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Maternal Vaccination in Argentina: Tetanus, Diphtheria, and Acellular Pertussis Vaccine Effectiveness During Pregnancy in Preventing Pertussis in Infants <2 Months of Age

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Background. In 2011, Argentina experienced its highest pertussis incidence and mortality rates of the last decade; 60% of deaths were among infants aged <2 months. In response, a dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine was recommended for all pregnant women at ≥20 weeks of gestation. Although recent studies suggest that maternal Tdap vaccination is effective at preventing infant disease, no data have come from low- or middle-income countries, nor from ones using whole-cell pertussis vaccines for primary immunization.

Methods. We conducted a matched case-control evaluation to assess the effectiveness of maternal Tdap vaccination in preventing pertussis among infants aged <2 months in Argentina. Pertussis case patients identified from September 2012 to March 2016 at 6 hospital sites and confirmed by polymerase chain reaction testing were included. Five randomly selected controls were matched to each case patient by hospital site and mother's health district. We used multivariable conditional logistic regression to calculate odds ratios (ORs). Vaccine effectiveness (VE) was estimated as (1 – OR) × 100%.

Results. Seventy-one case patients and 300 controls were included in the analysis. Forty-nine percent of case patients and 78% of controls had mothers who were vaccinated during pregnancy. Overall Tdap VE was estimated at 80.7% (95% confidence interval, 52.1%–92.2%). We found similar VE whether Tdap was administered during the second or third trimester.

Conclusions. Tdap vaccination during pregnancy is effective in preventing pertussis in infants aged <2 months in Argentina, with similar effectiveness whether administered during the second or third trimester of pregnancy.

Keywords. infant pertussis; maternal immunization; pregnancy; Tdap; vaccine effectiveness.

In Argentina, the largest peak of reported pertussis in the last decade occurred in 2011, with 10 395 suspected cases reported [1]. Seventy-six deaths occurred; 97% were in infants <1 year of age, and 60% were in infants <2 months of age [1]. At the time, the immunization schedule included doses of whole-cell pertussis vaccine at 2, 4, and 6 months of age followed by booster doses at 15–18 months and 6 years of age [2]. The schedule also included an adolescent dose of acellular pertussis vaccine (tetanus toxoid, reduced diphtheria toxoid, acellular pertussis [Tdap]) at 11 years.

Following the 2011 peak, the Argentina Ministry of Health in February 2012 recommended a dose of Tdap vaccine for all pregnant women at ≥20 weeks of gestation, with the intent of reducing morbidity and mortality in young infants [3]. The initial recommendation was for Tdap vaccine to be given during a single pregnancy; by 2016, the recommendation had been updated to include a dose with every pregnancy [3, 4]. In the first year of implementation, national Tdap coverage among pregnant women reached 51%, and by 2016, it was >65% (unpublished data, Ministerio de Salud y Desarrollo Social de Argentina).

Maternal Tdap vaccination has been recommended in multiple countries as an additional protective measure for infants [5–7]. Young infants are especially vulnerable to severe disease and death due to pertussis, and transplacental transfer of maternal antibodies to infants may provide protection during the susceptible period before primary immunization begins [8, 9]. Recent studies have demonstrated the effectiveness of maternal Tdap vaccination in preventing infant disease; however, these

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studies took place in high-income countries and among populations that use acellular pertussis vaccine for primary immunization [10–16]. Evidence of the effectiveness of this strategy in low- or middle-income countries and among populations that use whole-cell pertussis vaccines is lacking. The aim of this study was to evaluate the effectiveness of maternal Tdap vaccination in preventing pertussis among infants <2 months of age in Argentina, a middle-income country that uses whole-cell vaccine for the primary immunization series.

METHODS

Study Design and Population

We conducted a multisite, matched case-control study in Argentina to assess the effectiveness of maternal Tdap vaccination in preventing pertussis among infants <2 months of age. The study was conducted over 2 time periods (24 September 2012–31 March 2014; 1 December 2014–31 March 2016) to attain required sample size. Six reference hospital sites in 4 provinces (Buenos Aires, Neuquén, Tucumán, and Salta) participated in the study. Hospital del Niño Jesús (children's hospital, Tucumán), Hospital de Niños "Pedro de Elizalde" (children's hospital, Buenos Aires), and Hospital de Niños "R. Gutierrez" (children's hospital, Buenos Aires) participated during both time periods. Hospital "H. Heller" (general hospital, Neuquén) participated during the first time period only. Hospital Eva Perón (general hospital, Tucumán) and Hospital Público Materno Infantil (maternity and children's hospital, Salta) participated during the second time period only.

The study population included infants <2 months of age; potential case patients and controls were identified at participating hospital sites. For case patients and their matched controls, age was calculated based on date of cough onset of the case. Pertussis cases were identified through routine hospital surveillance. According to Argentina's national case definitions, a clinical case of infant pertussis was defined as acute cough illness and at least 1 of the following symptoms: paroxysmal cough, inspiratory whoop, posttussive vomiting, cyanosis, or apnea [17]. Cases included in the study met the national clinical case definition and were laboratory confirmed by conventional or real-time polymerase chain reaction (PCR). For conventional PCR, *IS481* and pertussis toxin promoter region were the targets specified; for real-time PCR, *IS481* and *ptxS1* were used [18]. Exclusion criteria for potential case patients included history of prematurity (born at <37 weeks' gestational age), history of adoption, prior enrollment in the study as either a case patient or control, lack of any contact between the case patient and his mother subsequent to birth (eg, due to death or divorce), or maternal residence outside of Argentina from the 20th week of pregnancy until delivery.

For each case, we attempted to enroll 5 controls, matched on mother's residential health district and receipt of healthcare at a participating hospital within the same province as the hospital at which the case patient was identified. Trained study personnel systematically visited all ambulatory clinics, emergency rooms, and hospital wards within each hospital site, and reviewed daily patient attendance logs to identify and randomly select potential controls. Potential controls were excluded if they met the following criteria: presence of respiratory or cough illness on the date of the matched case patient's cough onset, diagnosis of pertussis prior to the matched case patient's cough onset date, history of immunosuppressive condition, history of a sibling already enrolled in the evaluation, history of prematurity (born at <37 weeks' gestational age), history of adoption, prior enrollment as a control, lack of any contact between the control and his mother, or maternal residence outside of Argentina from the 20th week of pregnancy until delivery.

Trained study personnel contacted the parent or guardian of each potential study participant to obtain informed consent and conduct an interview, using a standardized protocol and abstraction form. Collected information included date of birth, sex, mother's residential health district, mother's education level, breastfeeding history, and family characteristics (number and age of household members, and any history of respiratory illness among household members). In addition, clinical data were collected from both the participant and mother's medical chart, including estimated gestational age at delivery and history of congenital disease (ie, neurologic disease, cardiac anomalies, or genetic disorders). Questions about participant family characteristics were made specifically with reference to the 1 month preceding the matched case patient's cough onset.

Tdap vaccination history of study participants' mothers was collected from vaccination cards, and supplemented by immunization registries. If vaccination history was available in both sources but discrepant, the vaccination card was the definitive source. Using these sources, Tdap vaccination date was recorded for all doses received, including adolescent and adult doses; vaccine brand data were not available. If neither source was available or if they did not contain the relevant information, mothers of study participants were asked to verbally confirm Tdap vaccination status; vaccination date was not collected in this setting. Although the first dose of primary immunization is not recommended until 2 months of age, vaccination history of study participants was reviewed to verify whether pertussis vaccinations had been received.

We classified participants' mothers as vaccinated during current pregnancy if Tdap vaccination date was confirmed by vaccination card or immunization registry; we also considered participants' mothers to be vaccinated if no record of Tdap vaccination date was found in the vaccination card or registry, but Tdap receipt during the current pregnancy was confirmed verbally by the mother. For those participants with known date of vaccination, we estimated trimester of Tdap administration. The gestational age at time of Tdap administration was estimated by

calculating the number of weeks between vaccination and the gestational age at delivery (first trimester: 1–13 weeks' gestation; second trimester: 14–26 weeks' gestation; third trimester: 27–42 weeks' gestation).

We classified participants' mothers as unvaccinated if no record of Tdap vaccination date was found in the vaccination card or registry, and nonreceipt was confirmed by the mother. In addition, participants' mothers were classified as unvaccinated if Tdap was received within 2 weeks prior to delivery, or if Tdap vaccination occurred outside of the current pregnancy (eg, during the postpartum period, a previous pregnancy, or adolescence).

Statistical Analysis

Assuming Tdap coverage of 40% among mothers of controls and 60% vaccine effectiveness (VE), 69 cases and 345 controls were needed to estimate VE with 80% power and .05 level of significance. Bivariable comparison of demographic characteristics between cases and controls was performed using conditional logistic regression. Wilcoxon rank-sum test was used to compare median values. To estimate the association between infant pertussis and maternal Tdap receipt during pregnancy, we used conditional logistic regression to calculate odds ratios (ORs), accounting for matching factors (mother's residential health district and attendance in a participating hospital within the same province). To account for additional confounding factors, multivariable modeling was performed to estimate adjusted ORs. Demographic characteristics found to be significant at $P < .05$ in the bivariable model were included in the multivariable models. Characteristics included in the adjusted analyses were participant age in weeks; history of congenital disease; history of household with ≥3 members <18 years of age; and history of household member with respiratory illness. While history of breastfeeding was not significantly different between cases and controls in bivariate analyses, it was included in multivariable models due to the possibility of placental antibody transfer in breast milk.

VE was calculated as: 1 – (OR) × 100%. Participants whose mothers were Tdap unvaccinated were the reference group in all models. Cases and controls were excluded from analyses if there was documentation of inadvertent administration of >1 Tdap dose during the current pregnancy.

The primary analysis measured Tdap VE in study participants whose mothers received a dose of Tdap during the current pregnancy. Separate analyses calculated VE based on timing of Tdap administration by trimester of pregnancy; because Tdap administration date was necessary, these analyses excluded those participants who only gave verbal affirmation of Tdap vaccination. To assess the stability of the VE estimates, we performed several subgroup analyses by restricting the analytic population based on source of maternal Tdap vaccine history, Tdap receipt only in current pregnancy, or participant age in weeks.

Epi Info version 7.2 (Centers for Disease Control and Prevention [CDC], Atlanta, Georgia) was used for data collection and management; all analyses were conducted in SAS software version 9.3 (SAS Institute, Cary, North Carolina).

Human Subjects Approval

To conduct the study in accordance with institutional policies involving human subjects, participating hospitals obtained approval from local ethics, teaching, and research committee institutional review boards (IRBs). This activity was determined by human subjects review at CDC to be a nonresearch public health program evaluation; thus, IRB review was not required.

RESULTS

Seventy-one case patients and 301 matched controls were enrolled in the study. One control was excluded due to mother's receipt of Tdap twice during the current pregnancy; therefore, 71 cases and 300 controls were included in the final analyses.

Demographic, medical, and vaccine characteristics of participants and their mothers are listed in Table 1. Median age of study participants was 28 days (range, 1–60 days); controls were significantly younger than cases (25 days vs 38 days; $P < .0001$). All case patients were hospitalized at the time of enrollment, compared to 44% (133/300) of controls, and there was 1 death within 8 days of pertussis cough onset date. Controls were more likely to have a history of congenital disease (12% vs 3%; $P = .02$) whereas cases were more likely to be part of families with ≥3 household members <18 years of age (66% vs 51%; $P = .02$) or to have a household member with respiratory illness (69% vs 20%; $P < .0001$).

Maternal vaccination history was verified by vaccination card or immunization registry for 94% (67/71) of case patients and 93% (279/300) of controls; 7% (25/371) overall were verbally confirmed by the mother. Forty-nine percent (35/71) of case patients and 78% (234/300) of controls had mothers who were vaccinated with Tdap during pregnancy, a difference that was statistically significant ($P < .0001$). Of the 256 participants whose mothers had documentation of Tdap vaccination date, 1 mother received Tdap during the first trimester, 59% (152/256) were vaccinated in the second trimester, and 40% (103/256) were vaccinated in the third trimester; there was no difference in vaccination timing between cases and controls (Table 1; Figure 1).

Overall, 269 women were classified as vaccinated and 102 were classified as unvaccinated. Of vaccinated mothers, 93% (249/269) had received a Tdap dose only during the current pregnancy; the remaining 7% (20/269) had also received Tdap at an additional earlier time point (such as during a previous pregnancy or postpartum period, or during adolescence). Of those mothers who were not vaccinated during this pregnancy, 76% (78/102) had never received Tdap previously, whereas 16% (16/102) had received Tdap at an earlier time point. Only 2%

Table 1. Characteristics of Study Participants

Characteristic	Cases (n = 71)	Controls (n = 300)	*P* Value
Participant demographic characteristics			
Enrollment province			NA[a]
Buenos Aires	21 (30)	84 (28)	
Neuquén	1 (1)	2 (0.3)	
Salta	21 (30)	88 (29)	
Tucumán	28 (39)	126 (42)	
Sex			.42
Female	28 (39)	135 (45)	
Male	43 (61)	165 (55)	
Age at enrollment, wk[b]			.001
<1	1 (1)	48 (16)	
1 to <2	1 (1)	38 (13)	
2 to <3	2 (3)	47 (16)	
3 to <4	10 (14)	36 (12)	
4 to <5	17 (24)	34 (11)	
5 to <6	8 (11)	40 (13)	
6 to <7	10 (14)	25 (8)	
7 to <8	13 (18)	19 (6)	
8 to <9	9 (13)	13 (4)	
Median (range), d	38 (6–60)	25 (1–60)	<.0001[c]
Participant medical characteristics			
Gestational age at delivery, wk			.56
37–39	50 (70)	201 (67)	
40–42	21 (30)	99 (33)	
Median (range), wk	39 (37–41)	39 (37–42)	.87[c]
Breastfeeding			.05
Breastfed	70 (99)	274 (91)	
Not breastfed	1 (1)	26 (9)	
Congenital disease present[d]			.02
Yes	2 (3)	36 (12)	
No	69 (97)	264 (88)	
Hospitalized at time of enrollment			
Yes	71 (100)	133 (44)	.99
No	0 (0)	167 (56)	
Maternal and family characteristics			
Mother's age, median (range), y	23 (14–40)	24 (13–42)	.33[c]
Mother's education level			.22
Primary school or less	35 (49)	122 (41)	
Secondary or more	36 (51)	178 (59)	
No. of household members <18 y of age[e]			.02
<3	24 (34)	147 (49)	
≥3	47 (66)	153 (51)	
Median (range), no.	3 (1–9)	3 (1–14)	.001[c]
No. of household members ≥18 y of age[e]			
Median (range), no.	2 (1–13)	3 (1–9)	.4[c]
Household member with respiratory illness[e]			<.0001
Yes	49 (69)	59 (20)	
No	22 (31)	241 (82)	
Vaccination characteristics			
Tdap vaccination status for current pregnancy			<.0001
Unvaccinated	36 (51)	66 (22)	
Vaccinated	35 (49)	234 (78)	
Tdap vaccination status for current pregnancy			.0001
Unvaccinated	36 (51)	66 (23)	
Vaccinated during second trimester[f]	20 (28)	132 (46)	

Table 1. continued

Characteristic	Cases (n = 71)	Controls (n = 300)	*P* Value
Vaccinated during third trimester[f]	15 (21)	88 (31)	
Median gestational age at vaccination, wk (range)	25 (18–37)	25 (11–39)	.79[c]
Source of maternal Tdap vaccination status			.87
Vaccination card	52 (73)	204 (68)	
Immunization registry	15 (21)	75 (25)	
Maternal report	4 (6)	21 (7)	

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: NA, not applicable; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine.

[a]Cases and controls were matched on attendance at participating hospital within same province; thus, *P* value not calculated.

[b]Age calculated based on date of matched case's cough onset.

[c]Calculated by Wilcoxon rank-sum test.

[d]Congenital disease included neurologic disease, cardiac anomalies, and genetic disorders specific to reference period (the 1 month prior to matched case's cough onset date).

[e]Specific to reference period (the 1 month prior to matched case's cough onset date).

[f]Only included those participants whose mothers had documentation of Tdap vaccination date; first trimester defined as 1–13 weeks' gestation, second trimester as 14–26 weeks' gestation, third trimester as 27–42 weeks' gestation.

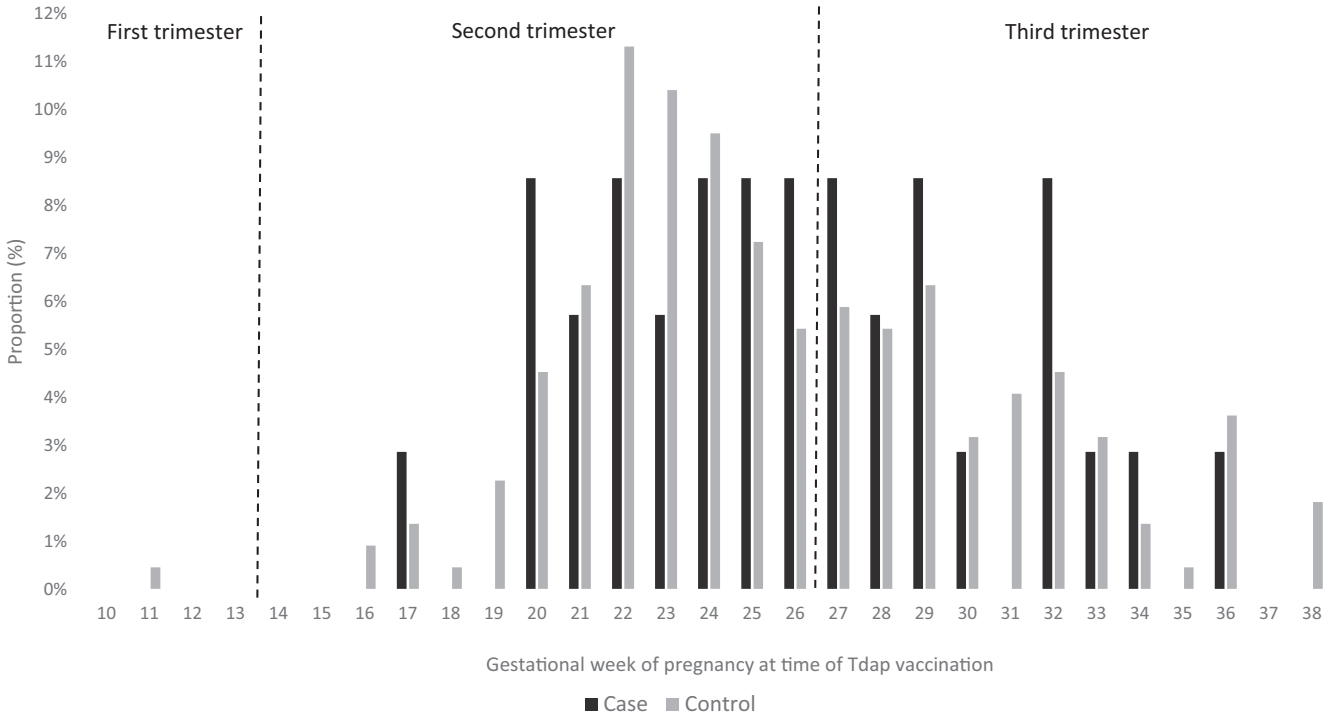

Figure 1. Timing of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccination during pregnancy, by gestational week. The proportion of cases and controls whose mothers who received Tdap during the current pregnancy are represented by black bars and gray bars, respectively. This analysis only included those participants whose mothers had documentation of Tdap vaccination date. First trimester was defined as 1–13 weeks' gestation, second trimester as 14–26 weeks' gestation, and third trimester as 27–42 weeks' gestation.

(2/102) of mothers classified as unvaccinated for the purpose of this analysis received a postpartum Tdap dose during the current pregnancy, and 6 (6% [6/102]) received a Tdap dose during the 14 days prior to delivery. Review of participant childhood vaccination history demonstrated that none had received the first dose of the whole-cell vaccine series at the time of enrollment.

The adjusted VE of Tdap during pregnancy in the prevention of pertussis among infants <2 months of age was 80.7% (95% confidence interval [CI], 52.1%–92.2%; Table 2). VE estimates were similar by timing of vaccination during pregnancy: the adjusted VE was 77.6% (95% CI, 39.1%–91.8%) for Tdap given during the second trimester and 82.7% (95% CI, 46.4%–94.4%) for Tdap given in the third trimester (Table 3). Due to the small

Table 2. Effectiveness of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccination During Pregnancy in Prevention of Pertussis Among Infants <2 Months of Age

	Cases	Controls	Unadjusted OR	Unadjusted VE, %	AOR[a]	Adjusted VE, %
Vaccination Status	(n = 71)	(n = 300)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
No Tdap during pregnancy	36	66	Reference	Reference	Reference	Reference
Tdap during pregnancy	35	234	0.28 (.16–.49)	72.1 (51.0–84.1)	0.19 (.08–.48)	80.7 (52.1–92.2)

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; VE, vaccine effectiveness.

[a]Adjusted model included the following characteristics: participant age in weeks; history of congenital disease; history of breastfeeding; history of household with ≥3 members <18 years of age; history of household member with respiratory illness.

Table 3. Effectiveness of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccination During Pregnancy, by Trimester, in Prevention of Pertussis Among Infants <2 Months of Age

	Cases	Controls	Unadjusted OR	Unadjusted VE, %	AOR[a]	Adjusted VE, %
Vaccination Status	(n = 71)	(n = 286)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
No Tdap during pregnancy	36	66	Reference	Reference	Reference	Reference
Tdap given during second trimester[b]	20	132	0.28 (.15–.54)	71.6 (46.4–85.1)	0.22 (.08–.61)	77.6 (39.1–91.8)
Tdap given during third trimester[b]	15	88	0.32 (.16–.64)	68.1 (35.6–84.2)	0.17 (.06–.54)	82.7 (46.4–94.4)

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; VE, vaccine effectiveness.

[a]Adjusted model included the following characteristics: participant age in weeks; history of congenital disease; history of breastfeeding; history of household with ≥3 members <18 years of age; history of household member with respiratory illness.

[b]Only included those participants whose mothers had documentation of Tdap vaccination date; first trimester defined as 1–13 weeks' gestation, second trimester as 14–26 weeks' gestation, third trimester as 27–42 weeks' gestation.

number of participants fulfilling criteria, we were unable to calculate VE estimates for doses given prior to the current pregnancy or postpartum.

Subgroup analyses were completed to evaluate the stability of the VE estimates. Restricting the population to those participants with maternal Tdap vaccination history confirmed by vaccine card or immunization registry, or restricting to those participants whose mothers had received Tdap vaccination only during the current pregnancy and not at previous time points, did not produce substantially different VE estimates (data not shown). Due to the significant difference in age between case patients and controls, subgroup analyses excluding all participants <3 weeks of age were completed. The resulting VE estimates were slightly higher than those in the primary analyses, but confidence intervals overlapped (data not shown).

DISCUSSION

Prompted by an alarming increase in pertussis-related infant mortality, Argentina became the first country in Latin America to implement maternal Tdap vaccination in 2012 [3, 4, 19]. Our findings demonstrate the effectiveness of this strategy in protecting infants during the susceptible period before primary immunization, and may be especially relevant for other middle-income and, potentially, low-income countries, including those where whole-cell vaccine is used.

Other studies have assessed the effectiveness of this strategy in preventing pertussis among infants <2 months of age [10–12, 14, 16]. Methodologies to estimate VE were diverse and included case-control, cohort, and screening designs. The studies also differed by setting, population, type of vaccine used for childhood series, and end-points evaluated. Despite these differences, it is reassuring that VE estimates across all studies were consistently high, ranging from 58% to 93%.

Recent immunogenicity evaluations have indicated that second trimester or early third trimester maternal vaccination may provide the highest antipertussis antibody titers to infants [20–23]. Because the specific antigen, antibody type, and concentration needed to provide protection are not well defined, the implications of these evaluations are unclear. To date, there are limited data on the relationship between vaccination timing and effectiveness. Results from 2 VE studies indicate that vaccination during the early third trimester is most effective in protecting infants <2 months of age [12, 14]. In contrast, we found little difference in VE when Tdap was administered during the second or third trimester. However, of participants vaccinated during the second trimester in our study, >80% were vaccinated in the second half of this trimester (weeks 20–26), suggesting that vaccination during the later stages of the second trimester may provide sufficient protection to infants.

Currently, international public health agencies such as the World Health Organization and Pan American Health Organization do not endorse routine maternal Tdap vaccination, likely due to lack of evidence regarding this strategy among populations that use whole-cell vaccine for the primary immunization series [24, 25]. One key concern is the potential for maternal antibodies to blunt the infant response to primary immunization. While there

is a growing literature base examining this question, the findings have been inconsistent, and the clinical significance of blunting is unclear [26–32]. In addition, the majority of these studies included acellular pertussis vaccine for primary immunization; it is not yet known if there will be a difference when immunizing with whole-cell vaccines. Regardless of the vaccine type used for primary immunization, if blunting of the infant antibody response does result in reduced protection against disease, there may be a shift in pertussis disease burden from younger to older infants. Studies evaluating the impact of maternal Tdap vaccination on older infants who have received their primary immunization, in addition to monitoring surveillance data in countries where maternal vaccination is recommended, will be critical to understanding this issue.

As with all case-control studies, there were certain limitations. Misclassification and selection biases may result in over- or underestimation of VE. Vaccination history of participants' mothers was confirmed through vaccination card or registry for the majority of participants; however, there was a small percentage for whom verbal report was the only method of confirmation. While misclassification of vaccination status may have occurred, restricting analyses to only those participants with card or registry-confirmed status did not result in substantially different VE estimates. Additionally, despite matching cases with controls, we found differences between them. Controls were more likely than cases to have a history of congenital disease, suggesting a potential selection bias that we could not control. Cases were more likely to be part of families with ≥3 household members <18 years of age, or to have a household member with respiratory illness; these differences likely convey risk of disease rather than selection bias.

Despite remaining questions, other countries in Latin American have also recommended routine Tdap vaccination during pregnancy [33]. Data collected in these countries, including routine surveillance, will provide additional information on the impact of this strategy. Two recent analyses from Argentina using national surveillance data and pediatric hospital data suggested that maternal Tdap vaccination was associated with a decrease in the number of infant cases, mortality, and hospitalization rates over time [34, 35]. While additional data are needed to understand the issue of blunting, findings from these studies and our own support the Argentinian recommendation for maternal Tdap vaccination during the second or third trimester of pregnancy.

Notes

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