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Effectiveness of acellular pertussis vaccine and evolution of pertussis incidence in the community of Madrid from 1998 to 2015

P. Latasa [a,*], L. García-Comas [a], A. Gil de Miguel [b,c], M.D. Barranco [d], I. Rodero [a], J.C. Sanz [e], M. Ordobás [a], A. Arce [a], M. Garrido-Estepa [e]

[a] Subdirectorate of Epidemiology, Health Department of the Community of Madrid, Madrid, Spain
[b] Department of Public Health, University Rey Juan Carlos, Madrid, Spain
[c] Subdirectorate of Promotion, Prevention and Health Education, Health Department of the Community of Madrid, Madrid, Spain
[d] Regional Public Health Laboratory, Health Department of the Community of Madrid, Madrid, Spain
[e] Health Technology Assessment Agency, Carlos III Health Institute, Madrid, Spain

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ABSTRACT

Introduction: Pertussis is a communicable disease that primarily affects infants. Vaccination has led to an important reduction in the incidence of the disease, however, resurgence of the disease has been observed. This study aimed to analyze the incidence of pertussis and assess the vaccination effectiveness (VE) of different schedules of acellular pertussis vaccination in the community of Madrid.

Methods: Pertussis cases notified to the Mandatory Disease Reporting System from 1998 to 2015 were analyzed. Five comparison periods were created: 1998–2001 (reference), 2002–2005, 2006–2009, 2010–2012 and 2013–2015. The incidence ratio (IR) between inter-epidemic periods was analyzed using a Poisson regression. VE was calculated using the screening method. Vaccine status data were collected from the vaccine registry.

Results: In total, 3855 cases were notified. Inter-epidemic periods were observed every 3–4 years. The incidence increased (IR: 5.99, $p < 0.05$) in the 2013–2015 period, particularly among infants younger than 1 month (IR: 32.41, $p < 0.05$). Vaccination data were available in 89% of cases. For those receiving the last dose at ≤6-month VE was 89.9% (95% confidence interval (CI): 87.3–92.0) after one year of follow-up, and 85.5% (95% CI: 82.4–88.1) after 11 years of follow-up. For those receiving the last dose at 18-months VE decreased from 98.8% (95% CI: 98.3–99.1) to 85.1% (95% CI: 81.9–87.7) in the same period, and for those receiving the last dose at 4-year VE decreased from 99.6% (95% CI: 99.3–99.7) to 79.3% (95% CI: 74.6–83.1).

Conclusions: B. pertussis is circulating in our population, as shown by the epidemic peaks and increased incidence of pertussis in recent years. VE increased with the number of doses and decreased with the follow-up period. The effect of this and other vaccination strategies must be monitored to control the disease.

1. Introduction

Pertussis is a highly transmissible bacterial infectious disease caused by *Bordetella pertussis*. Pertussis affects individuals of all ages, although infants younger than 6 months are the most vulnerable age group, with high rates of complications and mortality. Mild symptomatology of prolonged cough commonly occurs in adolescents and adults. Indeed, up to 13–20% of cases of prolonged cough in adolescents and adults result from infection by *B. pertussis* [1].

The main source of infection for young children are other household members, particularly parents and older siblings [2–7]. Transmission occurs through direct contact with infected persons; their contagiousness is very high, and reported attack rates in unvaccinated children within household contact studies ranged between 58 and 100% [8].

There may be waning of vaccine- and infection-induced immunity [9,10] but vaccination is still the most effective preventive strategy to control pertussis transmission in the population.

Vaccination programs have been introduced worldwide since the 1950s, initially with whole-cell vaccines (diphtheria, tetanus,

* Corresponding author at: Servicio de Epidemiología, Subdirección de Epidemiología, Dirección General de Salud Pública, Consejería de Sanidad, Comunidad de Madrid, c/ San Martín de Porres, 6-1ª planta, 28035 Madrid, Spain.
E-mail address: pello.latasa@salud.madrid.org (P. Latasa).

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pertussis - DTPw). Subsequently, in the 1990s, many countries began to vaccinate using acellular vaccines (aP), which have a better safety profile. In Spain, the DTPw vaccine was marketed in the 1960s and was administered in 2 annual campaigns to children younger than 1 year. In 1975, the component Pw was introduced in the child vaccination schedule with 3 doses at 3, 5 and 7 months of age. In 1996, the vaccination schedule was changed to 2, 4 and 6 months and a 4th dose was included at 18 months of age. In 1999, the DTPw vaccine was replaced by the DTPa vaccine in the community of Madrid. In 2000, a 5th dose was added at 4 years of age. In 2011, a 6th dose was added at 14 years of age and the type of vaccine was modified, replacing the high-load vaccine with low-load vaccines administered at 4 and 14 years of age. In 2013, the age of vaccination for the 5th dose was changed from 4 to 6 years. The Common Child Vaccination Schedule approved by the Interterritorial Council of the National Health System in March 2013 [11] recommends the administration of DTPa at 2, 4 and 6 months of age, with 2 booster doses at 18 months and 6 years of age [12]. The community of Madrid adopted these recommendations by publishing the child vaccination schedule of the community of Madrid in January 2014 [13].

Pertussis has reemerged in many countries despite the maintenance of high vaccine coverage [1,14–23]. Thus, vaccination may protect against severe forms of the disease, albeit with a more limited effectiveness regarding protection against infection.

The community of Madrid relies on the Epidemiological Surveillance System, which covers its entire population of nearly 6.5 million people, one of the largest populations in the country, to study the distribution and characteristics of the disease. Nearly 20% of pertussis cases notified in Spain from 2007 to 2014 occurred in the community of Madrid [24].

This study aimed to analyze the changes in pertussis incidence from 1998 to 2014 and assess the vaccination effectiveness (VE) of different schedules of aP in the community of Madrid.

2. Method

2.1. Study population

Cases of pertussis in residents of the community of Madrid that were notified through the Epidemiological Surveillance System from 1998 to 2015 were included. Cases of pertussis in infants with a date of birth from January 2001 to December 2015, and who had been vaccinated with all aP doses, were selected from the notified cases to study VE.

2.2. Data collection

Data were collected from the Mandatory Disease Reporting Surveillance System. The definition of a case for epidemiological surveillance purposes is that found in the Epidemiological Surveillance Network of the community of Madrid [25], based on clinical and laboratory criteria. Suspected, probable and confirmed cases with the following definitions were analyzed in this study:

- Suspected: Any case that agrees with the clinical case definition that is not laboratory-confirmed and is not epidemiologically related to a laboratory-confirmed case.
- Probable: A clinically compatible case that meets one of the presumptive diagnostic laboratory criteria.
- Confirmed: Clinically compatible laboratory-confirmed case or epidemiologically related to a laboratory-confirmed case.

Basic data were collected using a standardized form including patient identification and clinical, diagnosis, vaccine and epidemiological data. Clinical data were revised by consulting data from the Electronic Health Records and asking the respective physicians when necessary. Data on the vaccination status was obtained from the Community of Madrid Vaccination Register, which collects nominal information on the vaccines administered throughout its population, with data available since the end of 2004.

2.3. Statistical analysis

The incidence of pertussis cases (cases per 100,000 inhabitants) was analyzed in the period from 1998 to 2015 by age group in years (<1, 1 to 4, 5 to 9, 10 to 14, 15 to 49 and ≥50 years of age) and months (<1, 1, 2, 3 to 5, 6 to 8 and 9 to 11 months) for the subgroup of infants younger than 1 year.

The years were grouped into 5 periods according to epidemic cycles and changes in the vaccination schedule: 1998–2001, 2002–2005, 2006–2009, 2010–2012 and 2013–2015. The incidence ratios (IRs) of each period were calculated using a Poisson regression.

Cases with complete information on vaccination status were selected to study VE. The doses administered were considered valid if at least 15 days had elapsed from the date of vaccination to the date of onset of symptoms, which is necessary to generate an immune response. VE was calculated using the screening method [26] based on the comparison between the ratio of vaccinated cases and the ratio of the vaccinated population. The approach described by Farrington [27], which adjusts VE to possible confounders using logistic regression models, was used. The model required data on the vaccination coverage of each analysis subgroup. The follow-up period from the vaccination was calculated as the time elapsed between the date of the last dose and the date of onset of symptoms. VE was calculated with a 95% confidence interval (95% CI) for at least 1, 2, 3, 4 and 5 doses, according to the cumulative follow-up period. The short- (1 year) and long-term (12 years) evolution and annual evolution of pertussis were calculated for the recommended vaccination schedule for specific age groups: ≤6 months (≤3 doses), 18 months (4 doses) and ≥4 years (≥5 doses) to reduce the age effect on VE. Statistical significance was set at $p < 0.05$. The statistical analysis was performed in STATA v12.

3. Results

3.1. Incidence

An inter-epidemic period was observed every 3–4 years. At epidemic peaks, the increases in incidence occurred in all age groups, although they were more pronounced in infants younger than 1 year. After a decline in incidence in 2012, a new inter-epidemic period began in the 2013–2015 period (Table 1 and Figs. 1). The highest peaks occurred in 2015 (incidence: 12.41 cases per 100,000 inhabitants), followed by 2011 (6.29 cases per 100,000 inhabitants) and 2014 (5.75 cases per 100,000 inhabitants).

The IRs are outlined in Table 1 using the 1998–2001 inter-epidemic period as the reference. The overall incidence increased 6-fold in the 2013–15 period ($IR_{2013\text{-}15} = 5.99$). Although the inter-epidemic period started in 2013, and in previous inter-epidemic periods the rates increased for 1–2 years, the incidence was still increasing in 2015. Incidence rate observed in 2015 was the highest observed since 1998.

The incidence in infants younger than 1 year increased from 50.76 in the 1998–2001 period to 304.93 cases per 100,000 inhabitants in the 2013–2015 period, peaking in the last period. The highest incidence of the 5- to 9-year age group occurred in the

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