Vaccine 37 (2019) 6342–6347

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Paediatric hospitalizations due to whooping cough in Spain (1997–2017)

Ruth Gil-Prieto [a,*], Stefan Walter [b,c], Jesús San-Román-Montero [d], Patricia Marín-García [e], Alba González-Escalada [f], Angel Gil-de-Miguel [a]

[a] Area of Preventive Medicine & Public Health, Rey Juan Carlos University, Madrid, Spain
[b] Fundación de Investigación, Hospital Universitario de Getafe, Madrid, Spain
[c] Dept. of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA
[d] Area of Medicine, Rey Juan Carlos University, Madrid, Spain
[e] Area of Medical Immunology, Rey Juan Carlos University, Madrid, Spain
[f] Area of Medical Microbiology, Rey Juan Carlos University, Madrid, Spain

ARTICLE INFO

Article history:
Received 23 January 2019
Received in revised form 1 September 2019
Accepted 6 September 2019
Available online 13 September 2019

Keywords:
Whooping cough
Pertussis
Vaccine
Spain
Epidemiology
Hospitalizations

ABSTRACT

This epidemiological survey estimates the burden of whooping cough in infants up to 12 months old in Spain during a twenty-one-year period (1997–2017). The survey was conducted by reviewing data from the Spanish Surveillance System for Hospital Data. All hospitalizations due to whooping cough for infants, reported during the 1997–2017 period, were analysed. Codes were selected from the International Classification of Diseases, 9th Revision, Clinical Modification diagnosis codes 033.0–033.9. To explore the latest national outbreak and the implementation of vaccination in pregnant women, analyses were stratified to compare the following periods: 1997–2010, 2011–2015 and 2016–2017. A total of 13,352 hospital discharges for whooping cough in infants up to 12 months old were reported. A total of 6850 discharges in the period 1997–2010, 5271 in the period 2011–2015 and 1231 in 2016–2017 were identified. The annual hospitalization rate prior to 2011 was 131.02 cases per 100,000 infants; in 2011–2015, the rate was significantly higher (250.13 cases per 100,000 infants) and in 2016–2017 it decreased (157.69 cases per 100,000 infants). Most of the cases (n = 11,446) occurred in infants under 4 months of age, with hospitalization rates of 328.80, 670.81 and 385.84 cases per 100,000 infants up to 4 months of age in the periods 1997–2010, 2011–2015 and 2016–17, respectively. Thirty-four deaths occurred in the period 1997–2010, 36 in the period 2011–2015 and 4 in 2016–2017. All of the deaths occurred in infants under 4 months old. The case fatality rate did not vary significantly across the study periods. Whooping cough infections concentrate in infants up to 4 months of age in Spain. Public health measures such as vaccination of pregnant women, caregivers, health care professionals and relatives, especially young parents, could reduce the hospitalization burden during the current outbreak.

1. Introduction

Whooping cough is a highly transmissible infectious disease caused by the bacteria *Bordetella pertussis*. It affects individuals of all ages, especially children younger than age 5. Infants face the highest risk of hospitalization and death [1,2]. Pertussis is preventable through vaccination, and babies from 0 to 6 months of age, when vaccination has not yet been completed, are the most affected. The main sources of infection in non-vaccinated children are parents, siblings and caregivers [3].

During recent years, the incidence of whooping cough has increased worldwide, even in developed countries, despite high vaccination coverage [4–7]. Several explanations for this phenomenon include the waning of vaccine-induced/natural immunity, the switch from TDwP to TDaP and better diagnostic techniques [8–10]. In recent years, different countries have implemented different vaccination strategies such as maternal immunization, trying to prevent pertussis in infants [11–13].

The numerous modifications to the vaccination strategies in Spain make it difficult to attribute the increased incidence of whooping cough to the waning of vaccine-induced immunity. Pertussis vaccination began in Spain in the 1960s, with TDwP in two annual campaigns in infants <1 year old. In 1975, TDwP was introduced into the vaccination schedule with three doses at 3, 5, and 7 months. A fourth dose was added in 1996 (with doses at 2, 4, 6, and 18 months). In 1999/2000, the whole-cell vaccine was switched to an acellular vaccine (TDaP) with a five-dose schedule at 2, 4, 6, and 18 months and 4 years of age. No more changes were made in the vaccination

* Corresponding author at: Area of Preventive Medicine & Public Health, Avda. Atenas s/n, 28922, Rey Juan Carlos University, Madrid, Spain.
E-mail address: ruth.gil@urjc.es (R. Gil-Prieto).

https://doi.org/10.1016/j.vaccine.2019.09.017
0264-410X/

schedule until 2011, right after the latest national and international pertussis outbreak; at that time, a sixth dose of Tdap at 14 years old was added. In 2013, the dose at 4 years was changed and given instead at 6 years; in 2014–2015, the Public Health Commission recommended the vaccination of pregnant women in their 3rd term, and the sixth dose at 14 years old was eliminated. Different Spanish regions adopted modifications to this schedule.

The Spanish database for hospital surveillance, Conjunto Mínimo Básico de Datos; CMBD), covers 99.5% of the Spanish population and includes more than 98% of admissions to hospitals in the public health care system and 70% of the private hospitals. It provides a complete record of all centralized hospital discharges and is not subject to the limitations of outpatient surveillance systems [14–16]. CMBD has been previously used for research purposes, including epidemiological studies of different infectious diseases [17–19].

This epidemiological retrospective study was performed to obtain information on population-based estimates of the burden of hospitalization for whooping cough in infants up to 12 months old in Spain during a 21-year period (1997–2017).

2. Methods

All whooping cough-related hospitalizations in infants up to 12 months old reported in any diagnostic position from January 1st, 1997 through December 31st, 2017 were analysed. International Classification of Diseases, 9th revision, Clinical Modification or ICD-9-CM (CIE-9-MC) codes for whooping cough were selected: (033.0–033.9: 033.0 Whooping cough due to *bordetella pertussis*; 033.1 Whooping cough due to *bordetella parapertussis*; 033.8 Whooping cough due to other specified organism; 033.9 Whooping cough, unspecified organism).

The CMBD database contains admission and discharge date, age, sex, geographical region, diagnosis and discharge status for all hospitalizations in the country. The unit of analysis is the hospital discharge.

The annual hospitalization rate was calculated. For these rates, data from population municipal records for infants were used as the denominators. For the population denominators by month of age, we assumed a constant birth rate during the year in order to associate the precise hospitalization date with the population at risk in any given month. The case-fatality rate (CFR), that informs on the severity of the cases, was calculated by dividing the number of deaths by the total number of hospitalizations related to whooping cough (%). The average length of stay at the hospital (ALOS) was calculated.

All analyses were stratified by age. The same age, sex and epidemiological characteristics distributions were assumed for the population and for hospitalizations not covered by CMBD.

To explore the latest national outbreak and the recent recommendation for vaccination in pregnant women [20], analyses were stratified comparing the periods 1997–2010; 2011–2015 and 2016–2017.

The recommendation for vaccination in pregnant women had to be officially implemented in all the Spanish Autonomous Regions by the end of 2015. Between January 2014 and January 2016, all regions were complying with the measure [20]. Therefore, 2016 was the first year in which pertussis vaccination during pregnancy had been carried out in all regions.

3. Statistics

The chi-square test was used to assess significant differences in proportions, ANOVA was used for multiple comparisons and Poisson regression models were used to assess differences in the hospitalization rates during the study period including by age group. To evaluate whether the introduction of the vaccination recommendation in pregnant women was associated with a significant reduction of pertussis in infants, we leveraged the fact that the now universal recommendation (with costs covered by the social security scheme) was introduced heterogeneously in Spain between January of 2014 and January 2016 using a difference in difference approach [21,22].

In all tests, the significance level used was $p < 0.05$.

Statistical analyses were performed using the R Software (version 3.4.3).

The patient information was anonymised and de-identified prior to the analysis. The local ethics committee (Comité de Ética de la Investigación de la Universidad Rey Juan Carlos) ruled that no formal ethics approval was required for this study.

4. Results

A total of 13,352 hospital discharges for whooping cough in infants under 12 months old were reported during the study period in Spain, with an annual hospitalization rate of 164.51 cases per 100,000 infants (CI 95% 161.72–167.30). The mean age of the patients was 2 months (SD: 1.78, interquartile range (IQR): 1–3 Months), and most of the cases (n = 11.446, 86%) occurred in infants under 4 months of age, with a rate of 423.08 hospitalizations (CI 95% 415.35–430.82) per 100,000 infants up to 4 months of age. The average length of stay at the hospital was 7.7 days (IQR: 3–9).

Seventy-four deaths occurred among these hospitalized patients in the period 1997–2017; all of them occurred in infants under 4 months old with a case-fatality rate of 0.55% (CI 95%: 0.43–0.68%), 89% of them (n = 66) were younger than 2 months of age.

Table 1 shows the hospitalization rates and case-fatality rates for the different age groups in the study period and shows how whooping cough hospitalizations concentrates in infants 0–3 months-old, reaching a hospitalization rate in the second month of live of 715 cases per 100,000 and a case fatality rate of 1.88% in the first month of live.

No statistically significant differences were found by sex in hospitalization rates, or case-fatality rates.

Taking into account the increase in rates starting in 2010–2011 and to explore the latest national outbreak and the potential impact of the recommendation to vaccinate pregnant women, analyses were stratified to compare the periods 1997–2010, 2011–2015 and 2016–2017 (Table 2). In the period 1997–2010, which comprised 14 years, 6850 hospitalizations due to whooping cough were reported489hospitalizations per year, compared to 5,271 hospitalizations reported in 2011–2015 and 1231 reported in 2016–2017.

Table 2 summarizes the main findings of this analysis, showing statistically different annual hospitalization rates of 131.02, 250.13 and 157.69 cases in 1997–2010, 2011–2015 and 2016–2017, respectively.

When the analysis is gathered by month of age, it can be observed that most of the cases (n = 11,446) occurred in infants under 4 months of age, with hospitalization rates of 328.80, 670.81 and 385.84 cases per 100,000 infants up to 4 months of age in the periods 1997–2010, 2011–2015 and 2016–17, respectively. In fact, the increase in hospitalization rates in the period 2011–2015 compared to the previous 1997–2010 is only significant in infants 0–4 months old. Similarly, the significant decrease in the period 2016–2017 compared to 2011–2015, only occurs in infants 0–3 months old.

Of the 74 deaths, 34, occurred in the period 1997–2010, 36 in 2011–2015 and 4 in 2016–2017, which corresponds to a case-fatality rate of 0.5%, 0.7%and 0.5%; respectively (see Supplementary

Table 1
Hospitalization and case-fatality rate due to whooping cough by month of age in infants in Spain (1997–2017).

Age in month	N	Hospitalization rate (per 100,000) (95%-CI)	N (deceased)	Case fatality rate (%) (95%-CI)
[0,1)	1597	236.12 (224.56; 247.69)	30	1.88 (1.21; 2.54)
[1,2)	4839	715.47 (695.38; 735.55)	36	0.74 (0.5; 0.99)
[2,3)	3411	504.33 (487.45; 521.21)	7	0.21 (0.05; 0.36)
[3,4)	1599	236.42 (224.84; 247.99)	1	0.06 (−0.06; 0.19)
[4,5)	908	134.25 (125.53; 142.98)	0	0 (0; 0)
[5,6)	378	55.89 (50.26; 61.52)	0	0 (0; 0)
[6,7)	211	31.2 (26.99; 35.41)	0	0 (0; 0)
[7,8)	113	16.71 (13.63; 19.79)	0	0 (0; 0)
[8,9)	101	14.93 (12.02; 17.85)	0	0 (0; 0)
[9,10)	76	11.24 (8.71; 13.76)	0	0 (0; 0)
[10,11)	58	8.58 (6.37; 10.78)	0	0 (0; 0)
[11,12)	61	9.02 (6.76; 11.28)	0	0 (0; 0)
Total (<12 M)	13,352	164.51 (161.72; 167.3)	74	0.55 (0.43; 0.68)

Table 2
Hospitalization and case-fatality rate due to whooping cough by age in month and period in Spain.

	Hospitalization rate (per 100,000)/CI 95%					Case-fatality rate (%)/CI 95%				
Age in Month	1997–2010	2011–2015	P*	2016	P**	1997–2010	2011–2015	P*	2016	P**
[0,1)	176.05 (163.6; 188.49)	397.48 (368.05; 426.9)	<0.001	202.91 (168.33; 237.49)	<0.001	0.017 (0.01; 0.03)	0.021 (0.01; 0.03)	0.658	0.015 (−0.01; 0.04)	0.891
[1,2)	550.86 (528.88; 572.84)	1150.29 (1100.41;1200.16)	<0.001	644.09 (582.61; 705.56)	<0.001	0.006 0; 0.01)	0.01 (0.01; 0.01)	0.233	0.002 (0; 0.01)	0.221
[2,3)	392.95 (374.37; 411.53)	789.26 (747.87; 830.64)	<0.001	481.14 (427.97; 534.32)	<0.001	0.004 (0; 0.01)	0 (0 ; 0)	0.073	0.003 (0 ; 0.01)	0.415
[3,4)	195.33 (182.22; 208.44)	346.23 (318.75; 373.7)	<0.001	215.21 (179.6; 250.82)	<0.001	0 (0; 0)	0.002 (0; 0)	0.866	0 (0; 0)	1
[4,5)	116.14 (106.03; 126.25)	167.42 (148.3; 186.54)	<0.001	166.02 (134.73; 197.3)	0.985	NA	NA	NA	NA	NA
[5,6)	52.56 (45.76; 59.37)	63.78 (51.97; 75.59)	0.105	56.87 (38.55; 75.2)	0.608	NA	NA	NA	NA	NA
[6,7)	30.07 (24.92; 35.22)	30.18 (22.06; 38.31)	1	41.50 (25.85; 57.16)	0.22	NA	NA	NA	NA	NA
[7,8)	16.76 (12.91; 20.6)	14.81 (9.11; 20.5)	0.666	21.52 (10.25; 32.79)	0.339	NA	NA	NA	NA	NA
[8,9)	13.54 (10.09; 17)	14.81 (9.11; 20.5)	0.795	24.60 (12.55; 36.65)	0.15	NA	NA	NA	NA	NA
[9,10)	12.39 (9.09; 15.7)	8.54 (4.22; 12.86)	0.25	10.76 (2.79; 18.73)	0.791	NA	NA	NA	NA	NA
[10,11)	7.80 (5.18; 10.43)	7.40 (3.38; 11.43)	0.999	16.91 (6.92; 26.9)	0.065	NA	NA	NA	NA	NA
[11,12)	7.80 (5.18; 10.43)	11.39 (6.4; 16.38)	0.23	10.76 (2.79; 18.73)	1	NA	NA	NA	NA	NA
Total ≤ 12	131.02 (127.92; 134.12)	250.13 (243.39; 256.87)	<0.001	157.69 (148.89; 166.49)	<0.001	0.006 (0; 0.01)	0.008 (0.01; 0.01)	0.346	0.004 (0; 0.01)	0.292

Differences were statistically significant ($p < 0.05$) over the study period. Test for differences in proportions.
* Comparison of 1997–2010 vs. 2011–2015.
** Comparison of 2011–2015 vs. 2016.

Fig. 1). All of them occurred in infants younger than 4 months of age. No statistically significant differences were found in case-fatality rates.

On the other hand, Fig. 1 shows the variation during the study period in the annual hospitalization rate in infants up to 12 months of age. A well-known cyclic epidemic pattern can be seen during the period with an increase in rates starting in 2010 and reaching a peak in 2015 with 386.87 hospitalizations per 100,000 infants up to 12 months old (CI 95:367.6–406.1) In 2016, after the recommendation of vaccination for pregnant women implemented in all the Spanish regions, the hospitalization rate started to decrease (195.50 (CI 95% 181.4–208.9) hospitalization per 100,000 in 2016 and 119.50 (CI 95% 108.6–130.4) hospitalization per 100,000 in 2017.

In order to evaluate the potential impact of the implementation of the recommendation of pregnant women vaccination in Spain a difference in difference model was used [21,22]. This model analyzed the country in three different groups of authonomous regions regarding the moment of recommendation onset: (a) those implementing the vaccination in pregnant women in 2014, (b) those implementing it in 2015 and (c) those implementing it in 2016. Those regions implementing the vaccination the latest, reached hospitalizations rates in 2015 that were two-fold of those rates in the regions that had already recommended vaccination in pregnant women in 2014 or 2015 (Fig. 2). Overall the introduction of the vaccination recommendation was associated with a reduction of 20% in the incidence of hospitalization (HR = 0.80, 95%-CI 0.75–0.85, $p < 0.001$) when compared to no recommendation adjusting for time trend and group specific effects.

5. Discussion

This retrospective study reports the epidemiology of severe whooping cough infections in Spain over a period of twenty-one years. The main finding of this study is that an important increase in the hospitalization rates due to whooping cough infection in

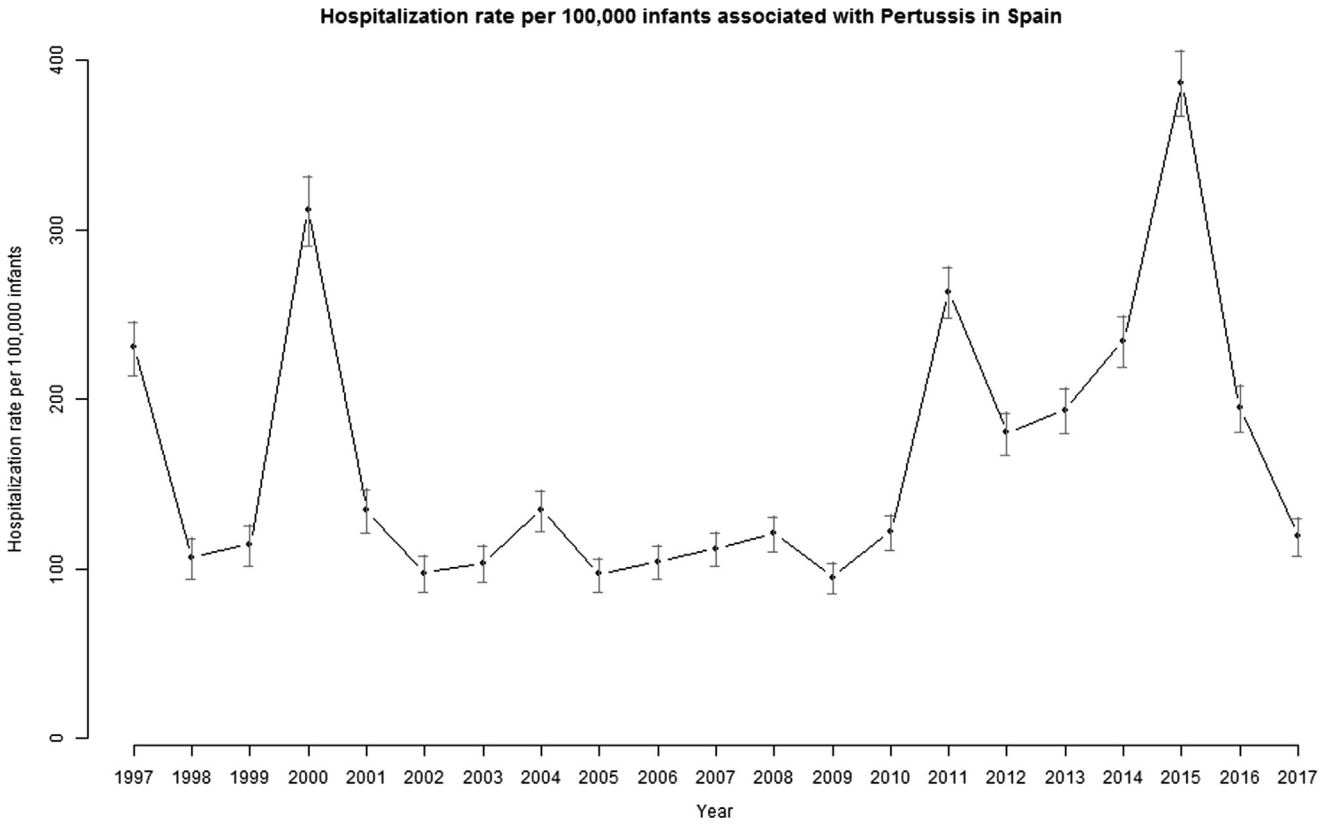

Fig. 1. Hospitalization rate per 100,000 infants associated with Pertussis in Spain.

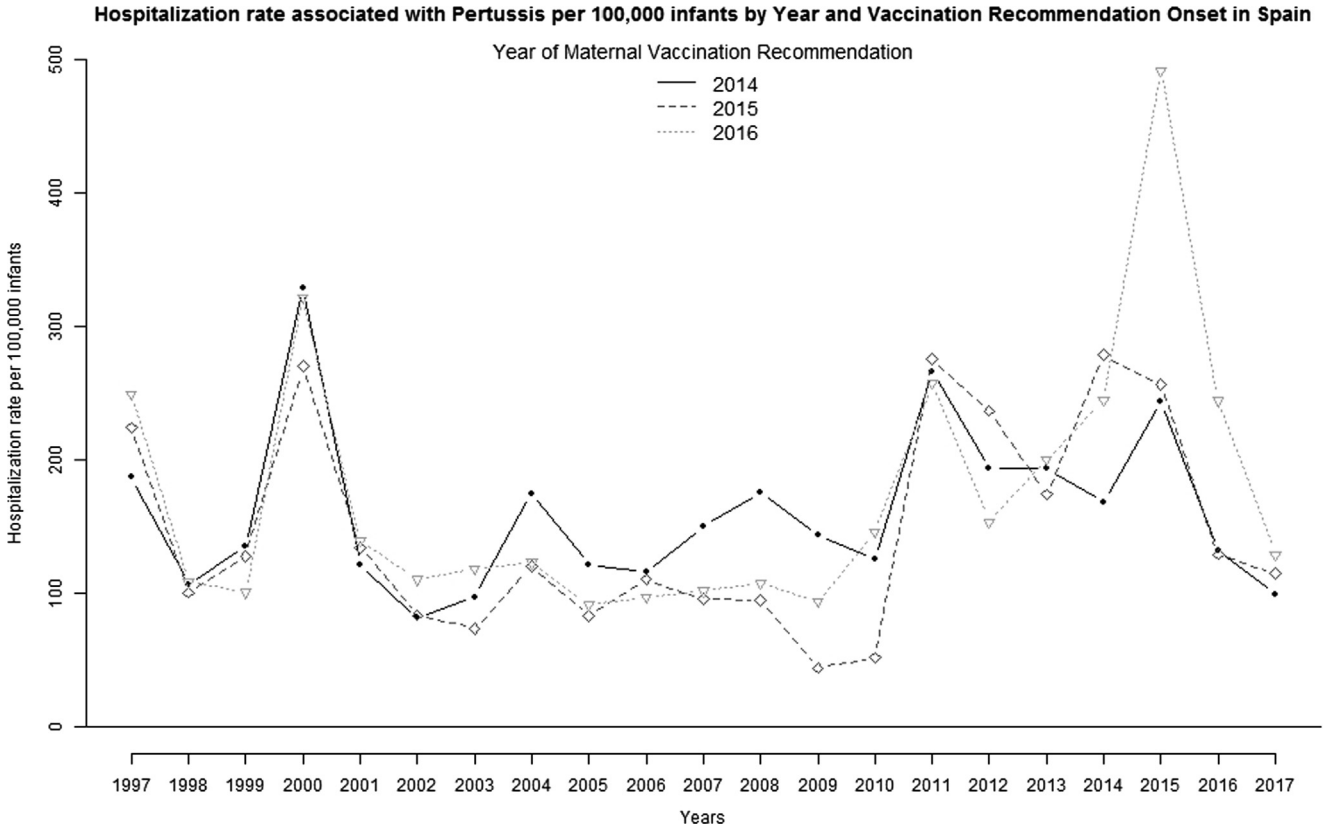

Fig. 2. Hospitalization rate associated with Pertussis per 100,000 infants by year and vaccination recommendation onset in Spain.

Spain has been observed since 2011, especially due to the increase in hospitalizations among infants up to 4 months old; the increase continued until 2016, when the impact of the vaccination recommendation for pregnant women was observed. These findings are in line with the results published in Eurosurveillance [23] for Spain; this study extends the previous analyses from Spain published before the last national and international outbreak starting in 2011 [24,25] and supports the epidemiologic data from around the world [2].

Vaccination has been proven to reduce disease severity and hospitalizations [26–28]; although an increase in cases has been reported in all ages even in the contexts of sustainable high vaccination rates, the increase may be due to the waning of natural and vaccine immunity or better diagnosis and reporting, among other reasons. Most of the hospitalizations and all the deaths in our study occurred in infants younger than 4 months of age, when the first vaccination has not yet been completed. This finding highlighted the need to reinforce the cocoon strategy and focus preventive strategies on infants.

In recent years, different countries have implemented different vaccination strategies and public health measures to end the important increase in pertussis cases. The results regarding the impact on the disease are starting to be seen in the UK [29], Australia [30] and the US [31], and studies of cost-effectiveness have found that vaccinating pregnant women with aP-containing vaccines to prevent neonatal and unvaccinated infants from pertussis-associated disease is likely to be cost-effective from different perspectives [32,33]. Maternal Tdap vaccination have shown to be highly protective against infant pertussis, especially in the first 2 months of life [34].

The National Spanish Public Health Commission, taking into account the epidemiological data as well as evidence of the safety, effectiveness and efficiency of the available vaccines, in 2014–5 recommended the administration of one dose of Tdap vaccine in pregnant women in the 3rd term, regardless of their vaccination status; this recommendation should have been implemented in all the Spanish regions by January 2016. Our results show an important decrease in hospitalizations and deaths in 2016 and 2017 compared to 2015. Unfortunately, our database does not allow us to have information on the individuaĺs mother's vaccination status, but the data do allow us to hypothesize a major impact of vaccination on hospitalizations, as vaccination coverage with Tdap in pregnant women in Spain was 82.7% (ranging from 73.4 to 95.5% in the different regions) in 2016 and 80.7% (ranging from 70.4 to 92.6% in the different regions) in 2017 [35].

The information presented in this article will allow the comparison of new data after the consolidated implementation in all regions of this new preventive strategy and will serve to confirm whether this decreasing trend continues or is due to epidemic fluctuations.

This study has some limitations related to the use of a nationwide hospital database. The reliability of hospital-based surveillance depends on the quality of the discharge report and the clinical history, as well as on the quality of the codification process [16]. Potential biases associated with coding or the assumption of causality between the disease and potential complications could result in misclassification. CMBD does not provide information regarding laboratory confirmation. However, we assumed that a differential diagnosis of severe pertussis infection had been confirmed, as it is a notifiable disease in Spain.

6. Conclusion

Most of the whooping cough infections and all deaths occurred in infants < 4 months of age in Spain. The hospitalization rate was significantly higher beginning in 2011 and did not decrease until 2016, after vaccination of pregnant women was recommended. Public health measures such as vaccination of pregnant women, caregivers, health care professionals and relatives, especially young parents, could reduce the hospitalization burden during the current outbreak.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: RGP has received travel and research grants and has participated in advisory boards from Sanofi and Merck.

AGM has received travel and research grants and has participated in advisory boards from Sanofi, Merck, Pfizer.

JSRM has received travel and research grants from Sanofi.

SW, PMG, AGE have no conflict of interests.

Acknowledgement

The authors thank the Subdirección General del Instituto de Información Sanitaria for providing the information on which this study is based.

Funding information

This research study is part of the research activities of the "Cathedra in Vaccines Research from Rey Juan Carlos University", which is sponsored by Sanofi Pasteur Spain.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.09.017.

References

[1] World Health Organization. Pertussis vaccines: WHO position paper - September 2015. Wkly Epidemiol Rec 2015;90(35):433–58.
[2] Tan T, Dalby T, Forsyth K, Halperin SA, Heininger U, Hozbor D, et al. Pertussis across the globe: recent epidemiologic trends from 2000 to 2013. Pediatr Infect Dis J 2015;34(9):e222–32.
[3] Forsyth K, Plotkin S, Tan T, Wirsing von König CH. Strategies to decrease pertussis transmission to infants. Pediatrics 2015;135(6):e1475–82. https://doi.org/10.1542/peds.2014-3925.
[4] Centers for disease control and prevention. Pertussis outbreak trends. http://www.cdc.gov/pertussis/outbreaks/trends.html Ultimo acceso 13 de febrero de 2018.
[5] Amirthalingam G, Gupta S, Campbell H. Pertussis immunisation and control in England and Wales, 1957 to 2012: a historical review. Euro Surveill 2013;18(38). pii: 20587. Review, Sep 19.
[6] Cherry JD. Epidemic pertussis in 2012–the resurgence of a vaccine-preventable disease. N Engl J Med 2012 Aug 30;367(9):785–7. https://doi.org/10.1056/NEJMp1209051. Epub 2012 Aug 15.
[7] van der Maas NA, Mooi FR, de Greeff SC, et al. Pertussis in the Netherlands, is the current vaccination strategy sufficient to reduce disease burden in young infants? Vaccine 2013;31:4541–7. https://doi.org/10.1016/j.vaccine.2013.07.060.
[8] Klein NP, Bartlett J, Rowhani-Rahbar A, et al. Waning protection after fifth dose of acellular pertussis vaccine in children. N Engl J Med 2012;367(11):1012–9.
[9] Lavine JS, Bjørnstad ON, de Blasio BF, et al. Short-lived immunity against pertussis, age-specific routes of transmission, and the utility of a teenage booster vaccine. Vaccine 2012 Jan 11;30(3):544–51. https://doi.org/10.1016/j.vaccine.2011.11.065. Epub 2011 Nov 26.
[10] Shapiro ED. Acellular vaccines and resurgence of pertussis. JAMA 2012 Nov 28;308(20):2149–50. https://doi.org/10.1001/jama.2012.65031.
[11] Ghaswalla P, Poirrier JM, Packnett ER, Irwin DE, Gray SR, Buck PO. Maternal immunization in the U.S.: A nationwide retrospective cohort study. Am J Prev Med 2019 Sep;57(3):e87–93. https://doi.org/10.1016/j.amepre.2019.04.013.
[12] Winter K, Zipprich J, Harriman K. Pertussis in California: A tale of 2 epidemics. Pediatr Infect Dis J 2018 Apr;37(4):324–8.
[13] Skoff TH, Blain AE, Watt J, Scherzinger K, McMahon M, Zansky SM, et al. Impact of the US Maternal Tetanus, diphtheria, and acellular pertussis vaccination

program on preventing pertussis in infants <2 months of age: a case-control evaluation. Clin Infect Dis 2017 Nov 29;65(12):1977–83.
[14] Ministerio de Sanidad y Consumo. Clasificación internacional de enfermedades 9 revisión, modificación clínica. 1996. p. 375–6. Available in: http://www.msssi.gob.es/estadEstudios/estadisticas/normalizacion/clasifEnferm/fichas/home.htm (consulted 11.05.13).
[15] Rivero Cuadrado A. El conjunto mínimo básico de datos en el SNS: inicios y desarrollo actual. Rev Fuentes Estadísticas 2000;49:18–9. Available in: http://www.ingesa.msc.es/estadEstudios/documPublica/pdf/grds-2001.pdf (consulted 10.05.13).
[16] Peiro S, Librero J. Evaluación de la calidad a partir del conjunto mínimo de datosbásicos al alta hospitalaria. RevNeurol 1999;29:651–61.
[17] Gil-Prieto R, San Martín M, de Andrés AL, Alvaro-Meca A, González A, de Miguel AG. Hospital-acquired rotavirus infections in Spain over a ten-year period (1998–2007). HumVaccin. 2009;5(11):748–53.
[18] Gil-Prieto R, García-García L, Alvaro-Meca A, González-Escalada A, Viguera Ester P, Gil De Miguel A. The burden of hospitalizations for meningococcal infection in Spain (1997–2008). Vaccine 2011;29(34):5765–70.
[19] Gil Prieto R, San Román Montero J, Gómez Alejandre C, Alvaro Meca LA, Rivero A, Gil de Miguel A. Epidemiology of pneumococcal meningitis hospitalisations in pediatric population in Spain (1998–2006). Vaccine 2009;27(20):2669–73.
[20] María de Viarce Torres de Mier, Noemí López-Perea, Josefa Masa Calles y la Red Nacional de Vigilancia Epidemiológica (RENAVE). Centro Nacional de Epidemiología. CIBERESP. ISCIII. RENAVE. Situación de la Tos ferina en España, 1998-2016. Análisis preliminar del Impacto de la Vacunación de Tos ferina en Embarazadas. Madrid, 25 de abril de 2018. URL: http://revista.isciii.es/index.php/bes/article/view/1060/1303 (Last consulted August 30th 2019).
[21] Wooldridge J. Econometric analysis of cross section and panel data. 2nd ed. Cambridge, MA: MIt Press; 2010. p. 130–2.
[22] Gil-Prieto R, Walter S, Gonzalez-Escalada A, Garcia-Garcia L, Marín-García P, Gil-de-Miguel A. Different vaccination strategies in Spain and its impact on severe varicella and zoster. Vaccine 2014 Jan 3;32(2):277–83.
[23] Sizaire V, Garrido-Estepa M, Masa-Calles J, et al. Increase of pertussis incidence in 2010 to 2012 after 12 years of low circulation in Spain. Euro Surveill 2014;19(32). Aug 14, pii: 20875.
[24] Santos JM, Gil R, Alvaro A, Gil A. Epidemiologia de las hospitalizaciones atribuibles a infección por *Bordetella Pertussis* en población general en Espala (1999-2015). Vacunas 2008;9(2):50–6.
[25] Fernández-Cano MI, Armadans-Gil L, Alvarez-Bartolomé M, Rodrigo-Pendás JÁ, Campins-Martí M. Hospitalization due to whooping cough in Spain (1997–2011). Enferm Infecc Microbiol Clin 2014 Dec;32(10):638–42.
[26] Crespo I, Toledo D, Soldevila N, Jordán I, Solano R, Castilla J, Caylà JA, Godoy P, Muñoz-Almagro C, Domínguez Á, Working Group on the Transmission of Pertussis in Households. Characteristics of hospitalized cases of pertussis in Catalonia and Navarra, two regions in the North of Spain. PLoS One 2015;10(10).
[27] Barlow RS, Reynolds LE, Cieslak PR, Sullivan AD. Vaccinated children and adolescents with pertussis infections experience reduced illness severity and duration, Oregon, 2010–2012. Clin Infect Dis 2014 Jun;58(11):1523–9.
[28] Wymann MN, Richard JL, Vidondo B, Heininger U. Prospective pertussis surveillance in Switzerland, 1991–2006. Vaccine 2011 Mar 3;29(11):2058–65.
[29] Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet 2014;384:1521–8.
[30] Perrett KP, Nolan TM. Immunization during pregnancy: impact on the infant. Paediatr Drugs 2017 Aug;19(4):313–24.
[31] Centers for disease control and prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women–advisory committee on immunization practices (ACIP), 2012. MMWR Morb Mortal Wkly Rep, 2013;62(7):131–5.
[32] Van Bellinghen LA, Dimitroff A, Haberl M, Li X, Manton A, Moeremans K, et al. Is adding maternal vaccination to prevent whooping cough cost-effective in Australia? Hum Vaccin Immunother 2018 May;17:1–11.
[33] Hoshi SL, Seposo X, Okubo I, Kondo M. Cost-effectiveness analysis of pertussis vaccination during pregnancy in Japan. Vaccine 2018 Aug 16;36(34):5133–40.
[34] Baxter R, Bartlett J, Fireman B, Lewis E, Klein NP. Effectiveness of vaccination during pregnancy to prevent infant pertussis. Pediatrics 2017;139(5). https://doi.org/10.1542/peds.2016-4091. May, pii: e20164091, Epub 2017 Apr 3.
[35] Coberturas de Vacunación. DATOS ESTADÍSTICOS. SECRETARIA GENERAL DE SANIDAD Y CONSUMO. DIRECCIÓN GENERAL DE SALUD PÚBLICA,CALIDAD E INNOVACIÓN SUBDIRECCIÓN GENERAL DE PROMOCIÓN DE LA SALUD Y VIGILANCIA EN SALUD PÚBLICA. URL: https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/docs/CoberturasVacunacion/Todas_las_tablas2017.pdf [last consulted August 30th 2019].