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Cover Letter

Dr Gregory A Poland
Editor-in-Chief, Vaccine

Paris, 6 December 2018

Dear Dr Poland

We are pleased to submit our paper '*ADVANCE system testing: vaccine benefit studies using multi-country electronic health data - the example of pertussis vaccination*' to your Journal, Vaccine for the ADVANCE supplement. This paper describes the proof-of-concept study assessing the ADVANCE system to estimate the benefits of pertussis vaccination. It is the fourth of the series of 10 papers that will be included in the supplement.

On behalf of all co-authors

Dr Myint **Tin Tin Htar**

***Author Agreement**

I, , Dr. Myint Tin Tin Htar declare that all authors have seen and approved the final version of the manuscript being submitted. We warrant that the article is our original work that has not been previously published and is not under consideration for publication elsewhere

Dr Myint Tin Tin Htar

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***Declaration of Interest Statement**

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒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.

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 2015were 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 ranged between 0.15 (95% CI: 0.12; 0.19) and 1.15 (95% CI: 1.07; 1.23), and the trend 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 investigate the incidence of pertussis and pertussis-related complications in vaccinated children.

ADVANCE system testing: vaccine benefit studies using multi-country electronic health data - the example of pertussis vaccination

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Abstract

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70 **Keywords:** Pertussis vaccination; pertussis-related complications; database study; feasibility
71 study; children; pertussis incidence
72

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]. Four proof-of-concept (POC) studies were designed to assess the feasibility of establishing the processes and systems proposed for generating the required data to perform benefit/risk (B/R) monitoring of vaccines [2-5]. These studies assessed the feasibility for generating data for coverage, benefit, risk, and the benefit-risk model. For these POC studies 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. 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. 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 [6].

Material and Methods

2.1 Study design

Full details of the study design can be obtained in the protocol, registered on the ENCePP (EUPAS) registry [5]. The study 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) [7]. 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 [8].

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 vaccines (either as a single component or part of a multivalent vaccine product). We defined four periods of exposure as follows: aP-0 – first 14 days after the receipt of the first dose (when children were considered to not yet be protected), aP-1 – from 14 days after the first dose until 14 days after the second dose, aP-2 –

from 14 days after the second dose until 14 days after the third dose, and aP-3 – from 14 days after the third dose 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 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) [9, 10]. 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 and by year for children who had received at least one dose and by 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 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; their contribution was 7,695 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 4,615 pertussis cases were identified in the study cohort during 8,576,043 person-years of follow-up with 79.6% of the follow-up time being post-dose 3. The overall incidence (/1 000 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 by database and year in children who had received at least one dose are summarised in **Figure 1** and **Supplementary data Table S2**. The pertussis IRs decreased with the number of doses of vaccines received in most databases (**Figure 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 to 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 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 and therefore it was not possible to calculate HRs (**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 consistently 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 [11]. However, even with seven databases covering almost 3 million vaccinated children, it was not always possible to estimate HRs reliably for pertussis-related complications in vaccinated children who developed pertussis due to the low number of cases and complications in these cases. Only 4,615 children developed pertussis following vaccination among the 2.9 million vaccinated children and only 89 of these developed

196 pneumonia and 7 developed generalised convulsions within one month of the pertussis
197 diagnosis and none died within three months of the pertussis diagnosis. Consequently, we
198 were not able to calculate HRs for all outcomes in all databases, and we could not calculate
199 any HRs by vaccine type, i.e. aP or wP vaccines.
200 Our results show that the incidence of pertussis in children who had received at least one dose
201 of pertussis vaccine from 2003 onwards was relatively low in the UK and relatively high in
202 Spain. We did not observe any major differences between the results from the two UK
203 databases, THIN and RCGP RSC, in the same calendar years. Although these databases do
204 not cover the whole population they are representative of the UK population, with a small
205 overlap in practices captured by the databases [12, 13]. The trend observed in our study was
206 similar to that reported for confirmed pertussis observed over the last decade in children aged
207 <5 years in the UK, although our IRs were lower since they are for vaccinated children only,
208 whereas the reported national rates were for the whole population, vaccinated or not [14, 15].
209 For Denmark, we observed a similar trend over time for the pertussis incidence rate in the SSI
210 (national) and AUH (regional) databases, except in SSI we observed peaks in the incidence
211 rates in 2004 and 2012, similar to those reported for laboratory-confirmed pertussis in the
212 whole Danish population [16]. In SSI The pertussis IRs were higher in the national SSI
213 database than those in the regional AUH database, generally; this may be due to differences in
214 population dynamics. For Spain, a higher incidence of pertussis was observed in the regional
215 SIDIAP database than in the multi-regional BIFAP database but the trends since 2001 in the
216 two databases were similar. The difference in incidence could be due to the different
217 geographical coverage and the coding which differed between the databases [17].
218 In the UK, there were no cases of pneumonia after pertussis diagnosis in the vaccinated cohort
219 that comprised more than 900,000 children. In RCGP RSC, pneumonia is one of the
220 conditions specifically monitored and the participating practices receive feedback about their

data quality for these conditions, so it is likely that the data are reliable [18]. 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 to 3% [19, 20]. 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 estimated IRs were coherent with those from national surveillance databases based on confirmed pertussis, although our analysis included all pertussis cases (both suspected and confirmed). It was difficult to make appropriate and reliable comparisons with pertussis or complication IRs in the literature because the confirmation information or predictive values were not always available. The databases included in our study were from different clinical settings (GP only, hospital only or hospital and GP data) and had different coding comportments (at regional or national levels), thus only the comparison of the trends over the time for estimates of incidence and complication rates seemed to be meaningful [17].

However, it is important to remember that the aim of this POC study was to assess the methodological aspects of the design, conduct and reporting of studies for vaccine benefit-risk monitoring activities using the proposed ADVANCE system. One aspect of this assessment was to show that the results described in this publication are plausible, but they 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.

Conflicts of interest

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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340 **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	9,708	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	7,695	2,886,367

341 *PEDIANET included only children 0-14 years of age

342

Table 2: Exposure, follow-up time, number of pertussis cases and pertussis incidence rates (per 1,000 person-years) in children aged 0 to 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	2,820	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

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	6,789	18.6 (4.1; 84.0)	9	6,791	NA	1	6,799	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	1,932		5	2,002		0	2,007	
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	1,608		2	1,616		0	1,618	
PEDIANET (Italy)	Reference cohort aP	18	2,482	NA	1	2,499	NA	0	2,500	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

352 **Figure legends**

353 Figure 1: Pertussis incidence rate per 1000 person-years for children who had received at least

354 one dose of pertussis vaccine by database and year followed from 1st dose to age 5 years

355 Figure 2: Incidence of pertussis according to the type and number of vaccine doses received

Figure 1

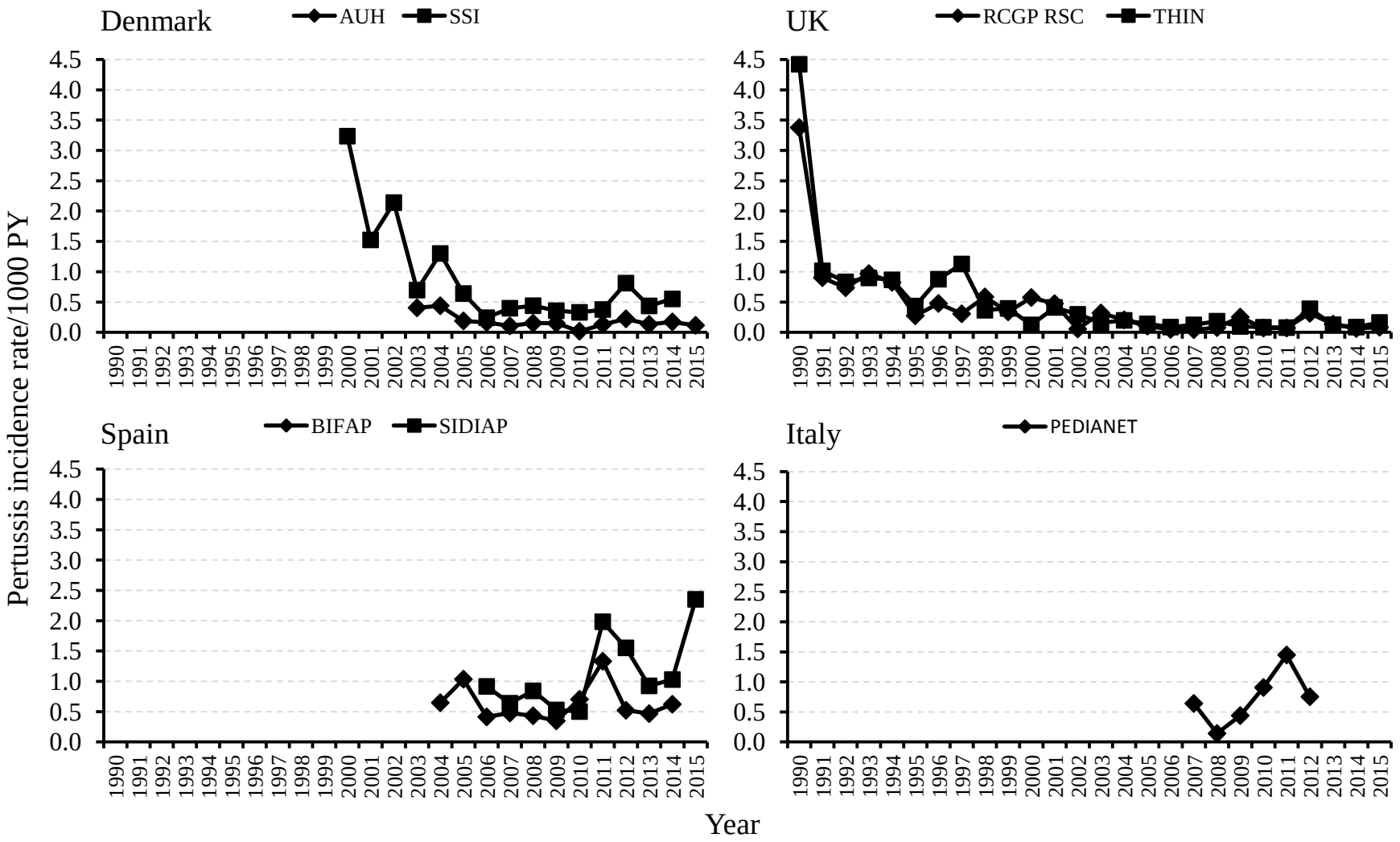
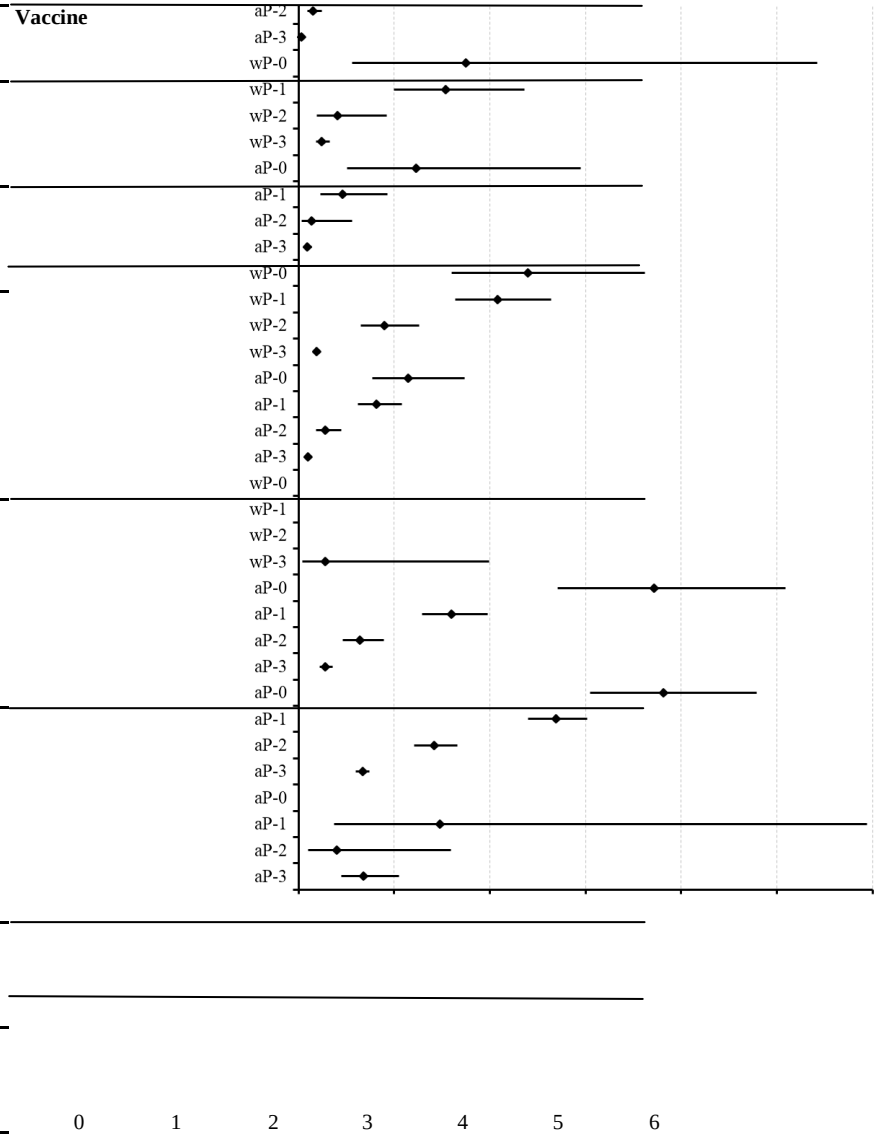

Denmark
AUH
SSI
UK
RCGP RSC
THIN
Spain
BIFAP
SIDIAP
Italy
PEDIANET
Pertussis incidence rate/1000 PY
Year

Figure 2

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



Supplementary data

Table S1: Codes used for extraction of data for outcomes: pertussis and pertussis-associated complications

Variable	Operational definition*
Pertussis	ICD-9: 033.9 Whooping cough, unspecified organism; 484.3 Pneumonia in whooping cough ICD-10: A37 READ-CTv3: A33y. A33yz; A33z.; Ayu39; Ayu3A; H243.; X70I8; XE0Qw; XE0Qw; XM00D READ v2: A33.. Ayu39; Ayu3A; H243. ICPC: R71 String text was also used in BIFAP
Confirmed pertussis	see above but with laboratory confirmation
Pneumonia	ICD-9 480–487 ICD-10: (J12–J18) READ-Ctv3: H20z. H222. H223. H22yz H22z. H23.. H26.. H2700 X100E X100H X100J X100M XE0YG XE0YJ XM0rv READ-v2: H20. H222. H223. H22yz H22z. H23.. H25.. H26.. H26.. H2700 ICPC: R81 String text was also used in BIFAP
Death	Code for death or reason for exit from population
Generalised convulsion	ICD-9: 779 ICD-10: P90 READ-CTv3: Q480. X75Z0 READ-v2: F25H. Q480. ICPC: none String text was also used in BIFAP
Age	From date of birth calculation
Calendar month	From calculated follow-up time
Gender	From population input files
Pertussis vaccination	From vaccination files, coded as aPe, uPe, wPe by dose

Table S2: Pertussis annual incidence rates (IR) per 1000 person years (PY) and their 95% confidence intervals in each database in pertussis vaccinated children followed from 1st dose to age 5 years

Database (country)	Year	PY	Number of pertussis events	IR	95% CI
AUH (Denmark)	2003	4944	2	0.40	0.10; 1.62
	2004	15952	7	0.44	0.21; 0.92
	2005	26512	5	0.19	0.08; 0.45
	2006	36758	6	0.16	0.07; 0.36
	2007	47029	5	0.11	0.04; 0.26
	2008	52751	8	0.15	0.08; 0.30
	2009	53469	8	0.15	0.07; 0.30
	2010	53680	1	0.02	0.00; 0.13
	2011	53961	7	0.13	0.06; 0.27
	2012	53802	12	0.22	0.13; 0.39
	2013	52960	7	0.13	0.06; 0.28
	2014	52143	9	0.17	0.09; 0.33
	2015	52087	6	0.12	0.05; 0.26
SSI (Denmark)	2000	199701	188	0.94	0.82; 1.09
	2001	259367	247	0.95	0.84; 10.8
	2002	316134	600	1.90	1.75; 2.06
	2003	332900	176	0.53	0.46; 0.61
	2004	302307	361	1.19	1.08; 1.32
	2005	292786	185	0.63	0.55; 0.73
	2006	286216	69	0.24	0.19; 0.31
	2007	281810	112	0.40	0.33; 0.48
	2008	280212	123	0.44	0.37; 0.52
	2009	280511	100	0.36	0.29; 0.43
	2010	282434	93	0.33	0.27; 0.40
	2011	284089	107	0.38	0.31; 0.46
	2012	283409	230	0.81	0.71; 0.92
	2013	279859	122	0.44	0.37; 0.52
	2014	194178	107	0.55	0.46; 0.67
RCGP RSC (UK)	1990	592	2	3.38	0.84; 13.51
	1991	2219	2	0.90	0.23; 3.60
	1992	4078	3	0.74	0.24; 2.28
	1993	6194	6	0.97	0.44; 2.16
	1994	8483	7	0.83	0.39; 1.73
	1995	10969	3	0.27	0.09; 0.85
	1996	12584	6	0.48	0.21; 1.06
	1997	13082	4	0.31	0.11; 0.81
	1998	13690	8	0.58	0.29; 1.17
	1999	14797	5	0.34	0.14; 0.81

Database (country)	Year	PY	Number of pertussis events	IR	95% CI
	2000	15667	9	0.57	0.30; 1.10
	2001	16905	8	0.47	0.24; 0.95
	2002	17914	1	0.06	0.01; 0.40
	2003	18793	6	0.32	0.14; 0.71
	2004	19425	4	0.21	0.08; 0.55
	2005	19502	2	0.10	0.03; 0.41
	2006	21207	1	0.05	0.01; 0.33
	2007	22997	1	0.04	0.01; 0.31
	2008	25652	2	0.08	0.02; 0.31
	2009	27844	7	0.25	0.12; 0.53
	2010	28239	2	0.07	0.02; 0.28
	2011	28193	2	0.07	0.02; 0.28
	2012	28714	9	0.31	0.16; 0.60
	2013	29750	4	0.13	0.05; 0.36
	2014	31816	2	0.06	0.02; 0.25
	2015	35426	3	0.08	0.03; 0.26
THIN	1990	1131	5	4.42	1.84; 10.62
	1991	4928	5	1.01	0.42; 2.44
	1992	9610	8	0.83	0.42; 1.66
	1993	14483	13	0.90	0.52; 1.55
	1994	19643	17	0.87	0.54; 1.39
	1995	25348	11	0.43	0.24; 0.78
	1996	30825	27	0.88	0.60; 1.28
	1997	35487	40	1.13	0.83; 1.54
	1998	41194	15	0.36	0.22; 0.60
	1999	48181	19	0.39	0.25; 0.62
	2000	57123	7	0.12	0.06; 0.26
	2001	77907	32	0.41	0.29; 0.58
	2002	97751	29	0.30	0.21; 0.43
	2003	112769	18	0.16	0.10; 0.25
	2004	126734	25	0.20	0.13; 0.29
	2005	129107	18	0.14	0.09; 0.22
	2006	138233	12	0.09	0.05; 0.15
	2007	146135	18	0.12	0.08; 0.20
	2008	152379	28	0.18	0.13; 0.27
	2009	155103	15	0.10	0.06; 0.16
	2010	154863	13	0.08	0.05; 0.14
	2011	154166	12	0.08	0.04; 0.14
	2012	151686	59	0.39	0.30; 0.50
	2013	142856	18	0.13	0.08; 0.20
	2014	128520	11	0.09	0.05; 0.15
	2015	73683	12	0.16	0.09; 0.29
BIFAP (Spain)	2004	9266	6	0.65	0.29; 1.44

Database (country)	Year	PY	Number of pertussis events	IR	95% CI
	2005	22208	23	1.04	0.69; 1.56
	2006	28988	12	0.41	0.24; 0.73
	2007	33472	16	0.48	0.29; 0.78
	2008	34703	15	0.43	0.26; 0.72
	2009	37271	13	0.35	0.20; 0.60
	2010	35542	25	0.70	0.48; 1.04
	2011	39061	52	1.33	1.01; 1.75
	2012	49734	26	0.52	0.36; 0.77
	2013	49214	23	0.47	0.31; 0.70
	2014	28929	18	0.62	0.39; 0.99
SIDIAP (Spain)	2006	25105	23	0.92	0.61; 1.38
	2007	68863	44	0.64	0.48; 0.86
	2008	79467	67	0.84	0.66; 1.07
	2009	85206	45	0.53	0.39; 0.71
	2010	85634	43	0.50	0.37; 0.68
	2011	86210	171	1.98	1.71; 2.30
	2012	85660	133	1.55	1.31; 1.84
	2013	80999	75	0.93	0.74; 1.16
	2014	77708	80	1.03	0.83; 1.28
	2015	76932	181	2.35	2.03; 2.72
PEDIANET (Italy)	2007	4679	3	0.64	0.21; 1.99
	2008	7067	1	0.14	0.02; 1.00
	2009	6828	3	0.44	0.14; 1.36
	2010	6615	6	0.91	0.41; 2.02
	2011	6215	9	1.45	0.75; 2.78
	2012	3984	3	0.75	0.24; 2.33

Supplemental Files

Click here to download Supplemental Files: Supplementary data file_06DEC2018.docx