

Received:

4 April 2018

Revised:

18 July 2018

Accepted:

31 January 2019

Cite as:

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in preventing whooping cough
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Spain.

Heliyon 5 (2019) e01207.

doi: [10.1016/j.heliyon.2019.e01207](https://doi.org/10.1016/j.heliyon.2019.e01207)



Effectiveness of dTpa vaccination during pregnancy in preventing whooping cough in infants under 3 months of age. Bizkaia, Basque Country, Spain

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Abstract

In response to an increase in the incidence of whooping cough in recent years, the Basque Country established a vaccination programme for pregnant women in the last trimester of the pregnancy seeking to protect young infants, a population that is at high risk of developing severe whooping cough. In the present study, based on the screening method, we assessed the effectiveness of this measure to prevent whooping cough in infants under 3 months of age. We found a vaccine effectiveness of 89% and 95% CI 72–96%. While the incidence of this disease remains high, we recommend continuing to vaccinate pregnant women in the last trimester of pregnancy.

Keyword: Vaccines

1. Introduction

The incidence of whooping cough has increased in recent years, even in countries with high vaccine coverage [1, 2]. The Basque Country (Spain) has not been spared from this increase: in 2010, the incidence of whooping cough was 0.19 cases per 100,000 people, rising to 89.82 per 100,000 (599.39 in infants under 1 year old) in 2015. In response to the marked increase in the number of cases, and seeking to protect infants under 1 year of age, a population that is at high risk of developing severe illness or complications from whooping cough, a campaign started in the Basque Country on 1 February 2015 to give women between week 27 and 36 of pregnancy the diphtheria, tetanus and acellular pertussis (whooping cough) (dTpa) vaccine. This measure provides, on the one hand, direct protection through transplacental transmission of antibodies to the foetus, and on the other, it prevents mothers being a source of infection [3]. Other countries such as the UK and the USA have also adopted this vaccination strategy in pregnant women.

In this study, we assessed the effectiveness of vaccinating pregnant women between 27 and 36 weeks of pregnancy in the prevention of whooping cough in infants under 3 months of age.

2. Material and methods

2.1. Cases of whooping cough and calculation of the incidence rate

The cases of whooping cough in infants were identified by reviewing the following sources of information:

- National registry of notifiable diseases: diagnoses of whooping cough are required to be notified to the corresponding Epidemiology Unit by all clinicians in both public and private providers (data being retrieved for the province of Bizkaia).
- The minimum data set of admissions to hospitals in the province: considering cases when the condition that was the main reason for hospital admission was assigned ICD-9 codes 033.0 (whooping cough due to *Bordetella pertussis*) or 033.9 (whooping cough due to a non-specified organism).
- The Basque Microbiological Information System (SIMCAPV): which registers all polymerase chain reaction tests with results positive for *Bordetella pertussis* obtained through all public laboratories and the main private ones in the region.

To calculate the rates, we used data from the 2015 Basque census (EUSTAT, Basque Statistics Office), in which Bizkaia was found to have a population of 1,138,852 people, of whom 9237 were under 1 year old. The data on cases comes from individual

questionnaires which are required to be completed for each diagnosis of whooping cough; for this study, these questionnaires were expanded to include the following items: mother vaccinated (yes/no), the date and week of vaccination, and the week of delivery.

2.2. Estimation of dTpa coverage among pregnant women in Bizkaia

The study period ran from 1 February 2015 (when vaccination started to be recommended) until 31 January 2016. For the numerator, we obtained basic patient data on women born before 31 December 1996 (women over 18 years of age) who had been vaccinated with dTpa (Boostrix[®], GlaxoSmithKline; intramuscular; sets AC37B133AB, AC37B136AI, AC37B146AC, AC37B149AF, AC37B159DD, AC37B168CL, AC37B159EG, AC37B188AA), in this period. We excluded women over 50 years of age (date of birth before 1965), and in the case of women aged between 46 and 50 years old, we checked whether they were pregnant. We checked the sets of the vaccines to avoid that Td, DTPa vaccines could be erroneously registered as dTpa. For the denominator, we used a registry of metabolic diseases that lists all the newborn infants in the Basque Country. We selected the newborn infants of mothers who were resident in Bizkaia in the study period (i.e., between 1 February 2015 and 31 January 2016). We considered the number of multiple pregnancies and the number of babies born in each of them to adjust the figure to the number of pregnancies.

2.3. Calculation of effectiveness of the vaccine to prevent cases of whooping cough in infants under 3 months of age

We used a case-coverage approach, the screening method [4], that makes it possible to estimate vaccine effectiveness when we do not have controls. Specifically, the effectiveness of the vaccine is calculated as follows (equation (1)):

$$\text{Effectiveness} = 1 - [(\text{PCV} * (1 - \text{PPV})) / (1 - \text{PCV}) * \text{PPV}]. \quad (1)$$

Where PCV is the proportion of cases vaccinated, that is, the proportion of infants with whooping cough whose mothers had been vaccinated; and PPV is the proportion of the population vaccinated, that is, the dTpa coverage in pregnant women. The 95% confidence intervals were obtained with the statistical software R (version 3.5.1; The R foundation for statistical computing).

3. Results

In 2015, 1035 cases of whooping cough were reported in Bizkaia, more than 95% of them confirmed using polymerase chain reaction (PCR) analysis in nasopharyngeal swabs. This represents the greatest increase in the number of cases in the last 20

Table 1. Cases of whooping cough and incidence rate per 100,000 people by age group. Bizkaia. 2014 and 2015. Notifiable disease surveillance system.

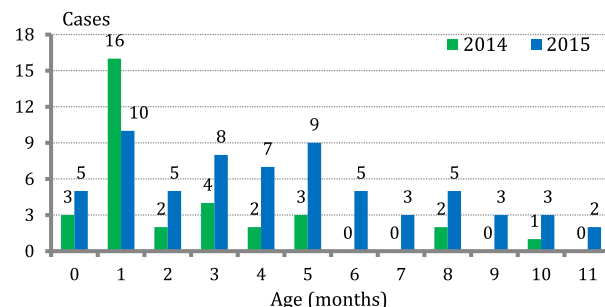
Age group (years)	2014		2015	
	Cases	Incidence rate	Cases	Incidence rate
<1	33	340.35	65	670.38
1–4	32	78.09	226	551.53
5–9	8	15.21	300	570.5
10–14	4	8.10	184	372.42
15–24	0	0	28	30.81
25–44	22	6.96	112	35.41
45–64	2	0.60	90	26.88
≥65	1	0.41	30	12.16
Total	102	8.94	1035	90.67

years. The increase was not homogeneous across all age groups. Table 1 shows the cases and the incidence rates of whooping cough in 2014 and 2015. Infants under 1 year of age were the group with the highest incidence in 2015, 670.38 cases per 100,000, though not the group which saw the sharpest rise in incidence since 2014. Among under-1-year-olds, the highest incidence rates in 2014 and 2015 were in 2-month-old infants (see Fig. 1).

Interestingly, the incidence of whooping cough in recent years has not been reflected in an increase in hospitalization (see Fig. 2), with 14 hospital admissions in both 2014 and 2015, despite the markedly different incidence rates.

3.1. Effectiveness of vaccinating pregnant women to prevent whooping cough in infants under 3 months of age

dTpa coverage in pregnant women aged between 18 and 50 years old between 1 February 2015 and 31 January 2016 in Bizkaia was 93.7%. In this province, 19 cases

**Fig. 1.** Cases of whooping cough in under-1-year-olds by age (in months) in Bizkaia in 2014 and 2015. Notifiable disease surveillance system.

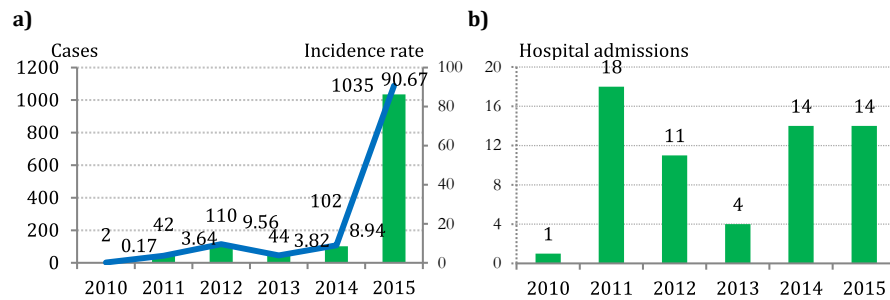


Fig. 2. a) Cases of whooping cough and incidence rate per 100,000 people. b) Number of hospital admissions for whooping cough between 2010 and 2015.

Table 2. Characteristics of the cases of whooping cough considered in this study.

Case no.	Sex ^a	Age (days)	Maternal vaccination	Week of pregnancy at vaccination	Week of birth
1	m	46	yes	27	39
2	m	64	yes	27	40
3	m	61	yes	28	32
4	f	31	yes	28	39
5	m	88	yes	28	32
6	f	2	yes	29	38
7	m	28	yes	30	39
8	f	18	yes	30	39
9	f	55	yes	30	41
10	f	47	yes	31	38
11	m	27	yes	34	36
12	f	52	yes	36	40
13	f	51	no	-	40
14	m	36	no	-	40
15	m	42	no	-	39
16	m	33	no	-	41
17	f	32	no	-	38
18	m	12	no	-	38
19	m	69	no	-	39

^a Male: m; female: f.

of whooping cough in infants under 3 months of age were reported to the notifiable disease surveillance system. Table 2 shows some characteristics of the cases of whooping cough considered in this study. Based on the Farrington equation [4], the vaccine effectiveness was calculated to be 89% and 95% confidence interval [CI]: 72–96%.

4. Discussion

The administration of the dTpa vaccine during pregnancy is considered to be safe [5]; and it has been shown that infants less 2 months of age whose mothers had been vaccinated have a higher concentration of antibodies [6]. Further, the vaccine has been found to have an effectiveness of 58% to prevent hospitalizations in infants [7] and shown to be cost-effective [8]. Vaccination of pregnant women is considered to be better than cocooning [9], a strategy that has the drawbacks of it being difficult to define the close contacts of young infants and greater economic costs. Nevertheless, there are also some uncertainties surrounding the vaccination of pregnant women, such as the potential interference of maternal antibodies in the immune response of young infants (known as blunting).

We estimated the effectiveness of this vaccine using the screening method, the validity of which is constrained by the accuracy of the vaccine coverage calculation. In relation to this, there are various potential sources of bias in our study. First, the denominator is the number of infants born in the period of time coinciding with that of the vaccination. Logically, these figures do not correspond to children born from vaccinated women. Nevertheless, we believe that these data can be extrapolated, since the number of births per month remains relatively stable. Secondly, this study does not include women who were born after 31 December 1996. We used this cut-off to avoid any influence of the Td vaccine (tetanus, diphtheria) for 16-year-olds, despite the risk of missing the youngest pregnant women (in the study period, there were 61 births to women younger than the cut-off age living in Bizkaia). Thirdly, it is possible that some of the vaccinations recorded were given for reasons other than pregnancy, for example, contact with a person with whooping cough. Lastly, since we included infants up to 3 months of age, the first vaccines at 2 months of age might have influenced the results. If, however, we limit the study to children aged under 60 days old, before the first dose of whooping cough vaccine, the number of cases would be 15, 9 of whose mothers had been vaccinated. This yields a vaccine effectiveness of 90%, very similar to the figure of 89% obtained including infants under 3 months of age.

The vaccine effectiveness we have estimated (89% (95% CI, 72–96)) is close to that found in other studies. Notably, Amirthalingam et al. [10] reported an effectiveness of 91% (95% confidence interval [CI]: 85–95%) in preventing the disease in infants under 2 months of age. A subsequent case-control study [11] found an effectiveness of 93% (95% CI: 81–97%). More recently, in another case-control study, Bellido-Blasco et al. found a vaccine effectiveness of 90.9 % (95% CI: 56.6–98.1%) in infants under 3 months of age in the Region of Valencia (Spain) [12].

5. Conclusions

Vaccination for dTpa in pregnant women in the third trimester of pregnancy was introduced in the Basque Country in February 2015. Using the screening method,

the effectiveness of this vaccination programme to prevent whooping cough in infants under 3 months of age was found to be 89% (95% CI, 72–96).

In the light of these results, while there continues to be a high incidence of whooping cough, we recommend continuing with the programme to vaccinate pregnant women in the third trimester of pregnancy. Additionally, we recommend using the screening method to determine the effectiveness of the vaccination programme in the whole region of the Basque Country.

Declarations

Author contribution statement

Patricia Sancho Uriarte, Sabino San José Rodríguez, Itxaso González Sancristobal, Nerea Muniozgueren Agirre: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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