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ORIGINAL RESEARCH ARTICLE

Reduction of Direct Health Costs Associated with Pertussis Vaccination with Acellular Vaccines in Children Aged 0–9 Years with Pertussis in Catalonia (Spain)

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Abstract

Objectives The aim of this study was to assess direct health costs in children with pertussis aged 0–9 years who were vaccinated, partially vaccinated, and unvaccinated during childhood, and to assess the association between pertussis costs and pertussis vaccination in Catalonia (Spain) in 2012–2013.

Methods Direct healthcare costs included pertussis treatment, pertussis detection, and preventive chemotherapy of contacts. Pertussis patients were considered vaccinated when they had received 4–5 doses, and unvaccinated or partially vaccinated when they had received 0–3 doses of vaccine. The Chi square test and the odds ratios were used to compare percentages and the *t* test was used to compare mean pertussis costs in different groups, considering a $p < 0.05$ as statistically significant. The correlation between pertussis costs and study variables was assessed using the Spearman's ρ, with a $p < 0.05$ as statistically significant. Multiple linear regression analysis (IBM-SPSS program) was used to quantify the association of pertussis vaccination and other study variables with pertussis costs.

Results Vaccinated children with pertussis aged 0–9 years had significantly lower odds ratios of hospitalizations (OR 0.02, $p < 0.001$), laboratory confirmation (OR 0.21, $p < 0.001$), and severe disease (OR 0.02, $p < 0.001$) than unvaccinated or partially vaccinated children with pertussis of the same age. Mean direct healthcare costs were significantly lower ($p < 0.001$) in vaccinated patients (€190.6) than in unvaccinated patients (€3550.8), partially vaccinated patients (€1116.9), and unvaccinated/partially vaccinated patients (€2330). Multivariable linear regression analysis showed that pertussis vaccination with 4–5 doses was associated with a non-significant reduction of pertussis costs of €107.9 per case after taking into account the effect of other study variables, and €200 per case after taking into account pertussis severity.

Conclusions Direct healthcare costs were lower in children with pertussis aged 0–9 years vaccinated with 4–5 doses of acellular vaccines than in unvaccinated or partially vaccinated children with pertussis of the same age.

Key Points for Decision Makers

Severe pertussis was less frequent in children with pertussis aged 0–9 years vaccinated during childhood with 4–5 doses of acellular vaccines.

Mean direct health costs were lower in children with pertussis aged 0–9 years vaccinated during childhood with 4–5 doses of acellular vaccines.

Pertussis vaccination with 4–5 doses of acellular vaccines was associated with a non-significant reduction of pertussis costs of €107.9 per case taking into account all study variables, and €200 per case taking into account pertussis severity.

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1 Introduction

Pertussis is a highly communicable vaccine-preventable disease caused by the *Bordetella pertussis* bacterium. The typical symptoms of pertussis include paroxysmal coughing, whooping, and vomiting. Pertussis occurs in all population groups, but it is more frequent and severe in children aged 0–9 years [1, 2]. Major complications of pertussis include pneumonia, encephalopathy, and hypoxia, which require hospitalization [1, 2]. In the US in 2016, 95% of total cases and 69% of hospitalizations occurred in individuals aged < 10 years, and 11.4% of cases, 35% of hospitalizations, and 86% of deaths occurred in infants aged < 1 year [3]. Pertussis is characterized by three phases of disease: catarrhal (1–2 weeks), paroxysmal (4–6 weeks), and convalescent. During the first weeks, irritating non-productive coughing changes into deep spams of paroxysmal coughing. After a week of paroxysmal coughing, the disease reaches its peak severity and begins to subside. Pertussis is spread from person to person by respiratory droplets, and it is among the most contagious diseases due to its high transmission to susceptible individuals (attack rates of 80–90%) and its long period of transmission (21 days from symptom onset) [1, 2].

The current pertussis prevention strategy in Spain is based on three measures: (1) acellular pertussis vaccination before the age of 7 years, (2) intensive epidemiological surveillance, and (3) rigorous outbreak control [4, 5]. The pertussis immunization program in Catalonia, a region in Northeast Spain with 7.5 million inhabitants, includes four doses of the diphtheria, tetanus, and acellular pertussis (DTaP) vaccine at 2, 4, 6, and 18 months, as well as a booster dose (dTap) at 3–6 years (4–6 years of age until 2003–2004) [5]. Two types of pertussis vaccines are available, whole-cell vaccines based on killed pertussis bacterium, and acellular vaccines based on one or more highly purified pertussis proteins that serve as immunogens (molecules that generates pertussis immunity). Whole-cell vaccines contain bacterium components that result in a high incidence of adverse effects [1, 2]. In Spain, pertussis vaccination with the diphtheria, tetanus, and whole-cell pertussis (DTwP) vaccine was introduced in 1960, and whole-cell vaccines were replaced by acellular vaccines in 2002 to avoid the high reactogenity of whole-cell vaccines [5]. The coverage of the pertussis vaccine increased in Spain from < 80% before 1990 to > 90% since 1990, and the mean vaccination coverage per year achieved after introducing the acellular pertussis vaccines was 91.6% for the 2003–2012 period [6]. The incidence of pertussis decreased in Catalonia from 20.5 per 100,000 in 1990 to 0.4 per 100,000 in 2002 [5]. Nevertheless, the incidence of pertussis has increased in Catalonia since 2002, reaching 49 per 100,000 in 2015 [7]. In 2015, infants aged < 1 year had the highest incidence of pertussis, with 497 per 100,000 [7]. The rise in pertussis incidence in Catalonia since 2002 highlights the growing vulnerability of infants who are too young to complete pertussis vaccination [8].

An evaluative study carried out in Catalonia and Navarra (Spain) in 2013 found that pertussis vaccination during childhood was 60% effective in preventing pertussis among children aged 1–9 years with household contacts of pertussis [9]. The study showed that pertussis vaccination during childhood was effective in preventing pertussis in the household of confirmed cases, where pertussis transmission is high [9]. Several evaluative studies have found pertussis vaccination effectiveness ranging from 12 to 75% in preventing pertussis during outbreaks [10–12]. At present, however, no information is available regarding the association between pertussis costs and pertussis vaccination in infants and children. The objectives of this study were to evaluate direct health costs in children with pertussis aged 0–9 years vaccinated and unvaccinated/partially vaccinated during childhood in Catalonia (Spain), and to assess the association between pertussis costs and pertussis vaccination during childhood in children with pertussis aged 0–9 years.

2 Methods

Direct health costs, defined as the medical care expenditure for the detection, treatment, and preventive chemotherapy of contacts related to pertussis, were determined in children with pertussis aged 0–9 years, both vaccinated and unvaccinated/partially vaccinated during childhood, detected by the epidemiological services in Catalonia (Spain) from 1 January 2012 to 31 December 2013.

2.1 Pertussis Cases

All children with pertussis aged 0–9 years detected by passive and active epidemiological surveillance in Catalonia in 2012 and 2013 were included in the study. Patients aged 0–9 years fulfilling the clinical criteria of pertussis reported to the epidemiological services (passive surveillance) were confirmed by laboratory tests (polymerase chain reaction (PCR), culture) or by an epidemiological link to a confirmed case of pertussis [4, 13]. A case fulfilled the clinical criteria of pertussis when the patient had a cough illness lasting 14 or more days along with paroxysms of coughing, inspiratory whoop, or post-tussive vomiting [4, 13]. A case of pertussis was confirmed by the epidemiological criteria when the patient had been exposed to a confirmed case of pertussis and pertussis symptoms began $\leq$ 28 days after the onset of symptoms in the confirmed case [4]. The laboratory tests used to confirm pertussis infections included real-time PCR and culture of a biological sample (nasopharyngeal swab). PCR is able to detect the genomic material of *B. pertussis* in a nasopharyngeal swab obtained from pertussis patients.

Active epidemiological surveillance was used to detect cases of pertussis in children aged 0–9 years among household contacts of pertussis cases detected by passive epidemiological surveillance. In this study, an individual aged 0–9 years was considered a household contact of a confirmed pertussis case if she or he had contact with the pertussis patient in the patient's household for $\geq$ 2 h during the pertussis transmission period (from the onset of symptoms in the confirmed case to 21 days later). All parents of contacts aged 0–9 years were contacted by telephone to ask about pertussis symptoms in their children. Children aged 0–9 years with symptoms fulfilling the clinical criteria of pertussis were confirmed by laboratory tests (PCR, culture) or by an epidemiological link to the confirmed case of pertussis [4, 13]. Pertussis cases among household contacts were confirmed by the epidemiological criteria when pertussis symptoms began $\leq$ 28 days after the onset of symptoms in the previously confirmed case of pertussis.

Pertussis cases were classified according to the chain of transmission into the following categories: primary, co-primary, secondary, and tertiary [4]. Primary cases of pertussis were those not epidemiologically linked to a previously confirmed case of pertussis. Co-primary cases were those where the coughing illness started 0–6 days after the symptoms began in the primary case. Secondary cases were those where the coughing illness symptoms started 7–28 days after the symptoms began in the primary case. Tertiary cases were those where the coughing illness symptoms started 7–28 days after the symptoms began in a secondary case.

All participants or their parents provided written informed consent to participate in the study; to collect vaccination, sociodemographic, and epidemiological information; and to obtain nasopharyngeal swabs to confirm pertussis cases.

2.2 Vaccination Status and Epidemiological Information

A questionnaire was used to record the pertussis vaccines received, clinical information, sociodemographic and epidemiological variables, and chemotherapy given to contacts. The questionnaires were completed by the nine epidemiological services of the four provinces of Catalonia (Barcelona, Tarragona, Lleida, Girona). The pertussis vaccination status was determined taking into account pertussis vaccines received at 2, 4, 6, and 18 months, and at 4–6 years of age. Pertussis patients were considered vaccinated when they had received 4–5 doses, partially vaccinated when they had received 1–3 doses and unvaccinated when they had not received any dose of pertussis vaccine. The pertussis vaccination status was verified from medical records. Immunity after vaccination is gradually built up after each vaccination dose, but individuals have completed vaccination only after the fourth and fifth doses of vaccine [4, 14–16]. The last two doses of vaccine are considered crucial since they increase the immunity level and assure long-term immunity after adolescence [1, 16]. The pertussis-related clinical information included pertussis symptoms, hospitalization, intensive care unit (ICU) care, and pertussis complications (secondary pneumonia). Pertussis cases were classified into the following disease severity categories: severe, moderate, and mild [17–19]. A pertussis case was considered severe when it required hospitalization or presented secondary bacterial pneumonia; it was considered moderate when it presented paroxysmal cough but did not require hospitalization or had a secondary bacterial pneumonia; and it was considered mild when it was not a severe or moderate case of pertussis.

2.3 Pertussis Costs

Direct health costs in 2012–2013, defined as the medical care expenditure for the detection and treatment of pertussis and for chemotherapy of contacts, were calculated in vaccinated, partially vaccinated, and unvaccinated pertussis patients aged 0–9 years. Pertussis costs in different pertussis vaccination groups were calculated using the IBM-SPSS Version 18 statistical program (IBM-SPSS, Chicago, IL, USA). Direct health costs were divided into three categories: pertussis detection costs, treatment costs, and chemotherapy of contacts costs. Chemotherapy is given to contacts of pertussis patients for preventing pertussis (chemoprophylaxis) because they have a higher risk of pertussis. Treatment costs included hospitalization, ICU care, primary health care and outpatient medical visits, and pharmacological therapies. Detection costs included PCR costs and *B. pertussis* culture and isolation costs. Hospital costs were determined for each hospitalized pertussis patient from the length of hospital stay of each patient and the mean cost per day in hospitals in Catalonia in 2012–2013.

Direct health costs were calculated taking into account resources used in 2012–2013 and the cost per unit of health resource in 2012–2013 [20]. Treatment costs were calculated using mean wholesale prices in 2012–2013 for drugs and the cost per medical visit in 2012–2013 for both outpatient and primary healthcare medical visits [20]. Pertussis costs were calculated by taking into account a cost of

€414.06 per day in hospitals (€2239.03/5.4 days), €185.96 for treatment costs in pertussis cases with a secondary bacterial pneumonia not requiring hospitalization, €132.48 for anti-pertussis therapy in moderate cases, €83.48 for anti-pertussis therapy in mild cases, €5.9 for chemotherapy in the household contacts of pertussis cases (chemoprophylaxis), €59 for the first medical visit, and €39 for the second and third medical visit. The cost per day in hospitalized pertussis patients assumed in this study was determined by dividing the mean cost per hospitalized patient (€2239.03) [21] for all hospitalized patients in Catalonia in 2012 by the mean length of hospital stay (5.4 days) [22] in Catalonia in 2012. Treatment costs in different types of patients were calculated using mean wholesale prices in 2012–2013 for drug costs, and the costs per medical visit in 2012–2013 [20]. Treatment costs in patients with pneumonia not requiring hospitalization were determined by taking into account that these patients require three medical visits (€59 for first visit, €39 for second and third visit [23]) and antibiotic therapy (€48.96) [24]. The cost of ICU care was determined for each pertussis patient from the length of ICU stay of each patient and the cost per day in ICUs (€2061/day) [25]. The cost per day in hospitalized patients and patients requiring ICU care included treatment, radiology, laboratory analysis, and stay costs [21]. Treatment costs in moderate pertussis cases were determined by taking into account that they required two medical visits (€59 for first visit, €39 for second visit [23]), anti-pertussis antibiotic therapy, and symptomatic therapy (€10). Treatment costs in mild pertussis cases were determined by taking into account that they required one medical visit (€49) and antibiotic therapy. The costs associated with antibiotic therapy in moderate and mild cases were determined by using the mean wholesale price in 2012–2013 of azithromycin at 10 mg/kg/12 h for 1 day and 5 mg/kg/12 h for 4 days [4]. The costs associated with chemotherapy of contacts to prevent pertussis (chemoprophylaxis) were determined by using the mean wholesale price of azithromycin in 2013 at 10 mg/kg/12 h (500 mg in adults) for 1 day and 5 mg/kg/12 h (250 mg/day in adults) for 4 days [4, 26].

2.4 Statistical Analysis

The statistical analysis of the results was carried out using IBM-SPSS Version 18 (IBM-SPSS, Chicago, IL, USA) [27]. The Chi square test (Fisher's exact test when necessary) and the odds ratios were used to compare percentages in different groups, considering a $p < 0.05$ as statistically significant. Total and mean care costs were calculated for different epidemiological and clinical variables. Mean pertussis costs were calculated for individuals that had received 0, 1, 2, 3, 4, and 5 doses of pertussis vaccine, and for vaccinated (4–5 doses) and unvaccinated/partially vaccinated individuals (0–3 doses). The t test was used to compare mean costs in different groups, considering a $p < 0.05$ as statistically significant. The correlation between total health costs and pertussis vaccination and other dichotomous variables was assessed using the Spearman's rank correlation (ρ), considering a $p < 0.05$ as statistically significant. Binary dummy variables were developed for the following variables: pertussis vaccination (vaccinated with 4–5 doses vs. unvaccinated/partially vaccinated); severity of disease (severe vs. moderate/mild disease); sex; type of pertussis case (primary/co-primary vs. secondary/tertiary); pertussis confirmation (based on laboratory results vs. based on epidemiological link); and pertussis detection by passive surveillance (detection by passive surveillance vs. detection by active surveillance). The correlation between total health costs and variables age and number of doses of pertussis vaccine received was assessed using the Pearson's correlation coefficient (r), considering a $p < 0.05$ as statistically significant. The correlation between pertussis costs and each number of doses of pertussis vaccine (0, 1, 2, 3, 4, and 5) received during childhood was assessed using the Spearman's rank correlation (ρ), considering a $p < 0.05$ as statistically significant. Dose-specific binary dummy variables (dose vs. other doses) were used for assessing the correlation between pertussis costs and each number of doses of pertussis vaccine received.

Multivariable linear regression analysis was used to assess and quantify the association of acellular pertussis vaccination with 4–5 doses and other study variables with total pertussis costs in pertussis cases. In the multivariable linear regression models, the correlation coefficient obtained for dichotomous independent variables indicates the cost increase or decrease associated with the category labeled 1, while the correlation coefficient obtained for continuous independent variables indicates the variation in total costs for a one-unit change in the independent variable when all of the other independent variables are held constant. Two models were developed: full model and reduced model. The full multivariable regression model included the following independent variables: pertussis vaccination with 4–5 doses, severity of disease, age, sex, laboratory pertussis confirmation, type of pertussis case, and pertussis detection by passive surveillance. The reduced model was developed for two reasons: (1) to obtain an optimal multivariable model with a lower number of variables than the full model, and (2) to reduce the effect of the correlation among independent variables (collinearity) on their regression coefficients. The reduced model was developed using the forward variable selection method (IBM-SPSS program), taking into account a probability-of-F-to-enter ≤ 0.05 and probability-of-F-to-remove ≥ 0.10 for including variables in the model. The variable pertussis vaccination was also included in the reduced model if it was not selected by the forward variable selection method. The multivariable linear regression models were assessed using the multiple R and the F test, considering a $p < 0.05$ as statistically significant [27]. The multiple R is the correlation coefficient between the observed and predicted values for the dependent variable (direct health costs). R ranges between 0 and 1. A significant multiple R indicates that the predicted cost obtained using the model is a better estimation than using the mean. The F test was used to evaluate the null hypothesis that the population value of the multiple R is 0. The significance of the F test indicates the probability of obtaining a multiple R equal to or higher than the value obtained in the study when the true population values is 0.

The same multiple linear regression analysis was carried out using the variable natural logarithm of total costs (ln costs) as dependent variable and all study independent variables. The multivariable linear regression models with the variable ln of costs as dependent variable were assessed using the multiple R and the F test, considering a $p < 0.05$ as statistically significant.

The assumptions of linearity, normal distribution, and equal variance around the mean of the expected outcomes required to develop multivariable linear regression models were assessed by plotting the standardized residuals (difference between observed and predicted values) against the independent variables and the estimated outcomes [27].

3 Results

3.1 Pertussis Cases

During the 2-year study period, 586 cases of pertussis were detected by passive and active epidemiological surveillance in children aged 0–9 years in Catalonia (Spain) (Fig. 1). Of these, 449 (76.6%) cases were reported to and confirmed by the epidemiological services (passive epidemiological surveillance), and 137 (23.4%) cases were detected by active epidemiological surveillance among 2794 household contacts of 641 pertussis cases confirmed during the study period. Subsequently, 579 (98.8%) pertussis cases with validated information on the pertussis vaccines received during childhood were included in the study (Fig. 1). Of these, 262 pertussis cases (45.3%) were considered vaccinated as they had received 4–5 doses of acellular pertussis vaccine, 159 (27.5%) were considered partially vaccinated as they had received 2–3 doses, 158 (27.3%) were considered unvaccinated since they had not received any dose of pertussis vaccine; and 317 (54.8%) were considered unvaccinated or partially vaccinated (Fig. 1). All vaccinated and partially vaccinated patients had received only acellular pertussis vaccines, including the DTaP and dTap (diphtheria, tetanus, acellular pertussis) vaccines, the pentavalent (diphtheria, tetanus, acellular pertussis, hepatitis B, and *Haemophilus influenzae* type b) vaccine, and the hexavalent (diphtheria, tetanus, acellular pertussis, hepatitis B, polio, and *Haemophilus influenzae* type b) vaccine.

Table 1 presents the clinical and epidemiological characteristics for vaccinated, partially vaccinated, unvaccinated, and unvaccinated/partially vaccinated patients of pertussis in children aged 0–9 years detected in Catalonia (Spain) in 2012 and 2013. Table 2 presents the odds ratios comparing the clinical and epidemiological characteristics for vaccinated patients and unvaccinated patients and for vaccinated patients and unvaccinated/partially vaccinated patients. The study found that vaccinated pertussis patients had a significantly lower percentage of hospitalizations, laboratory-based pertussis confirmation, severe disease, secondary pertussis, detection by passive surveillance, pneumonia, apnea, and post-tussive vomiting than unvaccinated patients or than unvaccinated/partially vaccinated patients (Tables 1, 2). The odds ratios ranged from 0.02 for hospitalizations and severe disease to 0.68 for post-tussive vomiting for the comparison between vaccinated and unvaccinated/partially vaccinated patients; and from 0.01 for hospitalizations and severe disease to 0.74 for paroxysms of coughing for the comparison between vaccinated and unvaccinated patients (Table 2). In contrast, vaccinated patients had a significantly higher percentage of mild and moderate disease, individuals aged 1–9 years, detection by active surveillance, primary cases, and epidemiological link-based confirmation than unvaccinated and unvaccinated/partially vaccinated patients (Table 2). The percentage of patients that required ICU care was lower in vaccinated patients than in unvaccinated and unvaccinated/partially vaccinated patients, but differences were not statistically significant.

3.2 Pertussis Costs

Table 3 presents total and mean treatment, detection, and chemotherapy of contacts costs in cases of pertussis in children aged 0–9 years for vaccinated, partially vaccinated, unvaccinated and unvaccinated/partially vaccinated patients. Total direct health costs in pertussis cases were €788,575.6; €49,948.8 in vaccinated patients and €738,626.8 in unvaccinated or partially vaccinated patients. Pertussis costs in vaccinated and unvaccinated/partially vaccinated patients represented 6.3 and 93.7% of total pertussis costs, respectively, although vaccinated and unvaccinated/partially vaccinated patients represented 55.2 and 54.8% of total pertussis cases. Seventy-one percent of

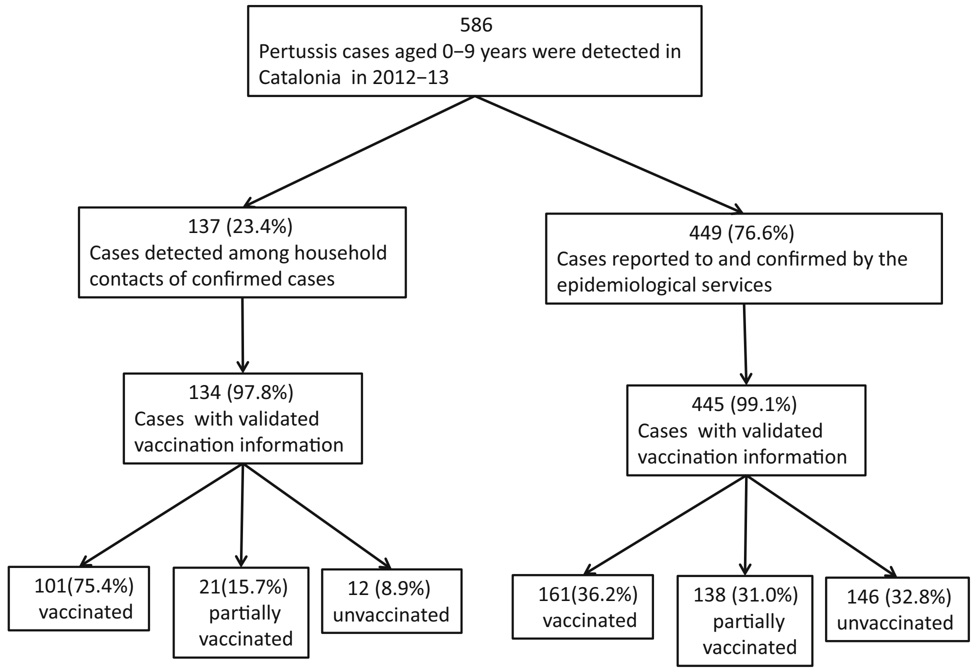

Fig. 1 Flow diagram of the study to assess the economic benefits of pertussis vaccination with acellular vaccines in pertussis patients aged 0–9 years. Catalonia (Spain), 2012–2013

total costs occurred in unvaccinated patients, 22.5% in partially vaccinated patients, and 6.3% in vaccinated patients. Mean total treatment, detection, and chemotherapy of contacts costs were significantly lower in vaccinated patients than in unvaccinated, partially vaccinated and unvaccinated/partially vaccinated patients (Table 3). Mean total treatment and detection costs were significantly lower in partially vaccinated patients than in unvaccinated patients (Table 3).

Table 4 presents total and mean health costs in pertussis patients that had received from 0 to 5 doses of acellular pertussis vaccine. Mean pertussis costs per case decreased with the number of doses of vaccine received from €3550.8 in unvaccinated patients to €186.4 in patients that had received five doses. Mean pertussis costs were significantly ($p < 0.001$) lower in pertussis patients vaccinated with 4 and 5 doses of vaccine than in those vaccinated with 0, 1, and 2 doses (Table 4). The bivariate linear correlation between pertussis costs and number of doses of acellular pertussis vaccines received was statistically significant ($r = -0.28$, $p < 0.001$). Spearman's rank coefficient assessing the correlation between pertussis costs and each one of the doses of vaccine received showed, however, that only the fourth and fifth dose of vaccine had a significant negative correlation with pertussis costs, with values of $\rho = -0.23$ ($p < 0.001$) for the fourth dose and $\rho = -0.25$ ($p < 0.001$) for the fifth dose (Table 4).

Table 5 presents mean direct health costs per patient in vaccinated, partially vaccinated, unvaccinated and unvaccinated/partially vaccinated pertussis patients aged 0–9 years for different clinical and epidemiological variables. Mean pertussis costs were significantly lower in vaccinated than in unvaccinated/partially vaccinated patients in males and females, severe and moderate pertussis, primary/co-primary and secondary/tertiary cases, and in cases detected by passive epidemiological surveillance. Mean pertussis costs were lower in hospitalized patients vaccinated during childhood than in unvaccinated/partially vaccinated patients, but differences were not statistically significant.

Table 5 also presents the comparison of mean pertussis costs between different clinical and epidemiological groups for all pertussis patients and for vaccinated, partially vaccinated, unvaccinated and unvaccinated/partially vaccinated patients. Mean pertussis costs were significantly higher in patients aged < 1 year than in those aged 1–3 and 4–9 years in unvaccinated, partially vaccinated and unvaccinated/partially vaccinated patients. Mean pertussis costs were significantly higher in severe cases than in moderate and mild cases in unvaccinated, partially vaccinated and unvaccinated/partially vaccinated patients. In pertussis patients vaccinated during childhood, mean pertussis costs were significantly higher in cases of moderate pertussis than in cases of mild pertussis, and mean costs were higher in severe cases than in moderate and mild cases, but differences were not statistically significant. Mean pertussis costs were significantly higher in cases detected by passive epidemiological surveillance than in cases detected by active surveillance in vaccinated, partially vaccinated, unvaccinated and unvaccinated/partially vaccinated patients.

Table 1 Clinical and epidemiological characteristics of pertussis patients aged 0–9 years by vaccination status in Catalonia (Spain), 2012–2013

Clinical and epidemiological variable	Vaccination status of pertussis patients[a]			
	Vaccinated [n = 262] % (95% CI)	Partially vaccinated [n = 159] % (95% CI)	Unvaccinated [n = 158] % (95% CI)	Unvaccinated or partially vaccinated [n = 317] % (95% CI)
Sex				
Male	51.1 (44.9–57.4)	52.2 (44.1–60.3)	50.6 (42.5–58.7)	51.4 (45.8–57.1)
Female	48.9 (42.6–55.1)	47.8 (47.8–55.9)	49.4 (41.2–57.5)	48.7 (42.9–54.2)
Age (years)				
0	0.0 (0–1.4)	70.4 (63.0–77.8)	81.0 (74.6–87.4)	75.7 (70.8–80.6)
1–3	24.4 (19.0–29.8)	24.5 (17.5–31.5)	8.2 (3.6–12.8)	16.4 (12.2–20.6)
4–9	75.6 (70.2–81.0)	5.0 (1.3–8.7)	10.8 (5.6–15.9)	7.9 (4.8–11.0)
Severity of disease				
Severe	1.9 (0.6–4.4)	30.8 (23.3–39.3)	63.3 (55.5–71.1)	47.0 (41.3–52.5)
Moderate	81.7 (76.8–86.5)	59.7 (51.8–67.9)	31.0 (23.5–38.5)	45.4 (39.8–51.1)
Mild	16.4 (11.7–21.1)	9.4 (4.6–14.3)	5.7 (1.8–9.6)	7.6 (4.5–10.6)
Type of pertussis case by pertussis transmission				
Primary/co-primary	71.0 (65.3–76.7)	62.9 (55.1–70.7)	61.4 (53.5–69.3)	62.1 (56.6–67.6)
Secondary/tertiary	29.0 (23.3–34.7)	37.1 (29.3–44.9)	38.6 (30.7–46.5)	37.9 (32.4–43.3)
Pertussis detection by passive and active epidemiological surveillance[b]				
Passive	61.5 (55.4–67.5)	86.8 (81.2–70.7)	92.4 (87.9–96.8)	89.6 (86.1–93.1)
Active	38.5 (32.4–44.6)	13.2 (7.6–18.8)	7.6 (3.1–12.0)	10.4 (6.9–13.1)
Confirmation of pertussis				
PCR/culture	68.7 (63.9–74.5)	91.2 (86.5–95.9)	91.1 (86.4–95.9)	91.2 (87.9–94.5)
Epidemiological link	31.3 (25.5–37.1)	8.8 (4.1–13.5)	8.9 (4.1–13.6)	8.8 (5.5–12.1)
Pertussis complications and vaccination status				
Hospitalization	1.9 (0.6–4.4)	30.8 (23.3–38.3)	63.3 (55.5–71.1)	47.0 (41.3–52.5)
ICU care	0.0 (0–1.4)	2.5 (0.7–6.3)	10.8 (5.6–15.9)	6.6 (3.7–9.5)
Pneumonia	0.0 (0–1.4)	0.6 (0–3.4)	2.5 (0.7–6.3)	1.6 (0.5–3.6)
Paroxysms of coughing	83.6 (78.9–88.3)	89.3 (84.2–94.4)	87.3 (81.8–92.8)	88.3 (84.6–92.0)
Apnea	14.1 (9.4–18.1)	31.0 (23.7–38.3)	48.1 (38.7–54.9)	38.8 (33.3–44.3)
Post-tussive vomiting	43.1 (36.9–49.3)	53.4 (45.4–61.5)	51.3 (43.2–59.4)	52.4 (46.7–58.0)

CI confidence interval, *ICU* intensive care unit, *PCR* polymerase chain reaction

[a]Children were considered vaccinated when they had received 4 or 5 doses of pertussis vaccine at 2, 4, 6, and 18 months and at 4–6 years of age; partially vaccinated when they had received 1–3 doses of vaccine; and unvaccinated when they had received 0 doses

[b]Pertussis cases were detected by passive epidemiological surveillance when they were reported to and confirmed by the epidemiological services, and by active epidemiological surveillance when they were detected among household contacts of confirmed cases

3.3 Bivariate Correlation Among Pertussis Costs and Independent Variables

Pertussis costs and pertussis severity correlated significantly with all independent study variables, except the variables of sex and type of pertussis case by pertussis transmission (primary vs. secondary/tertiary). Pertussis costs correlated significantly with the following variables: pertussis severity ($\rho = 0.60$, $p < 0.001$); vaccination with 4–5 doses of pertussis vaccine ($\rho = -0.40$, $p < 0.001$); age ($r = -0.22$, $p < 0.001$); laboratory pertussis confirmation ($\rho = 0.46$, $p < 0.001$); and pertussis detection by passive epidemiological surveillance ($\rho = 0.45$, $p < 0.001$). Pertussis costs did not correlate with the variables of sex ($\rho = 0.03$, $p = 0.407$) and type of pertussis case by pertussis transmission ($\rho = 0.01$, $p = 0.935$).

Pertussis severity correlated significantly with the following variables: pertussis costs ($\rho = 0.60$, $p < 0.001$); pertussis vaccination ($\rho = -0.51$, $p < 0.001$); age ($\rho = -0.58$, $p < 0.001$); laboratory pertussis confirmation ($\rho = 0.25$, $p < 0.001$); detection by passive epidemiological surveillance ($\rho = 0.30$, $p < 0.001$); and doses of pertussis vaccine received ($\rho = -0.58$, $p < 0.001$). Pertussis severity did not correlate with the variables sex ($\rho = 0.01$,

Table 2 Comparison of the clinical and epidemiological characteristics of vaccinated, unvaccinated, and partially vaccinated children with pertussis in Catalonia (Spain), 2012–2013

Clinical and epidemiological variable	Comparison of pertussis patients by vaccination status[a]			
	Vaccinated (n = 262) vs. unvaccinated/partially vaccinated (n = 317)		Vaccinated (n = 262) vs. unvaccinated (n = 158)	
	OR (95% CI)	p value	OR (95% CI)	p value
Sex				
Male	0.99 (0.71–1.37)		1.02 (0.69–1.51)	
Female	1.01 (0.73–1.40)		0.98 (0.66–1.45)	
Age (years)				
0				
1–3	1.65 (1.09–2.48)	0.016	3.10 (1.93–6.73)	< 0.001
4–9	36.13 (22.0–59.35)	< 0.001	35.66 (14.47–45.45)	< 0.001
Severity of disease				
Severe	0.02 (0.01–0.05)	< 0.001	0.01 (0.01–0.03)	< 0.001
Moderate	5.36 (3.65–7.85)	< 0.001	9.92 (6.26–15.7)	< 0.001
Mild	2.40 (1.41–4.07)	< 0.001	3.25 (1.56–6.76)	< 0.001
Type of pertussis case by pertussis transmission				
Primary/co-primary	1.49 (1.05–2.12)	0.028	1.54 (1.02–2.33)	0.042
Secondary/tertiary	0.67 (3.84–8.33)	0.028	0.65 (0.43–0.98)	0.042
Pertussis detection by passive and active epidemiological surveillance[b]				
Passive	0.18 (0.13–0.34)	< 0.001	0.13 (0.07–0.25)	< 0.001
Active	5.40 (3.48–8.33)	< 0.001	7.63 (4.06–14.3)	< 0.001
Pertussis detection				
PCR/culture	0.21 (0.13–0.34)	< 0.001	0.21 (0.12–0.39)	< 0.001
Epidemiological link	4.69 (2.95–7.52)	< 0.001	4.69 (2.57–8.53)	< 0.001
Pertussis complications				
Hospitalization	0.02 (0.01–0.05)	< 0.001	0.01 (0.01–0.03)	< 0.001
ICU care				
Pneumonia				
Paroxysms of coughing	0.67 (0.42–1.08)		0.74 (0.42–1.30)	
Apnea	0.25 (0.16–0.38)	< 0.001	0.18 (0.11–0.30)	< 0.001
Post-tussive vomiting	0.68 (0.49–0.95)	0.028	0.72 (0.49–1.07)	

CI confidence interval, *ICU* intensive care unit, *PCR* polymerase chain reaction

[a]Children were considered vaccinated when they had received 4 or 5 doses of pertussis vaccine at 2, 4, 6, and 18 months and at 4–6 years of age; partially vaccinated when they had received 1–3 doses of vaccine; and unvaccinated when they had received 0 doses

[b]Pertussis cases were detected by passive epidemiological surveillance when they were reported to and confirmed by the epidemiological services, and by active epidemiological surveillance when they were detected among household contacts of confirmed cases

p = 0.852) and type of pertussis case by pertussis transmission (ρ = 0.04, p = 0.334).

Pertussis vaccination with 4–5 doses of vaccine correlated significantly with all study variables except sex. Pertussis vaccination correlated with the following variables: severity of disease ($\rho = -0.51$, $p < 0.001$); age ($\rho = 0.80$, $p < 0.001$); laboratory pertussis confirmation ($\rho = -0.28$, $p < 0.001$); pertussis detection by passive epidemiological surveillance ($\rho = -0.33$, $p < 0.001$); and type of pertussis case by pertussis transmission (ρ = 0.09, p = 0.025). Pertussis vaccination did not correlate with the variable sex ($\rho = -0.01$, p = 0.948).

3.4 Multiple Linear Regression Analysis

The multiple linear regression models were developed based on the assumption of linearity, normal distribution, and equal variance around the mean of the expected outcomes. The linear relationship was assessed by plotting the residuals against the independent variables and the estimated outcomes, which resulted in points distributed

Table 3 Treatment, detection, and chemotherapy of contacts mean costs in pertussis patients aged 0–9 years by pertussis vaccination status. Catalonia (Spain), 2012–2013

Pertussis vaccination status[b]	Treatment costs (€)				Pertussis detection costs (€)				Chemotherapy of contacts costs (€)				Total pertussis costs (€)[a]				*n*
	Total	Mean	SD	%	Total	Mean	SD	%	Total	Mean	SD	%	Total	Mean	SD	%	
Vaccinated	34,428.0	131.4*	78.1	4.6	11,143.1	42.5*	23.3	40.4	4377.8	16.7*	13.9	38.4	49,948.8	190.6*	88.8	6.3	262
Partially vaccinated	165,780.0	1042.6**	2843	22.1	8263.3	52.0**	14.2	30.0	3551.8	22.3	19.3	31.1	177,595.1	1116.9**	2843	22.5	159
Unvaccinated	549,403.4	3477.2	8326	73.3	8153.1	51.6	15.0	29.6	3475.1	22.0	16.6	30.5	561,031.7	3550.8	8329	71.2	158
Partially vaccinated or unvaccinated	715,183.4	2256.1	6322	95.4	16,416.5	51.8	14.6	59.6	7026.9	22.2	18.0	59.6	738,626.8	2330.1	6324	93.7	317
Total cases	749,611.4	1294.7	4793	100	27,559.5	47.6	19.6	100	11,404.7	19.7	16.4	100	788,575.6	1362.0	4796	100	579

SD standard deviation

*$p < 0.001$ for vaccinated patients vs. other groups, **$p < 0.05$ for partially vaccinated patients vs. other groups

[a]Total pertussis costs: treatment costs + pertussis detection costs + chemotherapy of contacts costs

[b]Children were considered vaccinated when they had received 4 or 5 doses of pertussis vaccine at 2, 4, 6, and 18 months and at 4–6 years of age; partially vaccinated when they had received 1–3 doses of vaccine; and unvaccinated when they had received 0 doses

symmetrically above and below a straight line [27]. The normal distribution and equal variance around the mean of the expected outcomes could be assumed because the sample of individuals was higher than 100 [28].

Table 6 presents the full and reduced multivariable linear regression models quantifying the effects of pertussis vaccination with 4–5 doses and other study variables on pertussis costs. The full multivariable regression model including all study variables showed that pertussis vaccination with 4–5 doses was associated with a non-significant reduction in pertussis costs of €107.9 per case after taking into account the effect of other variables. In the full model, the effect of different variables ranged from a cost increase of €4259 for severe cases to a cost reduction of €145 for cases detected by passive surveillance. In the full model, however, only the variable pertussis severity was statistically significant. The full model was associated with a statistically significant multiple R of 0.412 ($p < 0.001$) and statistically significant F statistic of 16.6 ($p < 0.001$).

The reduced model included the variable pertussis severity, selected by the forward variable selection method (IBM-SPSS program), and the variable pertussis vaccination. In the reduced model, pertussis vaccination was associated with a non-significant reduction of €200 per case and pertussis severity increased pertussis costs by €4300 (Table 6). The reduced model was associated with a statistically significant multiple R of 0.407 ($p < 0.001$) and statistically significant F statistic of 57.3 ($p < 0.001$).

Table 7 presents the full and reduced multivariable linear regression models using the variable ln of costs as dependent variable. In the full multivariable regression model including all study variables, pertussis vaccination with 4–5 doses was associated with a regression coefficient of -0.01 after taking into account the effect of other variables. In the full model, the regression coefficients ranged from 2.20 for pertussis severity to -0.02 for age. In the full model, however, only the variable pertussis severity was statistically significant. The full model was associated with a statistically significant multiple R of 0.809 ($p < 0.001$) and a statistically significant F statistic of 154 ($p < 0.001$).

The reduced model included the variable pertussis severity, selected by the forward variable selection method (IBM-SPSS program), and the variable pertussis vaccination. In the reduced model, pertussis vaccination with 4–5 doses, pertussis vaccination was associated with a significant regression coefficient of -0.149 ($p < 0.05$) after taking into account the effect of other variables (Table 7). The reduced model was associated with a statistically significant multiple R of 0.804 ($p < 0.001$) and a statistically significant F statistic of 527 ($p < 0.001$).

Table 4 Total direct healthcare costs in pertussis cases detected in Catalonia (Spain) according to the number of doses of acellular pertussis vaccine received during childhood (2, 4, 6, 18 months, and 3–6 years)

Doses of acellular pertussis vaccine	Total cost (€)	Mean costs (€)	95% confidence interval	Spearman's rank coefficient[a]		n
				ρ	p value	
0	56,1031.7	3550.8*	2252.1–4849.5	0.31	< 0.001	158
1	148,647.4	1982.0[§]	1088.2–2875.7	0.21	< 0.001	75
2	13,930.7	480.4	267.7–693.0	− 0.11	0.310	29
3	15,017.1	273.0	179.4–366.7	− 0.02	0.077	55
4	28,882.9	193.8[†]	178.9–208.7	− 0.23	< 0.001	149
5	21,065.9	186.4[†]	172.0–200.9	− 0.25	< 0.001	113
Total	788,575.6	1362.0	971.3–1752.6			579

*$p < 0.001$ vs. 2, 3, 4, and 5 doses; [§]$p < 0.005$ vs. 2 doses; [†]$p < 0.05$ vs. 2 doses

[a]Spearman's rank coefficient (IBM-SPSS program) was determined using binary dummy variables (dose vs. other doses) to assess the correlation between total costs and each number of doses

4 Discussion

This study provided information on the economic benefits of pertussis vaccination during childhood in pertussis patients aged 0–9 years. The study found that total and mean direct health costs were lower in vaccinated than in unvaccinated/partially vaccinated children aged 0–9 years with pertussis. Total pertussis costs were €49,000 in vaccinated pertussis patients (6.3% of total costs) while they were €0.7 million (93.7% of total costs) in unvaccinated/partially vaccinated pertussis patients. Mean pertussis costs were significantly lower in vaccinated than in unvaccinated/partially vaccinated pertussis patients, for total cases (€191 vs. €2330), and for severe and moderate pertussis cases. The multivariable linear regression model showed that pertussis vaccination with 4–5 doses of acellular vaccine was associated with a non-significant reduction of €107.9 per case after taking into account the effect of other study variables (full model), and €200 per case after taking into account the effect of pertussis severity (reduced model).

The lower average cost per case in vaccinated compared with unvaccinated/partially vaccinated pertussis patients found in this study can be explained by the much lower frequency of severe pertussis, hospitalizations, intensive care and secondary pneumonia in vaccinated than in unvaccinated/partially vaccinated patients. The study found that the frequency of severe pertussis and hospitalization was 50 times lower in vaccinated than in unvaccinated/partially vaccinated patients (1.9 vs. 47%; OR 0.02), and that the frequency of intensive care assistance and secondary pneumonia was 0% in vaccinated patients and 6.6 and 1.6%, respectively, in unvaccinated/partially vaccinated patients. The higher percentage of severe pertussis found in this study among unvaccinated or partially vaccinated patients compared with vaccinated patients is consistent with the higher bacterial load (level of infection) found in another study among unvaccinated or partially vaccinated patients compared with vaccinated patients [29].

The average cost per case found in this study in vaccinated patients with severe pertussis (€576) was lower and the average cost found in unvaccinated/partially vaccinated patients with severe cases (€4738) was similar to the average cost per case found in the study assessing direct healthcare costs in all pertussis cases detected in Catalonia in 2012–2013 (€4437) [17]. This result can be explained by the lower average cost per case found in this study in hospitalized vaccinated patients than in hospitalized unvaccinated/partially vaccinated patients due to lower lengths of stay and pertussis complications among vaccinated hospitalized patients. In contrast, the average costs per case obtained in the study assessing direct healthcare costs in all pertussis cases detected in Catalonia in 2012–2013 in moderate (€186) and mild pertussis cases (€191) were not very different from those found in this study for vaccinated and unvaccinated/partially vaccinated patients with moderate and mild pertussis.

We have found that the average cost per case was significantly lower in vaccinated than in unvaccinated/partially vaccinated patients in both males and females, in severe and moderate pertussis, in primary and secondary cases, in cases confirmed by the epidemiological services and in cases detected among household contacts. These results were consistent with the results obtained in the multivariate linear regression analysis because both the bivariate and multivariate analyses indicated that direct health costs were lower in vaccinated pertussis patients than in unvaccinated or partially vaccinated patients, although pertussis vaccination was not significant in the multivariate models.

Table 5 Mean total health costs in vaccinated, partially vaccinated, and unvaccinated pertussis patients aged 0–9 years by epidemiological and clinical variables. Catalonia (Spain), 2012–2013

	Total cases			Pertussis vaccination status of pertussis patients [a]												p value for the *t* test for A vs. B
				Vaccinated (A)			Partially vaccinated			Unvaccinated			Unvaccinated or partially vaccinated (B)			
	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	
Total cases	1362.0	4796	579	190.6	89	262	1116.9	2843	159	3550.8	8329	158	2330.1	6324	317	< 0.001
Age (years)																
0	3000.0*	7141	240			0	1484.0†	3321	112	4326.5*	9084	128	3000.0*	7141	240	
1–3	239.3**	241	116	208.7	134	64	256.4	217	39	339.0	544	13	277.0	326	52	
4–9	183.0	62	223	189.9	84	198	173.3	45	8	166.6	47	17	168.8	46	25	
Sex																
Male	1205.6	3560	297	187.4	73	134	1314.5	3587	83	2758.2	5458	80	2042.7	4647	163	< 0.001
Female	1526.6	5823	282	194.0	100	128	901.2	1696	76	4322.8	10,472	78	2634.2	7716	154	< 0.001
Severity of disease																
Severe	4602.6*	8514	154	576.0	468	5	3178.0*	4510	159	5502.0§	9976	100	4737.8*	8624	149	< 0.001
Moderate	195.7*	31	358	191.5¶	31	214	206.0*	29	95	194.4	31	49	202.1	144	30	0.001
Mild	144.7	29	67	141.7	32	43	153.3	20	15	144.6	32	9	150.0	24	25	
Type of pertussis case by pertussis transmission																
Primary/co-primary	1459.2	5507	383	191.3	84	186	1115.2	3034	100	4245.0	10,004	97	2656.3	197	7492	<0.001
Secondary/tertiary	1171.9	2953	196	189.0	93	76	1119.9	2510	59	2446.9	4400	61	1794.5	120	3644	<0.001
Pertussis confirmation																
PCR/culture	1623.1	5287	469	208.3*	97	180	1177.8	2963	146	3840.1	8658	144	2504.3*	6587	289	<0.001
Epidemiological link with a case	246.4	639	110	151.8	36	82	487.1	726	14	575.7	4400	14	531.4	28	1237	
Pertussis detection by passive and active epidemiological surveillance[b]																
Passive	1713.1*	5422	445	209.1*	102	161	1227.1*	3029	138	3830.8*	8606	146	2526.7	284	5422	< 0.001
Active	195.9	251	134	161.1	39	101	392.9	601	21	144.0	34	12	302.433	491		
Pertussis complications																
Hospitalization	4691.6	8515	154	576.0	468	5	3178.0	2843	49	5502.0	9976	100	4737.8	149	862	
ICU care	18,349.0	17,181	21			0	14,228.1	2843	4	19,344.6	18,525	17	18,349.0	21	18,525	
Pneumonia	19,234.4	13,363	5			0	27,743.0		1	17,107.7	14,419	4	19,234.4	5	13,363	

ICU intensive care unit, *PCR* polymerase chain reaction, *SD* standard deviation

[a]Children were considered vaccinated when they had received 4 or 5 doses of pertussis vaccine at 2, 4, 6, and 18 months and at 4–6 years of age; partially vaccinated when they had received 1–3 doses of vaccine; and unvaccinated when they had received 0 doses

[b]Pertussis cases were detected by passive surveillance when they were reported to and confirmed by the epidemiological services, and by active surveillance when they were detected among household contacts of confirmed cases

p values for the *t* test for comparing mean costs in different epidemiological and clinical groups for each pertussis vaccination status and for all pertussis cases: *$p < 0.001$ vs. other groups; † $p < 0.001$ vs. 1–3 years old; ¶$p < 0.001$ vs. mild disease; §$p < 0.001$ vs. moderate disease; **$p < 0.05$ vs. 4–9 years

Table 6 Multiple variable linear regression models explaining the economic effects of pertussis vaccination and other study variables in pertussis patients aged 0–9 years in Catalonia (Spain), 2012–2013

	Regression coefficient (β)	p values
Full model including all study variables		
Pertussis vaccination with 4–5 doses[a]	− 107.9	0.852
Severity of disease	4259.3	< 0.001
Age	− 36.2	0.686
Laboratory pertussis confirmation[b]	105.4	0.872
Pertussis detected by passive surveillance[c]	− 145.4	0.820
Sex	302.1	0.410
Type of case primary or secondary/tertiary	517.7	0.200
Constant	− 80.2	0.896
Value of F	16.6	< 0.001
Value of multiple R	0.412	< 0.001
Reduced model[d]		
Pertussis vaccination with 4–5 doses[a]	− 200.1	0.638
Severity of disease	4300.4	< 0.001
Constant	308.7	0.355
Value of F	57.3	< 0.001
Value of multiple R	0.407	< 0.001

[a]Pertussis patients aged 0–9 years were considered vaccinated when they had received 4–5 doses of acellular pertussis vaccine at 2, 4, 6, and 18 months and at 4–6 years of age, and they were considered unvaccinated or partially vaccinated when they had received 0–3 doses of vaccine at 2, 4, 6, and 18 months and at 4–6 years of age

[b]Laboratory pertussis confirmation vs. confirmation by epidemiological link with a confirmed pertussis case

[c]Pertussis cases detected by passive epidemiological surveillance vs. active epidemiological surveillance

[d]The reduced multivariable model was developed using the forward method (IBM-SPSS program), taking into account a probability-of-F-to-enter ≤ 0.05 and probability-of-F-to-remove ≥ 0.10 for selecting variables, also including the variable pertussis vaccination if it was not selected

In another evaluative study, we found that mean pertussis costs were significantly higher in pertussis cases confirmed by the epidemiological services than in cases detected among household contacts [17]. In this study, we have found the same result for vaccinated, unvaccinated, and partially vaccinated pertussis patients. Pertussis costs were 30% higher in vaccinated patients and 748% higher in unvaccinated or partially vaccinated pertussis patients confirmed by the epidemiological services than in those detected among household contacts. This result shows that pertussis costs are higher in cases confirmed by the epidemiological services than in cases detected among household contacts independently of vaccination status. Active epidemiological surveillance activities in household contacts is therefore a consistent prevention strategy to reduce pertussis costs.

This is the first study assessing pertussis costs in pertussis patients aged 0–9 years vaccinated and unvaccinated during childhood. Several evaluative studies have assessed costs associated with pertussis infections in adolescents and adults [30–32]. O'Brien and Caro [30] calculated the healthcare costs for hospitalized pertussis patients from 1996 to 1999 using discharge databases from 1000 hospitals in four US states, finding a cost per stay of US$9586 in infants, US$4729 in children, and US$5683 in adolescents and adults. In the study, pertussis patients were identified by ICD-9 codes (033.0, 033.9), and the economic analysis was limited to examining the direct medical costs incurred during hospitalization; costs associated with outpatient care, ICU care, pertussis detection, and pertussis prevention were not included. Lee et al. [31] obtained a mean direct health cost per pertussis case of US$242 in adolescents and US$326 in adults in the US in 2002. Including indirect costs due to workdays lost and reduced productivity increased total pertussis costs by 64% (US$397) in adolescents and 137% (US$773) in adults [31]. In another study, Pichinero and Treanor [32] evaluated pertussis costs in the 107 cases reported in Monroe county (NY, USA) from 1989 to 1994, finding that hospitalization costs and indirect costs due to lost workdays represented 51 and 33% of the total pertussis costs, respectively. These studies showed the economic impact of pertussis infections, but they did not assess the association between pertussis vaccination and pertussis costs, and the economic benefits associated with pertussis vaccination.

Table 7 Multivariable linear regression models explaining the economic effects of pertussis vaccination and other study variables on pertussis costs in pertussis patients aged 0–9 years, using the variable ln of costs as dependent variable. Catalonia (Spain), 2012–2013

	Regression coefficient (β)	p values
Full model including all study variables		
Pertussis vaccination with 4–5 doses[a]	− 0.010	0.924
Severity of pertussis	2.201	< 0.001
Age	− 0.021	0.178
Laboratory pertussis confirmation[b]	0.195	0.089
Pertussis detected by passive surveillance[c]	0.083	0.453
Sex	− 0.004	0.945
Type of case primary or secondary/tertiary	0.008	0.905
Constant	5.094	< 0.001
Value of F	154.2	< 0.001
Value of multiple R	0.809	< 0.001
Reduced model[d]		
Pertussis vaccination with 4–5 doses[a]	− 0.149	0.047
Severity of disease	2.265	< 0.001
Constant	5.303	< 0.001
Value of F	527.9	< 0.001
Value of multiple R	0.804	< 0.001

[a]Pertussis patients aged 0–9 years were considered vaccinated when they had received 4–5 doses acellular pertussis vaccine at 2, 4, 6, and 18 months and at 4–6 years of age, and they were considered unvaccinated or partially vaccinated when they had received 0–3 doses of vaccine at 2, 4, 6, and 18 months and at 4–6 years of age

[b]Laboratory pertussis confirmation vs. confirmation by epidemiological link with a confirmed pertussis case

[c]Pertussis cases detected by passive epidemiological surveillance vs. active epidemiological surveillance

[d]The reduced multivariable model was developed using the forward method (IBM-SPSS program), taking into account a probability-of-F-to-enter ≤ 0.05 and probability-of-F-to-remove ≥ 0.10 for selecting variables, including also the variable pertussis vaccination if it was not selected

In this study, multiple linear regression analysis was used to quantify the economic effects of pertussis vaccination with 4–5 doses of vaccine and other study variables on pertussis costs in patients aged 0–9 years. Alternative distribution-free methods, such as generalized estimating equations, could have been used, but the parametric linear regression method was chosen in this study to develop multivariate models for the following reasons. First, the assumptions of linearity, normal distribution, and equal variance around the mean of the expected outcomes were met. Second, when outcomes are reasonably modeled using a parametric method, it usually provides more adequate estimations of outcomes than models based on non-parametric methods [33]. Third, the results of the multiple regression analysis using the variable total costs as dependent variables were consistent with those obtained using the natural logarithm of total costs as dependent variables.

This study has several limitations. First, costs in moderate and mild cases could be higher than those calculated in this study because the minimum number of medical visits (one in mild cases and two in moderate cases) was assumed in these cases. A higher number of medical visits than those assumed in the study would result in higher pertussis costs. However, in a study carried out in 87 pertussis cases among families in a community setting, the average number of medical visits registered in pertussis cases after diagnosis was 1.6 [31]. Second, the multiple linear regression model developed in this study could have underestimated the economic effects of pertussis vaccination with 4–5 doses of vaccine in pertussis patients aged 0–9 years because pertussis vaccination correlated with pertussis severity and other independent variables. Nevertheless, the study showed that pertussis vaccination was significantly lower in vaccinated than in partially vaccinated/unvaccinated pertussis patients for both severe and mild pertussis cases. Third, the economic benefits associated with pertussis vaccination in pertussis patients aged 0–9 years were assessed in this study using clinical, epidemiological, and vaccination information from pertussis cases detected in Catalonia in 2012–2013. A randomized clinical trial could avoid all potential biases derived from the non-randomized design of the study. Nevertheless, it is not possible to develop randomized clinical trials for assessing the economic benefits of acellular pertussis vaccines in children because of cost limitations and for ethical reasons.

The results obtained in this study indicate that pertussis vaccination during childhood is one of the key pertussis prevention strategies to reduce the burden of pertussis and pertussis costs in individuals aged 0–9 years. First, 95 and 93.7% of the total and treatment costs occurred in unvaccinated or partially vaccinated patients. Second, pertussis patients that had received at least four doses of acellular pertussis vaccine during childhood had a lower mean cost than unvaccinated and partially vaccinated patients. Third, patients that had received at least four doses of acellular pertussis vaccine during childhood had less severe cases than unvaccinated and partially vaccinated patients. In another evaluative study, we found that pertussis vaccination during childhood was effective in reducing the incidence of secondary cases among household contacts aged 1–9 years [9].

Despite the good results found in this study for pertussis vaccination in individuals aged 0–9 years, pertussis cannot by controlled by the current pertussis vaccination strategy for several reasons. First, vaccine-induced immunity wanes with time [34, 35]. Second, herd immunity levels are not sufficient to block pertussis transmission in the community, and pertussis remains endemic with epidemics every 2–5 years [36, 37]. Third, pertussis can be transmitted from infected adolescents and adults to susceptible infants and children [1, 2, 8]. Fourth, acellular pertussis vaccines could be less efficacious than whole-cell vaccines [1, 2]. Consequently, the Global Pertussis Initiative has proposed several immunization strategies to improve disease control, including the selective immunization of pregnant women, the selective immunization of certain other population groups (close family contacts of newborns, healthcare and childcare workers), and the universal vaccination of adolescents and adults [16, 38, 39]. The selective immunization of pregnant women and other population groups can protect infants and high-risk individuals, but it would not be sufficient to avoid pertussis transmission in the community [8, 36, 37]. In contrast, universal pertussis vaccination programs with percentages of vaccination coverage of 79–84% could be sufficient to block pertussis transmission in the community [36], but this is a difficult and costly immunization strategy.

5 Conclusion

The study found that direct healthcare costs were lower in pertussis patients aged 0–9 years vaccinated with 4–5 doses of acellular vaccines than in unvaccinated or partially vaccinated patients of the same age.

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Author contributions PP-R designed the economic research and performed the calculations. All authors contributed to the design and implementation of the epidemiological research. EN, PG, GC, AD, and MJ supervised the epidemiological research. CM-A and PB supervised the laboratory confirmation of pertussis cases. PP-R wrote the manuscript with input from all authors. All authors discussed the results and contributed to the final manuscript.

Data Availability The datasets generated during and/or analyzed during the current study are not publicly available due to legal restrictions applied to epidemiological and health information, but are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

Ethical approval The Research Ethics Board of the University Hospital Sant Joan de Deu of Barcelona reviewed and approved the objectives and methodology of the study.

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Conflict of interest PP-R, EN, PG, GC, AD, MJ, CM-A, and PB declare that they have no conflict of interest.

Informed consent Written informed consent was obtained from all participants or their parents to participate in the study.

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