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MAJOR ARTICLE

Case-Control Study to Estimate the Association Between Tdap Vaccination During Pregnancy and Reduced Risk of Pertussis in Newborn Infants in Peru, 2019–2021

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Background. Despite widespread vaccination, pertussis has re-emerged as a serious public health concern worldwide. Since 2017, Peru has experienced an increase in pertussis cases exhibiting a higher risk of severity and death in young infants. Thus, a dose of the tetanus, diphtheria, and acellular pertussis (Tdap) vaccine is recommended for pregnant women in the third trimester. Although evidence suggests the maternal Tdap vaccine is safe and effective, its association with a reduced risk of pertussis in developing countries remains poorly investigated.

Methods. We conducted a case-control study to evaluate the association between Tdap vaccination during pregnancy and reduction in the risk of pertussis among infants aged <2 months in Peru. Pertussis cases and controls treated in healthcare facilities nationwide between 2019 and 2021 and confirmed by real-time polymerase chain reaction were included. The controls were randomly selected from test-negative patients. Odds ratios (ORs) and vaccine effectiveness (VE) were calculated using a multiple logistic regression model and $1 - (\mathrm{OR}) \times 100\%$, respectively.

Results. Fifty cases and 150 controls were included in the analysis. The mothers of 4% of cases and 16.7% of controls received Tdap vaccination during pregnancy, resulting in an OR of 0.19 (95% confidence interval [CI], .04–.86) and VE of 81% (95% CI, 14%–96%) for preventing pertussis in infants.

Conclusions. Peruvian infants <2 months old whose mothers received the Tdap vaccine in the third trimester of pregnancy had a significantly lower risk of pertussis. The Tdap vaccination is thus an effective intervention to reduce the burden of pertussis in at-risk populations.

Keywords. pertussis; maternal immunization; Peru; pregnancy; Tdap.

Pertussis (whooping cough) is a highly contagious respiratory infectious disease of major public health concern [1]. Despite universal introduction of pertussis vaccines, countries around the world, including Peru, have reported an increased incidence of the disease in the last 2 decades, primarily in infants [2, 3]. The resulting estimated global burden of pertussis is 5.1 million cases and >85 000 deaths in children under 1 year of age [4].

The re-emergence of pertussis has been explained by various factors, including improved disease detection via more-sensitive polymerase chain reaction (PCR)-based diagnostic tests, decreased vaccine-induced immunity, the transition from whole-cell vaccines to less-effective acellular vaccines, and pathogen adaptation [5]. The re-emergence of pertussis has been observed in all age groups [6]. However, infants younger than 3 months of age who are unvaccinated or only partially immunized are at increased risk of severe complications and death due to pertussis [7]. Adults and adolescents are considered the most important sources of infection due to waning immunity and asymptomatic transmission in this group [8]. The household is the most commonly identified source of infection in hospitalized infants under 6 months of age, with the mother representing 39% (95% confidence interval [CI], 33%–45%), the father representing 16% (95% CI, 12%–21%), and grandparents representing 5% (95% CI, 2%–10%) [9].

Various strategies have been proposed to protect the vulnerable population of newborns, including the cocooning strategy, in which postpartum mothers and close contacts are vaccinated against pertussis; however, implementation of this strategy is challenging, and evidence of its effectiveness is limited [10]. In 2011, the United States recommended that all women receive a single dose of the tetanus, diphtheria, and acellular pertussis (Tdap) vaccine in the third trimester of pregnancy [11], which the World Health Organization (WHO) considers to be the most cost-effective strategy for protecting infants during

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this susceptible period [12]. In addition to the United States [13], this strategy has been instituted in Argentina [14], the United Kingdom [15], Australia, Belgium, and Spain [16]. In Peru, the Ministry of Health recommended that beginning in January 2019, pregnant women should receive a single dose of the Tdap vaccine between weeks 27 and 36 of pregnancy as a temporary protective measure for infants until they receive the first dose of pertussis vaccine according to the national vaccination program [17].

This recommendation was based on evidence of maternal antibody transfer across the placenta, which is maximal in the 34th week of gestation [18]. In a randomized, double-blind, placebo-controlled clinical trial, vaccination of pregnant women with Tdap in the third trimester produced higher levels of antibodies against pertussis in neonates and 2-month-old infants compared with infants whose mothers received a placebo, suggesting potential passive protection of infants during the period of high risk of pertussis morbidity and mortality [19]. In addition, some studies reported that the sum of more than 1 antibody against pertussis at levels greater than detectable contribute to an increased protective effect [20, 21]. Preliminary data from the United Kingdom and Australia indicate that infants born to mothers who received Tdap vaccination during pregnancy have a reduced risk of pertussis at an early age [22]. It is interesting to note that a recent study found that although Tdap vaccination of pregnant women is highly effective in protecting infants under 3 months of age against severe pertussis (odds ratio [OR] = 0.06, $P = .004$, 95% CI = .01–.41; vaccine effectiveness [VE] = 94%, 95% CI = 59%–99%), but it has lower effectiveness at preventing mild disease (OR = 0.31, $P = .026$, 95% CI = .11–.87; VE = 69%, 95% CI = 13%–89%) [23]. This suggests that acellular pertussis vaccination might not be enough to prevent transmission of the disease and to disrupt pertussis circulation, as suggested by another study using nonhuman models [24].

Overall, although studies have demonstrated the safety of the Tdap vaccine [25] and its protective effect against pertussis in infants, the durability of passively acquired antibody is unclear, and precise serological correlation of protection against the disease are not yet known [26]. Differences in maternal vaccine type and suggested optimal timing of Tdap vaccine administration (between 16 and 39 weeks of gestation) could affect the estimated measure of association [25]. Furthermore, the available studies were mainly conducted in developed countries with differing epidemiological contexts and sociodemographic characteristics and in which acellular pertussis vaccines (aP) were implemented as part of the vaccination schemes, whereas whole-cell vaccines (wP) are used in Peru. The response of Tdap-induced antibodies in women immunized with wP in infancy may change from those immunized with aP and affect the effectiveness of the Tdap maternal vaccination in preventing infant pertussis [26]. These differences in vaccine type also represent a selective pressure for important allelic variations in the circulating *Bordetella pertussis* strains [27], so it is possible that the maternal acellular Tdap vaccine may not provide adequate protection against pertussis in the high-risk Peruvian population. Finally, no studies have examined the association between Tdap vaccination in pregnant women and the reduction in the risk of pertussis in infants in Peru. Such studies would be particularly relevant from a public health standpoint to monitor and strengthen evidence of prevention of infection and complications associated with pertussis in susceptible populations, as well as for evidence-based decision making by public health professionals (to update prevention strategies) and women themselves regarding vaccination during pregnancy. In this context, the present study examined whether administration of the maternal Tdap vaccine between 27 and 36 weeks of gestation is associated with a reduction in the risk of pertussis in infants <2 months of age treated in healthcare facilities nationwide.

METHODS

Study Design and Population

A case-control study was conducted in Peru to evaluate whether maternal Tdap vaccination is associated with a lower risk of pertussis in infants <2 months old. The study population consisted of infants under 2 months of age with suspected pertussis treated in healthcare facilities nationwide between 2019 and 2021, with clinical samples sent to the National Institute of Health of Peru (INS-Peru) for confirmatory diagnosis and epidemiological surveillance. According to the national vaccination program, the first dose of the diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenzae* type B pentavalent combination vaccine (DTP-HvB-Hib) should be administered at 2 months of age, which is why this age was selected as the limit, because any protective effect of the DTP-HvB-Hib vaccine must be excluded.

Inclusion and Exclusion Criteria

Cases were defined as infants aged <2 months, treated in healthcare facilities nationwide between 2019 and 2021, who were positive for *B pertussis* deoxyribonucleic acid (DNA) by multitarget quantitative PCR (qPCR) at INS-Peru. The multitarget qPCR method was developed by Tatti et al [28] and combines a Singleplex assay targeting pertussis toxin subunit S1 (*ptx*S1) and a multiplex assay based on the insertion sequences *IS*481, *pIS*1001, and *hIS*1001 for the detection and differentiation of *B pertussis*, *Bordetella parapertussis*, and *Bordetella holmesii*. This multitarget assay exhibits superior performance and specificity for the diagnosis of *B pertussis* infection compared with other PCR-based assays [28, 29].

The inclusion criteria for the controls were as follows: infants <2 months old, treated in healthcare facilities nationwide

between 2019 and 2021, with negative multitarget qPCR results for DNA of *B pertussis* or other *Bordetella* species. Cases or controls were excluded from the analysis if the maternal Tdap vaccination status was unknown, they had been vaccinated with the first dose of DTP-HvB-Hib pentavalent combination vaccine, or if the *B pertussis* multitarget qPCR test was indeterminate. Cases and controls were included in the analysis according to the above-mentioned eligibility criteria and selected through the Clinical, Epidemiological, and Laboratory Investigation Form for Pertussis. This form accompanies the clinical samples of infants aged <2 months with suspected pertussis treated in healthcare facilities nationwide that are sent to the INS-Peru for diagnostic confirmation and epidemiological surveillance. According to Peru's Ministry of Health, definition of pertussis clinical case in infants is defined as any acute respiratory infection with cough and at least 1 of the following symptoms: paroxysmal cough, inspiratory whoop, posttussive vomiting, apnea, or cyanosis [2]. The confirmed pertussis case definition was based on the criteria reported by the WHO (in 2000) and the US Centers for Disease Control and Prevention (in 2010) [30]. The controls were randomly selected from the total population of eligible noncases who were multitarget qPCR-negative for *B pertussis* DNA.

Exposure and Collection of Data

The exposure variable was maternal Tdap vaccination during pregnancy and coded as a binary variable indicating whether the infant's mother received a single dose of Tdap vaccine during the period of 27 to 36 weeks of gestation. Information on cases and controls was obtained from the Clinical, Epidemiological, and Laboratory Research Form for Pertussis. The form is filled out with clinical and epidemiological information including Tdap vaccination status of patients' mothers that is collected from clinical history and immunization registries. Demographic, clinical, and epidemiological variables were analyzed in both groups, including sex, infant age, days since symptom onset, geographic region, clinical symptoms of pertussis (paroxysmal cough, stridor, and vomiting after cough), hospitalization, length of hospital stay, complications due to pneumonia, maternal age at delivery, and maternal Tdap vaccination during pregnancy. Although the first dose of the DTP-Hbv-Hib vaccine is given starting at 2 months of age, it was verified whether infants had received the vaccine. The number of days since symptom onset was calculated as the difference between the date the symptoms began and the date of sampling. The geographic region was coded as a binary variable, within Lima or outside Lima, because there are differences in the maternal Tdap vaccination rate in Lima compared with other regions of the country [31]. The age of the infant was calculated as the difference between the infant's date of birth and the date of sampling. The mother's age at delivery was defined as the difference between the mother's and the infant's dates of birth. Information on status of vaccination with the first dose of the pentavalent DTP-HvB-Hib and maternal Tdap vaccine during pregnancy was validated using the vaccination records of the Ministry of Health of Peru, within the framework of pertussis epidemiological surveillance. Infants' mothers were classified as unvaccinated if Tdap vaccination occurred in a previous or posterior pregnancy.

Sample Size Calculation

This study analyzed 50 cases and 150 controls ($N = 200$), assuming a proportion of exposed cases and controls of 17% and 71%, respectively [32]. This should give 100% power to detect an OR = 0.08 with a 95% CI of 79.34%–96.49%. The minimum sample size was calculated using Epidat v4.3.

Statistical Analyses

Statistical analyses, including regression models, were performed using the Stata/MP v.15.10 program, considering a 95% CI and two-tailed $P < .05$ as statistically significant. Bivariate analyses were performed between each covariable and outcome using the χ^2 test, Fisher's exact test, and Wilcoxon signed-rank test, as appropriate. The association between maternal Tdap vaccination during pregnancy and pertussis in infants younger than 2 months of age was evaluated using a multiple logistic regression model, estimating the OR, adjusted for confounding variables such as sex, infant age, geographic region, and mother's age at delivery. The Tdap VE was calculated as $1 - \text{OR} \times 100\%$. Sex and age of the infant and mother at delivery were included as a priori confounders [33]. The region variable was selected to adjust for temporal and spatial variations in vaccine coverage [32].

Ethics Statement

This study was reviewed and approved by the Ethics in Research Committee of the INS-Peru (reference number OT-024-19) and Universidad Peruana Cayetano Heredia (reference number 103935).

Patient Consent Statement

Written informed consent for participation was not required due to the retrospective nature of this study, in accordance with national legislation and institutional requirements.

RESULTS

A total of 626 newborn infants with suspected pertussis were identified whose nasopharyngeal swab samples and clinical/epidemiological forms were referred to the INS-Peru for pertussis surveillance and diagnostic confirmation by multitarget qPCR between 2019 and 2021. From this group, 20 participants were excluded because they were older than 2 months of age, DTP-Hbv-Hib vaccination history of 2 cases and 13 controls was not available, and mothers of 9 cases and 101 controls did not register Tdap vaccine status. Thus, these participants

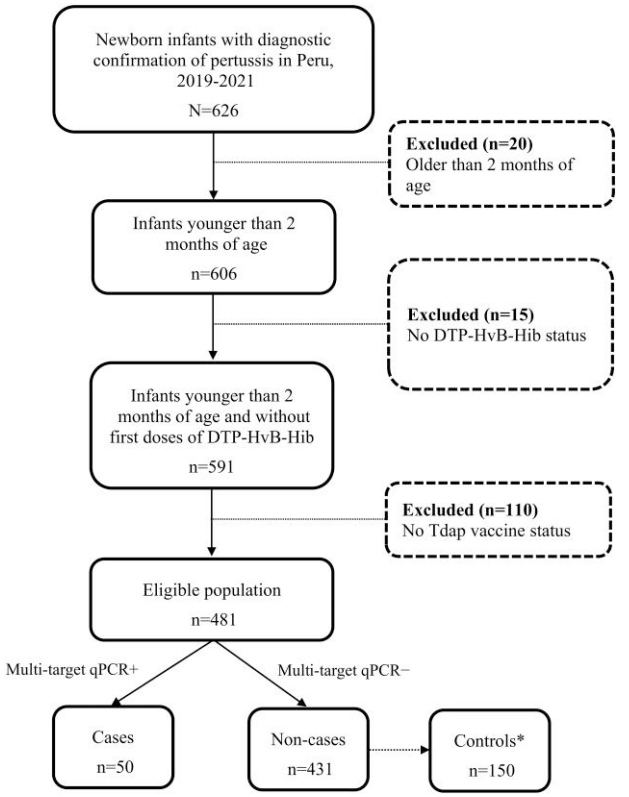

Figure 1. Flowchart of study participant selection. *A total of 150 controls were randomly selected from eligible noncases who were multitarget quantitative polymerase chain reaction (qPCR) negative for *Bordetella pertussis* DNA ($n = 431$). DTP-HvB-Hib, diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenzae* type B pentavalent combination vaccine; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine.

were not considered in the study, according to the inclusion and exclusion criteria. A total of 50 cases and 150 controls who were randomly selected from *B pertussis*-negative noncases were included in the analysis (Figure 1). This study analyzed the information contained in the form and the results of sample processing. The characteristics of the selected participants and their mothers are described in Table 1. Among all study participants ($N = 200$), males were predominant (52.0%). The median age of participants was 42 days (range, 11–61 days), and they presented classic pertussis symptoms such as paroxysmal cough (89.5%), stridor (47.5%), and vomiting after coughing (45.5%). The median number of days with symptoms at which the sample was taken was 6 days (range, 0–33 days). The mothers of 27 infants had been vaccinated with Tdap during gestation (Table 1).

Table 2 shows the results of bivariate analysis of the characteristics of infants and mothers between cases and controls. No statistically significant differences were found in the median age of infants between cases and controls (41.5 days vs 42 days; $P = .780$). The proportion of cases and controls exhibited statistically significant differences with regard to maternal

Table 1. Characteristics of Newborn Infants in the Study Population, 2019–2021 ($N = 200$)

Characteristic	*n* (%)
Infant Characteristics[a]	
Sex	
Male	104 (52.0)
Female	95 (47.5)
Age, Weeks	
1 to <2	3 (1.5)
2 to <3	12 (6.0)
3 to <4	15 (7.5)
4 to <5	26 (13.0)
5 to <6	43 (21.5)
6 to <7	33 (16.5)
7 to <8	39 (19.5)
8 to <9	29 (14.5)
Age, median (IQR), days	42 (11–61)
Days since symptom onset, median (IQR), days	6 (0–33)
Geographic Region	
Lima	109 (54.5)
Outside Lima	91 (45.5)
Clinical Symptoms	
Paroxysmal Cough	…
No	18 (9.0)
Yes	179 (89.5)
Stridor	…
No	69 (34.5)
Yes	95 (47.5)
Vomiting After Coughing	…
No	85 (42.5)
Yes	91 (45.5)
Hospitalization	
No	12 (6.0)
Yes	181 (90.5)
Duration of hospital stay, median (IQR), days	5 (0–32)
Pneumonia	
No	97 (48.5)
Yes	55 (27.5)
Maternal Characteristics	
Age at delivery, median (IQR), years	27 (14–48)
Maternal Tdap Vaccination During Pregnancy	
Unvaccinated	173 (86.5)
Vaccinated	27 (13.5)

Abbreviations: IQR, interquartile range; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine.

[a]Some values may not add to 100% due to missing data.

Tdap vaccination during pregnancy ($P = .029$). Four percent of cases (2 of 50) and 16.7% of controls (25 of 150) had mothers who were vaccinated with Tdap during pregnancy ($P = .029$). The median age of mothers in the case and control groups was 27 years (range, 15–46 years) and 26 years (range, 14–48 years), respectively ($P = .670$). Ninety-two percent of cases (46 of 50) were hospitalized, compared with 90% of controls (135 of 150), with no statistically significant difference ($P = .975$). A total of 58% of controls resided in the Lima region, compared with 44% of cases ($P = .085$) (Table 2). The

Table 2. Bivariate Analysis Comparing Newborn Infant Characteristics Between Cases and Controls, 2019–2021 (*N* = 200)

Characteristic	Cases (*n* = 50) *n* (%)	Controls (*n* = 150) *n* (%)	*P* Value
Infant Characteristics[a]			
Sex	…	…	.390[b]
Male	23 (46.0)	81 (54.0)	…
Female	26 (52.0)	69 (46.0)	…
Age, Weeks	…	…	.700[c]
1 to <2	1 (2.0)	2 (1.3)	…
2 to <3	1 (2.0)	11 (7.3)	…
3 to <4	5 (10.0)	10 (6.7)	…
4 to <5	7 (14.0)	19 (12.7)	…
5 to <6	11 (22.0)	32 (21.3)	…
6 to <7	11 (22.0)	22 (14.7)	…
7 to <8	8 (16.0)	31 (20.7)	…
8 to <9	6 (12.0)	23 (15.3)	…
Age, median (IQR), days	41.5 (13–61)	42 (11–61)	.780[d]
Days since symptom onset, median (IQR), days	7 (1–33)	6 (0–33)	.409[d]
Geographic Region	…	…	.085[b]
Lima	22 (44.0)	87 (58.0)	…
Outside Lima	28 (56.0)	63 (42.0)	…
Clinical Symptoms	…	…	…
Paroxysmal Cough	…	…	.570[c]
No	3 (6.0)	15 (10.0)	…
Yes	46 (92.0)	133 (88.7)	…
Stridor	…	…	.235[b]
No	14 (28.0)	55 (36.7)	…
Yes	27 (54.0)	68 (45.3)	…
Vomiting After Coughing	…	…	.087[b]
No	15 (30.0)	70 (46.7)	…
Yes	26 (52.0)	65 (43.3)	…
Hospitalization	…	…	.975[b]
No	3 (6.0)	9 (6.0)	…
Yes	46 (92.0)	135 (90.0)	…
Duration of hospital stay, median (IQR), days	6 (1–32)	5 (0–31)	.152[d]
Pneumonia	…	…	.598[b]
No	23 (46.0)	74 (49.3)	…
Yes	11 (22.0)	44 (29.3)	…
Maternal Characteristics	…	…	…
Age at delivery, median (IQR), years	27 (15–46)	26 (14–48)	.670[d]
Maternal Tdap Vaccination During Pregnancy	…	…	.029[c]
Unvaccinated	48 (96.0)	125 (83.3)	…
Vaccinated	2 (4.0)	25 (16.7)	…

Abbreviations: IQR, interquartile range; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine.

[a]Some values may not add to 100% due to missing data.

[b]*P* value calculated by χ^2 test.

[c]*P* value calculated by Fisher exact test.

[d]*P* value calculated by Wilcoxon rank-sum test.

distributions according to sex (*P* = .390), clinical features (paroxysmal cough [*P* = .570], stridor [*P* = .235], vomiting after coughing [*P* = .087]), median length of hospital stay (*P* = .152), and complications due to pneumonia (*P* = .598) showed no statistically significant differences between cases and controls (Table 2).

Table 3 shows the crude and adjusted models used to predict the ORs of associations between each independent factor and pertussis. The unadjusted OR for the association between the maternal Tdap vaccine administered between 27 and 36 weeks of pregnancy and the reduced risk of pertussis in infants younger than 2 months of age was 0.21 (95% CI, .05–.91) (Table 3). After adjusting for the confounding variables sex, infant age, geographic region, and mother's age at delivery, infants younger than 2 months of age born to mothers who received the Tdap vaccine between 27 and 36 weeks of pregnancy (OR = 0.19; 95% CI, .04–.86; *P* = .031) had an 81% lower risk of pertussis than infants younger than 2 months of age born to

Table 3. Regression Models Predicting Reduced Risk of Pertussis Infection Among Newborn Infants in Peru, 2019–2021 (*N* = 200)

	Crude Model[a]		Adjusted Model[b]	
Characteristic	OR (95% CI)	*P* Value		*P* Value
Sex				
Male	Ref.		Ref.	
Female	1.33 (.70–2.53)	.391	1.51 (0.76–2.98)	.236
Infant age	1.00 (.97–1.02)	.922	1.01 (0.98–1.03)	.637
Geographic Region				
Lima	Ref.		Ref.	
Outside Lima	1.76 (0.92–3.35)	0.087	1.85 (0.94–3.66)	.076
Maternal age at delivery	1.01 (.97–1.06)	.632	1.02 (0.97–1.08)	.343
Maternal Tdap Vaccination During Pregnancy				
Unvaccinated	Ref.		Ref.	
Vaccinated	.21 (.05–.91)	.038	0.19 (0.04–0.86)	.031

Abbreviations: CI, confidence interval; OR, odds ratio; Ref., reference; Tdap, tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine.

[a]Analyzed by logistic regression.

[b]Analyzed by multiple logistic regression, adjusted per all listed variables.

mothers who did not receive the Tdap vaccine, indicating 81% effectiveness of the Tdap vaccine in preventing pertussis in infants (95% CI, 14%–96%).

After adjusting for confounders, no associations were observed between pertussis and sex (OR = 1.51; 95% CI, .76–2.98; $P = .236$), infant age (OR = 1.01; 95% CI, .98–1.03; $P = .637$), geographic region (OR = 1.85; 95% CI, .94–3.66; $P = .076$), or maternal age at delivery (OR = 1.02; 95% CI, .97–1.08; $P = .343$) (Table 3).

DISCUSSION

The sustained increase in morbidity and mortality associated with whooping cough that has occurred since 2017, mainly in infants under 3 months of age, led the Ministry of Health of Peru to implement Tdap vaccination in pregnant mothers in 2019 [2, 7]. We present the first case-control study in Peru to evaluate whether administration of maternal Tdap vaccine between 27 and 36 weeks of gestation is associated with a reduced risk of pertussis in infants younger than 2 months of age. Our results demonstrate that infants <2 months old whose mothers were vaccinated with Tdap in the third trimester of pregnancy had an 81% lower risk of pertussis than infants born to mothers who did not receive the vaccine, suggesting that this strategy is effective (VE = 81%; 95% CI, 14%–96%) for protecting the infant during the first months of life and before primary immunization [3].

It is interesting to note that these results are consistent with those obtained in a case-control study from Argentina, another country using the whole-cell vaccine for primary pertussis immunization, where the Tdap vaccine was 80.7% (95% CI, 52.1%–92.2%) effective in preventing pertussis in infants <2 months of age [34]. In a study that analyzed 58 cases of infants younger than 8 weeks of age with pertussis in comparison with 55 controls, mothers of 10 infants with whooping cough (17%) had received the vaccine during pregnancy, compared with 39 mothers of 55 controls (71%), indicating a significant association between maternal prenatal vaccination and pertussis in infants (OR = 0.07; 95% CI, .03–.19), with a VE = 93% (95% CI, 81%–97%) after adjustment for sex, geographic area, and birth period [32]. Our results are also consistent with those reported by a study based on a laboratory-confirmed case coverage method as part of the pertussis surveillance system in England, where the authors found that the introduction of maternal Tdap vaccination provided protection against pertussis in infants younger than 2 months of age (VE = 90%; 95% CI, 82%–95%) and reduced disease-associated cases, hospitalizations, and deaths [35]. Despite differences between these studies in terms of design, population, locality, and type of vaccine used in primary immunization, the evaluation of the maternal Tdap vaccination strategy in Peru shows a comparable and high VE, probably due to the protection conferred to the infant through passive transfer of antibodies and the indirect effect of protecting the mother from whooping cough and potentially reducing the risk of transmission of the disease to the infant [32].

The main limitation of this study is the lack of control over the type of data recorded in the Clinical, Epidemiological, and Laboratory Investigation Form, which can lead to bias and misclassification, potentially resulting in over- or underestimation of the OR and VE [36]. However, validation of information, including maternal Tdap vaccination history, reduced the risk of recall bias and exposure misclassification. The analysis based on information from the form also made it impossible to control for other potential confounders, including mothers' breastfeeding status, gestational age, number of people in the household, daycare attendance, smoking, and maternal education [37]. For example, mothers who choose to be vaccinated may exhibit different characteristics—such as educational

attainment—than those who do not [38], which could introduce a protective bias into the effect of maternal vaccination. According to a study by Quinn et al [39], the mother's educational attainment and exposure to school-age children at home are associated with pertussis in infants.

Because the controls presented pertussis symptomatology (Table 2) and were selected based on negative PCR diagnostic results for DNA of *B pertussis* or other *Bordetella* species to avoid potential cross-protective effects, there was a possibility of misclassification of this group due to imperfections of the molecular test. However, no statistically significant differences were found between cases and controls in terms of the number of days with symptoms when sampled for PCR ($P = .409$) (Table 2), suggesting a low probability that the controls were false negatives. On the other hand, there may have been bias in the selection of cases, because patients who died of severe pertussis before being diagnosed would be excluded, thus biasing the protective effect of the Tdap vaccine toward cases with mild disease [36]. Nevertheless, in this study, more than 90% (46 of 50) of the cases were hospitalized, including nonsevere cases and those with complications of pneumonia (Table 2), suggesting that this effect was limited.

Because this study uses test-negative controls, some mild cases of pertussis are likely being missed. This is explained because individuals who come to healthcare facilities usually are more likely to have severe symptoms that suggest Tdap vaccination is effective for protecting the Peruvian infants against severe pertussis. However, this medical help-seeking behavior is affected not only by severity of symptoms, but also by others factors including age, gender, socioeconomic status, access to healthcare, proximity to testing facilities, personality, and insurance coverage. Several studies have supported that theses bias are controlled by a test-negative design, and it can generate valid estimates based on factors that lead individuals to come to healthcare facilities, which are the same on both those who test positive and those who test negatives [40]. Although severe pertussis has been associated with hospitalization, definition of pertussis severity is complex, and information such as duration of stay, level of hospitalization, use of oxygen, and intravenous therapy as well as clinical features including presence of complications is required. Furthermore, pertussis severity must be evaluated using these variables and based on a scoring system that has to be validated to be applicable to hospitalized children in specified country settings [41].

CONCLUSIONS

Despite these limitations, this study analyzed valuable information at the national level and provides robust evidence demonstrating that maternal Tdap administration during pregnancy is a highly effective intervention for protecting infants against pertussis, particularly for the Peruvian population at higher risk. It is thus crucial to communicate this information to both pregnant women and health professionals to promote greater acceptance of the vaccine at the national level and in low- and middle-income countries that recommend the whole-cell vaccine in their primary immunization schedule.

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Author contributions. EJ-L planned and designed the study. FV, MPS, and HH contributed to data collection. EJ-L performed the analyses, interpretated the data, and drafted the manuscript. MPS and MP contributed to writing the manuscript and provided ideas for the submission. All authors reviewed and approved the final manuscript.

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Potential conflicts of interest. All authors: No reported conflicts of interest.

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