



Reduced pertussis disease severity in infants following the introduction of pertussis vaccination of pregnant women in Spain, 2015–2019

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ARTICLE INFO

Keywords:

Bordetella
Whooping Cough
Pertussis Vaccination
Pregnancy

ABSTRACT

Background: Maternal pertussis vaccination during the third trimester of pregnancy was implemented in 2015 in Spain, reaching a national coverage of 84% in 2019. In this ecological study, we investigated whether there was a change in the disease severity for pertussis in infants upon introduction of prenatal pertussis vaccination.

Methods: We performed a time-trend analysis of infant pertussis hospitalizations during 2005–2019 in Spain using national register data. Annual hospitalization rates per 100,000 population and the mean length of hospitalization were calculated for infants < 3 months of age (target group benefiting from the prenatal vaccination) and a reference group aged 3–11 months. We compared overall rates and annual percent changes of the above variables in both groups for the time period before (2005–2014) and after vaccination introduction (2015–2019), using segmented Poisson regression.

Results: During the pre-vaccination period, infants aged 0–2 months had a 5-times higher rate of pertussis hospitalization and spent on average 50 % longer in hospital than the reference group. After the maternal vaccination introduction, the hospitalization rate decreased more rapidly in infants aged 0–2 months than in infants aged 3–11 months: annual reduction of 34 % (95 % CI: 31–38) versus 26 % (95 % CI: 21–31) in the hospitalization rate and 13 % (95 % CI: 11–15) versus 6 % (95 % CI: 2–9) in the mean hospital stay, respectively. In 2019, the mean hospital stay for pertussis was about 4.5 days in both groups.

Conclusions: Maternal pertussis vaccination in Spain led to a reduction in disease severity in the target group as compared to older infants, highlighting the need for increased efforts on educating healthcare professionals on the importance of maternal vaccinations.

1. Introduction

The bacterium *Bordetella pertussis* causes pertussis or whooping cough, a vaccine-preventable respiratory disease which is re-emerging worldwide including in populations with high vaccine coverage [1]. Pertussis affects all age groups but typically manifests itself as a childhood disease with the most severe forms occurring in infants during the first months of life. Pertussis vaccination during pregnancy can protect infants through passive immunity, i.e. active transfer of maternal antibodies that protect them until the primary immunization series. Studies

indicate vaccinating pregnant women with acellular pertussis vaccine is safe for mother and infant, immunogenic, with efficient transplacental transfer of antibodies, and effective in preventing severe pertussis in young infants [2–4]. In addition, there is an important benefit of protecting mothers against pertussis infection as they are often a source of infection for infants in the household [5].

The World Health Organization (WHO) estimated that there were 24.1 million cases of pertussis in 2014 globally, with 160,700 associated deaths in children under 5 years of age. Of these, 92,500 (58 %) were estimated to have occurred in Africa and involved mostly infants: 85,900

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<https://doi.org/10.1016/j.vaccine.2024.03.028>

Received 26 August 2023; Received in revised form 21 February 2024; Accepted 11 March 2024

Available online 25 March 2024

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(53 %) [6]. In the last decade, an increase in cases of pertussis has also been observed in high-income countries with long-standing high vaccination coverage [7–9], such as Spain [10].

In Spain, pertussis has been present in epidemic proportions since 2010, with the last wave between 2014 and 2019, peaking in 2015 [11–13]. Children, and particularly infants under 1 year of age have the highest incidence and hospitalization rate for pertussis, although, case fatality risk is low. From 2010 to 2019, there were 42 deaths of children under 1 year of age with a case fatality rate of 5.7 per 1,000 [14].

The current pertussis immunization schedule in Spain is based on 4 doses of Diphtheria/Tetanus/Pertussis (DTPa) vaccine (primary vaccination with 2 doses at 2 and 4 months, and boosters at 11 months and 6 years of age). This schedule was introduced in 2017, replacing the old one with 5 doses at 2, 4, 6 and 18 months and 6 years of age [15].

While some autonomous regions of Spain introduced this intervention 1–2 years earlier, [13,17], pertussis vaccination of mothers during the third trimester of pregnancy (Tdap) was implemented nationwide in 2015, with a recommendation to vaccinate between the 27th and 36th week of gestation, but ideally during the 28th and 32nd week [16]. The maternal vaccination coverage at the national level estimated during 2017–2019 was high (80–84 %), with some regional variation [18].

The implementation of this public health intervention is expected to reduce disease severity and improve clinical outcomes in infants, particularly in the first 3 months of life [13,19]. In this study, we aim to assess the impact of pertussis vaccination in pregnant women on disease severity, such as decrease in the hospitalization rate and length of hospitalization in infants aged less than 3 months.

2. Material and methods

2.1. Data collection

Information on cases hospitalized with pertussis during 2005–2019 in Spain was obtained from the National Hospitalization Registry (NHR-CMBD) and included data on date of birth, sex, region of residence, date of hospital admission, date of discharge and primary and secondary hospitalization diagnoses (1–20).

In our ecological study, pertussis cases were defined as those hospitalizations including one or more International Classification of Diseases 10th or 9th edition (ICD-10 or ICD-9) diagnostic codes (A37.00, A37.01, A37.80, A37.81, A37.90, A37.91 or O33.0, O33.8, O33.9, 484.3, respectively) as their primary or secondary diagnosis in NHR-CMBD [20,21]. Parapertussis cases were excluded unless the case had one of the ICD codes described above. This exclusion was motivated by the fact that parapertussis infection is a less serious disease than pertussis [22] and may therefore lead to an underestimation of the effect of the vaccine on disease severity.

Population data by sex, age group, region and calendar year were obtained from the National Statistics Institute (INE). In addition, data on pertussis vaccine coverage in pregnant women was obtained from the Vaccination Information System of the Ministry of Health (SIVAMIN) and through a request to each autonomous region as well as the Ministry of Health for any unpublished data on vaccine coverage.

2.2. Data analysis

We calculated hospitalization rates per 100,000 population for pertussis by sex, age group and calendar year. The effect of prenatal vaccination on the rate of hospitalization for pertussis in infants was

assessed using a segmented Poisson regression model in an interrupted time series design [23]. This ecological design is generally applied in natural experiments to evaluate the impact of an intervention introduced at a known point in time. The design extends the basic ITS by adding a control group that is not exposed to the intervention. The control group is used to account for external trends and factors that might otherwise bias the evaluation of the intervention's effect.

The trend of annual hospitalization rates in infants under 3 months - the target group for prenatal vaccination - was estimated before and after the introduction of the maternal pertussis vaccination. To account for the non-linearity of the trend, three periods were considered in the segmented analysis, namely 2005–2009, 2010–2014 and the period in which prenatal vaccination had been implemented countrywide (2015–2019). To control for underlying fluctuations in the epidemic and time-varying confounders, the model included for comparison a reference group of infants aged 3 to 11 months, an age range in which infants started their primary immunization series against the disease. Since the prenatal vaccination has no direct effect on the group of children aged 3–11 months, this group was used as a control to assess the share of the reduction in hospital admissions in 0–2 months age group potentially attributable to the prenatal vaccination. A random effect related to the region of residence was also included in the model to address geographical heterogeneity.

Changes in the population over time (the birth rate has fallen by 30 % over the last decade in Spain) were taken into account by including population as an offset [24]. Populations by age, region, and calendar year were inferred for the two age groups assuming that the age distribution (in months) was uniform in the population of infants under one year.

Annual percentage change (APC) was calculated to describe trends by period and age group. This standardized measure was obtained directly from the Poisson regression model and allows trends to be easily compared between periods and groups. The difference in trend between the two age groups over a given period was tested through the interaction term between the period and the age group [25] (see [Supplementary Material](#) for details). A significant interaction was not expected in the absence of an effect of prenatal vaccination on the hospitalization rate. Finally, the above analyses were also applied to the hospital stay length (in days). All analyses were performed using R (version 4.2) and R Studio statistical software [26].

3. Results

A total of 10,621 pertussis hospital admissions were reported during 2005–2019 in Spain of infants under 1 year of age, constituting the majority of all age groups (91 %). The hospitalization rate in infants under 1 year of age fluctuated over the study period and reached its peak in 2015 with 1,504 hospitalizations (421 pertussis cases per 100,000 population) (Fig. 1). Overall, hospitalization rates for girls were similar to those for boys, although slightly higher (Table 1). However, the rate of hospitalization was more than 5 times higher in children aged 0–2 months compared to those aged 3 to 11 months (overall, 418 vs. 77 hospitalizations per 100,000 child-years). Similarly, the average duration of hospitalization was shorter (5.6 days) in children aged 3 to 11 months than in those aged 0 to 2 months (7.6 days) and this difference was similar for both sexes (Table 1).

During the period before the introduction of maternal pertussis vaccination (2005–2014), the hospitalization rate (per 100,000 population) was 406 for children aged 0–2 months and 71 for children aged

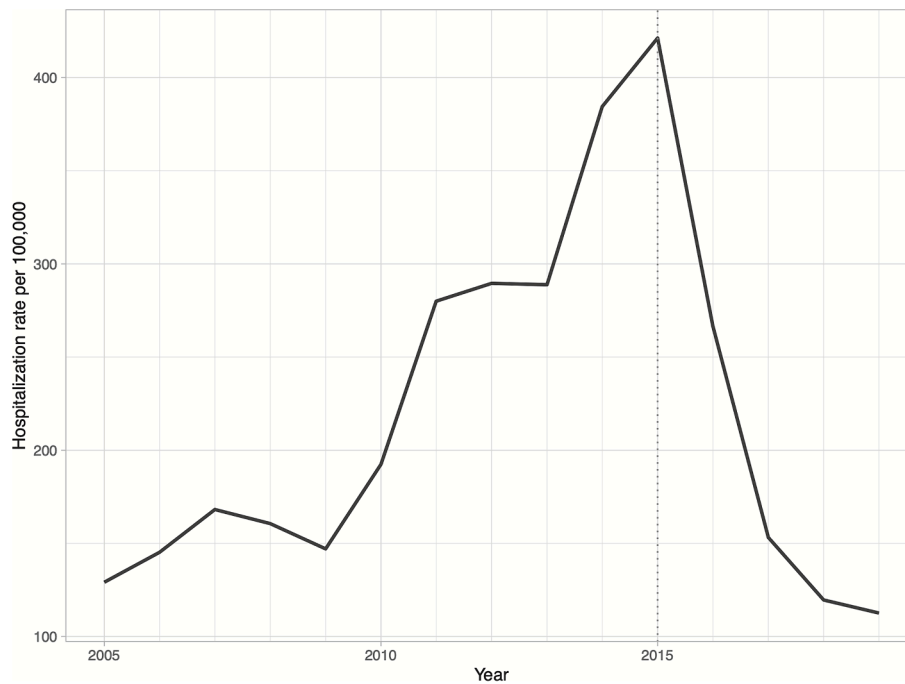


Fig. 1. Annual hospitalization rate for pertussis in children aged less than 1 year in Spain, 2005–2019.

Table 1

Number of hospitalizations for pertussis, population-years at risk, hospitalization rate (per 100,000), and average length of stay (in days) among infants, by sex, age group and calendar year (2005–2019) in Spain.

Age (months)	Hospitalizations		Population-years		Hospitalization rate		Average length stay	
	0–2	3–11	0–2	3–11	0–2	3–11	0–2	3–11
Males								
2005	119	62	48,072	147,718	247.5	42.0	8.3	6.7
2006	129	85	54,155	150,276	238.2	56.6	7.1	6.8
2007	129	87	52,348	147,550	246.4	59.0	9.0	6.7
2008	156	91	51,799	159,448	301.2	57.1	7.3	5.5
2009	147	71	58,111	161,930	253.0	43.8	7.0	4.5
2010	196	86	58,916	158,100	332.7	54.4	7.6	6.1
2011	367	198	57,037	171,193	643.4	115.7	8.4	5.6
2012	246	138	55,668	160,601	441.9	85.9	8.6	4.6
2013	298	129	55,576	161,175	536.2	80.0	7.2	5.4
2014	312	147	52,200	148,204	597.7	99.2	7.8	6.6
2015	522	263	52,144	156,433	1,001.1	168.1	7.5	5.8
2016	197	145	49,530	144,343	397.7	100.5	6.6	5.1
2017	136	94	49,545	150,872	274.5	62.3	5.7	4.2
2018	108	60	45,979	132,202	234.9	45.4	5.3	4.6
2019	73	43	37,596	100,119	194.2	42.9	4.2	4.0
Overall	3,135	1,699	778,677	2,250,165	402.6	75.5	7.4	5.6
Females								
2005	126	68	46,952	139,592	268.4	48.7	8.6	6.5
2006	148	64	48,724	133,131	303.8	48.1	9.5	5.5
2007	159	85	48,203	136,331	329.9	62.3	12.4	6.6
2008	198	85	52,485	147,880	377.2	57.5	8.5	6.5
2009	155	71	51,647	152,573	300.1	46.5	6.8	5.1
2010	194	88	52,048	152,230	372.7	57.8	7.2	6.3
2011	382	202	55,454	166,361	688.9	121.4	7.8	6.0
2012	246	134	52,242	156,262	470.9	85.8	8.4	4.9
2013	257	116	51,984	142,862	494.4	81.2	8.3	6.0
2014	312	151	48,928	142,803	637.7	105.7	7.6	5.7
2015	495	235	49,313	143,696	1,003.8	163.5	7.7	4.9
2016	208	148	47,073	135,921	441.9	108.9	5.7	4.9
2017	120	84	45,819	140,844	261.9	59.6	6.2	4.8
2018	92	68	43,366	127,130	212.1	53.5	5.0	4.5
2019	82	66	37,226	114,428	220.3	57.7	4.3	5.2
Overall	3,174	1,665	731,466	2,132,044	433.9	78.1	7.8	5.5

Table 2
Annual percent change in hospitalization rate for pertussis in infants by age group and period in Spain, 2005–2019.

	2005–2009		2010–2014		2015–2019	
	APC ^a (%)	95 % CI ^b	APC ^a (%)	95 % CI ^b	APC ^a (%)	95 % CI ^b
Age group 0–2 months	8.29	(4.09, 12.66)	16.51	(12.77, 20.37)	–34.34	(–37.83, –30.66)
3–11 months	7.52	(2.56, 12.72)	16.96	(12.53, 21.57)	–26.12	(–30.61, –21.34)

^a Annual percentage change.
^b Confidence interval.

3–11 months. The mean length of hospital stay was 8 days in 0–2 month-olds and 6 days in 3–11 month-olds. Hospitalization rates and mean length of hospital stay by sex, age group, and calendar year are shown in Table 1.

Before the introduction of the prenatal vaccine (2005–2014), the annual percentage changes (APC) in the hospitalization rate for pertussis were not significantly different between the two age groups. However, during the period following the introduction of the vaccine (2015–2019), the annual reduction in the pertussis admission rate was significantly more pronounced in the 0–2 month age group (34.3 %, 95 % CI: 30.7–37.8) than in the 3–11 month age group (26.1 %, 95 % CI:

21.3–30.6) (see Table 2). The estimated trends in hospitalization rates from 2005 to 2019 in both age groups and the effect of prenatal pertussis vaccination are shown in Fig. 2.

Regarding the average length of stay, it was also observed that the APC was similar in the two age groups before the prenatal vaccination period. But the difference between these two groups observed after the introduction of the vaccine was even more pronounced than that estimated for the hospitalization rate. During 2015–2019, there was an annual reduction of 12.6 % (95 % CI: 10.4–14.7) in children aged 0–2 months compared to an average reduction of 5.5 % (95 % CI: 2.5–8.5) in those aged 3–11 months (Table 3) regarding the length of

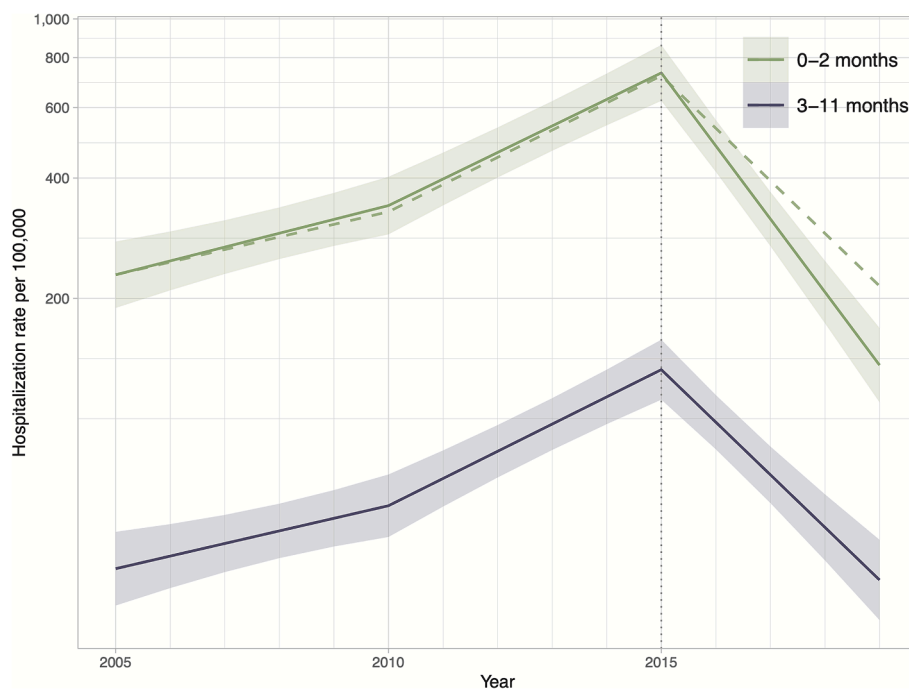


Fig. 2. Estimated pertussis hospitalization rate (in log-scale) for pertussis by year and by age group adjusted for region in Spain, 2005–2019. The dashed curve assumes the same trend in both age groups (no interaction between age and period).

Table 3
Annual percent change in mean length of hospital stay for pertussis in infants by age group and period in Spain, 2005–2019.

	2005–2009		2010–2014		2015–2019	
	APC ^a (%)	95 % CI ^b	APC ^a (%)	95 % CI ^b	APC ^a (%)	95 % CI ^b
Age group 0–2 months	–2.75	(–4.37, –1.09)	–1.33	(–2.55, –0.09)	–12.57	(–14.73, –10.36)
3–11 months	–3.13	(–5.42, –0.78)	–0.99	(–2.75, 0.80)	–5.53	(–8.50, –2.45)

^a Annual percentage change.
^b Confidence interval.

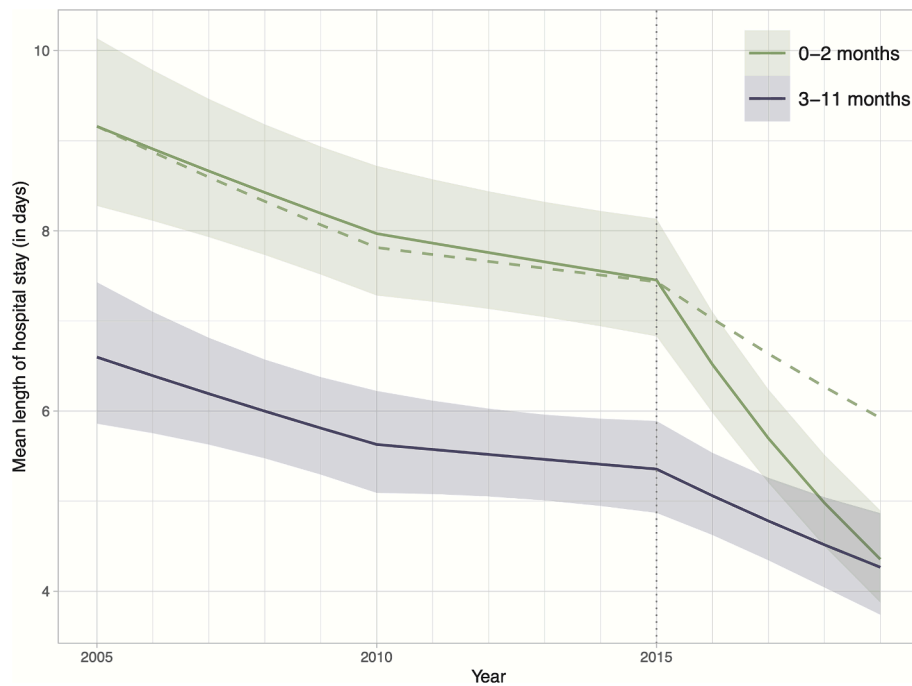


Fig. 3. Estimated mean of hospital stay (in days) for pertussis by year and by age group adjusted for region in Spain, 2005–2019. The dashed curve assumes the same trend in both age groups (no interaction between age and period).

hospitalization. In 2005, the mean length of hospital stay was 8.5 days for children aged 0–2 months and 6.6 for children aged 3–11 months; whereas in 2019, the mean length of hospital stay for these two age groups was similar and close to 4.5 days. Trends in the mean length of hospital stay during 2005–2019 in both age groups and the effect of prenatal pertussis vaccination are shown in Fig. 3.

4. Discussion

As our results suggest, vaccinating women against pertussis during their third trimester of gestation appears to be an effective method of preventing severe forms of the disease in infants, reducing hospitalizations and especially the length of hospital stay. Our results are consistent with another recent ecological study in United States, where Tdap vaccination was associated with a reduction in pertussis incidence in infants younger than 2 months, narrowing the gap with infants aged 6–11 months [27]. Another study from Canada identified a crude reduction in incidence among infants aged 3 months or less over time; however, in an interrupted time series analysis, the publication of national recommendations for antenatal Tdap immunization (NACI) in every pregnancy was not associated with a statistically significant decrease in the monthly pertussis trends [28]. This finding most likely reflects suboptimal antenatal Tdap coverage with past research finding that immunization was undertaken in only 25 % of pregnancies one year after the publication of NACI guidance [29].

The time of vaccination was brought forward in Spain. Initially, Tdap vaccination was recommended for women between the 28th and 36th week of gestation, then between 28th and 32nd week, and currently a dose of vaccine is recommended in each pregnancy starting at week 27, but preferably during the week 27–28 [30]. Similarly, in other countries recommendations to vaccinate are being advanced to the second trimester of pregnancy to ensure that premature infants are also protected [31].

In Spain, any vaccine included in the national vaccination schedule is fully funded by the National Health System (NHS) and provided free of charge to the population [32,33]. Given the Tdap vaccine accessibility in Spain and the low cost associated with the maternal vaccination

assumed by the government (21 Euros (€) per vaccine administered, including the cost of the vaccine of €14,95 and an administration cost of €6), [34] it seems to be an effective intervention in reducing the number of days in neonatal care and pediatric units. This was also demonstrated in a study in Catalonia, where direct healthcare costs were lower in children vaccinated with 4–5 doses of acellular pertussis vaccines than in unvaccinated or partially vaccinated children with pertussis of the same age [35].

Since almost all children with pertussis under the age of 6 months are typically hospitalized, [36] the impact of the intervention was more relevant to the length of hospital stay than hospitalization rates. Throughout the study period, the number of deaths from pertussis was very low. Although we have refrained from using the fatality ratio to assess the effect of the vaccine, the number of deaths amongst all pertussis cases decreased from 9 in 2015 to 1 annual case of death during 2016–2018, with no deaths in 2019 in children aged less than 3 months [14]. There were some other possible health outcomes such as most common pertussis' complications including pneumonia, apnea, convulsions and encephalopathy [37]. However, the data in NHR-CMBD was not complete enough to allow this analysis. In addition, it would be difficult to relate any of these diagnoses and their respective ICD-9/ICD-10 diagnostic codes directly to pertussis as some children could have been born prematurely and could have suffered from these comorbidities regardless of pertussis. Although more recent data was available, we decided to limit our analyses to 2019. The COVID-19 pandemic with its preventive measures aimed at reducing transmission of viral and bacterial respiratory diseases could have had an impact on the natural fluctuations of pertussis and ultimately lead to overestimating the effect of the vaccine [12,38].

While we observed a significant decrease in disease severity in infants aged less than 3 months after the introduction of maternal pertussis vaccination, we cannot infer a causal relationship between the vaccination and improved health outcomes as this is an ecological study. Although we had detailed information on pertussis cases in terms of demographics and hospitalization, we did not know whether their mothers were vaccinated or not. This study is therefore subjected to an ecological fallacy that may lead to an underestimation of the impact of

vaccination on the group of children aged 0–2 months. However, given no major changes in the National Hospitalization Registry and case definition during the study period (except for the change of ICD-9 to ICD-10 in 2015) and overall increasing trend in the national prenatal vaccination coverage reaching 84 % in 2019, [18] we assume that the observed reduction in severity in infants is most likely attributed to the maternal Tdap vaccine.

Another possible source of underestimation of the effect of the maternal Tdap vaccine is the fact that the reference group of infants aged 3–11 months might have also been affected by the vaccination of pregnant women due to the persistence of antibodies beyond 2 months or reduction in transmission of pertussis in households.

Similarly, natural fluctuations in pertussis incidence could lead to underestimating/overestimating the effect of the intervention. However, analysis of pertussis trends prior to maternal vaccine introduction in children aged 0–2 months and 3–11 months should mitigate these biases [27]. Moreover, although the incidence of pertussis changes over time, the severity of the infection was not expected to change. Therefore, while the hospitalization rate can be affected by variations in circulation of pertussis in the population with mostly small children being hospitalized, the analysis of length of hospital stay should not be greatly affected by these variations.

Another potential limitation of our study is the fact that the vaccination of pregnant women was not introduced at the same time at the national level. Certain Spanish regions started to vaccinate mothers in 2014, although the coverage was small [17]. In addition, official data on vaccine coverage in pregnant women was available by autonomous regions only as of 2017 [18]. Data prior to that was limited and of varying completeness in regions, therefore vaccine coverage was not included in our model.

Lastly, we did not have any information on breast-feeding practices in mothers of pertussis' cases. Due to a possibility of passive transfer of antibodies through maternal milk, older children would also be protected through breastfeeding, and as we are comparing both groups, this could have led to an underestimation of the effect of intervention.

5. Conclusions

In summary, maternal prenatal pertussis vaccination seems to be effective in preventing severe disease in young infants aged 0–2 months in Spain. It is important to advocate for pertussis vaccination in pregnant women as well as timely immunization series in children to prevent serious disease in infants. This can be achieved through increased efforts on educating healthcare and particularly antenatal care professionals on the importance of maternal vaccinations. They should provide a recommendation to vaccinate, and explain the vaccine benefits and potential risks to pregnant women. Advice from healthcare professionals has been shown to be very effective in improving vaccination uptake [39].

Author contributions

A. P., O. N., N. L. P., and J. M. C. were involved in the conception and design of the study. A. P. and O. N. were involved in data acquisition, data analysis and wrote the first draft of the manuscript. All authors were involved in data interpretation and refining the manuscript, and all authors reviewed and approved the final version of the manuscript.

CRedit authorship contribution statement

Andrea Parisi: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing, Validation, Visualization. **Olivier Nuñez:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Noemí López-Perea:** Conceptualization, Methodology, Writing

– review & editing. **Josefa Masa-Calles:** Conceptualization, Methodology, Writing – review & editing, Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgements

The authors thank Nadine Zeitmann (Robert Koch Institute, Berlin, Germany) for the review of the manuscript.

Disclaimer

AP was supported by the European Programme for Intervention Epidemiology Training, European Centre for Disease Prevention and Control, Sweden. The funder played no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. All authors attest they meet the ICMJE criteria for authorship.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2024.03.028>.

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