	HANFORD	4,056	5	4,061	1.23
QUEEN OF THE VALLEY HOSPITAL	NAPA	1,624	2	1,626	1.23
HENRY MAYO NEWHALL MEMORIAL HOSPITAL	VALENCIA	2,506	3	2,509	1.20
LONG BEACH MEMORIAL MEDICAL CENTER	LONG BEACH	11,699	14	11,713	1.20
LA PALMA INTERCOMMUNITY HOSP	LA PALMA	844	1	845	1.18
KAISER FOUNDATION HOSPITAL SAN JOSE	SAN JOSE	4,265	5	4,270	1.17
PACIFIC HOSPITAL OF LONG BEACH	LONG BEACH	853	1	854	1.17
PROVIDENCE TARZANA MEDICAL CENTER	TARZANA	5,179	6	5,185	1.16
WATSONVILLE COMMUNITY HOSPITAL	WATSONVILLE	2,590	3	2,593	1.16
MERCY SOUTHWEST HOSPITAL	BAKERSFIELD	5,187	6	5,193	1.16
O'CONNOR HOSPITAL	SAN JOSE	6,053	7	6,060	1.16
WHITE MEMORIAL MEDICAL CENTER	LOS ANGELES	7,803	9	7,812	1.15
SCRIPPS MERCY HOSPITAL CHULA VISTA	CHULA VISTA	3,479	4	3,483	1.15
KAISER HOSPITAL: SOUTH BAY	HARBOR CITY	4,355	5	4,360	1.15
REGIONAL MEDICAL CENTER OF SAN JOSE	SAN JOSE	876	1	877	1.14
JOHN F. KENNEDY MEMORIAL HOSPITAL	INDIO	4,454	5	4,459	1.12
LOMPOC VALLEY MEDICAL CENTER	LOMPOC	892	1	893	1.12
CITRUS VALLEY MEDICAL CENTER-QV CAMPUS	WEST COVINA	8,114	9	8,123	1.11
SALINAS VALLEY MEMORIAL HOSPITAL	SALINAS	3,631	4	3,635	1.10
NORTHRIDGE HOSPITAL MEDICAL CENTER	NORTHRIDGE	2,732	3	2,735	1.10
LOS ALAMITOS MEDICAL CENTER	LOS ALAMITOS	2,756	3	2,759	1.09
RIVERSIDE COMMUNITY HOSPITAL	RIVERSIDE	7,411	8	7,419	1.08
SIERRA NEVADA MEMORIAL HOSPITAL	GRASS VALLEY	932	1	933	1.07
GLENDALE MEMORIAL HOSPITAL	GLENDALE	3,739	4	3,743	1.07

Facility name	Facility City	Non cases	Cases <4 months	Total births*	Rate per 1,000 births
COTTAGE HOSPITAL	SANTA BARBARA	4,689	5	4,694	1.07
MEMORIAL MEDICAL CENTER	MODESTO	3,858	4	3,862	1.04
UCSD MEDICAL CENTER	SAN DIEGO	4,864	5	4,869	1.03
LOMA LINDA UNIVERSITY MEDICAL CENTER	LOMA LINDA	5,871	6	5,877	1.02
UCI MEDICAL CENTER	ORANGE	2,973	3	2,976	1.01
NATIVIDAD MEDICAL CENTER	SALINAS	4,957	5	4,962	1.01
MARSHALL HOSPITAL	PLACERVILLE	995	1	996	1.00
EL CENTRO REGIONAL MED CNTR	EL CENTRO	1,997	2	1,999	1.00
CALIFORNIA HOSPITAL MEDICAL CENTER	LOS ANGELES	8,122	8	8,130	0.98
CONTRA COSTA REGIONAL MEDICAL CENTER	MARTINEZ	4,117	4	4,121	0.97
PARKVIEW COMMUNITY HOSPITAL MED. CNTR.	RIVERSIDE	4,187	4	4,191	0.95
MEMORIAL HOSPITAL OF GARDENA	GARDENA	2,098	2	2,100	0.95
MONTEREY PARK HOSPITAL	MONTEREY PARK	3,158	3	3,161	0.95
BAKERSFIELD MEMORIAL HOSPITAL	BAKERSFIELD	6,453	6	6,459	0.93
FOUNTAIN VALLEY REG HOSP & MED CTR	FOUNTAIN VALLEY	6,530	6	6,536	0.92
COMMUNITY MEMORIAL HOSPITAL - SAN BUENAVENTURA	VENTURA	5,489	5	5,494	0.91
ANAHEIM MEMORIAL MEDICAL CENTER	ANAHEIM	3,305	3	3,308	0.91
ST. LOUISE REGIONAL HOSPITAL	GILROY	1,103	1	1,104	0.91
GLENDALE ADVENTIST MEDICAL CENTER	GLENDALE	4,793	4	4,797	0.83
HOLLYWOOD PRESBYTERIAN MEDICAL CENTER	LOS ANGELES	7,303	6	7,309	0.82
SUTTER SOLANO MEDICAL CENTER	VALLEJO	1,226	1	1,227	0.81
EAST LOS ANGELES DOCTORS HOSPITAL	E. LOS ANGELES	1,231	1	1,232	0.81
WHITTIER HOSPITAL	WHITTIER	6,171	5	6,176	0.81
SHARP MARY BIRCH HOSPITAL	SAN DIEGO	18,555	15	18,570	0.81
TORRANCE MEMORIAL MEDICAL CENTER	TORRANCE	6,238	5	6,243	0.80
PALOMAR MEDICAL CENTER	ESCONDIDO	6,337	5	6,342	0.79
ARROWHEAD REGIONAL MEDICAL CENTER	COLTON	5,087	4	5,091	0.79
SIMI VALLEY HOSPITAL AND HEALTHCARE SERVICE	SIMI VALLEY	1,311	1	1,312	0.76
ONTARIO MEDICAL CENTER	ONTARIO	3,934	3	3,937	0.76
SUTTER TRACY COMMUNITY HOSPITAL	TRACY	1,312	1	1,313	0.76
POMONA VALLEY HOSPITAL MEDICAL CENTER	POMONA	13,477	10	13,487	0.74
KAWEAH DELTA DISTRICT HOSPITAL	VISALIA	8,364	6	8,370	0.72
KAISER FOUNDATION HOSPITAL	FONTANA	7,221	5	7,226	0.69
SUTTER DAVIS HOSPITAL	DAVIS	2,910	2	2,912	0.69
KAISER FOUNDATION HOSPITAL	RIVERSIDE	5,892	4	5,896	0.68

Facility name	Facility City	Non cases	Cases <4 months	Total births*	Rate per 1,000 births
MARIAN MEDICAL CENTER	SANTA MARIA	5,898	4	5,902	0.68
SUTTER ROSEVILLE MEDICAL CENTER	ROSEVILLE	5,986	4	5,990	0.67
GOOD SAMARITAN HOSPITAL	LOS ANGELES	7,585	5	7,590	0.66
COMM HOSP LOS GATOS-SARATOGA	LOS GATOS	1,529	1	1,530	0.65
VENTURA COUNTY MEDICAL CENTER	VENTURA	3,121	2	3,123	0.64
PRESBYTERIAN INTERCOMMUNITY HOSPITAL	WHITTIER	7,989	5	7,994	0.63
SAN JOAQUIN COMM HOSP - FBC	BAKERSFIELD	6,406	4	6,410	0.62
SANTA ROSA MEMORIAL HOSPITAL	SANTA ROSA	1,618	1	1,619	0.62
SUTTER MEDICAL CENTER	SANTA ROSA	3,237	2	3,239	0.62
ST. ROSE HOSPITAL	HAYWARD	1,621	1	1,622	0.62
KAISER FOUNDATION HOSPITAL IRVINE	IRVINE	4,872	3	4,875	0.62
DESERT REGIONAL MEDICAL CENTER	PALM SPRINGS	6,503	4	6,507	0.61
DELANO REGIONAL MEDICAL CENTER	DELANO	1,633	1	1,634	0.61
GARDEN GROVE HOSPITAL & MED. CNTR.	GARDEN GROVE	3,462	2	3,464	0.58
ANTELOPE VALLEY HOSPITAL	LANCASTER	10,471	6	10,477	0.57
KAISER PERMANENTE MEDICAL CENTER	SANTA CLARA	8,755	5	8,760	0.57
MONTCLAIR HOSPITAL MEDICAL CENTER	MONTCLAIR	1,760	1	1,761	0.57
MERCY MEDICAL CENTER - COMMUNITY	MERCED	5,457	3	5,460	0.55
MISSION HOSP REGIONAL MED CTR	MISSION VIEJO	5,485	3	5,488	0.55
JOHN MUIR MEDICAL CENTER	WALNUT CREEK	5,619	3	5,622	0.53
RONALD REAGAN UCLA HEALTH SYSTEM	LOS ANGELES	3,796	2	3,798	0.53
ALTA BATES MEDICAL CENTER	BERKELEY	13,417	7	13,424	0.52
SUTTER DELTA MEDICAL CENTER	ANTIOCH	1,949	1	1,950	0.51
LAC USC MEDICAL CENTER	LOS ANGELES	1,951	1	1,952	0.51
MERCY GENERAL HOSPITAL	SACRAMENTO	3,956	2	3,958	0.51
MERCY MEDICAL CENTER	REDDING	3,959	2	3,961	0.50
ST. JOSEPH HOSPITAL	ORANGE	10,010	5	10,015	0.50
FREMONT MEDICAL CENTER	YUBA CITY	4,055	2	4,057	0.49
LODI MEMORIAL HOSPITAL	LODI	2,066	1	2,067	0.48
ACMC-HIGHLAND CAMPUS	OAKLAND	2,196	1	2,197	0.46
KAISER FOUNDATION HOSPITAL MORENO VALLEY	MORENO VALLEY	2,196	1	2,197	0.46
KAISER HOSPITAL: OAKLAND	OAKLAND	4,492	2	4,494	0.45
TULARE DISTRICT HOSPITAL	TULARE	2,308	1	2,309	0.43
DAMERON HOSPITAL	STOCKTON	2,391	1	2,392	0.42
ST. JOSEPH'S MEDICAL CENTER	STOCKTON	4,857	2	4,859	0.41
VICTOR VALLEY COMMUNITY HOSPITAL	VICTORVILLE	2,474	1	2,475	0.40
HEMET VALLEY MEDICAL CENTER	HEMET	2,583	1	2,584	0.39
EDEN MEDICAL CENTER	CASTRO VALLEY	2,616	1	2,617	0.38
EMANUEL HOSPITAL	TURLOCK	2,632	1	2,633	0.38
CEDARS SINAI MEDICAL CENTER	LOS ANGELES	13,200	5	13,205	0.38
LITTLE COMPANY OF MARY HOSPITAL	TORRANCE	5,315	2	5,317	0.38
SUTTER MEMORIAL HOSPITAL	SACRAMENTO	10,800	4	10,804	0.37
MARIN GENERAL HOSPITAL	GREENBRAE	2,738	1	2,739	0.37

Facility name	Facility City	Non cases	Cases <4 months	Total births*	Rate per 1,000 births
SADDLEBACK MEMORIAL MED CENTER	LAGUNA HILLS	5,500	2	5,502	0.36
KAISER HOSPITAL: BALDWIN PARK	BALDWIN PARK	5,584	2	5,586	0.36
GARFIELD MEDICAL CENTER	MONTEREY PARK	8,711	3	8,714	0.34
SAN GABRIEL VALLEY MEDICAL CENTER	SAN GABRIEL	5,860	2	5,862	0.34
KAISER FOUNDATION HOSPITAL	REDWOOD CITY	2,992	1	2,993	0.33
SEQUOIA HOSPITAL	REDWOOD CITY	3,226	1	3,227	0.31
HUNTINGTON MEMORIAL HOSPITAL	PASADENA	6,711	2	6,713	0.30
KAISER FOUNDATION HOSPITAL	WALNUT CREEK	7,079	2	7,081	0.28
KAISER HOSPITAL: LOS ANGELES, CADILLAC	LOS ANGELES	3,545	1	3,546	0.28
GOOD SAMARITAN HOSPITAL	SAN JOSE	7,125	2	7,127	0.28
PIONEERS MEMORIAL HOSPITAL	BRAWLEY	3,638	1	3,639	0.27
KAISER HOSPITAL: BELLFLOWER	BELLFLOWER	7,298	2	7,300	0.27
METHODIST HOSPITAL OF SACRAMENTO	SACRAMENTO	3,651	1	3,652	0.27
DOCTORS MEDICAL CENTER	MODESTO	7,630	2	7,632	0.26
METHODIST HOSPITAL OF SOUTHERN CALIF	ARCADIA	3,825	1	3,826	0.26
KAISER HOSPITAL: SANTA ROSA	SANTA ROSA	3,873	1	3,874	0.26
LOS ROBLES HOSPITAL AND MEDICAL CENTER	THOUSAND OAKS	3,877	1	3,878	0.26
LUCILE PACKARD CHILDREN'S HOSPITAL	PALO ALTO	8,308	2	8,310	0.24
UNIV. OF CALIFORNIA MED CENTER	SAN FRANCISCO	4,242	1	4,243	0.24
MERCY SAN JUAN HOSPITAL	CARMICHAEL	4,318	1	4,319	0.23
ST. JUDE MEDICAL CENTER	FULLERTON	4,355	1	4,356	0.23
KAISER HOSPITAL: SAN DIEGO	SAN DIEGO	8,729	2	8,731	0.23
EL CAMINO HOSPITAL	MOUNTAIN VIEW	8,847	2	8,849	0.23
ST. JOHN'S REGIONAL MEDICAL CENTER	OXNARD	4,494	1	4,495	0.22
KAISER FOUNDATION HOSPITAL SOUTH SACRAMENTO	SACRAMENTO	4,801	1	4,802	0.21
REDLANDS COMMUNITY HOSPITAL	REDLANDS	5,146	1	5,147	0.19
KAISER FOUNDATION HOSPITAL ROSEVILLE	ROSEVILLE	10,408	2	10,410	0.19
PROVIDENCE ST. JOSEPH MEDICAL CENTER	BURBANK	5,239	1	5,240	0.19
HOAG MEMORIAL HOSPITAL	NEWPORT BEACH	12,150	2	12,152	0.16
CALIFORNIA PACIFIC MEDICAL CENTER	SAN FRANCISCO	10,074	1	10,075	0.10

*Births occurring in 2013 or 2014 with a gestational age of ≥24 weeks and a birth weight of ≥500 grams