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Advance system testing: Vaccine benefit studies using multi-country electronic health data – The example of pertussis vaccination

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ABSTRACT

The Accelerated Development of VAccine benefit-risk Collaboration in Europe (ADVANCE), a public-private consortium, implemented and tested a distributed network system for the generation of evidence on the benefits-risks of marketed vaccines in Europe. We tested the system by estimating the incidence rate (IR) of pertussis and pertussis-related complications in children vaccinated with acellular (aP) and whole-cell (wP) pertussis vaccine. Data from seven electronic databases from four countries (Denmark: AUH and SSI, Spain: SIDIAP and BIFAP, UK: THIN and RCGP RSC and Italy: Pedianet) were included in a retrospective cohort analysis. Exposure was defined as any pertussis vaccination (aP or wP). The follow-up time started 14 days after the first dose. Children who had received any pertussis vaccine from January 1990 to December 2015 were included (those who switched type, or had unknown type were excluded). The outcomes of interest were confirmed or suspected pertussis and pertussis-related pneumonia and generalised convulsions within one month of pertussis diagnosis and death within three months of pertussis diagnosis. The cohort comprised 2,886,367 children ≤5 years of age. Data on wP and aP vaccination were available in three and seven databases, respectively. The IRs (per 100,000 person-years) for pertussis varied largely and ranged between 0.15 (95% CI: 0.12; 0.19) and 1.15 (95%

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CI: 1.07; 1.23), and the trends over time was consistent with those observed from national surveillance databases for confirmed pertussis. The pertussis IRs decreased as the number of wP and aP vaccine doses increased. Pertussis-related complications were rare (89 pneumonia, 7 generalised convulsions and no deaths) and their relative risk (vs. non-pertussis) could not be reliably estimated. The study demonstrated the feasibility of the ADVANCE system to estimate the change in pertussis IRs following pertussis vaccination. Larger sample sizes would provide additional power to compare the risk for complications between children with and without pertussis. The feasibility of vaccine-type specific effectiveness studies may be considered in the future.

1. Introduction

ADVANCE is a public-private collaboration aiming to develop and test a system for rapid benefit-risk monitoring of vaccines using existing healthcare databases in Europe using a distributed network approach similar to that used in other post-licensure vaccine safety studies [1,2]. The processes and systems for generating the data required to perform benefit/risk (B/R) monitoring of vaccines were developed and evaluated through proof of concept (POC) studies [3–6]. These POC studies consisted of four individual studies assessing the feasibility of generating data for coverage, benefit, risk, and the benefit-risk model. The research question was considered as a proxy for the introduction of a hypothetical new vaccine when benefit-risk monitoring would be needed, which is one of the scenarios in which the ADVANCE system could be used in the future. For this purpose, we assessed if the initial benefit-risk profile of pertussis vaccines was maintained after the switch from whole cell pertussis (wP) vaccines to acellular pertussis (aP) vaccines. It should be noted that these POC studies were undertaken for system testing and not to inform clinical, regulatory or public health decisions on pertussis vaccination.

Here we present the results from the benefit POC study. The specific objective was to determine the feasibility of using available electronic healthcare databases to estimate the incidence of pertussis following different doses of wP and aP vaccination and pertussis-associated complications (pneumonia, generalised convulsions and death) following pertussis disease to inform the benefit/risk model [7].

2. Material and methods

2.1. Study design

Full details of the study design can be found in the protocol, registered in the ENCePP (EUPAS) registry [6]. This was a retrospective dynamic cohort analysis.

2.2. Electronic healthcare databases used

Seven of the 19 European healthcare databases identified in ADVANCE participated in this POC study from Denmark (n = 2), Spain (n = 2), UK (n = 2) and Italy (n = 1) (Table 1) [8]. Details about the extraction, management, transformation, sharing, and analyses of the data using the ADVANCE system workflows and methodology can be found in paper 2 in this supplement [9].

2.3. Population studied

The source population consisted of children in the participating databases that were followed from first dose of pertussis vaccination until administration of the pre-school-entry booster or their sixth birthday (or death or transfer out of the database), which ever occurred first. To be eligible, date of birth and start and end of follow-up dates had to be available, i.e., no missing dates were allowed. Day, month and year were required for start and end of follow-up dates but date of birth could be rounded to an arbitrary day in the registered birth month. Children registered within three months of birth with a logical recorded series of pertussis vaccination (i.e., Dose 0 before Dose 1, etc.) were eligible. Only children who had received at least one dose of a single type of pertussis vaccine, i.e., only aP or wP, were included; those who switched from one type to the other or who had any doses with unknown type were excluded. The study period start and end dates varied between databases, depending on data availability (Table 2).

2.4. Exposure

The exposure of interest was aP- or wP-containing vaccine (either as a single component or part of a multivalent vaccine product). We defined four periods of vaccine exposure as follows: aP-0 – first 14 days after the first dose (when children were considered not to be protected yet); aP-1 – from 14 days post-dose 1 to 14 days post-dose 2; aP-2 – from 14 days post-dose 2 to 14 days post-dose 3; and aP-3 – from 14 days post-dose 3 until the end of follow-up.

2.5. Outcomes analysed

The outcomes analysed in children from first dose up to school-entry booster vaccination, 6th birthday, death or leaving the database, were the incidence rates (IRs) of pertussis following pertussis vaccination, non-fatal pertussis-related convulsions and pneumonia leading to hospitalisation within 1 month of pertussis diagnosis, and death within 3 months of pertussis diagnosis.

A set of codes were generated to identify confirmed and possible pertussis events in the databases using the ADVANCE Codemapper to map codes to the different coding systems used in the databases: 033.9; 484.3 (ICD-9), A37 (ICD-10), A33y, A33yz; A33z.; Ayu39; Ayu3A; H243.; X70I8; XE0Qw; XE0Qw; XM00D (Read version 2 or Clinical Terms version 3), A33 Ayu39; Ayu3A; H243(READ-V3) and R71 (ICPC) (Supplementary Table S1) [10,11]. The database codes used for pertussis-associated complications are summarised in Supplementary Table S1.

2.6. Statistical analyses

Incidence rates (IRs) for pertussis (per 1000 person-years) were calculated by dividing the number of events by the person-time of follow-up, overall, by year and by dose for children who had received at least one dose. This was done by calendar year and by exposure period. For the analyses of pertussis complications children diagnosed with pertussis after having received one or more doses of pertussis vaccine were identified ('break-through' pertussis cases) and were matched on birth-year and month to 100 children who had been vaccinated, but had not been diagnosed with pertussis (non-pertussis controls). Kaplan-Meier curves were

Table 1
Overall numbers of individuals in each database and numbers of children aged <6 years included in the benefit cohort.

	Denmark		UK		Spain		Italy	
	AUH	SSI	RCGP RSC	THIN	BIFAP	SIDIAP	PEDIANET*	Total
Type of database	Regional	National	National	National	National	Regional	Regional	
Data period	2002–2015	2000–2014	1995–2015	1996–2015	2003–2014	2006–2015	2006–2013	
Number of persons in full population file (any age)	1,725,165	7,512,032	3,017,610	11,696,261	7,541,864	7,096,695	9708	38,599,335
Number of children (0–5 years) included in the final benefit cohort	143,399	1,004,854	151,764	770,849	288,476	519,330	7695	2,886,367

AUH: Aarhus University Hospital; SSI; Statens Serum Institut; RCGP RSC: Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC); THIN: The Health Improvement Network; BIFAP: Base de Datos Para la Investigación Farmacoepidemiológica en Atención Primaria; SIDIAP: Institut Universitari d'Investigació en Atenció Primària Jordi Gol.
* PEDIANET included only children 0–14 years of age.

Table 2
Exposure, follow-up time, number of pertussis cases and pertussis incidence rates (per 1000 person-years) in children aged 0–5 years who had received at least one dose of whole-cell pertussis (wP) or acellular pertussis (aP) containing vaccine (follow-up started 14 days after the first dose)*.

Database (country)	Date or period of wP to aP switch	Vaccine used	Total follow-up (person-years)	Number of pertussis cases	Incidence rate/1000 person-years (95% CI)
AUH (Denmark)	1997	aP	556,048	83	0.15 (0.12; 0.19)
SSI (Denmark)	1997	aP	4,155,943	2820	0.68 (0.65; 0.70)
RCGP RSC (UK)	2004	aP + wP	474,732	109	0.23 (0.19; 0.28)
THIN (UK)	2004	aP + wP	2,229,848	487	0.22 (0.20; 0.24)
BIFAP (Spain)	2000–2004	aP + wP	370,343	229	0.62 (0.54; 0.70)
SIDIAP (Spain)	2000–2004	aP	751,786	862	1.15 (1.07; 1.23)
PEDIANET (Italy)	Before 1996	aP	37,343	25	0.67 (0.45; 0.99)

* Children were followed up until 6th birthday, pre-school booster dose, death, leave database or the end of the study, whichever occurred earliest.

estimated for pertussis-associated complication outcomes, pneumonia, convulsions and death. Cox regression models for these outcomes were fitted to compare children with pertussis diagnosis and their controls. Using the probabilities estimated with the Kaplan-Meier method and the hazard ratios obtained from the Cox regression, 'excess probabilities' of the different events were calculated, with their 95% CIs.

3. Results

3.1. Characteristics of population

The source population included over 38 million persons of all ages in seven databases from Denmark, Italy, Spain and the UK (4 national databases and 3 regional databases) (Table 1). A total of 2,886,367 children <6 years of age were included in the study cohort. The national Danish database SSI contributed data for 1,004,854 children (35%) and the national UK database, THIN, contributed data for 770,849 children (27%). The smallest contribution was from the Italian regional paediatric database, PEDIANET, which contributed data for 7695 children (0.3%).

Data on aP vaccination were available in all databases and data for wP vaccination were available in three (RCGP RSC, THIN, BIFAP) (Table 2).

3.2. Incidence of pertussis

A total of 4615 pertussis cases were identified in the study cohort over 8,576,043 person-years of follow-up with 79.6% of the follow-up time being post-dose 3. The overall incidence (/1000 person-years) for pertussis in the study cohort (aged 0 to 5 years) ranged from 0.15 (95% CI: 0.12; 0.19) in the AUH database to 1.15 (95% CI: 1.07; 1.23) in the SIDIAP database (Table 2). The incidence rates of pertussis from 1st dose to 5 years of age by database and year in children who had received at least one dose are summarised in Fig. 1 and Supplementary data Table S2. The pertussis IRs decreased with the number of doses of vaccines received in most databases (Fig. 2). The IRs after one dose of wP and aP ranged from 0 to 2.08 and 0.46 to 2.69, respectively. Post-dose 3 the IRs ranged from 0.19 to 0.28 and 0.03 to 0.68, respectively.

3.3. Complications following pertussis diagnosis

There were 89 cases of pneumonia within one month after pertussis diagnosis, with no cases in the UK (RCGP RSC and THIN) and Italian (PEDIANET) databases. Thus the HRs for pneumonia in breakthrough cases compared with vaccinated non-pertussis controls was calculated with data from the two Danish and two Spanish databases (Table 3). The HRs of pneumonia in pertussis cases versus children without pertussis ranged from 4.1 (95% CI: 2.2; 7.8) to 24.6 (95% CI: 19.1; 31.7). There were seven cases of generalised convulsions within one month after pertussis diagnosis (five in SSI and two cases in SIDIAP), with a relative risk of 1.99 (95% CI: 0.8; 4.8) in SSI and 4.6 (95% CI: 1.1; 19.2) in SIDIAP (Table 3). No deaths occurred within three months of pertussis diagnosis therefore the HRs were not calculated (Table 3).

The planned analyses for pertussis-related complications in five age groups (2–3 months, 4–5 months, 6–11 months, 12–23 months, 24 months or older) could not be done because of the low number of events. The 'excess probabilities' of the different complication events were calculated but were too small to be reliably interpreted (data not shown).

4. Discussion

In this study we showed it was possible to estimate pertussis IRs following wP or aP vaccination overall, over time and by the number of doses received demonstrating that data from the participating healthcare databases can be used to estimate vaccine effectiveness. We observed that the IRs for pertussis decreased as the number of aP and wP doses increased. This is consistent with our current knowledge, i.e. protection increases with the number of doses [12]. However, even with data from seven databases covering almost 3 million vaccinated children, it was not always

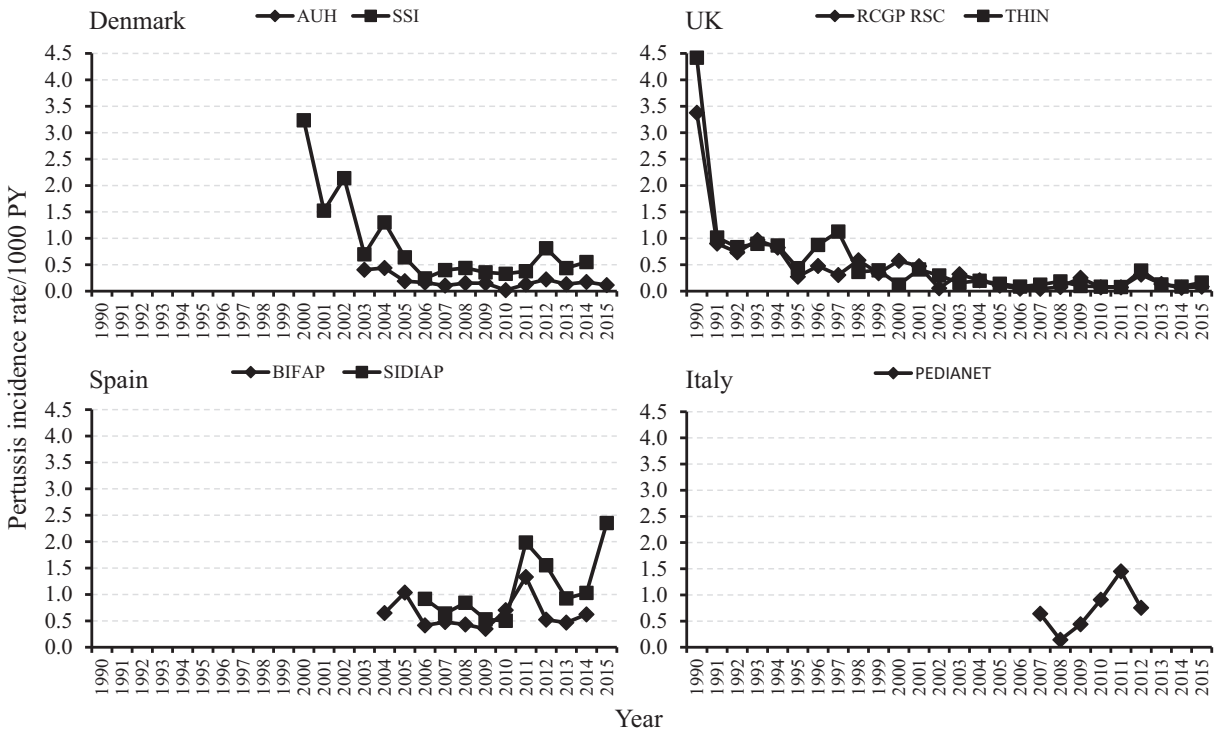

Fig. 1. Pertussis incidence rate per 1000 person-years for children who had received at least one dose of pertussis vaccine by database and year followed from 1st dose to age 5 years.

possible to estimate HRs reliably for pertussis-related complications in vaccinated children who developed pertussis versus those without pertussis due to the low number of cases and the low incidence of complications in these cases. Only 4615 children developed pertussis following vaccination among the 2.9 million vaccinated children and only 89 of them developed pneumonia and 7 developed generalised convulsions within one month of the pertussis diagnosis and none died within three months of the pertussis diagnosis. Low numbers of events were also observed in the comparison group (children who did not develop pertussis after vaccination). Consequently, we were not able to calculate HRs for all outcomes in all databases, and we could not calculate the HRs by vaccine type, i.e. aP or wP vaccines. Importantly, in this study we estimated the incidence of pertussis in vaccinated children over time for different periods with different programmes and heterogeneous vaccine coverage rates. However, we intentionally did not attempt to estimate the vaccine effectiveness, or to estimate the impact of the vaccination programme as incidence rate reduction between two different time points (wP vaccine periods compared to those aP periods.

Our results show that the incidence of pertussis in children who had received at least one dose of pertussis vaccine from 2003 onwards was lowest in the UK and highest in Spain. We did not observe any major differences between the results from the two UK databases, THIN and RCGP RSC, in the same calendar years. Although these databases do not cover the whole population, they are representative of the UK population, with a small overlap in practices captured by both databases [13,14]. The trend observed in our study was similar to that reported for confirmed pertussis observed over the last decade in children aged <5 years in the UK, although our IRs were lower since they are for vaccinated children only, whereas the reported national rates were for the whole population, vaccinated or not [15,16].

For Denmark, we observed a similar trend over time for the pertussis incidence rate in the SSI (national) and AUH (regional) databases, except we observed peaks in the incidence rates in 2004 and 2012 in the SSI database, similar to those reported for laboratory-confirmed pertussis in the whole Danish population [17]. The pertussis IRs were generally higher in the national SSI database than in the regional AUH database; this may be due to differences in population dynamics. For Spain, a higher incidence of pertussis was observed in the regional SIDIAP database than in the multi-regional BIFAP database but the trends since 2001 in the two databases were similar. The observed differences in incidences could be due to the different geographical coverage and the coding which differed between the databases [18].

In the UK, there were no cases of pneumonia after pertussis diagnosis in the vaccinated cohort that comprised more than 900,000 children. In RCGP RSC, pneumonia is one of the conditions specifically monitored and the participating practices receive feedback about their data quality for this conditions, so it is likely that the data are reliable [19]. The HRs for pneumonia following pertussis in vaccinated children was similar in Denmark and Spain with overlapping 95% CIs. The rates of pneumonia following pertussis in our vaccinated cohorts, where this could be calculated were similar to previously reported rates of between 0 and 3% [20,21]. The generalised convulsion rates in the vaccinated cohorts were extremely low and available in only two databases. The numbers of cases of generalised convulsions and death after pertussis in vaccinated children in the participating databases were too low to allow accurate interpretation.

The trends of estimated IRs were coherent with those from national surveillance databases based on confirmed pertussis. Our analysis included all pertussis cases (both suspected and confirmed). No chart reviews or specific analyses on confirmed or suspected cases were performed for pertussis but the predictive values were previously checked for some complications, such as pneumonia, in BIFAP database [22]. It was not possible to make appropriate and reliable comparisons with the IRs for pertussis and pertussis-related complications in the literature because the

Database (country)	Study period	Person/ years	Number of cases	Incidence/1,000 p/y (95% CI)	Vaccine type-dose
SSI (Denmark)	2000-2014	31,842	136	4.27 (3.61; 5.05)	aP-0
		207,158	556	2.68 (2.47; 2.92)	aP-1
		707,027	647	0.91 (0.85; 0.99)	aP-2
		3,209,916	1,481	0.46 (0.44; 0.49)	aP-3
AUH (Denmark)	2003-2015	5,488	15	2.73 (1.65; 4.53)	aP-0
		34,286	38	1.11 (0.81; 1.52)	aP-1
		106,635	16	0.15 (0.09; 0.24)	aP-2
		409,638	14	0.03 (0.02; 0.06)	aP-3
RCGP RSC (UK)	1990-2015	4,066	5	1.75 (0.56; 5.42)	wP-0
		17,280	8	1.54 (1.00; 2.36)	wP-1
		14,407	2	0.41 (0.19; 0.92)	wP-2
		229,051	20	0.24 (0.18; 0.33)	wP-3
		1,716	3	1.23 (0.51; 2.95)	aP-0
		13,631	21	0.46 (0.23; 0.93)	aP-1
		14,562	6	0.14 (0.03;0.56)	aP-2
		180,019	44	0.09 (0.06; 0.14)	aP-3
THIN (UK)	1990-2015	19,928	23	2.40 (1.60; 3.62)	wP-0
		58,741	48	2.08 (1.64; 2.64)	wP-1
		66,866	19	0.90 (0.65; 1.26)	wP-2
		1,171,790	114	0.19 (0.16; 0.22)	wP-3
		9,566	23	1.15 (0.77; 1.74)	aP-0
		32,683	68	0.82 (0.62; 1.08)	aP-1
		38,780	35	0.28 (0.18; 0.45)	aP-2
		831,494	157	0.10 (0.08; 0.12)	aP-3
BIFAP (Spain)	2003-2014	227	0	0	wP-0
		1,105	0	0	wP-1
		834	0	0	wP-2
		3,5721	1	0.28 (0.04; 1.99)	wP-3
		10,497	39	3.72 (2.71;5.09)	aP-0
		53,130	85	1.60 (1.29; 1.98)	aP-1
		53,229	34	0.64 (0.46; 0.89)	aP-2
		247,75	70	0.28 (0.22; 0.36)	aP-3
SIDIAP (Spain)	2006-2015	19,882	76	3.82 (3.05; 4.79)	aP-0
		107,818	290	2.69 (2.40; 3.02)	aP-1
		106,510	151	1.42 (1.21; 1.66)	aP-2
		517,575	345	0.67 (0.60; 0.74)	aP-3
PEDIANET (Italy)	2006-2013	291	0	0	aP-0
		1,347	2	1.48 (0.37; 5.94)	aP-1
		5,037	2	0.40 (0.10; 1.59)	aP-2
		30,668	21	0.68 (0.45; 1.05)	aP-3

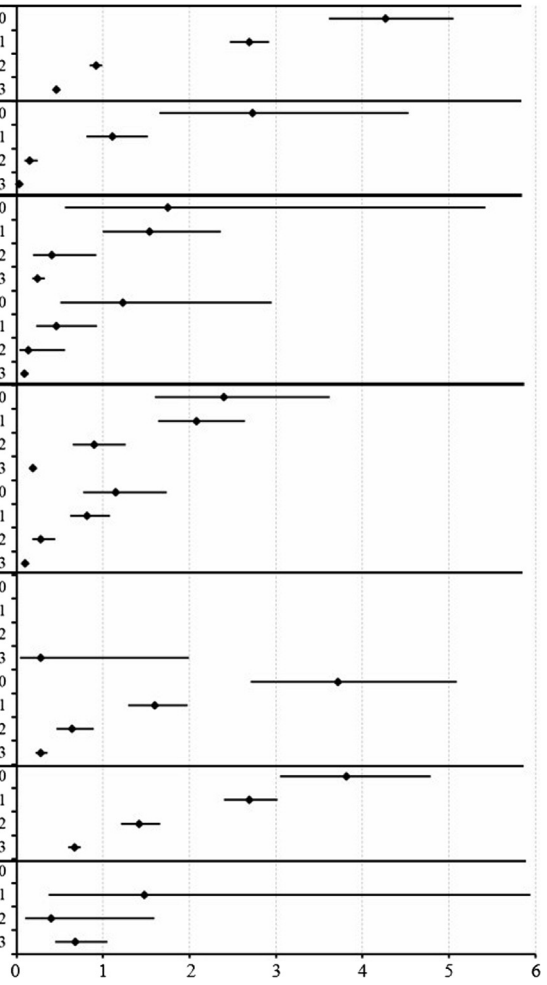

Fig. 2. Incidence of pertussis according to the type and number of vaccine doses received.

confirmation information or predictive values were not always available. Although comparison of IR among databases for the outcomes studied in the ADVANCE project by age, calendar year and sex were performed in order to assess the external validation as a first step before the analytical studies (Ref to fingerprint paper), the databases included in our study were from different clinical settings (GP only, hospital only or hospital and GP) and with different coding comportments (at regional or national levels), thus only the comparison of the trends over the time for estimates of pertussis incidence and pertussis-related complication rates seemed to be meaningful [18].

However, it is important to remember that the purpose of this POC study was to assess the methodological aspects of the design, conduct and reporting of studies for vaccine benefit-risk monitoring activities through the distributed data network the proposed by ADVANCE which is similar to that developed in the United States [2]. Although the vaccine effectiveness and the impact of vaccination programmes were not fully evaluated, we estimated the incidence of pertussis over time in vaccinated children as well as the incidence rate per dose, which, by some means, indicated the benefits of pertussis vaccines. The results, however, are not intended to inform regulatory or clinical decisions.

In conclusion, our results demonstrate the feasibility of estimating incidence rates for specific pertussis and pertussis-related complications outcomes using the ADVANCE distributed data system in the databases included in this study. Due to the low incidences of pertussis-related complications, larger sample sizes and inclusion of more databases would provide additional power.

Disclaimer

The results described in this publication are from the proof of concept studies conducted as part of the IMI ADVANCE project with the aim of testing the methodological aspects of the design, conduct and reporting of studies for vaccine benefit-risk monitoring activities. The results presented relate solely to the methodological testing and are not intended to inform regulatory or clinical decisions on the benefits and risks of the exposures under investigation. This warning should accompany any use of the results from these studies and they should be used accordingly. The views expressed in this article are the personal views of the authors and should not be understood or quoted as being made on behalf of or reflecting the position of the agencies or organisations with which the authors are affiliated.

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Table 3
Pertussis-related complications in children who had received at least one dose of pertussis vaccine compared with matched controls.

Data source (country)	Study group	Pneumonia (within one month)			Generalised convulsions (within one month)			Death (within three months)		
		Yes	No	Hazard ratio (95% CI)	Yes	No	Hazard ratio (95% CI)	Yes	No	Hazard ratio (95% CI)
AUH (Denmark)	Reference cohort aP	11	6789	18.6 (4.1; 84.0)	9	6791	NA	1	6799	NA
	Pertussis cohort aP	2	66		0	68		0	68	
SSI (Denmark)	Reference cohort aP	313	200,387	24.6 (19.1; 31.7)	251	200,499	1.99 (0.8; 4.8)	45	200,655	NA
	Pertussis cohort - aP	75	1932		5	2002		0	2007	
RCGP RSC (UK)	Reference cohort aP or wP	8	10,871	NA	18	10,861	NA	0	10,879	NA
	Pertussis cohort - aP	0	41		0	41		0	41	
	Pertussis cohort wP	0	115		0	115		0	115	
THIN (UK)	Reference cohort aP or wP	6	43,953	NA	13	43,946	NA	6	43,953	NA
	Pertussis cohort - aP	0	182		0	182		0	182	
	Pertussis cohort wP	0	261		0	261		0	261	
BIFAP (Spain)	Reference cohort aP or wP	77	27,991	15.4 (3.6; 66.3)	30	28,038	NA	4	28,064	NA
	Pertussis cohort - aP	2	306		0	308		0	308	
	Pertussis cohort wP	0	3		0	3		0	3	
SIDIAP (Spain)	Reference cohort aP	242	161,358	4.1 (2.2; 7.8)	43	161,557	4.6 (1.1; 19.2)	18	161,582	NA
	Pertussis cohort aP	10	1608		2	1616		0	1618	
PEDIANET (Italy)	Reference cohort aP	18	2482	NA	1	2499	NA	0	2500	NA
	Pertussis cohort aP	0	29		0	29		0	29	

NA: could not be estimated; * 5 pertussis non-exposed children were matched for each pertussis exposed child.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Maria de Ridder, Toon Braeye, Ana Correa, Chris McGee, Talita Duarte-Salles, Consuelo Huerta, Elisa Martín-Merino, Lara Tramontan, Giorgia Danieli, Gino Picelli, Nicoline van der Maas, Klara Berensci, Hanne-Dorthe Emborg, Daniel Weibel and Kaat Bollaerts declared no conflicts of interest. Myint Tin Tin Htar is employed by Pfizer and holds company shares/stock options. Simon de Lusignan declared he has received funding through his University to conduct enhanced surveillance of influenza vaccine (GSK), and is a member Seqirus and Sanofi Pasteur advisory boards for which he received personal payment within the limits defined by his university. Lisen Arnheim-Dahlström declared that her organisation has received funding from SPMSD, MSD and GSK for population-based, observational studies that she has conducted and that she is currently employed by Celgene AB. Ulrich Heininger declared that he is a member of the Global Pertussis Initiative (GPI) Steering Committee, which is funded by an educational grant from Sanofi Pasteur. Miriam Sturkenboom declared that she has received grants from Novartis, CDC and Bill & Melinda Gates Foundation, for work unrelated to the submitted work.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.08.078.

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