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ADVANCE system testing: Can safety studies be conducted using electronic healthcare data? An example using pertussis vaccination

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ABSTRACT

Introduction: The Accelerated Development of Vaccine benefit-risk Collaboration in Europe (ADVANCE) public-private collaboration, aimed to develop and test a system for rapid benefit-risk monitoring of vaccines using healthcare databases in Europe. The objective of this proof-of-concept (POC) study was to test the feasibility of the ADVANCE system to generate incidence rates (IRs) per 1000 person-years and incidence rate ratios (IRRs) for risks associated with whole cell- (wP) and acellular- (aP) pertussis vaccines, occurring in event-specific risk windows in children prior to their pre-school-entry booster.

Methods: The study population comprised almost 5.1 million children aged 1 month to <6 years vaccinated with wP or aP vaccines during the study period from 1 January 1990 to 31 December 2015. Data from two Danish hospital (H) databases (AUH and SSI) and five primary care (PC) databases from, UK (THIN and RCGP RSC), Spain (SIDIAP and BIFAP) and Italy (Pedianet) were analysed. Database-specific IRRs between risk vs. non-risk periods were estimated in a self-controlled case series study and pooled using random-effects meta-analyses.

Results: The overall IRs were: fever, 58.2 (95% CI: 58.1; 58.3), 96.9 (96.7; 97.1) for PC DBs and 8.56 (8.5; 8.6) for H DBs; convulsions, 7.6 (95% CI: 7.6; 7.7), 3.55 (3.5; 3.6) for PC and 12.87 (12.8; 13) for H; persistent crying, 3.9 (95% CI: 3.8; 3.9) for PC, injection-site reactions, 2.2 (95% CI 2.1; 2.2) for PC, hypotonic hypo-responsive episode (HHE), 0.4 (95% CI: 0.4; 0.4), 0.6 (0.6; 0.6) for PC and 0.2 (0.2; 0.3) for H; and somnolence: 0.3 (95% CI: 0.3; 0.3) for PC. The pooled IRRs for persistent crying, fever, and ISR, adjusted for age and healthy vaccinee period were higher after wP vs. aP vaccination, and lower for convulsions, for all doses. The IRR for HHE was slightly lower for wP than aP, while wP was associated with

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somnolence only for dose 1 and dose 3 compared with aP.
Conclusions: The estimated IRs and IRRs were comparable with published data, therefore demonstrating that the ADVANCE system was able to combine several European healthcare databases to assess vaccine safety data for wP and aP vaccination.

1. Introduction

The ADVANCE public-private collaboration aims to develop and test a system for rapid benefit-risk (B/R) assessment and monitoring of vaccines using health care databases in Europe and is following the distributed network approach that has been successful in several post-licensure vaccine safety studies [1,2]. Details on the rationale and system have been described elsewhere in this supplement [3,4]. Proof of concept (POC) studies were designed to test the system by assessing the feasibility of transforming data into evidence that would support B/R monitoring of vaccines. The aim of this study was to test the system's ability to generate results that could be benchmarked against other sources, not to generate new evidence. The POC studies addressed the comparative B/R of whole cell pertussis (wP) and acellular pertussis (aP) containing vaccines in children. The switch from wP to aP vaccines was used as a proxy for the introduction of a new vaccine, as an example of one of the scenarios where the ADVANCE system could be used in the future.

In this paper, we report the results from the comparison of safety outcomes after wP and aP vaccination, selected based on a literature review, which were used as input for the B/R analysis [5].

2. Methods

2.1. Study design and setting

A multi-database retrospective dynamic cohort study was conducted to estimate incidence rates (IRs) of specific safety outcomes after wP and aP vaccinations (risk period) and in a non-risk period. A self-controlled case series (SCCS) method, which uses only individuals with the event of interest, was used to estimate incidence rates (IRs) and incidence rate ratios (IRRs) for events of interest in defined risk periods after vaccination with wP- and aP-containing vaccines versus reference periods [6,7].

2.2. Data sources

Data were obtained from seven healthcare databases that passed the fit for purpose assessment in 2016 and that agreed to participate in the ADVANCE project (Table 1) [8]. This assessment included the evaluation of incidences of several health outcomes, population indicators and vaccine information in the databases [8,9]. There were two databases from Denmark: the regional Aarhus (AUH) and national Statens Serum Institute (SSI) hospital discharge databases which were linked to vaccination registries; two primary care medical record databases from Spain (including GP and family paediatricians): Base de Datos Para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP) and the Information System for Research in Primary Care (SIDIAP); two primary care medical record databases from the UK: the Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) database and The Health Improvement Network (THIN); and one family paediatrician database from an Italian network of family paediatricians that was linked to the Veneto region vaccination registry: PEDIANET [8,10]. Data extraction, management, transformation, sharing, and analyses followed the ADVANCE system workflows and methodology [4].

2.3. Study population and follow-up

The study population comprised all children registered in the databases aged between one month and <6 years. Follow-up started either with the start of the study period (1 January 1990) or when valid data (database specific) were available, or the date children were aged one month, whichever was the latest. The end of follow-up was defined as the earliest of the following dates: the end of the study period (31 December 2015) or the date of the first occurrence of any of the following: pre-school-entry pertussis booster, 6th birthday, transferring out of the database, date of last data recorded, or death.

2.4. Pertussis vaccination exposure

The exposure of interest was vaccination with wP- or aP-containing vaccines by dose. Databases generally provided pertussis vaccine information coded as wP- or aP-containing vaccines. If pertussis vaccines were not coded specifically into wP or aP, we used the date of the switch to assign the pertussis vaccine type.

Table 1
Summary of participating database characteristics.

	Country	Source/Type of data	Study period covered (years)	Date of wP to aP switch
AUH[1]	Denmark	Hospital, out- and inpatient diagnoses	2002–2015	1997
SSI[2]	Denmark	Hospital, out- and inpatient diagnoses	2000–2014	1997
RCGP RSC[3]	UK	GP	1990–2015	October 2004
THIN[4]	UK	GP	1990–2015	October 2004
BIFAP[5]	Spain	GP and family paediatricians	2003–2015	1997–2004 wP and aP; 2005+ aP only
SIDIAP[6]	Spain	GP and family paediatricians	2006–2015	1997–2004 wP and aP; 2005+ aP only
PEDIANET[7]	Italy	GP and family paediatrician	2006–2013	1996

aP: acellular pertussis; wP: whole cell pertussis; GP: general practitioner.
[1] Aarhus University Hospital: https://www.ncbi.nlm.nih.gov/pubmed/21152254.
[2] Statens Serum Institut: https://www.ssi.dk/English/RandD/Research%20areas/Epidemiology.aspx.
[3] Royal College of General Practitioners: http://www.rcgp.org.uk/clinical-and-research/our-programmes/research-and-surveillance-centre.aspx.
[4] The Health Improvement Network: https://www.ucl.ac.uk/pcph/research-groups-themes/thin-pub/database.
[5] Base de Datos Para la Investigación Farmacoepidemiológica en Atención Primaria: http://www.bifap.org/summary.php Información para el Desarrollo de la Investigación en Atención Primaria: http://bifap.aemps.es/.
[7] Epidemiological Information for Clinical Research from an Italian Network of Family Paediatricians: http://pedianet.it/en.

We included a transition period (during the switch from wP to aP vaccine) in which pertussis vaccines were coded as 'unknown' (uP). For databases that did not have reliable information about the dose, we imputed dose information based on the local immunisation schedule using the recommended age of vaccination as imputation rule. This was done for 2% of all vaccinations in BIFAP and for 2.8% in SSI [11].

2.5. Outcomes

The selection of the study outcomes of interest was based on events that have been reported to be related with wP or aP vaccination in trials or studies [12–15]. These events were: persistent crying, hypotonic hypo-responsive episode (HHE), somnolence, fever, generalised and febrile convulsions/seizures, extensive limb swelling, and injection-site reactions (ISRs; including limb swelling). Whenever available, we used Brighton Collaboration (BC) case definitions to define the outcomes of interest, and to create the case extraction algorithms based on the signs, symptoms and disease entities described in these definitions [16–21]. Cases were identified from the electronic healthcare databases using codes and text (Online Supplement Table 1) [22]. The codes for different terminologies were obtained using the Codemapper manual review of the data access providers and harmonization was conducted using a standardised quality workflow [4,23–25]. Based on expert opinion, post-aP or -wP vaccination exposure risk windows for each dose were defined as 0–24 h for persistent crying, 0–48 h for HHE and somnolence, 0–72 h for generalised fever and febrile convulsions/seizures, and 0–7 days for ISR including limb swelling.

2.6. Statistical analyses

We estimated IRs and IRRs for all databases by vaccine type and dose. Person-time of follow-up was categorised as during risk window or outside risk window and was not censored at the occurrence of an event, thus allowing each child to experience more than one event. Events were considered recurrent (i.e., counted as two separate events) if they were at least seven days apart. Follow-up time was classified by calendar year, age (months) and the different risk windows for each child in the cohort. This person-time was used as the denominator for the IR estimations and their 95% confidence intervals (CIs) were calculated using a Poisson distribution [26]. The IRs are presented as IRs within the risk period, outside the risk period (baseline IRs), and as overall IRs which included both risk and baseline periods.

For the SCCS analyses, follow-up was calculated from cohort entry for individuals without recorded pertussis vaccine exposure or one month before the first recorded pertussis vaccine exposure until one month after the last pertussis vaccine exposure for individuals with recorded pertussis vaccine exposure (Fig. 1). The non-risk period excluded the week before vaccination for the SCCS analyses to account for a potential healthy vaccinee effect just prior to vaccination. The SCCS models included age (in months) as a time-varying covariate, and all available aP or wP vaccine doses as exposure. The IRRs were adjusted for age in months and for the healthy vaccinee period. Random effects meta-analyses were performed by vaccine type and dose [27]. For wP, only data from the UK was used for the meta-analyses as the databases from the other countries contained little wP information due to their earlier switch from wP to aP [11]. Study heterogeneity was assessed by the chi-squared test for heterogeneity and quantified using the I^2 statistic.

We used SAS version 9.4 for the calculation of IRs and IRRs. SAS programs authored by Bart Spiessens and updated by Francois Haguinet were used for SCCS analyses. The meta-analyses were conducted using R.

2.7. Ethical considerations

The study protocol was approved by the approval committee of the local database and the ADVANCE steering committee. It was registered in the ENCePP registry (EUPAS13779) [28].

3. Results

3.1. Study population

We included data from seven European healthcare databases with a total source population of 38,599,335 persons (Table 1). The main reason for exclusion was outside age range during the study period. The study population comprised just over 5 million children aged <6 years, with 13,635,355 person-years of follow-up during the study period. The THIN database contributed 34.4% of the study population and PEDIANET contributed 0.2% (Table 2). The age and gender ratios for the children included in the SCCS analyses were similar between the databases (Table 3). The numbers of children exposed to wP and aP differed between the databases due to different periods for data availability and different dates for the wP to aP vaccine switch.

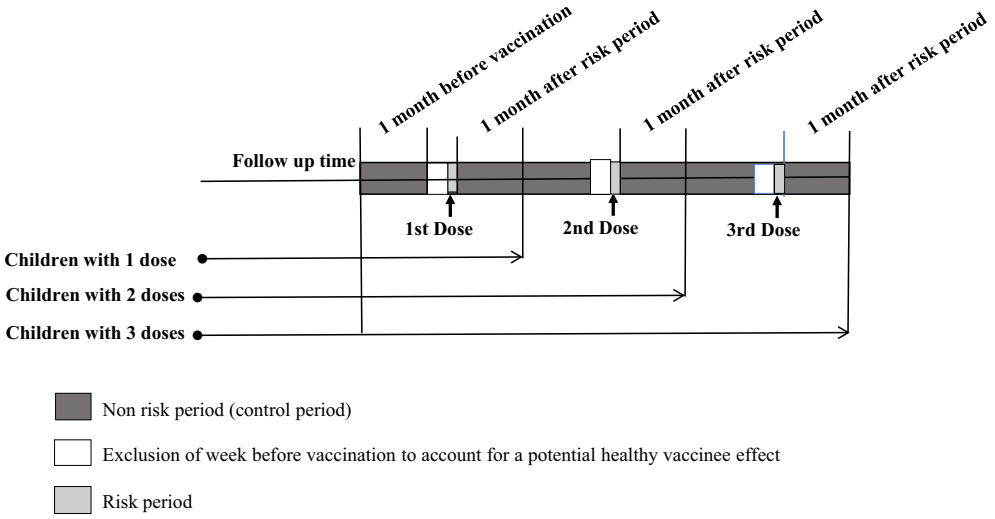

Fig. 1. Follow-up periods used in the SCCS analyses.

Table 2
Summary of type of database and numbers of individuals in each healthcare database.

	Denmark		UK		Spain		Italy	TOTAL
	AUH	SSI	RCGP RSC	THIN	BIFAP	SIDIAP	PEDIANET[1]	
Type of database	Regional	National	National	National	Multiregional	Regional	Regional	
Total number of persons (all ages)	1,725,165	7,512,032	3,017,610	11,696,261	7,541,864	7,096,695	9708[2]	38,260,474
Number of persons with unknown birth month (all ages) *EXCLUDED*	*21*	*27*	*0*	*10,453,631*[4]	*0*	*0*	*0*	*10,453,679*
Number of persons not having follow-up time in the study period (all age) *EXCLUDED*	*1,418,041*	*5,818,647*	*25,281*	*107,973*	*23*	*6'109'234*	*0*	*13,479,199*
Number of persons with eligible data[3]	305,461	1,687,703	434,931	1,899,704[5]	756,536	992,812	9,547	23,184,035
Number of children (0–5 years) included in the final study cohort	271,949	1,203,365[6]	387,003	1,735,910	568,400	872,580	9,079	5,048,286

[1] PEDIANET includes only children 0–14 years of age, data linked with vaccination data were available only for the 2006 and 2007 cohorts.
[2] With at least one day of follow-up between dose 1 and booster.
[3] No exclusion if not registered within one month of age.
[4] Including total database cohort (on date 20 Jan 2017) as in common data model, independent of study period.
[5] In the THIN database data protection regulations foresee that only children up to 15 years of age have birthdates with month and year recorded (i.e., valid birth date for the study), after 15 years of age only year of age will remain recorded in the database, therefore once a subject is 16 years old, they will be removed from the study due to insufficient birthdate information. This child cohort can provide valid data retrospectively until leaving the cohort at age 15 years.
[6] In a last data cleaning step, due to database information entry changes over time, SSI data has been restricted to the period 2000–2014.

Table 3
Characteristics of cases included in the SCCS analyses. The numbers exposed to wP and aP correspond to vaccination at any time.

	Denmark		UK		Spain		Italy	
	AUH	SSI	THIN	RCGP RSC	BIFAP	SIDIAP	PEDIANET	Total
Fever								
Total events (n)	8514	42,585	396,442	72,375	112,207	140,771	20,697	793,591
Mean age (years)	1.79	1.81	2.32	2.36	2.27	2.46	2.86	2.33
Male (%)	54.3	55.6	52.4	52.2	52.2	52.7	51.8	52.6
Exposed to wP (n)	0	0	85,491	10,226	1290	0	0	97,007
Exposed to aP (n)	6561	33,725	125,681	32,338	75,663	99,397	5012	378,377
Febrile and afebrile convulsions/seizures								
Total events (n)	13,869	62,973	11,602	7087	2114	6247	167	104,059
Mean age (years)	1.97	1.93	2.46	2.28	1.95	2.04	2.41	2.04
Male (%)	56.2	56.1	53.5	53.9	55.9	55.2	60.3	55.5
Exposed to wP (n)	0	0	3431	1648	26	0	0	5105
Exposed to aP (n)	8158	41,211	2627	2462	1661	4865	103	60,187
Persistent crying								
Total events (n)	0	0	11,468	4,167	13,662	0	471	29,768
Mean age (years)	NA	NA	0.83	0.77	0.83	NA	1.16	0.83
Male (%)	NA	NA	53.2	53.9	53.7	NA	53.3	53.5
Exposed to wP (n)c	0	0	3380	630	233	0	0	4243
Exposed to aP (n)	0	0	6554	2937	12,901	0	353	22,745
Injection-site reaction								
Total events (n)	448	2,296	10,380	1421	1571	2995	130	19,241
Mean age (years)	2.37	2.11	2.03	2.13	2.33	2.57	3.35	2.23
Male (%)	57.38	53.88	55.97	54.43	51.87	54.09	61.42	54.73
Exposed to wP (n)	0	0	2589	272	17	0	0	2878
Exposed to aP (n)	264	1839	5049	751	1325	2659	110	12,006
Hypotonic hypo-responsive episode								
Total events (n)	233	1225	2897	373	552	554	64	5898
Mean age (years)	1.16	1.19	2.38	2.29	1.81	2.03	2.74	2.01
Male (%)	42.8	50.3	53.9	53.4	59.3	56.1	58.7	53.9
Exposed to wP (n)	0	0	1198	111	9	0	0	1318
Exposed to aP (n)	198	1097	786	157	485	507	55	3285
Somnolence								
Total events (n)	15	72	2037	300	66	61	11	2562
Mean age (years)	2.64	2.74	1.79	1.88	2.23	2.53	1.72	1.89
Male (%)	26.7	38.7	51.6	52	51.5	53.1	36.4	51.2
Exposed to wP (n)	0	0	834	65	1	0	0	891
Exposed to aP (n)	7	55	830	175	59	58	9	1193

3.2. Incidence rates for risk outcomes

The highest number of events were recorded for fever (793,591 cases), followed by convulsions (104,059), persistent crying (29,768), ISR (19,241), HHE (5898), and somnolence (2562) (Table 3).

IRs for fever varied particularly in family paediatricians and primary care practitioners' databases, e.g., PEDIANET 489.8 (95% CI 483.1; 496.5) and BIFAP 183.6 (95% CI 182.6; 184.7) and were lower in hospital databases (8.6 (95% CI: 8.5; 8.6)) than in the primary care databases (96.9 (95% CI: 96.7; 97.1)). The overall IR for convulsions was 7.6 (95% CI: 7.6; 7.7) and the IR was higher in

hospital databases (IR = 12.9 (95% CI 12.8; 13.0) than in primary care databases (IR = 3.6 (95% CI: 3.5; 3.6) (Table 4). The overall IR for persistent crying was 3.9 (95% CI 3.8; 3.9), for injection-site reactions 2.2 (95% CI 2.1; 2.2), for HHE 0.4 (95% CI 0.4; 0.4) and for somnolence 0.3 (95% CI 0.3; 0.3).

The hospital databases (AUH, SSI) could not be used to estimate injection-site reactions, somnolence, or persistent crying. SIDIAP could not be used for persistent crying analyses, as there were no ICD-10 codes for this event. However, the other primary care databases either had free-text or more detailed codes.

The IRs for persistent crying, HHE, ISR, and somnolence were highest among infants and decreased after the first six months of life. The IRs for convulsions were highest in the hospital-based systems in Denmark where they peaked at around 18 months of age. The highest incidence for fever was recorded for children at around 18 months of age, in all PC databases. In all databases the IRs for all events were higher in the risk periods than in the non-risk periods (Table 4).

3.3. Self-controlled case series analyses

We included 793,591 cases of fever, 104,059 cases of febrile or afebrile convulsions/seizures, 29,768 cases of persistent crying, 19,241 cases of injection-site reactions, 5898, cases of HHE, and

Table 4
Summary of number of events and incidence rates (IRs) per 1000 person-years (PY) for safety outcomes after any dose of either wP or aP vaccine, by database (DB), type of database (primary care (PC) or hospital) and overall.

	Non-risk period			Risk period			Overall (non-risk + risk period)
	Number of events	PY	IR/1000PY (95% CI)	Number of events	PY	IR/1000PY (95% CI)	IR/1000PY (95% CI)
Fever							
BIFAP	110,719	601,535	184.1 (183; 185.2)	1488	9546	155.9 (148.1; 164)	183.6 (182.6; 184.7)
SIDIAP	139,083	1,451,435	95.8 (95.3; 96.3)	1688	17,465	96.7 (92.1; 101.4)	95.8 (95.3; 96.3)
RCGP RSC	71,831	1,006,079	71.4 (70.9; 71.9)	544	6060	89.8 (82.4; 97.6)	71.5 (71; 72)
THIN	393,135	4,501,524	87.3 (87.1; 87.6)	3307	28,911	114.4 (110.5; 118.4)	87.5 (87.2; 87.8)
PEDIANET	20,626	42,008	491 (484.3; 497.8)	71	252	281.9 (220.2; 355.6)	489.8 (483.1; 496.5)
PC DBs*	735,394	7,602,198	96.7 (96.5; 97)	7098	62,235	114.1 (111.4; 116.7)	96.9 (96.7; 97.1)
AUH	8,362	967,669	8.6 (8.5; 8.8)	152	5487	27.7 (23.5; 32.5)	8.8 (8.6; 8.9)
SSI	41,964	4,969,111	8.4 (8.4; 8.5)	621	28,655	21.7 (20; 23.5)	8.5 (8.4; 8.6)
Hospital DS**	50,326	5,936,780	8.5 (8.4; 8.6)	773	34,142	22.6 (21.1; 24.3)	8.56 (8.5; 8.6)
Overall	785,720	13,538,978	58.0 (57.9; 58.2)	7,871	96,377	81.7 (79.9; 83.5)	58.2 (58.1; 58.3)
Febrile and afebrile convulsions/seizures							
BIFAP	2088	601,535	3.5 (3.3; 3.6)	26	9,546	2.7 (1.8; 4)	3.5 (3.3; 3.6)
SIDIAP	6121	1,451,435	4.2 (4.1; 4.3)	126	17,465	7.2 (6; 8.6)	4.3 (4.2; 4.4)
RCGP RSC	7057	1,006,079	7 (6.9; 7.2)	30	6,060	5 (3.3; 7.1)	7 (6.8; 7.2)
THIN	11,515	4,501,524	2.6 (2.5; 2.6)	87	28,911	3 (2.4; 3.7)	2.6 (2.5; 2.6)
PEDIANET	166	42,008	4 (3.4; 4.6)	1	252	4 (0.1; 22.1)	4 (3.4; 4.6)
PC DBs*	26,947	7,602,198	3.5 (3.5; 3.6)	270	62,235	4.3 (3.8; 4.9)	3.55 (3.5; 3.6)
AUH	13,732	967,669	14.2 (14; 14.4)	137	5,487	25 (21; 29.5)	14.3 (14; 14.5)
SSI	62,520	4,969,111	12.6 (12.5; 12.7)	453	28,655	15.8 (14.4; 17.3)	12.6 (12.5; 12.7)
Hospital DBs**	76,252	5,936,780	12.8 (12.8; 12.9)	590	34,142	17.3 (15.9; 18.7)	12.87 (12.8; 13)
Overall	103,199	13,538,978	7.6 (7.6; 7.7)	860	96,377	8.9 (8.3; 9.5)	7.6 (7.6; 7.7)
Persistent crying, irritability							
BIFAP	13,425	606,306	22.1 (21.8; 22.5)	237	4,775	49.6 (43.5; 56.4)	22.4 (22; 22.7)
RCGP RSC	4011	1,009,126	4.0 (3.9; 4.1)	156	3,013	51.8 (44; 60.6)	4.1 (4; 4.2)
THIN	10,976	4,515,621	2.4 (2.4; 2.5)	492	14,422	34.1 (31.2; 37.3)	2.5 (2.5; 2.6)
PEDIANET	468	42,134	11.1 (10.1; 12.2)	3	126	23.8 (4.9; 69.6)	11.2 (10.2; 12.2)
PC DBs*	28,880	6.173.187	3.8 (3.7; 3.8)	888	31,071	28.6 (26.7; 30.5)	3.9 (3.8; 3.9)
Injection-site reactions							
BIFAP	1441	591,994	2.4 (2.3; 2.6)	130	19,088	6.8 (5.7; 8.1)	2.6 (2.5; 2.7)
SIDIAP	2547	1,433,980	1.8 (1.7; 1.9)	448	34,921	12.8 (11.7; 14.1)	2 (2; 2.1)
RCGP RSC	1334	999,911	1.3 (1.3; 1.4)	87	12,228	7.1 (5.7; 8.8)	1.4 (1.3; 1.5)
THIN	9680	4,472,440	2.2 (2.1; 2.2)	700	58,013	12.1 (11.2; 13.0)	2.3 (2.3; 2.3)
PEDIANET	128	41,756	3.1 (2.6; 3.6)	2	504	4 (0.5; 14.4)	3.1 (2.6; 3.7)
PC DBs*	15,130	7,539,697	2 (2; 2)	1,367	124,754	11 (10.4; 11.6)	2.2 (2.1; 2.2)
Hypotonic hypo-responsive episode							
BIFAP	451	603,920	0.8 (0.7; 0.8)	101	7,161	14.1 (11.5; 17.1)	0.9 (0.8; 1)
SIDIAP	483	1,455,800	0.3 (0.3; 0.4)	71	13,101	5.4 (4.2; 6.8)	0.4 (0.4; 0.4)
RCGP RSC	371	1,007,605	0.4 (0.3; 0.4)	2	4,534	0.4 (0.1; 1.6)	0.4 (0.3; 0.4)
THIN	2,858	4,508,769	0.6 (0.6; 0.7)	39	21,661	1.8 (1.3; 2.5)	0.6 (0.6; 0.7)
PEDIANET	64	42,071	1.5 (1.2; 1.9)	0	189	0 (0; 19.5)	1.5 (1.2; 1.9)
PC DBs*	4,227	7,617,782	0.6 (0.5; 0.6)	213	46,646	4.6 (4; 5.2)	0.6 (0.6; 0.6)
AUH	228	969,041	0.2 (0.2; 0.3)	5	4,115	1.2 (0.4; 2.8)	0.2 (0.2; 0.3)
SSI	1208	4,976,276	0.2 (0.2; 0.3)	17	21,490	0.8 (0.5; 1.3)	0.3 (0.2; 0.3)
Hospital DBs**	1436	5,945,317	0.2 (0.2; 0.3)	22	25,606	0.9 (0.5; 1.3)	0.2 (0.2; 0.3)
Overall	5663	13,563,100	0.4 (0.4; 0.4)	235	72,252	3.3 (2.8; 3.7)	0.4 (0.4; 0.4)
Somnolence							
BIFAP	62	603,920	0.1 (0.1; 0.1)	4	7,161	0.6 (0.2; 1.4)	0.1 (0.1; 0.1)
SIDIAP	60	1,455,800	0 (0; 0.1)	1	13,101	0.1 (0; 0.4)	0 (0; 0.1)
RCGP RSC	288	1,007,605	0.3 (0.3; 0.3)	12	4,534	2.7 (1.4; 4.6)	0.3 (0.3; 0.3)
THIN	1,976	4,508,769	0.4 (0.4; 0.5)	61	21,661	2.8 (2.2; 3.6)	0.5 (0.4; 0.5)
PEDIANET	10	42,071	0.2 (0.1; 0.4)	1	189	5.3 (0.1; 29.5)	0.3 (0.1; 0.5)
PC DBs*	2,396	7.617.783	0.1 (0.3; 0.3)	79	46.646	1.7 (1.3; 2.1)	0.3 (0.3; 0.3)

* Overall estimate including primary care (PC) databases: BIFAP, SIDIAP, RCGP RSC, THIN and PEDIANET.
** Overall estimates including hospital databases: AUH and SSI.

Table 5
Comparison of estimated and published incidence rate ratios (IRRs) for all risk outcomes (except somnolence).

	Estimates from this study		Zhang 2014 [15]		Jefferson 2003 [13]		Andrews 2010 [12]		Sun 2012 [14]	
	Risk window	IRR (95% CI)	Risk window	IRR (95% CI)	Risk window	IRR (95% CI)	Risk window	IRR (95% CI)	Risk window	IRR (95% CI)
Persistent crying										
wP all D					2–72 h	12.59 (1.91;83.00)	0d	6.51 (5.53; 7.66)		
							1-3d	1.44 (1.18; 1.75)		
wP D1	0–24 h	4.85 (4.43; 5.32)								
wP D2	0–24 h	2.36 (1.17; 4.73)								
wP D3	0–24 h	2.11 (1.80;2.47)								
aP D1	0–24 h	1.99 (1.66; 2.40)		1.29 (0.71; 2.34)						
aP D2	0–24 h	1.16 (0.88;1.53)		1.08 (0.83; 1.40)						
aP D3	0–24 h	1.29 (0.75;2.21)		1.06 (0.66; 1.68)						
Hypotonic-hypo-responsive episode										
wP all D					0–48 h	3.22 (0.39; 26.78)	0d	1.22 (0.30; 4.96)[c]		
							1-3d	0.62 (0.20; 1.99)[c]		
wP D1	0–48 h	1.70 (0.99; 2.94))								
wP D2	0–48 h	0.58 (0.38; 0.87)								
wP D3	0–48 h	1.28 (0.94; 1.74)								
aP all D				0.29 (0.02; 5.13)	0–48 h	0.29 (0.04; 2.28)	0d	3.22 (1.30; 7.98);		
							1-3d	1.56 (0.71; 3.39)		
aP D1	0–48 h	2.80 (1.52; 2.16)								
aP D2	0–48 h	1.73 (0.86; 3.48)								
aP D3	0–48 h	1.75 (0.79; 387)								
Fever										
wP D1	0–72 h	1.42 (0.78; 2.60)[a]			0-72h[b]	33.29 (28.48; 38.91)				
wP D2	0–72 h	1.40 (1.23; 1.59)								
wP D3	0–72 h	2.01 (1.67; 2.41)								
aP D1	0–72 h	1.09 (0.99; 1.21)		1.18 (0.73; 1.90)	0-72h[b]	1.10 (0.79; 1.53)				
aP D2	0–72 h	0.94 (0.87;1.02)		1.00 (0.91; 1.11)						
aP D3		1.12 (0.95; 1.33)		1.03 (0.94; 1.13)						
Convulsions										
wP all D					0–72 h	1.04 (0.16; 6.72)	0d	4.14 (1.92; 8.92)		
							1-3d	1.37 (0.63; 2.95)		
wP D1	0–72 h	1.20 (0.70; 2.05)								
wP D2	0–72 h	0.85 (0.42; 1.72)								
wP D3	0–72 h	1.34 (0.50; 3.56)								
aP D1	0–72 h	1.53 (1.02; 2.30)							0d	6.49 (3.10–13.61)
									1-3d	1.47 (0.62–3.50)
aP D2	0–72 h	0.99 (0.78; 1.26)							0d	3.97 (2.20–7.16);
									1-3d	1.52 (0.88–2.64)
aP D3	0–72 h	1.41 (0.98; 2.03)							0d	1.07 (0.73–1.57);
									1-3d	0.89 (0.70–1.14)
Injection-site reactions										
wP D1	0-7d	2.27 (1.73; 2.99)			0–72 h	11.49 (8.68; 15.22)[d]				
wP D2	0-7d	2.34 (2.09; 2.62)								
wP D3	0-7d	2.62 (1.69; 4.06)								
aP D1	0-7d	1.37 (1.12; 1.67)		1.29 (0.62; 2.68)	0–72 h	0.99 (0.67; 1.48) [d]				
aP D2	0-7d	1.77 (1.08; 2.89)		2.08 (0.54; 8.01)						
aP D3	0-7d	1.54 (1.11; 2.14)		1.13 (1.07; 1.20)						

Zang [15] is a Cochrane Review that pooled safety data from individual double-blind RCTs using a random-effects meta-analysis model. Jefferson et al. [13] included 49 RTCs and 3 cohort studies in fixed and random effect model meta analyses where safety was expressed as the Mantel Haenszel odds ratio (OR) and 95% CIs. Andrews et al. [12] and Sun et al. [14] were IRRs using a SCCS.

[a] Temperature ≥38 °C.
[b] Temperature >38 °C.
[c] Apnoea/collapse/cyanosis/pallor.
[d] Swelling/induration.

2562 cases of somnolence in the SCCS analyses (Table 4). Only RCGP RSC, THIN and BIFAP had data for children exposed to wP vaccine (Table 4). In these databases with information on wP and aP exposure, 11.51% of cases who had ≥1 risk event had been exposed to wP and 50.2% to aP (Table 4).

The pooled, age and healthy vaccinee period adjusted IRRs for risk versus non-risk periods were higher for wP than aP for all doses for persistent crying, fever, and injection-site reactions and for HHE the IIRs were lower IRRs for wP than aP. The IRs for somnolence were higher for wP only for dose 1 and 3 compared with those for aP. IRRs for convulsions are lower for wP than for aP for all doses (Supplemental Figs. 1–6). The results were statistically significant for persistent crying and injection-site reactions. The main objective of this proof of concept study was to compare our retrospective results with published findings, when possible (Table 5).

4. Discussion

The results of this POC study show that healthcare databases in ADVANCE can be used to generate reliable estimates for IRs and IRRs for a range of safety events. We showed that all databases cannot and should not be treated the same, as there can be important differences in rates based on where the data originate, i.e. in a primary care or hospital setting. Some events do not generally lead to hospitalisation and therefore hospital databases cannot be used to estimate the incidence of these events reliably and some events generally lead to hospitalisation, so that primary care databases cannot be used to estimate the incidence of these events. The incidence rates vary not only between primary care and hospital databases but also between primary care databases. The reasons for this are based on the characteristics of database and national health systems (i.e., population size, periods of data coverage, coding/entering of events, health care system and extraction algorithms) (refer to database characterization and fit for purpose assessment, M Sturkenboom – this JVAC issue). We tried to harmonize as much as possible through common data extraction protocols, code mapping, and iterative processes to verify data extractions. Additionally, a more detailed assessment is needed. Within the ADVANCE network, we included both primary care and hospital databases, which allowed us to estimate the incidences of different types of events The goal of estimating the IRs was to feed into a larger combined benefit-risk model comprising these databases, but also to test the databases for individual country/region specific future studies. The Danish databases (i.e., SSI and AUH) are overlapping. For the final benefit-risk model only SSI has been used.

In a Danish birth cohort study the IRs for febrile seizures were reported to be 2.92, 4.75 and 31.0 per 1000 person-years, within seven days after the first, second and third aP dose [14]. In our study we estimated the IRs for combined febrile and afebrile convulsions/seizures within three days after any aP dose to be 17.28 in the Danish hospital databases, which is within the range of the published data.

In a patient-reported survey, continuous crying for more than 3 h after wP was reported in 1.5% children and 0.4% following aP vaccination [29]. We found that 0.05% of the children showed persistent crying within 24 h following aP or wP vaccination; this lower rate is expected because not all persistent crying will be reported in clinical care.

In a SCCS study conducted using data for birth cohorts of children born between 2003 and 2006 from the GPRD database in the UK the risks were not estimated by dose, but for children who received at least one dose [12]. The risk windows differed since the GPRD study estimated risk for the day of vaccination separately whereas we took the first 24 h after vaccination as our risk window. The same differences in risk window length and analysis regarding the day of vaccination were also found for a Danish birth cohort study [14]. The results from two systematic reviews and two birth cohort database studies are summarised in Table 5 and compared with our estimates [12–15].

This proof of concept study was designed to test the capacity of the ADVANCE system to perform safety studies for events known to be associated with pertussis vaccination. We demonstrated that we were able to extract, share and pool data and generate evidence. In spite of this success there are some limitations. Since this study was focusing on testing the workflows and system, around a known topic, and no resources were available for validation, this was not conducted. Most of the data sources allow for chart validation, but it is costly. Future use of the system, especially when considering rare serious events, should have sufficient funding to enable validation of patients' dossiers [30]. We also demonstrated that primary care data sources are better suited to analyse less severe reactogenicity events compared with hospital databases, even if the absolute risks could be underestimated. If estimates of the absolute risks for these outcomes are need, secondary care databases should be complemented by primary data collection. In contrast, secondary care databases could be better situated for more severe outcomes that may not be recorded in primary care databases, since the children go directly to hospital. Injection-site reaction events are difficult to capture with electronic healthcare databases because the cause of the skin reaction is generally not recorded. Hence, we identified local skin reaction events that occurred in the risk window following vaccination in the SCCS. Therefore, the event 'injection-site reaction' was defined through all local skin reactions and symptoms with a temporal association with vaccination, not necessarily a causal association.

Second, we estimated risk windows based on vaccine prescriptions/administrations recorded in the databases. When using prescription databases, errors may occur due to delayed administration so that the date indicated in the database may not be the administration date. This will have a greater impact on outcomes with shorter risk windows. It may be important to perform validation studies to assess the accuracy between date of vaccine recording and its administration. The description of the ADVANCE Big Health Data ecosystem, it's functionality for future vaccine safety studies, the relation to other distributed vaccine information networks, and the processes are further described in the ADVANCE System's publication in this issue.

5. Conclusions

We demonstrated the feasibility of generating vaccine safety data based on secondary use of electronic health data from various databases in a distributed healthcare database network in Europe. As expected in Europe, the databases were heterogeneous, which emphasises the opportunities and synergies that could be created by working with common methods and protocols and data sharing, since some databases may be more appropriate for estimating certain outcomes than others. The quantification of the heterogeneity between databases is a pre-requisite for generating reliable evidence that is needed to inform future vaccine B/R monitoring and assessments.

6. 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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Declaration of Competing Interest

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Appendix A. Supplementary material

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