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Effectiveness of one and two doses of acellular pertussis vaccines against laboratory-confirmed pertussis requiring hospitalisation in infants: Results of the PERTINENT sentinel surveillance system in six EU/EEA countries, December 2015 – December 2019

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ABSTRACT

Background: Monitoring effectiveness of pertussis vaccines is necessary to adapt vaccination strategies. PERTINENT, Pertussis in Infants European Network, is an active sentinel surveillance system implemented in 35 hospitals across six EU/EEA countries. We aim to measure pertussis vaccines effectiveness (VE) by dose against hospitalisation in infants aged <1 year.

Methods: From December 2015 to December 2019, participating hospitals recruited all infants with pertussis-like symptoms. Cases were vaccine-eligible infants testing positive for *Bordetella pertussis* by PCR or culture; controls were those testing negative to all *Bordetella* spp. For each vaccine dose, we defined an infant as vaccinated if she/he received the corresponding dose >14 days before symptoms. Unvaccinated were those who did not receive any dose. We calculated (one-stage model) pooled VE as 100*(1-odds ratio of vaccination) adjusted for country, onset date (in 3-month categories) and age-group (when sample allowed it).

Abbreviations: PERTINENT, Pertussis in Infants European Network; PV, primary vaccination; wP vaccine, whole-cell pertussis vaccine; aP vaccine, acellular pertussis vaccine; VE, vaccine effectiveness.

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Results: Of 1,393 infants eligible for vaccination, we included 259 cases and 746 controls. Median age was 16 weeks for cases and 19 weeks for controls ($p < 0.001$). Median birth weight and gestational age were 3,235 g and week 39 for cases, 3,113 g and week 39 for controls. Among cases, 119 (46 %) were vaccinated: 74 with one dose, 37 two doses, 8 three doses. Among controls, 469 (63 %) were vaccinated: 233 with one dose, 206 two doses, 30 three doses. Adjusted VE after at least one dose was 59 % (95 %CI: 36–73). Adjusted VE was 48 % (95 %CI: 5–71) for dose one (416 eligible infants) and 76 % (95 %CI: 43–90) for dose two (258 eligible infants). Only 42 infants were eligible for the third dose.
Conclusions: Our results suggest moderate one-dose and two-dose VE in infants. Larger sample size would allow more precise estimates for dose one, two and three.

1. Introduction

Pertussis or whooping cough, caused by *Bordetella pertussis*, is a highly contagious vaccine-preventable respiratory disease. It is characterised by a violent cough, and although it can present as a mild disease in adults, the most severe complications usually occur in infants during the first weeks and months of life, when the disease is the most life-threatening.

The main objective of the pertussis vaccination programmes today is to reduce the risk of severe pertussis in infants, due to the high morbidity and mortality in this age group [1]. Yeung et al. estimated 160,700 pertussis related deaths worldwide in children aged <5 years in 2014, 53 % of these deaths occurring in infants aged <1 year [2]. In the pre-vaccine area, pertussis was a very common childhood infectious disease worldwide, causing many deaths every year. For instance, in the United States, there were 115,000 to 270,000 cases of pertussis and 5,000 to 10,000 deaths due to the disease each year [3]. Pertussis vaccines containing inactivated whole-cell *B. pertussis* bacterium were introduced in the 1940s in the United States and in the 1950s in Europe. It was followed by a substantial decrease of reported cases with only 1,010 cases reported in the United States in 1976 [4]. Unfortunately, several studies linked the use of whole-cell pertussis (wP) vaccines with serious adverse reactions which led to substantial decrease in vaccination coverage and pertussis resurgence in many countries in the 1970s [5]. In the 1980s, acellular pertussis (aP) vaccines based on purified specific *B. pertussis* antigens were developed. Clinical trials in the 1990s suggested that they were safer and provided a similar efficacy as wP vaccines. Most European countries progressively replaced wP with aP vaccines, recommending primary vaccination (PV) with first dose as early as six weeks of age, and a total of three doses in the first year of life. Nevertheless, the primary series varies a lot across countries and can be grouped with the "3p + 0" schedule (three primary doses at 2, 4 and 6 months), the "2p + 1" schedule (two primary doses at 3 and 5 months or 2 and 4 months and a booster dose at 11 or 12 months) and the "3p + 1" schedule (three primary doses in the first year of life and a booster dose in the second year) [6].

Despite more than 90 % coverage for the first three doses in most countries over the last two decades [7], pertussis remains an endemic disease with epidemic peaks every 2–5 years. The last major peak incidence in Europe occurred in 2012 and the European Centre for Disease Prevention and Control (ECDC) reported a substantial increase in pertussis reports in many EU/EEA Member States [8], most notable among infants and adolescents. Many hypotheses for the resurgence were postulated, including improved diagnostic methods and disease awareness, or genetic changes in the organism [9]. Additional studies suggested that aP vaccination might be less effective and lead to faster waning of vaccination-induced immunity than the traditional wP vaccination [5,10]. Since then, the overall notification rate remained high in many countries, the causal bacterial agent continues to circulate and there are still significant challenges to controlling pertussis in Europe [8]. It remains one of the world's leading causes of vaccine-preventable deaths with more than 150,000 cases of pertussis reported globally in 2018 according to the World Health Organisation (WHO) [11]. According to the ECDC, infants continued to be the group with the highest notification rate in all EU/EEA Member States in that same year, except for Estonia and Norway [8]. From 2020, a dramatic decline in pertussis incidence was observed at the EU/EEA level concomitant with the COVID-19 pandemic [12].

In response to the evolving epidemiology of the disease, from September 2015 to January 2020, the ECDC created and funded PERTINENT, "Pertussis in Infants European Network", a multi-country hospital-based active sentinel surveillance system to measure pertussis incidence and vaccine effectiveness (VE) in infants aged <1 year [13].

In this article, we present the PERTINENT VE estimates against hospitalisation for laboratory-confirmed pertussis after at least one dose of PV; after only one dose of PV and after two doses of PV in infants eligible for PV and based on a prospective test-negative design (TND) [14].

2. Methods

2.1. Study sites

Seven study sites from six European countries participated in PERTINENT: Czech Republic, France, Ireland, Italy, Norway, Catalonia and Navarra regions in Spain. All sites complied with the generic PERTINENT sentinel surveillance and VE protocols [15] and laboratory guidelines [16]. We organised site visits and a laboratory workshop to ensure harmonisation of practices and allow pooling of sites' data.

From late 2015 to early 2016, all study sites gradually implemented the generic protocol and initiated pertussis active surveillance in the 40 participating hospitals. The French site accounted for a large proportion of hospitals (n = 21) located throughout the country. In 2018, four out of the five Norwegian hospitals had to withdraw from the PERTINENT project. By February 2019, the remaining Norwegian hospital had to leave the study due to surveillance challenges.

All sites used the aP vaccine for PV in infants, but vaccination schedule varied across sites (Table 1).

2.2. Study population and eligibility criteria

The study population consisted of all infants aged <1 year, likely to be hospitalised in one of the participating hospitals if developing the following pertussis-like symptoms.

We raised participant hospital physicians' awareness of pertussis clinical presentation and asked them to test all hospitalised infants aged <1 year presenting with apnoea or cough associated with at least one symptom of paroxysmal cough, whoop or post-tussive vomiting. Infants with any respiratory symptoms and an epidemiological link with a pertussis confirmed case or those not meeting the above clinical presentation but with clinical suspicion for pertussis by a physician were also tested for pertussis.

We asked parents or legal guardians of all infants tested for pertussis to participate in the study. When required by site-specific research ethics committee, hospital teams requested an informed consent.

We restricted the analysis to infants eligible for vaccination according to sites' national immunisation recommendations.

2.3. Laboratory methods

Since aP vaccines are prepared with *B. pertussis* major toxins and antigens, we asked the hospital laboratories to ensure an accurate identification of the *Bordetella* species. The PERTINENT diagnostic algorithm included a triplex quantitative PCR (qPCR): first targeting IS*481* gene (in *Bordetella pertussis*, *Bordetella holmesii*, and some *Bordetella bronchiseptica* strains), pIS*1001* (*Bordetella parapertussis*-specific) and RNase P as the human internal control and two confirmatory singleplex tests for *Bordetella pertussis* (*ptxA-Pr*) and *Bordetella holmesii* (hIS*1001*) if IS*481* was positive [16].

2.4. Test-negative design and vaccination definition

We conducted a multi-centre case control study using TND in the participating hospitals. We defined a laboratory-confirmed *B. pertussis* case as an infant with suspicion of pertussis infection and testing positive for *B. pertussis* by PCR (DNA detection of *B. pertussis* in a nasopharyngeal aspirate or swab) or culture (isolation of *B. pertussis* from the prior-mentioned clinical specimen). Test-negative controls were those testing negative to all *Bordetella* species by PCR or culture. Due the team's availability constraints in the Catalan hospital, control recruitment was limited to the inclusion of three controls per case using a systematic consecutive approach based on the date of specimen collection.

For each aP vaccine dose, we defined an infant as vaccinated if she/he had received the corresponding dose >14 days before symptom onset. Unvaccinated infants were those who had not received any dose.

2.5. Exclusion criteria

We excluded all infants with missing information for laboratory results, date of onset, or vaccination status. We also excluded infants with contra-indication for pertussis vaccination, those sampled >4 weeks after symptom onset, those testing positive to other *Bordetella* species than *B. pertussis*, those with previous laboratory confirmed pertussis episode and those whose legal guardian did not give consent to participate. Infants who did not meet the study eligibility criteria and testing negative to *B. pertussis* were excluded from the analysis. We also excluded infants who received the first dose of PV within 14 days before symptom onset.

2.6. Analysis

2.6.1. VE after at least one dose of PV

For the estimation of VE after at least one dose of aP vaccine, we restricted the analysis to infants eligible to any of the three doses of PV and aged 2–11 months.

We described cases and controls by clinical presentations, severity, risk and protective factors (Table 2). We used Fisher's exact test to compare those characteristics between cases and controls.

We compared the odds of vaccination with at least one dose between cases and controls. Based on pooled site-specific data, we used a one-stage model with study site as a fixed effect. Using logistic regression, we estimated the odds ratio (OR) and adjusted for date of symptom onset (in 3-month categories) and age group (2, 3–11 months). We computed VE as 1 minus the adjusted OR, expressed as a percentage and with 95 % confidence intervals.

2.6.2. One-dose VE

To estimate VE after only one dose of pertussis PV, we excluded all infants who received more than one dose. We estimated one-dose VE in infants aged 2–11 months adjusting for date of symptom onset (in 3-month categories) and age group (2, 3, 4, 5–11 months).

This sub-population includes infants in the target age-group for the second, third or even fourth dose (i.e., booster dose). To allow for more accurate one-dose VE estimate, we restricted the analysis to infants in the target age group for the first dose only, according to sites' national immunisation schedule. We estimated one-dose VE in infants aged 2–5 months using logistic regression including site as fixed effect and adjusted for date of symptom onset (in 3-month categories) and age group (2, 3, 4–5 months).

2.6.3. Two-dose VE

To estimate VE after two doses of pertussis PV, we excluded all infants who received one dose only, those who received the second dose within 14 days before symptom onset and those who received more than two doses. We estimated two-dose VE in infants aged 2–11 months adjusting for date of symptom onset (in 3-month categories) and age group (2, 3–11 months).

Table 1
Characteristics of PERTINENT study sites, current vaccination recommendations in infants for the primary schedule, in adulthood, during pregnancy or as cocooning strategy, Europe, 1st December 2015–31st December 2019.

Study sites	Vaccination recommendations									Number of hospitals participating in PERTINENT
	Primary schedule in infants					Pregnancy	Cocooning	Adulthood		
	Year of introduction	Age in months			VC % in 2016[a]		Year of introduction	Year of introduction	Number of doses	
		1st dose	2nd dose	3rd dose	1st dose	3rd dose				
Czech Republic	2018[b]	3[b]	5[b]	11–13[b]	98 %	96 %	2016	No	1 dose only	6
France	2013	2	4	11	99 %	96 %	2022	2004	1 dose every 10 years	21
Ireland	1995	2	4	6	98 %	95 %	2013	2013	No	2
Italy	1995	3	5	11	95 %	94 %	2017	No	1 dose every 10 years	1
Spain, Catalonia	2016[c]	2[c]	4[c]	11[c]	98 %	97 %	2014	No	No	1
Spain, Navarra	2016[c]	2[c]	4[c]	11[c]			2015	No	No	4
Norway	1998	3	5	12	99 %	96 %	No	No	1 dose every 10 years	5 *(2015–2017)* 1 *(2018–2019)*

PERTINENT: Pertussis in Infants European Network; VC: Vaccination coverage.

[a] Diphtheria tetanus toxoid and pertussis (DTP) vaccination coverage [Internet]. [cited 2023 Jun 7]. Available from: https://immunizationdata.who.int/pages/coverage/dtp.html?CODE=CZE+FRA+IRL+ITA+ESP+NOR%26ANTIGEN=DTPCV3+DTPCV1%26YEAR=.

[b] Before 2018: doses at 2, 3, 4 and 10 months.

[c] Before 2016: doses at 2, 4 and 6 months.

Table 2
Characteristics of *Bordetella pertussis* cases and controls by age group, sex, laboratory components, clinical presentation, severity and risk/protective factors, hospitalised infants aged 2–11 months, PERTINENT study, Europe, 1st December 2015–31st December 2019.

Characteristics		Cases (n = 259)		Controls (n = 746)		p value
		N	%	N	%	
Demographic						
Age group	0–3 months	146	56.4	336	45.0	**0.002**
	4–11 months	113	43.6	410	55.0	
Sex	Female	118	45.6	360	48.3	0.471
	Male	141	54.4	386	51.7	
Laboratory						
Nasopharyngeal specimen collection	Aspirate or both aspirate and swab	196	77.5	491	66.9	**0.002**
	Swab only	57	22.5	243	33.1	
Clinical criteria						
Cough	Yes	256	98.8	720	96.8	0.115
	No	3	1.2	24	3.2	
Cough with paroxysms	Yes	227	87.6	487	68.3	**<0.001**
	No	32	12.4	226	31.7	
Whoop	Yes	84	52.8	80	13.1	**<0.001**
	No	75	47.2	531	86.9	
Post-tussive vomiting	Yes	120	47.2	384	53.0	0.126
	No	134	52.8	341	47.0	
Apnoea	Yes	126	48.6	163	22.2	**<0.001**
	No	133	51.4	571	77.8	
Cyanosis	Yes	123	47.7	127	17.2	**<0.001**
	No	135	52.3	610	82.8	
Epidemiological link	Yes	100	39.4	12	2.4	**<0.001**
	No	154	60.6	483	97.6	
Diagnosis by a clinician	Yes	205	79.5	216	29.3	**<0.001**
	No	53	20.5	522	70.7	
Severity						
Death	Yes	1	0.4	1	0.1	0.451
	No	257	99.6	738	99.9	
ICU	Yes	30	16.5	29	7.5	**0.002**
	No	152	83.5	357	92.5	
ECMO	Yes	3	1.6	0	0.0	**0.011**
	No	180	98.4	627	100.0	
Pneumonia	Yes	11	6.1	26	6.8	0.856
	No	170	93.9	356	93.2	
Encephalopathy	Yes	2	1.1	0	0.0	0.103
	No	179	98.9	382	100.0	
Seizure	Yes	6	3.3	1	0.3	**0.005**
	No	175	96.7	380	99.7	
Eating difficulties	Yes	34	21.8	277	46.5	**<0.001**
	No	122	78.2	319	53.5	
Kidney failure	Yes	3	1.9	0	0.0	**0.029**
	No	156	98.1	359	100.0	
Dehydration	Yes	8	4.7	55	9.6	**0.04**
	No	162	95.3	516	90.4	
Risk factors						
Premature < 37 weeks	Yes	41	16.0	115	23.1	**0.023**
	No	216	84.0	382	76.9	
Delivery type	Vaginal	184	73.0	335	69.8	0.392
	C-section	68	27.0	145	30.2	
Episode in pregnancy	Yes	2	1.4	1	0.3	0.209
	No	145	98.6	350	99.7	
Infant going to day care	Yes	21	8.2	71	10.6	0.326
	No	234	91.8	600	89.4	
Infant with babysitter	Yes	104	42.4	141	22.9	**<0.001**
	No	141	57.6	474	77.1	
Infant staying regularly with grandparents	Yes	71	28.2	99	20.1	**0.016**
	No	181	71.8	394	79.9	
Protective factors						
Breastfeeding	Yes	168	65.6	465	64.5	0.761
	No	88	34.4	256	35.5	
Mother vaccination in adulthood	Yes	84	35.4	215	47.8	**0.002**
	No	153	64.6	235	52.2	
Mother vaccination in pregnancy	Yes	39	20.3	120	33.8	**0.001**
	No	153	79.7	235	66.2	
Vaccinated at least 1 dose	Yes	119	45.9	469	62.9	**<0.001**
	No	140	54.1	277	37.1	
Number of doses	1 dose	74	28.6	233	31.2	**<0.001**
	2 doses	37	14.3	206	27.6	
	3 doses	8	3.1	30	4.0	

This sub-population includes infants in the target age-group for the first but also the third or even the fourth dose. To allow for more accurate two-dose VE estimate, we restricted the analysis to infants in the target age group for the second dose only, according to sites' national immunisation schedule. We estimated two-dose VE in infants aged 3–10 months using logistic regression including site as fixed effect and adjusted for date of symptom onset (in 3-month categories). Sample size did not allow adjustment for age group. When the number of cases per parameters in logistic regression was less than ten, we carried out a sensitivity analysis using Firth's method of penalised regression to correct for small sample bias [17].

For each of the three VE analyses described above, the age distribution of included infants varied. Therefore, we adapted the adjustment for age in each model accordingly. For each analysis, we used the Akaike information criterion to determine the best functional form for the infants' age (i.e., spline, 2-category, 3-category or 4-category variable).

All statistical analyses were performed using Stata Release 17 (StataCorp, College Station, TX, USA).

2.7. Data collection

Using a standardised questionnaire, we collected a common set of information: demographic, clinical and laboratory data, vaccination status of the infant, severity, risk and protective factors (Table 2). This set also included maternal vaccination status in adulthood and, in countries where it was recommended during the study period, vaccination during pregnancy. Data were collected through review of clinical case-patient notes, vaccination cards, interviews with parents or legal guardians, and extraction from patient registries.

2.8. Ethical statement

Each site complied with the local ethical procedures. The planning, conduct and reporting of the study was in line with the Declaration of Helsinki [18]. Ethical approval was not needed in Navarra as the PERTINENT study was considered part of the mandatory surveillance system. Other study sites sought ethical approval from a review board according to country-specific regulations (Catalonia: PIC-31-16, Czech Republic: SZU/05992/2019, France: CNIL authorisation for RENACOQ on 17 June 1996 and order published in the Official Gazette (BO) no. 96/31, Ireland: Royal College of Physicians in Ireland REC reference number 16.058 and Gen/499/16, Italy: Bambino Gesù Children's Hospital Ethical Committee: protocol n. 1064_OPBG_2016, Norway: Regional Committees for Medical and Health Research Ethics, South-East A (2015/956)).

3. Results

From 1 December 2015 to 31 December 2019, we screened and tested for *B. pertussis* 1,393 infants eligible for vaccination and aged 2–11 months, attending a PERTINENT hospital with pertussis-like symptoms.

3.1. VE after at least one dose of PV

After applying the exclusion criteria for the analysis of the VE after at least one dose of PV, we included 1,005 infants eligible for any dose,

with 259 cases and 746 controls (Fig. 1a). The ratio of the number of controls per case ranged from 1.2 in the Czech study site, up to 248 controls per case in the Norwegian site (supplementary Table S4).

Over this four-year study period, the number of *B. pertussis* cases by month of symptom onset was highest in August 2016 (n = 12), June 2017 (n = 16), July 2017 (n = 12) and August 2018 (n = 11). The highest number of controls was over the periods February–March–April 2016 (n = 34, 38 and 38), November–December 2016–January 2017 (n = 38, 62 and 38) and November 2017–December 2017 (n = 30 and 29) (Fig. 2a). Regardless of the year, August was the month of the year with the highest mean number of *B. pertussis* cases with symptom onset (n = 8.5). February-March were the months of the year with the highest mean number of *B. pertussis* negative controls with symptom onset (n = 22.3 and 22.8, respectively) (Fig. 2b).

Although additional laboratory tests were not conducted systematically for every patient nor reported by all study sites and all hospitals, test results for Respiratory Syncytial Virus (RSV) were available for 46 cases and 384 controls. Out of them, 10 cases (22 %) and 202 controls (53 %) were positive to RSV ($p < 0.001$). Rhinovirus tests results were available for 50 cases and 273 controls and included 37 cases (74 %) and 123 controls (45 %) positive ($p < 0.001$).

Out of the 253 cases and 734 controls with available type of specimen collection, 57 cases (23 %) and 243 controls (33 %) were diagnosed based on a nasopharyngeal swab collection only ($p = 0.002$) (Table 2).

One-hundred-forty-one cases (54 %) and 386 controls (52 %) were males ($p = 0.471$). The median age at inclusion was 16 weeks for cases versus 19 weeks for controls ($p < 0.001$). The median birth weight was 3,235 g (range: 700–4,780 g; interquartile range [IQR]: 780 g) for cases versus 3,113 g (range: 640–5,006 g; IQR: 830 g) for controls ($p = 0.045$). The median gestational week at birth was 39 for both cases (range: 25–42; IQR: 2) and controls (range: 24–43; IQR: 3) ($p = 0.215$). Out of the 257 cases and 497 controls with reported gestational week, 41 cases (16 %) and 115 controls (23 %) were born before 37 weeks ($p = 0.023$) (Table 2); 14 cases (5 %) and 37 controls (7 %) were born before 32 weeks ($p = 0.360$); 3 cases (1 %) and 13 controls (3 %) were born before 28 weeks ($p = 0.286$). Information being available for 245 cases and 615 controls, 104 cases (42 %) and 141 controls (23 %) had a regular babysitter at home ($p < 0.001$). Most of them were reported by the French study site (97 % of cases and 90 % of controls). Excluding this site, only 3 cases (2 %) and 14 controls (3 %) were reported as having a regular babysitter ($p = 0.074$). The proportion of cases and controls with risk and protective factors such as delivery type, childcare and breastfeeding were similar. Regarding vaccination of the mother in adulthood which covers up to four different vaccination strategies in place in the seven sites (i.e., vaccination in pregnancy, cocooning strategy, one dose every 10 years, one dose only in adulthood), 84 cases (35 %) and 215 controls (48 %) had a mother reported as vaccinated in adulthood ($p = 0.002$).

Among cases, 119 (46 %) were vaccinated: 74 with one dose, 37 two doses, 8 three doses. Among controls, 469 (63 %) were vaccinated: 233 with one dose, 206 two doses, 30 three doses. VE after at least one dose, adjusted for study site, date of symptom onset (in 3-month categories) and age groups (2, 3–11 months) was 59 % (95 %CI: 36–73) (Table 3a).

Out of the 182 cases with available information about ICU admission, 8 (27 %) of the ICU cases and 72 (47 %) of the non-ICU cases were vaccinated with at least one dose ($p = 0.044$).

3.2. One-dose VE

Out of the 1,005 infants eligible for any dose of PV, we excluded all infants vaccinated with more than one dose. In this one-dose analysis, we included 210 *B. pertussis* cases and 476 controls aged 2–11 months (Fig. 1b.1). Seventy cases (33 %) and 199 controls (42 %) were vaccinated with only one dose of PV > 14 days before symptom onset ($p =$

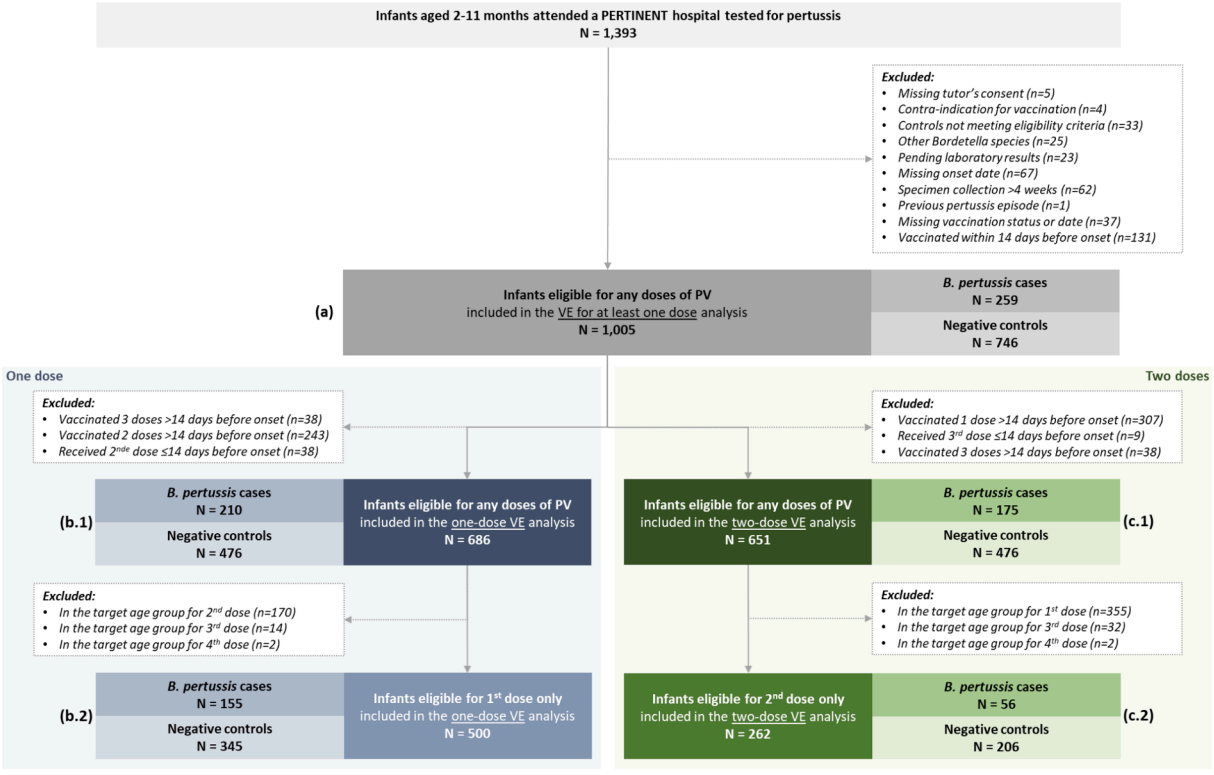

Fig. 1. Flowchart of hospitalised infants inclusion in or exclusion from the five analyses performed: (a) VE after at least one dose in infants 2–11 months; (b.1) One-dose VE in infants 2–11 months; (b.2) One-dose VE in infants 2–5 months; (c.1) Two-dose VE in infants 2–11 months; (c.2) Two-dose VE in infants 3–10 months of pertussis primary vaccination, PERTINENT study, Europe, 1st December 2015–31st December 2019. PERTINENT: Pertussis in Infants European Network; PV: primary vaccination; VE: vaccine effectiveness.

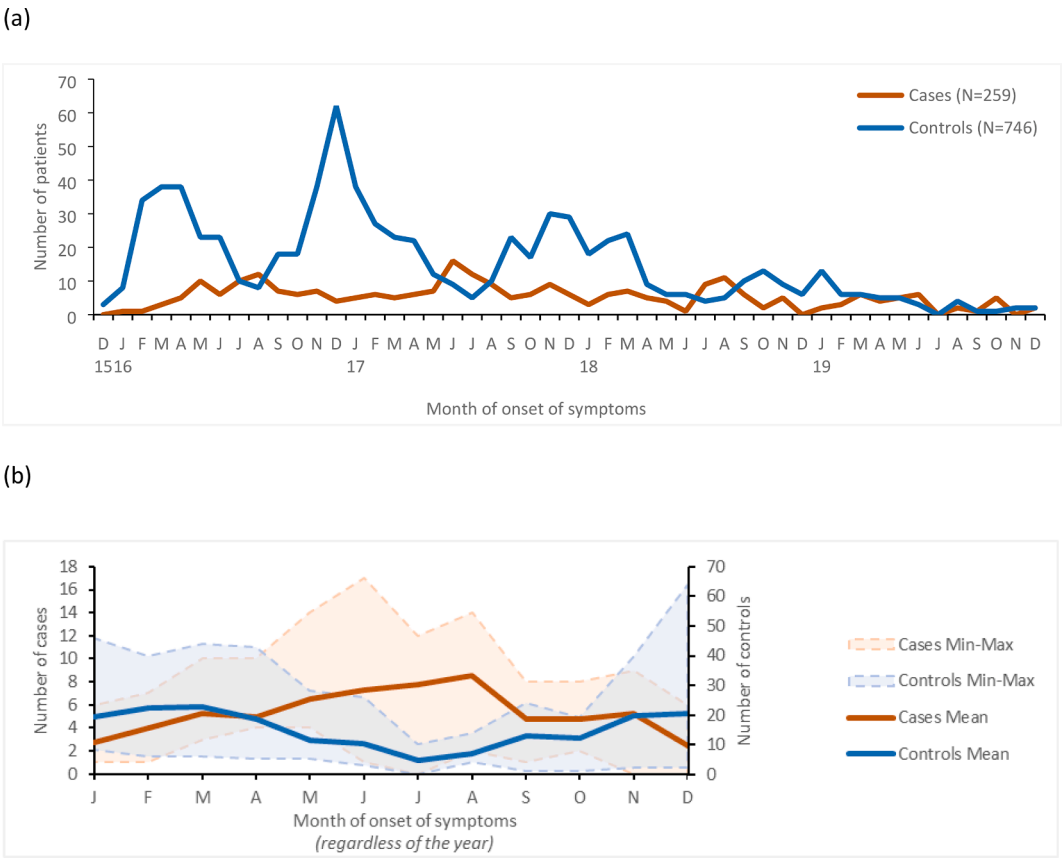

Fig. 2. *Bordetella pertussis* cases (N = 259) and controls (N = 746) (a) by month and year of symptom onset, (b) by month of symptom onset *(regardless of the year)*, hospitalised infants aged 2–11 months, PERTINENT study, Europe, 1st December 2015–31st December 2019.

Table 3
Adjusted vaccine effectiveness of the five analyses performed: (a) VE after at least one dose in infants aged 2–11 months; (b.1) One-dose VE in infants 2–11 months; (b.2) One-dose VE in infants 2–5 months; (c.1) Two-dose VE in infants 2–11 months; (c.2) Two-dose VE in infants 3–10 months of pertussis primary vaccination, in hospitalised infants, PERTINENT study, Europe, 1 December 2015–31 December 2019 (N = 1,005).

Adjustment variables		Df	N	Cases		Controls		Adjusted VE (95 % CI)
				Vacc.	N	Vacc.	N	
VE after at least one dose								
(a)	***Infants eligible for any dose of PV (2–11 months; 7 sites; N = 1,005)***							
	Site; Onset date (3-month); Age group (2, 3–11 months)	16	1,005	119	259	469	746	**59 (36–73)**
One-dose VE								
(b.1)	***Infants eligible for any dose of PV (2–11 months; 6 sites; N = 551)***							
	Site; Onset date (3-month);Age group (2, 3, 4, 5–11 months)	16	551	70	210	146	341	**56 (28–73)**
(b.2)	***Infants eligible for 1st dose only (2–5 months; 6 sites; N = 416)***							
	Site; Onset date (3-month);Age group (2, 3, 4–5 months)	15	416	45	155	91	261	**48 (5–72)**
Two-dose VE								
(c.1)	Infants eligible ***for any dose of PV (2–11 months; 7 sites; N = 651)***							
	Site; Onset date (3-month);Age group (2, 3–11 months)	15	651	35	175	199	476	**73 (50–86)**
(c.2)	***Infants eligible for 2nd dose only (3–10 months; 6 sites; N = 258)***							
	Site; Onset date (3-month)	13	258	32	56	176	202	**76 (43–90)**

Df: degree of freedom; VE: vaccine effectiveness; CI: confidence interval; PV: primary vaccination.

0.042).

Over the study period, the Norwegian site did not report any cases either unvaccinated or vaccinated with only one dose. Excluding this study site (135 controls including 53 vaccinated), one-dose VE adjusted by site, date of symptom onset (in 3-month categories) and age group (2, 3, 4 months and 5–11 months) was 56 % (95 %CI: 28–73) (Table 3b.1).

According to participating countries immunisation recommendations, the above-mentioned one-dose VE analysis includes infants already in the age group targeted for the second dose (n = 170), the third dose (n = 14) and even the fourth dose of PV (n = 2). Restricting the analysis among infants eligible for the first dose of PV only, we included 155 cases and 345 controls (Fig. 1b.2). Excluding the Norwegian site (84 controls including 9 vaccinated), 45 cases (29 %) and 91 controls (35 %) had received only one dose (p = 0.236). Adjusted one-dose VE was estimated at 48 % (95 %CI: 5–72) in infants aged 2–5 months (Table 3b.2).

3.3. Two-dose VE

Out of the 1,005 infants eligible for any dose of PV, we excluded all infants who received either one or three doses. In this two-dose analysis, we included 175 *B. pertussis* cases and 476 controls aged 2–11 months

(Fig. 1c.1). Thirty-five cases (20 %) and 199 controls (42 %) were vaccinated with two doses of PV > 14 days before symptom onset ($p < 0.001$).

Two-dose VE adjusted for site, date of symptom onset (in 3-month categories) and age group (2, 3–11 months) was 73 % (95 %CI: 50–86) (Table 3c.1).

According to participating countries immunisation recommendations, the above-mentioned two-dose VE analysis includes infants in the age group targeted for the first dose (n = 355) and not yet vaccinated at all, in the age group targeted for the third dose (n = 32) and even the fourth dose of PV (n = 2). Restricting the analysis among infants eligible for the second dose of PV only, we included 56 cases and 206 controls (Fig. 1c.2). Among them, 32 cases (57 %) and 180 controls (87 %) had received two doses ($p < 0.001$).

Over the study period, the Irish site did not report any cases in the age group targeted for the second dose only. Excluding this study site (4 vaccinated controls), adjusted two-dose VE was estimated at 76 % (95 % CI: 43–90) in infants aged 3–10 months using penalised logistic regression (Table 3c.2).

4. Discussion

Four years of active surveillance across 35 to 40 hospitals (with 5 withdrawals due to surveillance challenges) in 6 EU/EEA countries allowed us to include 1,005 infants eligible for any dose of PV in the PERTINENT VE study. Our results suggest that having received at least one dose of aP vaccine reduces the risk of being hospitalised for pertussis by almost 60 % in infants aged 2–11 months. Additionally, this comprehensive study served as a basis for conducting several dose-specific effectiveness analyses. Our findings indicate that receiving only one dose of aP vaccine halves the risk of being hospitalised for pertussis in infants eligible for the first dose only and aged 2–5 months. After two doses, VE was estimated between 73 and 76 %. Due to sample size limitations, we did not compute VE after three doses, nor VE by time since vaccination, nor by vaccine brand. Even though the sample size of each analysis did not allow for precise estimates or further adjustments and stratifications, we observed an increasing VE from dose to dose with VE estimates aligned with existing literature. In 2014, based on an Australian matched case-control study, Quinn et al. estimated that one-dose VE against hospitalisation was 55 % (95 %CI: 43–65) in infants <4 months and two-dose VE against hospitalisation was 83 % (95 %CI: 70–90) in infants <6 months of age [19]. Using a population-based retrospective case-control study design in a more recent study in Switzerland, Mack et. al. estimated that one-dose VE against hospitalisation was 42 % (95 %CI: 11–63) and two-dose VE against hospitalisation was 84 % (95 %CI: 70–92) [20].

Our study is subject to several limitations. Despite the implementation of a standardised generic protocol harmonising practices which enabled pooling of site data, there was a high heterogeneity between PERTINENT study sites in terms on national vaccination recommendations (Table 1) but also in terms of data collection and recruitment capacities. Even though all sites recommended at least one vaccination strategy in adulthood, they differed considerably across countries. Five sites recommended vaccination in pregnancy, two sites the cocooning strategy, three sites recommended one dose every 10 years and one site one dose only in adulthood. Additionally, vaccination status and vaccination date of the mother was not well collected in two of the seven sites. As a consequence, the VE estimates presented in the above analyses could not account for any maternal vaccination strategies. Nevertheless, in the context of the PERTINENT study, we presented in 2022, in an analysis restricted to the five sites recommending vaccination in pregnancy, our results on the effect of both vaccination in pregnancy and primary vaccination in infants aged 2–11 months. We found a similarly good VE of at least one dose of PV, irrespective of maternal vaccination (estimated at around 74–95 % when mothers were vaccinated in pregnancy and 68–94 % with unvaccinated mothers) [21]. Sample size limitations prevented us to conclude on a potential interaction between the two vaccinations. Regarding heterogeneity in terms of recruitment capacities, in the Catalan site, control recruitment was limited to three controls per case, as described in the protocol. But some sites such as the Czech, French and Italian sites, hardly managed to reach two controls per recruited case. In the Norwegian site, 248 controls were recruited while only one case vaccinated with two doses met the eligibility criteria. To check for a potential selection bias, we performed sensitivity analysis excluding the Norwegian data for the estimation of the VE after at least one dose and the two-dose VE estimates and results were very similar. Additionally, sample sizes were too small to measure VE by study site, and we used a one-stage approach on pooled data instead, with study site as fixed effect. In such analysis, we assume that the VE are the same in all sites, which is unlikely in our settings due to differences of vaccine brand, vaccine schedule, age at first dose, differences in circulating *Bordetella* strains or immunisation recommendations in adults. Therefore, larger sample size is required to estimate site-specific VE, statistical heterogeneity between sites and perform a "two-stage" model analysis including the confounding factors of interest.

Building upon the pilot study conducted by the PERTINENT Network which suggested a mild seasonality of the disease during summer [13,22], in this VE study, we observed a distinct counter-cyclical seasonality pattern between *B. pertussis* cases and controls, with peaks of disease incidence occurring at opposite times compared to control incidence. During periods of low recruitment of *B. pertussis* cases (i.e., winter period), there was a notable increase in the number of recruited controls.

Controls were more likely than cases to present with an RSV infection, aligning with the winter seasonality observed during control recruitment. RSV is known to circulate predominantly during late autumn, winter and early spring each year [3]. Date of symptom onset was an important potential confounding factor that we have strived to include with the highest precision possible in the VE estimation. In terms of co-infections, *B. pertussis* cases were more likely than controls to present with a co-infection with rhinovirus. While studies have confirmed the occurrence of RSV and *B. pertussis* co-infection in infants, limited information is available regarding rhinovirus co-infection [23,24]. This potential bias in clinical presentation needs to be quantified.

Given the possibility of pertussis atypical presentation in infants [13], we asked hospital teams to test for pertussis and include in the study any infants suspected for pertussis, even though some typical symptoms were missing [25]. However, clinicians may be more likely or less likely to test suspected pertussis cases according to vaccination status leading to selection bias. Including more unvaccinated infants may lead to an increase of unvaccinated cases in the study and an overestimation of the VE.

As described in the methods, all infants presenting with pertussis-like symptoms received a nasopharyngeal aspirate or swab that was then tested for pertussis by PCR or culture. However, nasopharyngeal swabs can be less sensitive than aspirate to isolate *B. pertussis* in infants [26]. Inclusion of false-negatives could lead to misclassification of unvaccinated cases as unvaccinated controls and an underestimation of the VE. A larger sample size is needed to perform sensitivity analysis excluding infants diagnosed only based on nasopharyngeal swabs.

TND is commonly used for assessment of influenza VE. Nevertheless, it is crucial to ascertain whether this design constitutes an appropriate methodology for estimating VE against severe pertussis in infants. To the best of our knowledge, we believe that this is the first prospective TND study at European level and in hospital settings, implemented to estimate VE against severe pertussis in infants. The main hypothesis of TND resides in the representation of the control group. Controls, consisting of infants hospitalised for pertussis-like symptoms but diagnosed with alternative respiratory illnesses (e.g., RSV), should mirror the pertussis vaccination experience of the source population. To confirm that the

likelihood of hospitalisation for non-pertussis respiratory infection is similar amongst both vaccinated and unvaccinated infants, implementation of large ad-hoc cohort studies in Europe or vaccination coverage studies in specific hospital catchment areas would be needed. Unfortunately, such studies were not feasible at the PERTINENT network level.

PERTINENT dose-specific VE estimates tend to be lower than previous estimations based on different study designs. One of the first studies estimating VE against hospitalisation due to pertussis in infants was performed in 2002 in Germany, early after the introduction of aP vaccine in the country. Based on a modified screening method, Juretzko and colleagues found a dose-dependent increase of VE against hospitalised laboratory-confirmed pertussis with a one-dose VE of 68 % and a two-dose VE of 92 % in infants [27]. However, comparing these estimates from the 2000′s at the hospital level with those from recent studies is challenging, mainly because of potential variations in hospitalisation behaviour over time. Even though our VE estimates are aligned with the recent literature, confidence intervals are large and we cannot conclude about a potential lower effectiveness that could explain the pertussis resurgence observed over the past ten years in Europe, before the COVID-19 pandemic. However, it is crucial to improve laboratory diagnostic methods across Europe to ensure the accurate differentiation of *B. pertussis* from other *Bordetella* species. Although aP vaccine may confer cross-immunity against other *Bordetella* thanks to some common virulence factors [28], it initially targets *B. pertussis* antigens. Culturing the pathogen and sequencing its genome are also key to monitor genetic variations in pertussis pathogens induced by vaccine selection pressure [9,29]. Considering other *Bordetella* species in VE studies as well as describing the ongoing genetic shift in the *B. pertussis* organism, for instance lacking pertactin (PRN), a common aP antigen [30], are factors that could contribute to a potential lower VE and further map the circulation of the pathogen.

5. Conclusion

While existing literature includes several case-control studies investigating dose-specific acellular pertussis VE against hospitalisation, our study stands out as the first independent and multi-country pertussis VE study in infants within the EU/EEA region, using TND in hospital settings.

Despite the concerning resurgence of pertussis in recent decades, our findings indicate that aP vaccine continues to offer a good effectiveness against hospitalisation for pertussis in infants aged 2–11 months. To further enhance protection for this vulnerable population, the consideration of pertussis vaccination during pregnancy is essential to protect younger infants aged <2 months who are not yet eligible to receive the first dose of aP vaccine. This vaccination strategy was also observed as protective in the context of the PERTINENT study [21]. Addressing this immunisation gap is of utmost importance for this age group with the highest risk of severe complications and mortality.

The implementation and sustainability of a large hospital-based surveillance network in Europe for all respiratory diseases including pertussis in infants, is crucial and can serve as a foundation for numerous VE studies. Such studies are necessary to investigate the diverse immunisation strategies currently implemented in EU/EEA (e.g., the so-called “2p + 1” vs. “3p + 1” primary course [8], vaccination in pregnancy, cocooning strategy in adults, etc.). Expanding the PERTINENT Network to increase our analysis sample sizes could allow for more robust and precise VE estimates, but also for estimating VE in fully immunised infants, VE by vaccine product, and for addressing the concerning aP vaccine waning immunity.

Additionally, the surveillance network has provided an opportunity to describe the circulating *Bordetella* species, and could support monitoring their potential genetic evolution and the impact of changes of vaccination strategies [31]. Even though most EU/EEA countries have sustained high routine immunisation coverage during the COVID-19 pandemic, especially for DTP, a significant drop in coverage worldwide was observed [32]; the impact of this drop needs to be closely monitored.

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Declaration of competing interest

No conflict of interest to declare except for Elmira Flem who has been employed since April 2019 by Merck & Co., Inc., North Wales, PA, USA. The work for the current study was conducted by Dr. Flem under the previous affiliation at the Norwegian Institute of Public Health.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

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