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ADVANCE system testing: Can coverage of pertussis vaccination be estimated in European countries using electronic healthcare databases: An example

Hanne-Dorthe Emborg [a,*,1], Johnny Kahlert [b,1], Toon Braeye [c], Jorgen Bauwens [d,e,f], Kaatje Bollaerts [g], Giorgia Danieli [h,i], Talita Duarte-Salles [j], Steffen Glismann [k], Consuelo Huerta-Alvarez [l], Simon de Lusignan [m,n,2], Elisa Martín-Merino [l], Chris McGee [m,n], Ana Correa [m], Lara Tramontan [h,i], Daniel Weibel [o,p,3], Miriam Sturkenboom [g,p,q]

[a] Statens Serum Institut, Artillerivej 5, DK-2300 Copenhagen, Denmark
[b] Aarhus University Hospital, Olof Palmes Alle 43-45, DK-8200 Aarhus, Denmark
[c] Sciensano, Rue Juliette Wytsmanstraat 14, 1050 Brussels, Belgium
[d] University Children's Hospital Basel, PO Box, CH 4033 Basel, Switzerland
[e] University of Basel, Switzerland
[f] Brighton Collaboration Foundation, Switzerland
[g] P-95 Epidemiology and Pharmacovigilance, Leuven, Belgium
[h] Consorzio Arsenàl.IT, Veneto Region, Italy
[i] PEDIANET, Padova, Italy
[j] Fundació Intitut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol I Gurina (IDIAPJGol), Barcelona, Spain
[k] GSK, Av. Fleming 20, 1300 Wavre, Belgium
[l] BIFAP Database, Spanish Agency of Medicines and Medical Devices, Madrid, Spain
[m] University of Surrey, Guildford, Surrey GU2 7XH, UK
[n] Royal College of General Practitioners Research and Surveillance Centre, 30 Euston Square, London NW1 2FB, UK
[o] Erasmus University Medical Center, PO Box 2014, 3000 CA Rotterdam, the Netherlands
[p] VACCINE.GRID Foundation, Spitalstrasse 33, Basel, Switzerland
[q] Julius Global Health, Julius Center, University Medical Center Utrecht, Heidelberglaan 100, the Netherlands

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ABSTRACT

Introduction: The Accelerated Development of VAccine beNefit-risk Collaboration in Europe (ADVANCE) is a public-private collaboration aiming to develop and test a system for rapid benefit-risk (B/R) monitoring of vaccines, using existing healthcare databases in Europe. The objective of this paper was to assess the feasibility of using electronic healthcare databases to estimate dose-specific acellular pertussis (aP) and whole cell pertussis (wP) vaccine coverage.

Methods: Seven electronic healthcare databases in four European countries (Denmark (n = 2), UK (n = 2), Spain (n = 2) and Italy (n = 1)) participated in this study. Children were included from birth and followed up to age six years. Vaccination exposure was obtained from the databases and classified by type (aP or wP), and dose 1, 2 or 3. Coverage was estimated using period prevalence. For the 2006 birth cohort, two

Abbreviations: ADVANCE, Accelerated Development of VAccine beNefit-risk Collaboration in Europe; aP, acellular pertussis; ATC, Anatomical Therapeutic Chemical Classification System; AUH, Aarhus University Hospital Denmark; BIFAP, Database for Pharmacoepidemiological Research in Primary Care Spain; B/R, benefit-risk; CumInc, cumulative incidence; DTP, diphtheria tetanus pertussis; DT, diphtheria tetanus; DTaP, diphtheria tetanus acellular pertussis; ECDC, European Centre for Disease Prevention and Control; PEDIANET, Family Paediatrician Database Veneto vaccine registry Italy; POC, Proof of Concept; PP_{FU}, Period Prevalence; RCGP RSC, Royal College of General Practitioners Research and Surveillance Centre UK; SIDIAP, Information System for Primary Care Research Spain; SSI, Statens Serum Institut Denmark; THIN, The Health Improvement Network UK; wP, whole cell pertussis.

* Corresponding author.
E-mail addresses: hde@ssi.dk (H.-D. Emborg), jok@clin.au.dk (J. Kahlert), toon.braeye@sciensano.be (T. Braeye), j.bauwens@brightoncollaboration.org (J. Bauwens), kaatje.bollaerts@p-95.com (K. Bollaerts), gdanieli@consorzioarsenal.it (G. Danieli), tduarte@idiapjgol.org (T. Duarte-Salles), steffen.x.glismann@gsk.com (S. Glismann), chuerta@aemps.es (C. Huerta-Alvarez), simon.delusignan@phc.ox.ac.uk (S. de Lusignan), emartinm@aemps.es (E. Martín-Merino), c.mcgee@surrey.ac.uk (C. McGee), accorrea1@googlemail.com (A. Correa), ltramontan@consorzioarsenal.it (L. Tramontan), daniel@weibelconsult.com (D. Weibel), m.c.j.sturkenboom@umcutrecht.nl (M. Sturkenboom).

[1] These authors contributed equally to the work and share first authorship.
[2] Current affiliation: Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK.
[3] Current affiliation: Weibel Consulting, Den Haag, Netherlands. European & Developing Countries Clinical Trials Partnership (EDCTP), Den Haag, Netherlands.

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estimation methods for pertussis vaccine coverage, period prevalence and cumulative incidence were compared for each database.

Results: The majority of the 2,575,576 children included had been vaccinated at the country-specific recommended ages. Overall, the estimated dose 3 coverage was 88–97% in Denmark (birth cohorts from 2003 to 2014), 96–100% in the UK (2003–2014), 95–98% in Spain (2004–2014) and 94% in Italy (2006–2007). The estimated dose 3 coverage per birth cohort in Denmark and the UK differed by 1–6% compared with national estimates, with our estimates mostly higher. The estimated dose 3 coverage in Spain differed by 0–2% with no consistent over- or underestimation. In Italy, the estimates were 3% lower compared with the national estimates. Except for Italy, for which the two coverage estimation methods generated the same results, the estimated cumulative incidence coverages were consistently 1–10% lower than period prevalence estimates.

Conclusion: This study showed that it was possible to provide consistent estimates of pertussis immunisation coverage from the electronic healthcare databases included, and that the estimates were comparable with the national estimates.

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1. Introduction

Whole cell pertussis (wP) vaccines have been available since the 1940s and were effective in reducing the number of pertussis cases and mortality [1,2]. However, due to common minor adverse reactions and less common severe systemic reactions to wP, acellular pertussis (aP) vaccines were developed and used from the mid-1990s [1]. Many countries replaced wP with aP, and Poland is the only country in Europe where wP vaccine is still included in the childhood vaccination programme [3].

World-wide, countries provide annual reports on national pertussis vaccine coverage estimates to WHO/UNICEF's Vaccine Preventable Diseases Monitoring System [4]. Electronic registration of vaccination is becoming more widespread in Europe, allowing countries to share vaccine coverage data for further analysis. In a survey by the European Centre for Disease Prevention and Control (ECDC) in 2016, 16 out of 27 EU/EEA countries reported that they had a national or sub-national vaccination information system, 5 countries reported they were piloting a system and 6 countries said they had plans to set up a system in the future [5]. Collations of data from these registries and other sources have shown that pertussis vaccine coverage in Europe is generally above 90%, although coverage has dropped in some countries in some years [6,7].

The Accelerated Development of VAccine beNefit-risk Collaboration in Europe (ADVANCE) is a public-private collaboration aiming to develop and test a system for rapid benefit-risk (B/R) monitoring of vaccines, using existing healthcare databases in Europe. A series of proof of concept (POC) studies were designed to assess the processes and system proposed for generating data on vaccination coverage, benefits and risks required to perform B/R monitoring. As a preparatory step to these studies, a systematic approach was used to characterise and assess the eligibility of these healthcare databases for their use in coverage and B/R studies [8].

The objective of this paper was to determine the feasibility of using electronic healthcare databases to estimate dose-specific vaccination coverage by age and its variation across birth cohorts, using aP and wP vaccination coverage as an example.

2. Material and methods

2.1. Databases

Nine of the 19 electronic European healthcare databases had recorded the pertussis vaccines and of these two databases were not able to provide data within the ADVANCE POC study deadline, leaving a total of seven databases for this study [8]. There was one regional and one national hospital discharge database linked to vaccination registries from Denmark (Aarhus University Hospital: AUH and Statens Serum Institut: SSI), one multiregional and one regional primary healthcare record database from Spain (Database for Pharmacoepidemiological Research in Primary Care: BIFAP and the Information System for Primary Care Research: SIDIAP), two national primary care medical record databases from the UK (The Health Improvement Network: THIN and Royal College of General Practitioners Research and Surveillance Centre: RCGP RSC) and one regional family paediatrician database linked to the Veneto vaccine registry from Italy (PEDIANET). SSI was the only database that used the national vaccination register when extracting aP and wP vaccines. Details about the extraction, management, transformation, sharing, and analyses of the data using the ADVANCE system workflows and methodology (common protocol, common data model and common analytics) can be found in another paper in this supplement [9]. In response to a survey, the database owners provided information on database characteristics such as representativeness, origin of data, population size, data-availability period, switch from wP to aP vaccines, historical pertussis vaccine schedules, availability of ATC-codes and doses, how information about dose was recorded and rounding rules for birth dates due to privacy (Table 1).

2.2. Study population

The eligible population comprised all children from birth to five years old, registered in any of the participating databases and identifiable through a unique anonymised patient-ID and with at least one day of follow-up during the overall study period: 1st January 1990 to 31st December 2015. Children were eligible for inclusion in the study population if they entered the database at the age of one month or younger during the study period (defined as start of follow-up). We defined end of follow-up, as the date of whichever of the following events occurred first: receipt of their preschool-entry pertussis booster, 6th birthday, end of study (varied across databases - see country specific study periods in Table 1), transferring out from the catchment of the database, or death. Children with incomplete dates of birth, start or end of follow-up were excluded. Rounding of birth dates was allowed.

2.3. Exposure

The exposure of interest was vaccination with any pertussis-containing vaccine in the study population during follow-up. In Denmark (AUH, SSI), the vaccine type was recorded at the time of administration. In the UK, the switch from wP to aP occurred in October 2004. Vaccines administered prior to 1st October 2004

Table 1
Characteristics of the seven participating databases.

Country	Denmark		Spain		United Kingdom		Italy
Database	AUH	SSI	BIFAP	SIDIAP	THIN	RCGP RSC	PEDIANET
Representativeness	Regional Whole	National Whole	Multi-regional Subset	Regional Subset	National Subset	National Subset	Regional Subset
Origin of data	Record linkage between different registries*		GP and primary care paediatricians	GP and paediatricians	GP	GP	Family paediatricians
Birth cohorts available for coverage estimation	2002–2015	1997–2014**	2002–2014***	2005–2015	1990–2015	1990–2015	2006–2007
Switch from wP to aP	1997	1997	1997–2004	1997–2004	2004	2004	1995
Percentage wP of all vaccinations recorded	0	2.1	1.7	0	64.3	47.7	0
ATC code available (%)	0	100	100****	0	0	0	0*****
Dose recorded (% missing)	Yes (35.4)	Yes (2.7)	Yes (23)	Yes (0)	Yes (<0.01)	No	Yes (0)
Dose derived (% missing)	Yes (0)	Yes (2.8)	Yes (2)	None	None	Yes (0)	None
Rounding of birthdates	None	None	None	Rounded to 1st of month	Rounded to 1st of month	Rounded to 1st of month	Rounded to 15th of month

AUH: Aarhus University Hospital Denmark; SSI, Statens Serum Institut Denmark; BIFAP: Database for Pharmacoepidemiological Research in Primary Care Spain; SIDIAP, Information System for Primary Care Research Spain; THIN, The Health Improvement Network UK; RCGP RSC: Royal College of General Practitioners Research and Surveillance Centre UK; PEDIANET: Family Paediatrician Database Veneto vaccine registry Italy.
* The general practioners register the pertussis vaccinations at the time of administration and afterward the vaccination data are linked to the population data.
** The study period was 1997 to September 2014.
*** The 2002 and 2003 birth cohorts were excluded from the coverage analyses since the vaccine type was unknown for the majority of the vaccines administered.
**** ATC code was derived based on the described antigen combinations, marketed vaccines at every calendar year of vaccination and age at vaccination according to the rules in the national scheme.
***** Could be derived from coded association information.

were recorded as wP, vaccines administered in October 2004 were recorded as uP (unknown) and vaccines administered from 1st November 2004 and onwards as aP. In Spain, aP vaccines were first introduced in 1997 and the switch from wP to aP vaccines occurred gradually until 2004. From 2005 onwards only aP vaccines were available, which means that the SIDIAP database only provided aP data (Table 1). In the Spanish BIFAP database, the antigens mentioned in the vaccination code recorded at the time of each administration was used to determine the vaccine type administered. In Italy, only aP were administered to the 2006 and 2007 birth cohort (Table 1). In all databases, when the vaccine type (aP or wP) could not be determined reliably, it was coded uP. If the dose number was not recorded in the database, it was derived based on the chronological sequence of administered doses and the age of the child. A child was assumed to be vaccinated on the day the vaccine dose was recorded. All records with missing patient-ID, dates or vaccine type were excluded from analysis.

2.4. Statistical methods

Vaccination coverage (per dose) was estimated as the percentage of the children in the study population who had received the specific vaccine dose by a certain age. Pertussis vaccine coverage was estimated by dose and by age (in weeks) in each birth cohort, using period prevalence, taking into consideration any children lost-to-follow-up (PP_{FU}). The PP_{FU}-estimate for children at a certain age (in weeks) was the number of children vaccinated with the first dose (D1), second dose (D2), and third dose (D3), respectively, divided by the total number of children in follow-up at that age (in weeks). For example, in the 2012 birth cohort, at five weeks of age, the number of children vaccinated with the first dose (D1), second dose (D2) and third dose (D3), respectively, was divided by the total number of children in the 2012 birth cohort and being follow-up at five weeks of age. At six weeks of age the total number of children still in the population and vaccinated with D1, D2 and D3 respectively, was divided by the total number of children still being followed-up in the 2012 birth cohort aged six weeks old etc. Thus the numerator and the denominator could decrease over time as children left the database. To compare between different methods to estimate pertussis coverage, for the 2006 birth cohort in each database the PP_{FU} coverage estimates were compared with the cumulative incidence (CumInc) of pertussis vaccination. The cumulative incidence was estimated for each birth cohort as the number of all vaccinated children at a certain age in weeks divided by the number of eligible children, i.e. those at the start of the follow-up period.

The age at vaccination per birth cohort, dose and vaccine type were estimated and presented in Cleveland dot plots as 10%, 50% (median) and 90% quantiles [10].

To assess the validity of the coverage estimates obtained in this study, the estimates were compared with the national coverage estimates that have been published by the public health institutes in each of the four countries that the databases originated from.

We did not report wP for the THIN-database before 2000, because birthdates were rounded to 1st of July at extraction, leading to inaccurate age of vaccination.

3. Results

3.1. Study population

The seven databases that participated showed large variation in their overall number of eligible persons (0.0097–1.2 millions) and availability of data during the overall study period: this varied from 2 to 26 years (Tables 1 and 2). The total study population across all databases comprised 2.575 million children aged <6 years (Table 2).

3.2. Pertussis vaccination data

In the BIFAP, RCGP RSC, AUH and SSI databases the vaccine dose was not recorded reliably for all records and had to be derived. Only the UK databases could provide a large proportion of data on wP vaccination coverage.

Across all birth cohorts within a database and across databases within a country, the majority of children were vaccinated at the

Table 2
Attrition table of seven databases (AUH and SSI from Denmark, RCGP RSC and THIN from UK, BIFAP and SIDIAP from Spain and PEDIANET from Italy).

	Denmark		UK		Spain		Italy	Total
	AUH	SSI	THIN	RCGP RSC	BIFAP	SIDIAP	PEDIANET	
Number of persons (all ages)	1,725,165	7,512,032	13,646,770	3,017,610	7,541,864	7,096,695	9,708	40,549,844
Number of persons born during the birth years of interest (1990–2015)	499,318	1,822,953	1,616,311	860,411	1,467,618	1,774,085	9,708	8,050,404
Number of persons without follow-up (<1 day of follow-up)	0	31,434	59,933	0	23	92,932	0	184,322
Number of persons with start of follow-up after the age of 1 month	310,765	571,787	1,206,165	814,171	1,174,425	1,213,193	0	5,290,506
Number of persons eligible for analysis	188,553	1,219,732	350,213	46,240	293,170	467,960	9708	2,575,576

AUH: Aarhus University Hospital, Denmark; SSI, Statens Serum Institut, Denmark; RCGP RSC: Royal College of General Practitioners Research and Surveillance Centre, UK; THIN, The Health Improvement Network, UK; BIFAP: Database for Pharmacoepidemiological Research in Primary Care Spain; SIDIAP, Information System for Primary Care Research Spain; PEDIANET: Family Paediatrician Database Veneto vaccine registry Italy.

recommended age of vaccination (Fig. 1). However, the 90% quantile for age at vaccination was higher than the recommended age of vaccination in some cases, indicating that a certain percentage of individuals in the birth cohorts were vaccinated late.

3.3. Pertussis vaccination coverage for dose 3

The coverage estimates (PP_{FU}) by age for dose 3 (D3) are summarised by database, birth cohort and type of vaccine (aP, wP) in Fig. 2. The coverage started to increase in all databases at the age when the D3 was recommended in the country. For example, the aP D3 for children is recommended at 12 months old in Denmark and the D3 coverage estimates in AUH and SSI were close to zero until just before the children were 12 months old, then increased rapidly after they were 12 months old to above 80% at 15 months of age in all birth cohorts. In general, the observed age of the D3-vaccination was similar across birth cohorts from the same database. Following the steep increase in coverage estimates, little change was observed until the end of the follow-up period. The differences in coverage reached at the end of the follow-up at 72 months old were between 0% and 8% between birth cohorts within the same database, except for the RCGP RSC and THIN databases. In these databases the differences were 21% and 27%, respectively, with the largest difference observed at the end of follow-up at 72 months of age (Fig. 2). Spikes at the end of the follow-up were due to small sample sizes, especially in the younger birth cohorts. The switch from wP to aP occurred in 2004 in the UK, therefore, the 2004 birth cohort from RCGP RSC is the only one with a substan-

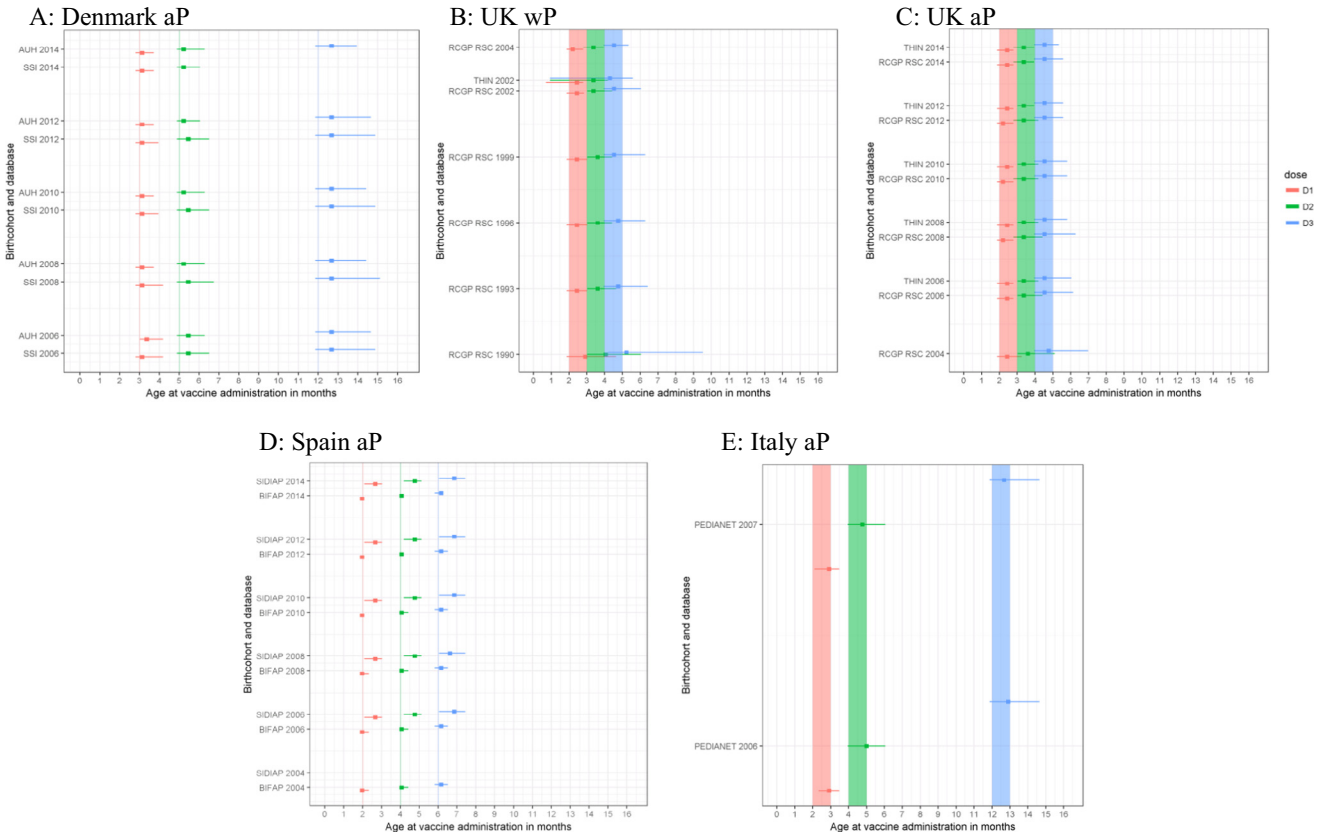

Fig. 1. Median age in weeks, at first (D1), second (D2) and third (D3) dose of whole cell (wP) or acellular (aP) pertussis vaccine and the 10% and 90% quantiles for age at vaccination for the entire birth cohort. A: aP vaccination from AUH and SSI in Denmark; B and C: wP and aP vaccination from RCGP RSC and THIN in the UK; D: aP vaccination from BIFAP and SIDIAP in Spain; E: aP vaccination from PEDIANET in Italy. The recommended ages of vaccination are indicated by the vertical lines and shaded areas. We show every second or third birth cohort only due to limited space. The SSI database provided data until September 2014, so that none of the children born in 2014 had reached the age of 12 month when the aP dose 3 is recommended in Denmark; thus this dose is missing for the 2014 birth cohort.

tially lower coverage for both aP and wP in 2004, compared with the other cohorts that included the switch from wP to aP. This was not observed in the THIN database since the vaccine type could not be determined during the switch in 2004.

3.4. Comparison of vaccination coverage estimation methods

We estimated coverage for the 2006 birth cohort in each database as a method, to compare the results with the estimation methods (PP_{FU} and CumInc). The CumInc estimates were consistently 1–10% lower at the end of follow-up in all databases, except for PEDIANET, where the two methods generated the same results (Fig. 3).

3.5. Comparison with national coverage rates

Comparison of national and estimated coverage rates was done for dose 3. Overall, the estimated coverage was 88–97% (birth cohorts from 2003 to 2014) in Denmark, 96–100% (2003–2014) in the UK, 95–98% (2004–2014) in Spain and 94% (2006–2007) in Italy (Table 3). The estimated coverage in the Danish SSI and AUH databases differed by 1–4% and 2–6%, respectively, compared with the national estimates. In the UK THIN and RCGP RSC databases, the estimated coverage differed by 2–5% and 1–6%, respectively, compared with the national estimates. In both Denmark and UK, our estimates were almost always higher. The estimated coverage in the Spanish BIFAP and SIDIAP databases differed both by 0–2% compared to the national estimates with no clear direction of the deviation. The coverage estimates from the Italian PEDIANET database were 3% lower than the national estimates.

4. Discussion

This study showed that it was possible to provide reliable estimates on pertussis vaccination coverage using data in the seven participating healthcare databases in four countries. The results showed that the ages when the pertussis doses were administered were comparable across up to 26 birth cohorts within the same database. We observed a steep increase in the period coverage prevalence estimates for dose 3 at almost the same age in all birth cohorts within each database. In addition, the observed age at vaccination was consistent with the recommended age for vaccination, as defined in the national guidelines, and the overall coverages obtained at the end of follow-up (72 months) were comparable to the national coverage estimates, which demonstrates the feasibility of obtaining accurate estimates for vaccination coverage using data from healthcare databases.

In addition to the information on the median age at vaccination, we also observed variability in age of vaccination, which confirms a delay in vaccination for a part of the population that has been reported in several countries [11–14]. The more recent birth cohorts had shorter follow-up time than the earlier birth cohorts, because of the retrospective nature of the study, which led to unequal truncation of follow-up time. For example: at the end of the study period the oldest child in 2014 birth cohort would be 730 days old (December 2015), and consequently, the median age for the third dose in this birth cohort would be expected to be lower than in the earlier birth cohorts because data for any children with late vaccination would be truncated in the later birth cohorts.

A review of the databases that were considered for the inclusion in this proof of concept study revealed differences in how data about the vaccine and the vaccine dose administered were recorded, and the level of information provided, in terms of the codes used and what free text was used [8]. Despite these differences, it was generally possible to identify the type of vaccine administered and the date of vaccination, derive the relevant doses and to obtain coverage estimates (overall, by birth cohort and age) close to the national estimates provided by public healthcare authorities. In the PRISM programme in the USA, DTP, DT and DTaP vaccination coverage was estimated to be 76% for the third dose, using data from three claims databases, compared with the estimated 91% vaccination coverage obtained through the National Immunization Survey, which is a bigger difference than what we observed [15]. However, previous studies have shown underreporting of childhood vaccination coverage when based on vaccination registers [16,17] and we cannot rule out that pertussis vaccine coverages was underreported in the databases included in this study and in the databases used for the national coverage estimation.

The high level of concordance between our coverage estimates and the national estimates was not expected because the inclusion criteria for this study (see Methods section) differed from those used for the national coverage estimation. We followed the birth cohorts up to 72 months (6th birthday) whereas most countries usually select an age closer to the recommended age of vaccination to be able to estimate vaccination coverage in relation to the national recommendations for vaccination (see references for national estimates in Table 3 for further details). In addition, if ecological data (i.e. total number of administered vaccines divided by the total number of children registered in the census) are used for national estimations like in Spain -, this could potentially result in larger deviations from the patient-level estimations used in our study.

The databases included in our study varied in size, geographical coverage and healthcare setting. The national registries have a more stable population with fewer individuals leaving or entering the database at different time points, compared with, for example GP databases, where the turnover of patients is expected to be higher, resulting in incomplete follow-up for a proportion of the population [8]. This could result in biased prevalence rates, if considered as complete follow-up, and thus compromise the coverage estimates [18]. In addition, we cannot rule out that a portion of the population has very little contact to the healthcare system and these children may not be registered in the databases and included in this study. In our study, we estimated vaccination coverage as a period prevalence, taking into consideration loss-to-follow-up. This approach can result in lower coverage estimates when vaccinated children leave the database faster than unvaccinated children and higher coverage estimates when unvaccinated children leave the database faster than vaccinated children. This could occur if vaccination schedules differ across regions in the same country, for example in a multi-regional database setting. However, this is less likely to be important across regions with homogeneous vaccination schedules.

Our results showed that vaccination coverage at the end of follow-up, estimated using PP_{FU} or CumInc were comparable (0–10% difference) for the 2006 birth cohorts (Fig. 3). This suggests that incomplete follow-up did not have a large impact on the coverage estimation in this study, possibly because incomplete follow-up was limited in this comparison. The inclusion of children who entered the database only within one month of birth limited the left-censoring, which may reduce bias in coverage estimates since the youngest children are also those who receive pertussis vaccine [19]. This inclusion criterion could increase bias in coverage estimation since children who have their first GP visit before one month of age might be those who are more likely to be vaccinated and, also, perhaps more likely to be vaccinated in compliance with the national guidelines [18]. Some of the participating databases round birth dates to the 1st or the 15th of the birth month which means that some children will only have two weeks to be enrolled

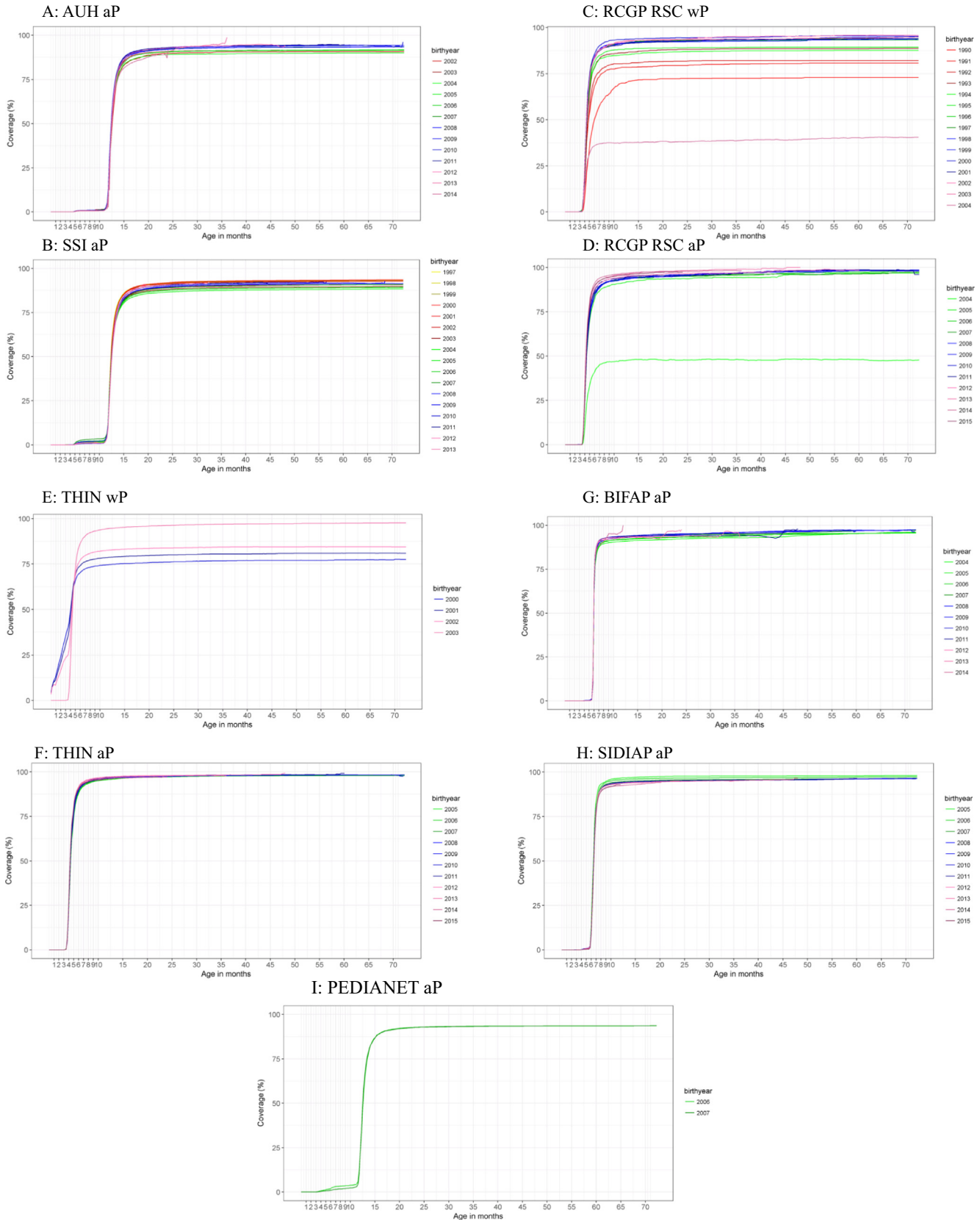

Fig. 2. Pertussis coverage by age for dose 3 estimated as period prevalence (PP_{FU}) by database, birth cohort and type of vaccine (wP or aP). A: AUH, Denmark, aP; B: SSI, Denmark, aP; C: RCGP RSC, UK, wP; D: RCGP RSC, UK, aP; E: THIN, UK, wP; F: THIN, UK, aP; G: BIFAP, Spain, aP; H: SIDIAP, Spain, aP; I:PEDIANET, Italy, aP.

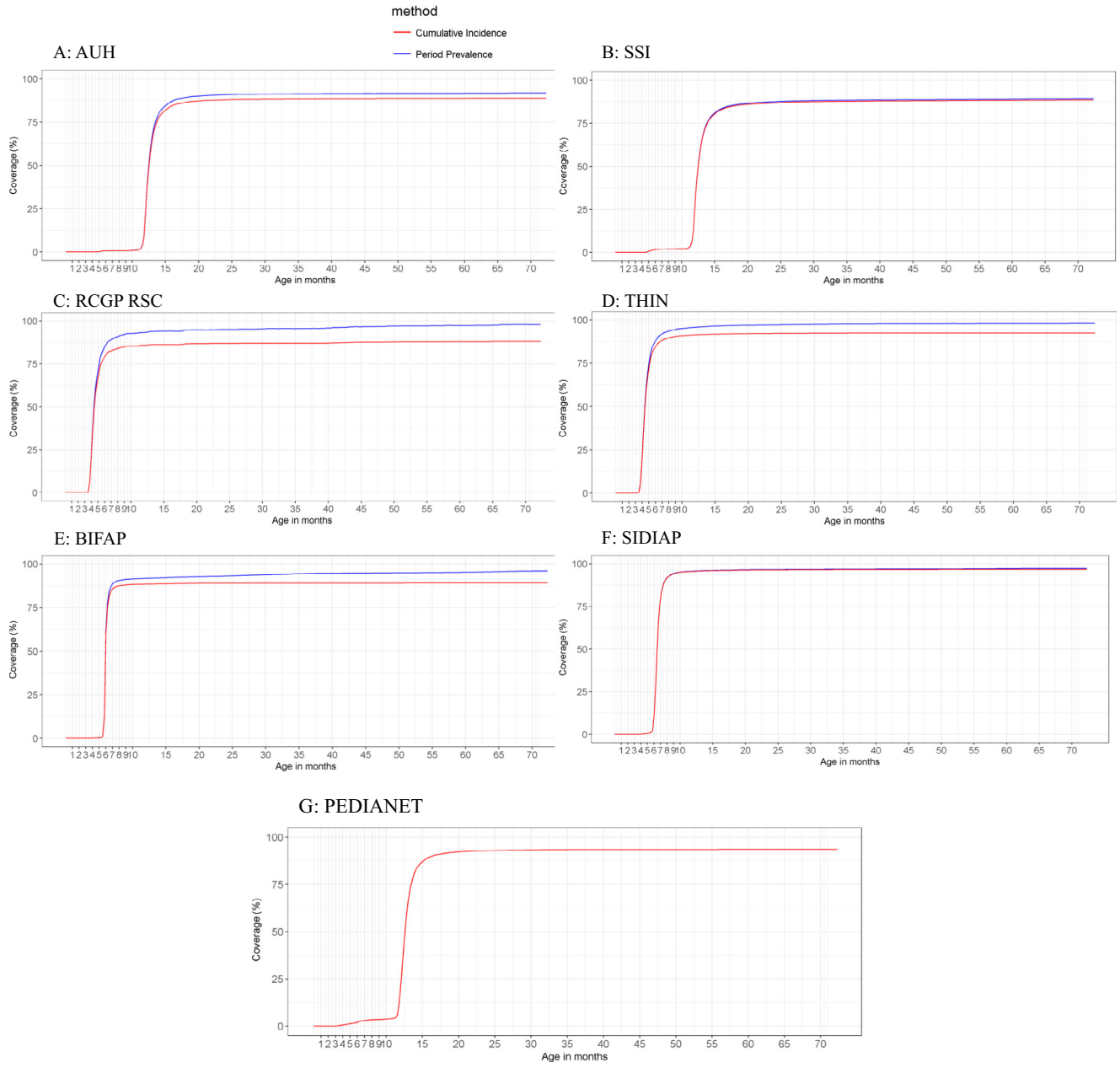

Fig. 3. Comparison of the monthly dose 3 pertussis vaccination coverage for 2006 birth cohorts using period prevalence (PP_{FU}) and cumulative incidence (CumInc) methods from birth up to 6th birthday. A: AUH and B: SSI from Denmark; C: RCGP RSC and D: THIN from the UK; E: BIFAP and F: SIDIAP from Spain; G: PEDIANET from Italy.

in the study population and others will have six weeks, which could potentially exclude a large number of children. This could also result in misclassification of age. If vaccination adherence and registration in the database after one month of age were dependent variables, the two coverage estimation methods would provide biased, overestimated or underestimated coverage estimates, depending on the direction of the dependency. The database used by SSI to estimate pertussis coverage is similar to the national vaccination register and consequently only the method differed between the SSI pertussis coverage estimates and the national estimates. The AUH, THIN and RCGP RSC databases comprise subsets of the data from which the national coverage estimates are derived. Thus these data are not entirely independent of the national estimates.

It was possible to estimate aP-containing vaccine coverage rates in all seven participating databases using the two estimation methods. However, it was only possible to estimate wP-containing vaccine coverage before and during the switch from wP to aP in two databases due to low numbers of registered wP vaccinations in the remaining five databases where the switch occurred prior to the study period.

In conclusion, we identified heterogeneity in the characteristics of the databases, which lead to challenges in defining inclusion criteria and taking incomplete follow-up into account, and thus for estimating pertussis vaccination coverage. We handled these elements in a homogenous manner across countries and were, therefore able to provide reliable pertussis coverage estimates.

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Table 3
Comparison of estimated database-specific dose 3 pertussis coverage (%) based on period prevalence (PP_{FU}) at the end of follow-up (after 72 months) with the national pertussis coverage estimates reported by a national authority.

Birth cohort	Denmark			UK			Spain			Italy	
	National*	AUH	SSI	National*	RCGP RSC	THIN	National*	BIFAP	SIDIAP	National*	PEDIANET
2003	88	92	90			98	98			97	
2004	87	92	89			98	97	96		97	
2005	86	90	88		97	98	96	96	98	96	
2006	87	92	89	93	98	98	98	96	97	97	94
2007	88	93	91	93	97	98	96	97	96	97	94
2008	89	94	91	93	99	98	97	97	96	97	
2009	89	94	92	95	98	98	96	96	96	96	
2010	90	94	92	94	98	98	97	97	96	96	
2011	89	95	92	95	96	99	97	98	96	96	
2012	91	94	92	95	98	99	96	95	96	96	
2013	91	97	90	94	100	98	96	97	95	96	
2014	91	89		95	98	97	97	97	95	95	

Denmark: https://www.ssi.dk/Smitteberedskab/Sygdomsovervaagning/VaccinationSurveillance.aspx?xaxis=Cohort&vaccination=3&sex=3&landsdel=100&show=&datatype=Vaccination&extendedfilters=False#HeaderText.
UK: https://www.gov.uk/government/publications/cover-of-vaccination-evaluated-rapidly-cover-programme-annual-data.
Spain: http://www.msssi.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/docs/TosFerina.pdf.
Italy: http://www.epicentro.iss.it/temi/vaccinazioni/dati_Ita.asp#pertosse.
AUH: Aarhus University Hospital Denmark; SSI, Statens Serum Institut Denmark; RCGP RSC: Royal College of General Practitioners Research and Surveillance Centre UK; THIN, The Health Improvement Network UK; BIFAP: Database for Pharmacoepidemiological Research in Primary Care Spain; SIDIAP, Information System for Primary Care Research Spain; PEDIANET: Family Paediatrician Database Veneto vaccine registry Italy.

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Declaration of Competing Interest

Hanne-Dorthe Emborg, Toon Braeye, Jorgen Bauwens, Kaatje Bollaerts, Giorgia Danieli, Talita Duarte-Salles, Consuelo Huerta Elisa Martin, Chris McGee, Ana Correa and Lara Tramontan declared no conflicts of interest. Johnny Kahlert declared that although he does not personally receive fees, honoraria, or grants he is employed at Department of Clinical Epidemiology, Aarhus University Hospital that receives research grants from various pharmaceutical companies administered by Aarhus University. Steffen Glismann is employed by the GSK group of companies and holds company shares. Simon de Lusignan declared he has received funding through his University to conduct enhanced surveillance of influenza vaccine (GSK), and is a member of Seqirus and Sanofi Pasteur advisory boards for which he received personal payment within the limits defined by his university. Daniel Weibel declared that he has received consultancy fees from GSK unrelated to the submitted work. 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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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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