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ADVANCE: Towards near real-time monitoring of vaccination coverage, benefits and risks using European electronic health record databases

Kaatje Bollaerts [a,*], Tom de Smedt [a], Chris McGee [b,c], Hanne-Dorthe Emborg [d], Marco Villa [e], Maria Alexandridou [a], Talita Duarte-Salles [f], Rosa Gini [g], Claudia Bartolini [g], Simon de Lusignan [b,c], Myint Tin Tin Htar [h], Lina Titievsky [i], Miriam Sturkenboom [a,j,k], Vincent Bauchau [l]

[a] P95 Epidemiology and Pharmacovigilance, Koning Leopold III laan 1, 3001 Heverlee, Belgium
[b] Royal College of General Practitioners Research and Surveillance Centre, London, UK
[c] Department of Clinical and Experimental Medicine, University of Surrey, Guildford, UK
[d] Statens Serum Institut, Artillerivej 5, 2300 Copenhagen, Denmark
[e] ATS della Val Padana, Cremona, Italy
[f] Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona, Spain
[g] Agenzia regionale di sanità della Toscana, Osservatorio di epidemiologia, Florence, Italy
[h] Pfizer, 23-25 Avenue du Dr Lannelongue, 75014 Paris, France
[i] Pfizer, 219 East 42nd St, NY, NY 10017, USA
[j] Julius Global Health, University Medical Center Utrecht, Heidelberglaan 100, the Netherlands
[k] VACCINE.GRID Foundation, Basel, Switzerland
[l] GSK, Av. Fleming 20, 1300 Wavre, Belgium

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ABSTRACT

Background: The Accelerated Development of VAccine beNefit-risk Collaboration in Europe (ADVANCE) is a public-private partnership aiming to develop and test a system for rapid benefit-risk (B/R) monitoring of vaccines using European electronic health record (eHR) databases. This proof-of-concept study aimed to test the feasibility of near real-time (NRT) monitoring of vaccination coverage, benefits and risks based on multiple European eHR databases, using acellular pertussis vaccination in children aged <6 years as test case.

Methods: A qualitative feasibility assessment on NRT monitoring was carried out using a survey and face-to-face discussion with ADVANCE data partners. Subsequently, a dynamic cohort study was conducted containing two distinct observation periods: a first period to establish a baseline (Jan 2014 to Mar 2018) and a subsequent 3-month period to test the actual feasibility of weekly NRT monitoring, based on which data latencies were calculated. An interactive web-application was additionally developed to facilitate the visual monitoring of vaccination coverage, the vaccine preventable disease incidence rates (benefits) and the incidence rates of adverse events (risks).

Results: Nine databases from four countries (Denmark, Italy, Spain and UK) participated in the qualitative feasibility assessment. Of them, five databases took part in the dynamic cohort study, with 5 databases providing baseline data and 3 databases participating to the NRT monitoring, providing data extractions on an almost weekly basis. The median data latency (time between event date and data release date) was between 1 and 2 weeks except for the benefit and risk events in one of the databases (latency 16 weeks).

Conclusion: Three European eHR databases successfully demonstrated the feasibility of providing data for weekly NRT monitoring, with short data latencies of 1–2 weeks for most events.

1. Introduction

Post-marketing near real-time (NRT) monitoring is used to detect vaccine safety alerts (i.e. deviations from the anticipated rate of selected adverse events) as not all adverse events are detected or confirmed during pre-licensure clinical trials, particularly rare or delayed-onset events or those they affect specific

* Corresponding author at: Vlierbeeklaan 18, 3010 Kessel-lo, Belgium.
E-mail addresses: kaatje.bollaerts@p-95.com (K. Bollaerts), tom.desmedt@p-95.com (T. de Smedt), c.mcgee@surrey.ac.uk (C. McGee), HDE@ssi.dk (H.-D. Emborg), marco.villa@ats-valpadana.it (M. Villa), maria.alexandridou@p-95.com (M. Alexandridou), tduarte@idiapjgol.org (T. Duarte-Salles), rosa.gini@ars.toscana.it (R. Gini), claudia.bartolini@ars.toscana.it (C. Bartolini), s.lusignan@surrey.ac.uk (S. de Lusignan), myint.tintinhtar@pfizer.com (M. Tin Tin Htar), lina.titievsky@pfizer.com (L. Titievsky), miriam.sturkenboom@p-95.com, m.c.j.sturkenboom@umcutrecht.nl (M. Sturkenboom), vincent.g.bauchau@gsk.com (V. Bauchau).

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subpopulations not enrolled in the trials [1]. Such NRT monitoring is usually implemented shortly after a new vaccine is released, when vaccine brands are switched or the target population is expanded. Apart from monitoring safety, the post-marketing surveillance of vaccination coverage and of the benefits of vaccination are often undertaken to provide data on the vaccine uptake and to assess if the impact on the vaccine preventable disease meets the expectations.

Electronic health record (eHR) databases are increasingly used for vaccine monitoring as they enable real-world effects, including rare events, to be studied in a larger, more widely geographical dispersed population without the need to initiate prospective data collection. The Vaccine Safety Datalink (VSD), a collaborative project between the US Center for Disease Control and Prevention (CDC) and eight healthcare organisations, is a pioneering example of large-scale vaccine monitoring, focused primarily on safety [2]. In Europe, most of the vaccine coverage, benefit and risk monitoring is done nationally [3]. The European NRT vaccine safety monitoring initiatives are based on a single national database or involve enhanced surveillance through the collection of additional data from patients [4–6].

The Innovative Medicines Initiative (IMI) funded the Accelerated Development of VAccine beNefit-risk Collaboration in Europe (ADVANCE) project to improve post-marketing vaccine monitoring in Europe. ADVANCE is a public-private partnership that aimed to develop and test a system for rapid benefit-risk (B/R) assessment and NRT B/R monitoring of vaccines in the post-market setting using a distributed network of European eHR databases [7].

A first set of proof-of-concept (POC) studies was conducted in 2016 to test the system and workflows for generating evidence based on eHR databases to inform the B/R assessment of vaccines in Europe [8–11]. The workflow for evidence generation and the characterisation of the European eHR databases are described elsewhere [3,7–11,14]. ADVANCE also piloted the use of an interactive dashboard for vaccine B/R monitoring based on simulated data mimicking the introduction of rotavirus vaccination in the UK [12,13]. Although the potential of such a dashboard was recognized by various potential end-users, the main concern was the availability of appropriate European data for monitoring, requiring frequent data updates and short latency between the occurrence of the events and their release date [12].

We here report on a study assessing the feasibility of NRT B/R monitoring in Europe using eHR databases. The objectives were: (1) to explore the capacity of European eHR databases to perform NRT monitoring and (2) to demonstrate the practical potential of B/R monitoring using an interactive dashboard populated with real-world evidence. The current study builds further upon the previous POC studies, assessing the feasibility of generating evidence from European eHR databases regarding vaccination coverage [8], the vaccine preventable disease or the benefits [9], and vaccine safety [10]. All three studies used pertussis vaccination in children (<6 years) as test case.

2. Materials and methods

2.1. Participating databases

To this study participated the nine ADVANCE eHR databases that successfully participated in the fit-for-purpose assessment related to the POC studies on pertussis vaccination in children [14]. A description of these databases is given in Table 1.

2.2. Qualitative feasibility assessment

The feasibility of conducting NRT monitoring of vaccination coverage, benefits and risks was first assessed using a paper-based survey. The survey, which was sent to the ADVANCE contact persons of the nine participating eHR databases, contained questions on the expected time required for the different data processing steps between the actual date of an event and releasing the data for statistical analysis (or monitoring). The following steps were distinguished: event date (i.e. date of assumed diagnosis for events recorded at primary care, date at hospital admission for events recorded at the hospital or vaccination date), system date (i.e. date on which the information is electronically recorded in the source database using the medical software), data collection date (i.e. data lock point or the cut-off point for data to be extracted and entered in the database for analysis or monitoring), internal and external release dates (i.e. date on which the data are ready for analysis internally by the data access providers and the date on which the data are shared with external parties) (Fig. 1). In addition, questions were asked about data delays and if there were

Table 1
Database description.

Country – database		Geographical coverage	Description
Denmark			
AUH	Aarhus Universitets Hospital	Regional	Population-based hospital discharge database linked to vaccination registries
SSI	Statens Serum Institut	National	Population-based hospital discharge database linked to vaccination registries
Italy			
ARS	Agenzia Regionale di Sanità, Tuscany region	Regional	Administrative databases
ATSVP	Agenzia di Tutela della Salute Val Padana (subarea Lombardy region)	Regional	Administrative databases
PEDIANET		Regional	Primary care medical record paediatric database linked to the Veneto vaccine registry
UK			
THIN	The Health Improvement Network	National	Primary care medical record databases with access provided through Erasmus University Medical Centre
RCGP RSC	Royal College of General Practitioners Research and Surveillance Centre	National	Primary care medical record databases with access provided through University of Surrey
Spain			
BIFAP	Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria	Multi-regional	Primary care medical record database
SIDIAP	Information System for Research in Primary Care	Regional	Primary care and hospital medical record database

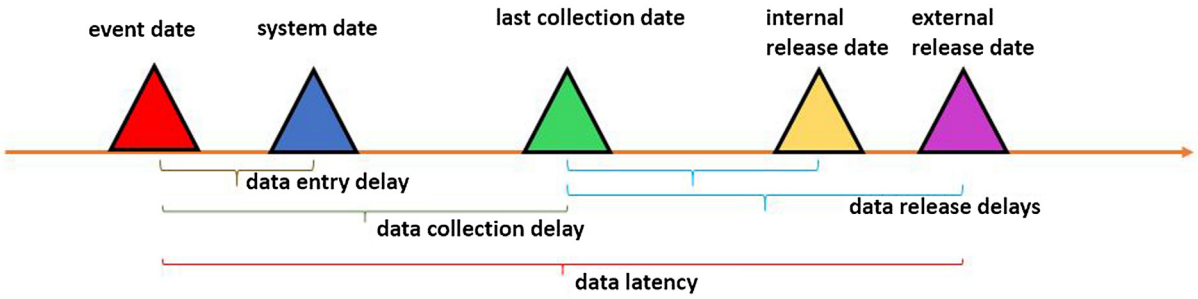

Fig. 1. Schematic representation of the chronological steps from event (exposure or outcome) to data release for statistical analysis (or monitoring).

any main barriers to implementing NRT monitoring. The following data delays were distinguished; data entry delay (i.e. difference in time between the event date and system date), data collection delay (i.e. difference in time between the event date and data collection date), data release delay (i.e. difference in time between last collection date and release date(s)) and the total data latency (i.e. difference in time between the event date and the release date (s)) (Fig. 1). The survey responses were discussed during a face-to-face meeting among the participating ADVANCE data partners.

2.3. Proof-of-concept study assessing NRT monitoring

Based on results of the qualitative feasibility assessment, databases were invited to participate in this POC study on NRT monitoring of coverage, benefits and risks using acellular (aP) vaccination as the test case. The study protocol was registered on the EU PAS Register (EUPAS26809) [15].

2.3.1. Study design and periods analysed

This study was a retrospective multi-database dynamic cohort study, with the observation period divided over two periods. The first period, that established the baseline, was from 1 January 2014 until March 2018. The second period, during which the feasibility of weekly NRT monitoring was tested, started immediately after the first period in March 2018 and lasted about three months, with the exact start and end dates being different for the different databases (Table S1). Databases were eligible for participation to the dynamic cohort study when they could provide data on exposure and events for the population of interest during the study period. Databases that can provide frequent data updates were eligible to also participate to the NRT monitoring.

2.3.2. Study population

The source population consisted of children in the participating databases from the start of the study period (1 January 2014) or first entry in the database (whichever occurred latest) until administration of the pre-school-entry booster, their sixth birthday, death, transfer out of the database or last data collection date (whichever occurred first). As this study is on NRT monitoring, exclusion criteria were kept to the minimum with only children with missing information on month and year of birth and date of start of follow-up being excluded.

2.3.3. Vaccination and health outcome events

The exposure of interest was vaccination with any acellular pertussis containing vaccine (either as a single component or part of a multivalent vaccine product) by dose (dose 1, dose 2 or dose 3). Risk outcomes were selected among events reported to be related to pertussis vaccination in trials or studies [10]. The risk outcomes of interest were febrile convulsions/seizures, fever, hypotonic hypo-responsive episodes (HHE), somnolence and persistent crying. The benefit outcome of interest (i.e. the vaccine preventable disease) was confirmed or probable pertussis.

For the risk outcomes, we identified medically attended events that occurred within post-vaccination pre-defined risk windows (febrile convulsions/seizures and fever: 0–3 days; HHE and somnolence: 0 to 2 days and persistent crying: 0–1 day post-vaccination) or that occurred within the baseline window of 10–15 days post-vaccination. The case definitions, risk windows and code lists were from the previous POC studies on vaccination coverage, benefits and risks [8–10].

2.3.4. Local data processing and sharing of aggregated data

All ADVANCE data partners worked in a distributed manner, following a common protocol, common data model (CDM) and common data transformation scripts [7]. In summary, individual-level data were extracted and transformed locally into three study-specific CDM files: the first file contained anonymised information on the children, the second file contained information on the vaccinations and the third file contained information on the benefit and risk outcomes of interest. These CDM files were then transformed locally into aggregated data outputs using common analytical scripts.

The aggregated data outputs contained information on the number of administered vaccine doses by calendar time (in weeks) and age (in weeks); the total number of vaccinated children and the number vaccinated within year-month birth cohorts by age (in weeks); the number of pertussis events by calendar time (in weeks) and the number of risk outcomes within the risk windows and within the baseline windows by calendar time (in weeks) as well as the corresponding person-time information. These were transferred from the local databases to a central server for further statistical analyses to generate input for the interactive dashboard. During the 3-month NRT monitoring period, the process of data collection and transformation into the CDM files was repeated on a weekly basis. Each time, data were collected from the start of the study (1st January 2014) until the data collection date.

2.3.5. Interactive dashboard

Data from the whole study period (i.e. baseline and NRT periods) were used for the interactive dashboard, which was developed to facilitate the visual monitoring of vaccination coverage, benefits and risks. The dashboard, which contained more than 20 interactive graphs, is freely accessible, after registration, from https://advance.p-95.com/brpertussis/ or from https://vac4eu.org/benefits-and-risk/.

To create input for the interactive dashboard, the total number of administered doses n_{ij} (dose1, dose2 and dose3) during week i in age group j was calculated for each database. In addition, the coverage at week i for birth-month cohort k was calculated by dividing the number of vaccinated children n_{ik} by the total number of children still in follow-up at week i, for children with follow-up that

started before the age of six weeks. The benefits were monitored by calculating the weekly pertussis incidence rates (per 100,000 person-years), with their corresponding exact Poisson 95% confidence intervals (CIs). To monitor safety, incidence rates (per 1000 person-years), with their corresponding exact Poisson 95% CIs, within the pre-defined outcome-specific risk windows and within the baseline risk windows were calculated cumulatively over time, combining all data from the start of the study period until week *i*.

2.3.6. Data latency

Data collected during the 3-month period of NRT monitoring were used to calculate data collection delays. This was done by comparing data in consecutive data extracts, excluding consecutive data extracts >1 week apart. For each data extract *i*, we kept only the data for newly added events (i.e. events present in data extract *i*, but that were not present in the previous data extract *i*-1). For each newly added event, the data collection delay was calculated as the difference between the event date and the date when the event appeared the first time. In addition, we assessed the time required from data collection to locally transforming the CDM files into aggregated data outputs for transfer to the central server.

2.3.7. Software

Different software was used (e.g. SQL server, DB visualizer, SQL management server, MSAccess, SAS) by the different data access providers to extract the data and transform them to the CDM files locally. R3.4.0 was then used for all subsequent data transformation steps. The dashboard was developed using Shiny R 3.4.4 [16].

2.3.8. Ethics

This study was a continuation of the earlier ADVANCE POC studies on vaccination coverage, benefits and risks [8–10]. The current study was performed in accordance with the ADVANCE Code of Conduct for the vaccination and risks events and with the ENCePP Code of Conduct for the benefit events [17,18].

3. Results

3.1. Qualitative feasibility assessment

Nine databases (AUH, SSI, ARS, ATSVP, PEDIANET, BIFAP, SIDIAP, THIN and RCGP RSC) participated in the qualitative feasibility assessment. Five of these databases (SSI, ARS, ATSVP, SIDIAP, and

Table 2
Main results from the database survey to assess the feasibility of NRT monitoring.

Country - database	Estimated time required between:			Is NRT monitoring feasible?	What is needed to implement NRT monitoring or further reduce data latencies?
	System date and data collection date	Data collection date and internal release date	Data collection date and external release date		
Denmark					
AUH	Up to 3 months	1 day	N.A.	Yes, but with delays	Registries are presently updated monthly. More frequent updates would reduce data latencies
SSI	<2 days	1 day	N.A.	Yes, but with delays.	Monitoring is resource intensive. Additional programs and procedures should be developed
Italy					
ARS	2 to 4 weeks	1 to 3 months	N.A.	Yes, but with delays. All data (with exception of exposure events) are received on a monthly basis, with an average of 45 days delay. Vaccination data incomplete before 2018, because vaccinations administered in primary care pediatrician practices that were not included in the available data	To decrease delays, an agreement with the regional healthcare system is needed to allow weekly updates to be received
ATSVP	4 weeks	<1 week	N.A.	Yes, pending feasibility	Political endorsement and dedicated personnel
PEDIANET	1 day	1 week	N.A.	Yes, but only for selected health outcomes. Vaccination data is not yet available	Time consuming activity, for which approval is needed
UK					
THIN Access provided through Erasmus University Medical Centre	Not provided	Not provided	greater than 6 months	No, not under the current licensing agreement with the Erasmus University Medical Centre	Change the licensing agreement to allow for weekly updates.
RCGP RSC Access provided through University of Surrey	<1 week	3 days	1 week	Yes	Weekly monitoring is possible, Delays in data recording where vaccination takes place outside general practice. Access to GPs may limit immediacy of reporting.
Spain					
BIFAP	Annual updating of information from Jan 1st to Dec 31st	1 to 3 months	1 to 3 months	No, not under the current agreements and governance model of the database	More frequent update would be necessary for NRT monitoring, However it is not possible under the current agreements and governance model of the database.
SIDIAP	2–14 months (annual updating of information from Jan 1st to Dec 31st)	2–3 months	N.A.	No, not under the current agreement with the Catalan Institute of Health	The Catalan Institute of Health receives data continuously. Need closer collaborate to get NRT data. Resources are also needed to set up system.

N.A. not applicable as data are not available for analysis by third party.

RCGP RSC) decided to also participate to the dynamic cohort study. AUH, the regional Danish database, did not participate as the procedure for data access authorisation had changed before the start of the study, making it unlikely to obtain approval on time. PEDIANET could not provide data for the study period as they have vaccination data only for the 2006 and 2007 birth cohorts. BIFAP decided to not participate as the database is updated annually. Finally, the initial access provider for THIN within the ADVANCE consortium (Erasmus Medical University Centre) no longer had the necessary license for THIN at the time of study (Table 2).

3.2. Proof-of-concept study for NRT monitoring

The five participating databases varied in size, with SSI providing data for 374,161 children (0–6 years) at the start of the observation period, RCGP RSC for 6362 children, ATSVP for 2492 children, ARS for 84,076 children and SIDIAP for 28,089 children. All databases provided baseline data for the vaccination, risk and benefit events, except ARS that did not provide data for the benefit events as they can only participate in studies compliant with the ENCePP Code of Conduct prohibiting partners from industry to be the principal investigator, which was the case for the benefit events [18]. Four databases decided to participate in the NRT monitoring. SIDIAP could not participate as the database is updated only annually. ARS could eventually also not participate as the anticipated improvement in their access to vaccination registry data was delayed beyond the period of this study. The three databases that could successfully participate in the NRT monitoring, provided 11 (SSI), 7 (ATSVP) and 11 (RCGP RSC) data extractions during the 3-month NRT monitoring period. All three databases were able to provide data extractions on a weekly basis (See Table S1 for data extraction dates).

3.2.1. Interactive dashboard

As the interactive graphs in the dashboard were developed for system testing only, they should not be used to inform clinical or regulatory decision making. As an example we provide graphical representations of the weekly incidence rate of fever (per 1000 person-years) estimated cumulatively over time, within the risk window of 0–3 days post-vaccination after dose 1 and within the baseline window (Fig. 2). No differences in the fever incidence rate in the dose 1 risk window and in the baseline incidence rates were observed, except for the RCGP RSC database.

3.2.2. Data latency

The majority of data collection delays for any vaccination dose were short for all three databases. The data for dose 1 are shown in Fig. 3 and Table 3; dose 2 and 3 are similar. The median

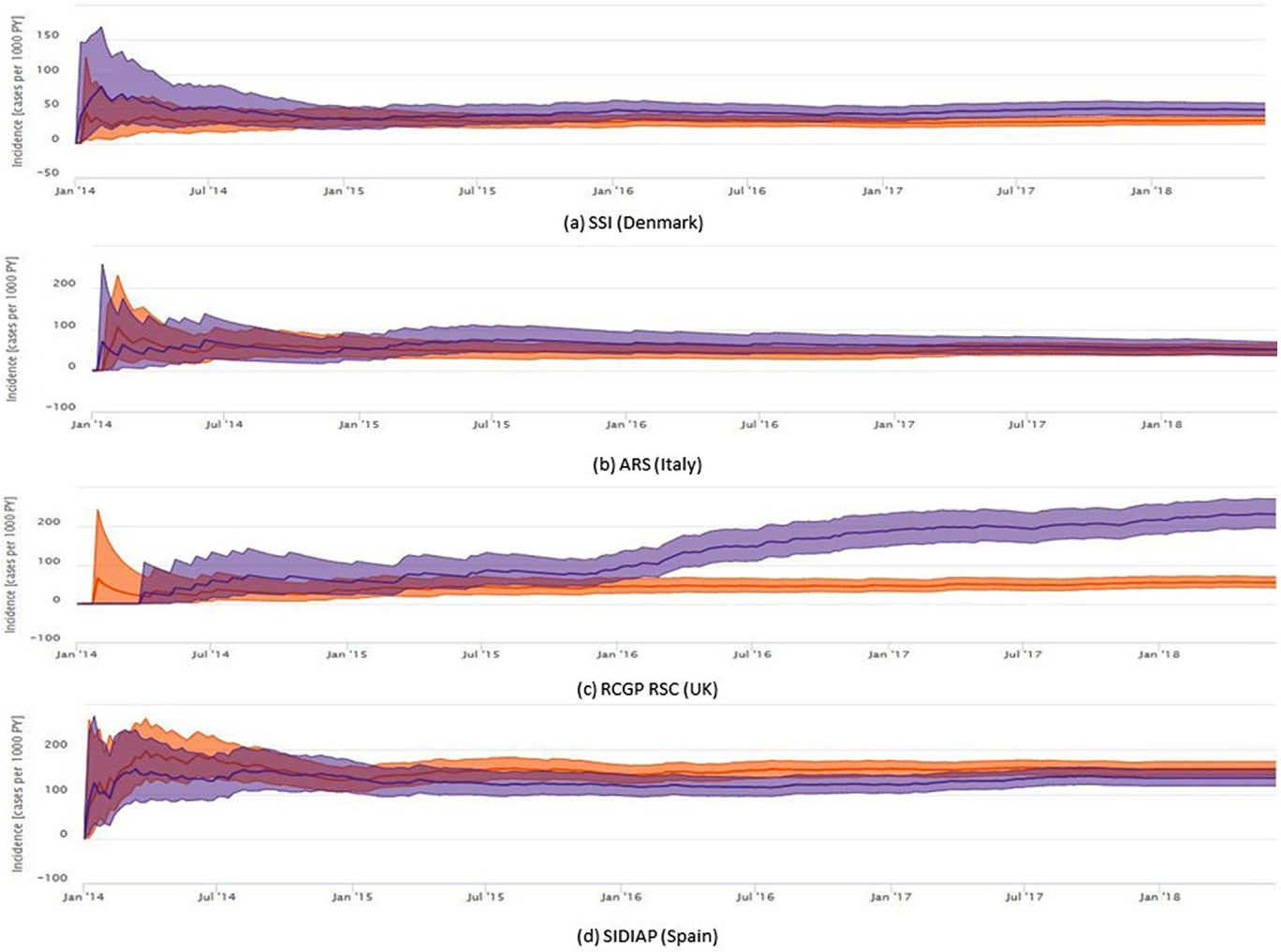

Fig. 2. An example of the dashboard interactive graphs for safety: incidence rate per 1000 person/years (95% confidence) within the risk window of 0 to –3 days post-dose 1 (purple) and within the baseline window (orange). Data from ATSVP are not shown as fever only few events were reported within the risk and baseline windows.

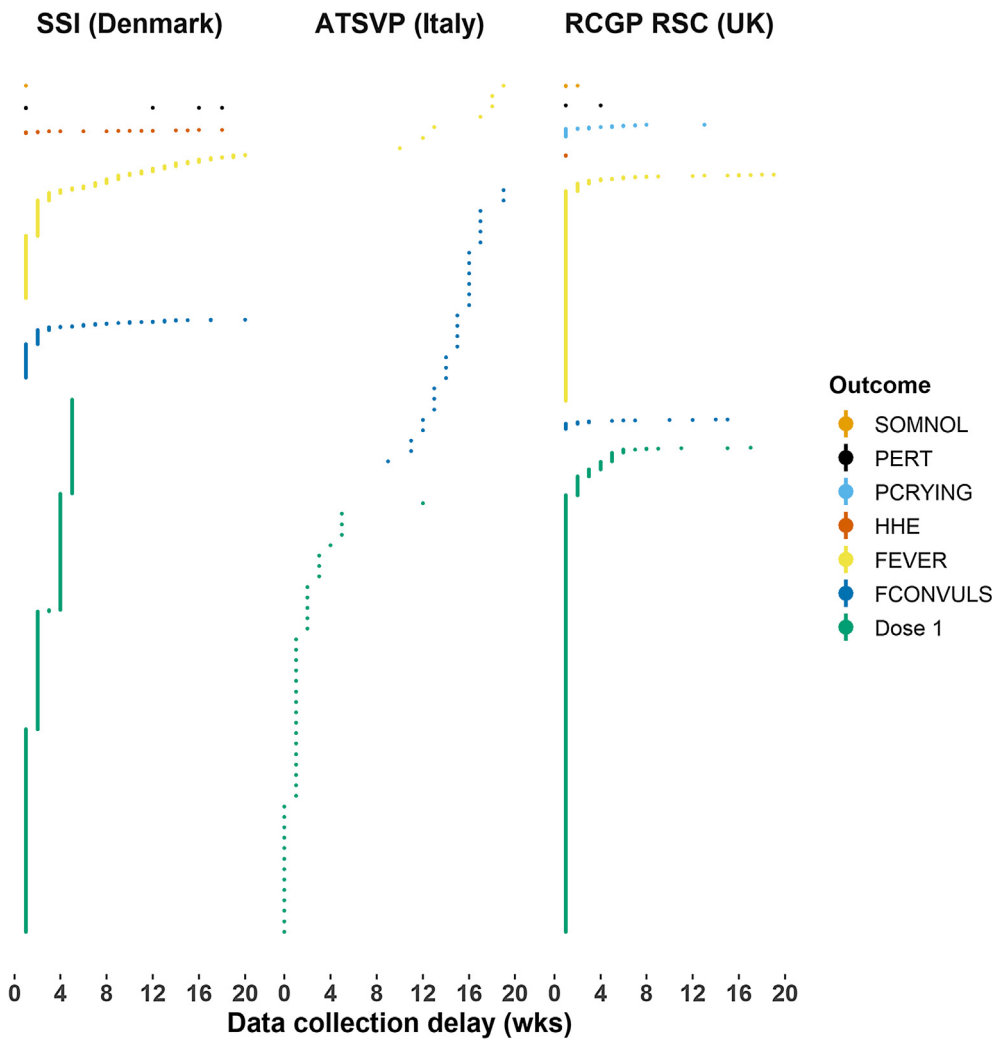

Fig. 3. Data collection delays (in weeks) ≤20 weeks, by event type and database (dose 2 and dose 3 data not shown). SOMNOL: somnolence; PERT: pertussis; FCONVULS: febrile convulsions; PCRYING: persistent crying; HHE: hypo-tonic hypo-responsive episodes.

Table 3
Percentage of data available for extraction at ≤4 weeks, ≤8 weeks and ≤20 weeks for safety, efficacy and vaccination doses in the three databases that provided data.

	SSI (Denmark)						ATSVP (Italy)						RCGP RSC (UK)					
	N	Min	Med	≤4 k (%)	≤8 wk (%)	≤20 wk (%)	N	Min	Med	≤4 wk (%)	≤8 wk (%)	≤20 wk (%)	N	Min	Med	≤4 wk (%)	≤8 wk (%)	≤20 wk (%)
All outcomes	2159	1	2	68.5	74.5	87.0							1362	1	1	94.0	96.4	97.5
Somnolence	2	1	1	100	100	100							6	1	1	83.3	83.3	83.3
Pertussis	7	1	12	42.9	42.9	85.7							3	1	1	100	100	100
Persistent crying													65	1	1	78.5	96.9	98.5
HHE	29	1	3	55.2	62.1	96.6	7	10	17	0	0	100	3	1	1	66.7	66.7	66.7
Fever	1577	1	2	62.7	68.9	83.1	27	9	15	0	0	100	1231	1	1	95.6	96.9	97.7
Febrile convulsions	544	1	1	86.0	91.7	97.6	34	9	15	0	0	100	54	1	1	77.8	87.0	94.4
All doses	12,396	1	2	79.3	98.5	98.5	266	0	1	82.3	83.5	85.0	7434	1	1	97.2	98.9	99.3
aPE dose 1	4924	1	2	81.5	99.1	99.1	60	0	2	63.3	68.3	70.0	2584	1	1	96.8	99.5	99.7
aPE dose 2	3649	1	4	76.0	97.8	97.8	111	0	1	82.9	82.9	85.6	2409	1	1	97.3	98.9	99.4
aPE dose 3	3823	1	1	79.6	98.4	98.4	95	0	1	93.7	93.7	93.7	2441	1	1	97.7	98.2	98.9

N: number of events; Min: minimum; Med: medium; HHE: hypo-tonic hypo-responsive episodes; aPE: acellular pertussis vaccine.

collection delays for vaccination events (all doses) were 2 (SSI), 2 (ATSVP) and 1 (RCGP RSC) weeks (Table 3). For the outcomes, the collection delays varied more, with median delays of 2 (SSI), 16 (ATSVP) and 1 (RCGP RSC) weeks (Fig. 3 and Table 3). For SSI and RCGP RSC, over 70% of the vaccination, risk and benefit events were collected within 4 weeks.

The time required for internal pre-processing and quality checks, mapping to the CDM files, transforming to aggregated data outputs and transferring to the central server was short, with on average of 1 to 2 days for SSI, 1 day for ATSVP and 3 days for RCGP RSC. In this POC study, uploading of the aggregated data outputs to the dashboard was not automated and took approximately 1 h.

4. Discussion

The results from this study demonstrated the practical feasibility of NRT monitoring of vaccination coverage, benefits and risks for some European eHR databases. This study focussed on the timeliness (i.e. data latencies) of the data capture while the previous POC studies focussed on the completeness of the medical information captured [8–10]. Five ADVANCE databases (SSI from Denmark, ARS and ATSVP from Italy, SIDIAP from Spain and RCGP RSC from the UK) participated in the dynamic cohort study. Three databases (SSI, ATSVP and RCGP RSC) also participated to the NRT monitoring, providing data extractions on a weekly basis over three months. The vaccination events showed a median delay of 1–2 weeks, whereas the delays for the benefit and risk outcomes were more varied across the databases, with those for, ATSVP (Italy) being longer compared with the other two databases. For all databases and all event types, the majority of data collection delays were $\leq$8 weeks. These data collection delays are good approximations of the total data latencies (i.e. time between event date and release date) as the data release delays (i.e. time between data collection and data release date) were a few days, at the most.

The data collection delays were calculated using a small number of events collected during a short three-month NRT monitoring period. The NRT monitoring period was deliberately kept short as providing weekly data extractions is resource-intensive. The reported data collection delays are, therefore, only indicative, and do not represent the actual distribution of delays. These delays varied between databases and types of event. The delays for the vaccination events may also vary within databases/countries depending on the type of vaccination. Particularly, school-based or travellers vaccinations are likely to be recorded with a longer delay, depending on the national organisation for vaccine administration.

Although this was a limited POC study, a change in the incidence of fever was observed in the UK. The dashboard showed an increase in the fever incidence from March 2016 onwards. This increase was only observed after dose 1 and dose 3 but not after dose 2 (Fig. 2). These observations suggest that the changes in fever incidence are probably related to the co-administration of Meningitis B, which was introduced in the UK routine childhood vaccination program on the 1st September 2015 [19,20].

The theoretical feasibility of using European eHR databases for NRT monitoring has been studied before. One study assessed recording delays (i.e. difference in time between the assumed date of diagnosis and the system date) for events of interest for vaccine safety monitoring in the Clinical Practice Research Datalink (CPRD) [4]. The CPRD is a UK primary care database currently containing data for over 5 million active patients [21]. The results from this study showed that over 70% of the events of interest had recording delays $\leq$30 days, which is comparable with the delays we observed for SSI and RCGP RSC. The same authors assessed the statistical power and time to signal using continuous sequential tests and concluded that using only CPRD data provided limited power to detect small to moderate increases in risk in a timely fashion and that larger sample sizes were required [5].

The three databases that participated in NRT monitoring during this POC study (SSI, ATSVP and RCGP RSC) currently have data for more than 11.3 million active individuals. The main reasons for non-participation were administrative (licensing and initial data-sharing agreements) and we could expect to have more participating databases, and therefore, more patient data in the future. For example, if ARS and SIDIAP had participated there would have been data for more than 22 million active individuals. If data for this number of individuals were available the performance of the NRT monitoring systems would be greatly improved, provided that any heterogeneity between databases can be accounted for.

To conclude, we demonstrated the practical feasibility of NRT monitoring using some European eHR databases. As such, we hope to have paved the way for other databases to take away the barriers to NRT monitoring. Continued capacity building and adequate resources are required to continue to develop and enhance a sustainable vaccine monitoring system in Europe with a wide geographical coverage and a sufficiently large sample size to monitor rare events also. To try to achieve this, the VAC4EU (Vaccine monitoring Collaboration for Europe) project was launched in March 2019 (https://vac4euorgdev.wpengine.com/).

5. 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 herein relate solely to the testing of these methodologies 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

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Tom de Smedt, Chris McGee, Hanne-Dorthe Emborg, Marco Villa, Talita Duarte-Salles, declared no potential conflicts of interest. Kaatje Bollaerts and Maria Alexandridou received consultancy fees from GSK for work unrelated to the submitted work. Rosa Gini declared that her institution is participating in studies funded by Novartis, Eli Lilly, and Daiichi outside the scope of this project. Claudia Bartolini declared she has received grants from PHARMO Institute for work outside the submitted work. 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. Myint TinTin Htar declared that she is employed by Pfizer and holds company shares. Miriam Sturkenboom declared that she has received grants from Novartis, CDC and Bill & Melinda Gates Foundation, for work unrelated to the submitted work. Lina Titievsky declared that she is employed by Pfizer and holds company stocks/shares. Vincent Bauchau declared that he is employed by GSK and holds company shares.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.08.012.

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