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Accelerated Development of VAccine beNefit-risk Collaboration in Europe

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Executive summary POC-1 studies on pertussis coverage, benefits, risks and B/R analysis

WP5 – Proof-of-concept studies of a framework

to perform vaccine benefit-risk monitoring

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Disclaimer: *The results described in this report 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.

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Executive summary

Accelerated development of vaccine benefit-risk collaboration in Europe (ADVANCE) is an ongoing collaborative European project that was initiated in 2013 and is scheduled to end in 2018. It is part of the Innovative Medicines Initiative (IMI), a joint undertaking by the European Union and pharmaceutical industry. (www.advance-vaccines.eu)

ADVANCE seeks to address the feasibility of establishing a public-private partnership to respond/evaluate relevant public health questions associated with the examination of benefits and risks of vaccines in a timely and efficient manner. Specifically, the ADVANCE vision is to deliver '*best evidence at the right time to support decision-making on vaccination in Europe*', and its mission is to establish a prototype of a sustainable and compelling system that rapidly provides the best available scientific evidence on post-marketing vaccination benefits and risks for well informed decisions. Consequently, ADVANCE involves the creation and assessment of an infrastructure (i.e. system) which could bring together different stakeholders and data sources in Europe.

As envisioned, the ADVANCE platform will ultimately provide evidence on the benefits and risks of vaccines at the request of different stakeholders. These requests/needs could arise under a number of scenarios including but not limited to: 1) inclusion of a new vaccine in a vaccination programme and/ or 2) an occurrence of a new unexpected safety issue and/or 3) when the benefit of the vaccine is questioned (e.g. waning immunity) and/ or 4) modification of indicated or targeted population(s). Under these scenarios, it would be possible to leverage the infrastructure of ADVANCE to investigate how the benefits and risks could also be monitored sequentially (cumulatively when data becomes available) to investigate whether the benefits, risks and composite measures of benefits/risk evolve over time.

Work Package 5 Overview

ADVANCE Work Package 5 (WP5) is one of the seven work packages (WPs) in the ADVANCE project. This WP focused on conducting and delivering the proof of concept (POC) studies to assess the feasibility of establishing the processes and systems that would generate the required inputs to carry out vaccine benefit risk (B/R) assessment. The first POC was aimed at the diagnosis of potential issues that would be encountered in a public private collaboration with a distributed network model approach to estimate vaccine coverage, benefits, risk and carry out a B/R analysis. There were 68 contributors to the ADVANCE POC-1.1 from research/academic institutes, public health institutes, regulatory authorities, small medium enterprises (SME), and vaccine market authorisation holders (MAHs), as part of the European Federation of Pharmaceutical Industrials and Associations (EFPIA) companies.

In brief, the specific objectives of WP5 fall under the following set of activities/tasks:

1 Systematic evaluation of available databases in Europe with a potential to be utilised in observational studies of vaccines. To achieve this, all potential databases identified through ADVANCE activities were surveyed and 'fingerprinted' to assess their eligibility. This involved a set of activities that produced a standard description of observational healthcare database contents to help understand the quality of the data and their suitability for vaccine B/R studies. In ADVANCE, this included meta-data plus outputs from standard programs that provide descriptions of the population, vaccines and events. The results of this eligibility assessment are summarised in this report and also served as the basis for the selection of databases to be included in pertussis POC described below.

2 Testing and establishment of systems, processes and tools which included implementation of an information technology (IT) infrastructure to enable the design and conduct of collaborative studies across different data sources and countries. This was complemented by the creation of ontologies, and vaccine and outcome mapping for the respective proof of concept studies. The ultimate test was to see if and how the systems, processes and tools could be used

3 Design and conduct of proof of concept studies for the coverage, benefit, risk and benefit-risk pillars using pertussis as a 'real world' case study to test the system to see if study protocols could be developed and performed.

ADVANCE adapted the distributed network model approach similar to that used in the Vaccine Safety Datalink (VSD), Sentinel, and the Canadian Network for Observational Drug Effect Studies (CNODES), requiring collaboration or in some cases, a partnership across different stakeholders. The important features of this approach include the joint development of common study protocols and data specifications including a common statistical analysis plan but where data extraction was done independently in the individual databases by different research teams using the common code with potential minor modifications based on the infrastructure and features of respective databases. Whereas the concepts of data pooling, standardised computer programmes and common protocols are the same in all initiatives, ADVANCE aimed to go beyond the approach used in CNODES and Sentinel by sharing and allowing pooling of both aggregated and anonymised person-level data (as required for certain designs). Some aspects of this model (common protocol, common programs, pooling of data) had already been tested in Europe in the Vaccine Adverse Events Monitoring and Communication (VAESCO) project[1] for the monitoring of pandemic influenza vaccine, that was funded by ECDC. However, in VAESCO no fingerprinting was done and no remote research environment (RRE) was available. Moreover, the statistical analyses and the principal investigator

[1] http://vaesco.net/vaesco.html

were limited to only one institution in VAESCO because no central server platform was available. A remote research environment that had been built for the FP-7 ARITMO (small molecules) project was used in ADVANCE to enable the multiple stakeholders, statisticians and principal investigators from a range of institutions to collaborate, in line with the lessons learned and recommendations published by ECDC from the VAESCO project. Additional innovations of ADVANCE compared with VAESCO include the use of the research procedures based on a draft Code of Conduct[2] and mapping of vaccines to standard terminology, as well as setting up a public-private partnership. In summary, ADVANCE is unique in having established a true public-private partnership, conducting systematic fingerprinting and using a central server as a research platform, while evaluating relevant facets of vaccines beyond safety, i.e., coverage, benefits, risks and benefit/risk assessment and monitoring. This first POC aimed to test the system and identify issues and lessons learned for subsequent improvement based on a retrospective analysis of data. In the next POC it is anticipated to determine the feasibility of conducting prospective monitoring of benefits and risks. WP5 will compile all the lessons learnt and provide recommendations for the way forward in a white paper that is currently due at the end of 2017.

Overview of pertussis proof of concept study

This report describes system testing for the generation of evidence for pertussis-containing vaccines using a proof of concept study, described below. This first POC study was designed using a 'pillar' approach where each pillar was under the responsibility of a different principle investigator. There were four pillars: coverage, benefits, risks and benefit-risk analysis. A multiple pillar approach was chosen so that as many individuals as possible could be involved and trained and also to allow databases to participate in different studies based on data eligibility, with further integration of activities within each team. The primary objective of this first POC was to test the currently-available systems using a real-world test case i.e., benefit-risk monitoring of vaccines in Europe.

Pertussis-containing vaccines was chosen as the test case for the first POC study, based on a set of *a priori* criteria established by the ADVANCE Steering Committee. The following research question was addressed: 'has the initial benefit-risk profile of pertussis vaccines been maintained after the switch from whole cell pertussis (wP) to acellular pertussis (aP) vaccines in children prior to receiving their pre-school-entry booster?' The switch from wP to aP vaccines was used as a proxy for the introduction of a new vaccine. The objectives of the POC were to determine the feasibility of using pre-identified electronic healthcare databases to identify and operationalise each pillar's specific outcomes (i.e. coverage for the coverage pillar, pertussis and pertinent clinical sequelae following

[2] Kurz X, Bauchau V, Mahy P, Glismann S, van der Aa LM, Simondon F. The ADVANCE code of conduct for collaborative vaccine studies. Vaccine. 2017; 35:1844-1855.

pertussis for the benefit pillar and potential safety events for the risk pillar) and to estimate the corresponding prevalence or incidence rates associated with these outcomes. The goal of the benefit/risk pillar was to use the information derived from the other three pillars, wherever feasible, in benefit/risk analyses and to perform a multi-criteria decision analysis (MCDA) using solicited preferences.

From the 19 databases in 8 countries available to or owned by ADVANCE partners, that were initially considered for the POC studies, 7 databases from 4 countries (Denmark (AUH and SSI), Italy (PEDIANET), Spain (SIDIAP and BIFAP) and UK (THIN and RCGP)) were ultimately included in the POC studies (see table 1). These databases were selected based on the pre-specified scientific criteria as well as operational considerations including but not limited to the timely ethics committee approvals and database holders/custodians review process. Overall, for the study period specified for the POC studies, these seven databases included data from more than 38 million subjects (all ages, with some double counting between AUH and SSI). The source population for each of the pillars was the paediatric population from birth to six years old or when the first pre-school booster dose was registered as having been received, which ever occurred earliest. The total study cohorts in each pillar varied in size because of the differences in the inclusion and exclusion criteria relevant for each pillar's research questions. Hence the study cohort for the coverage pillar included around 4.5 million children; the study cohort for the benefit pillar included 3 million children and 5 million children for the risk pillar. Data on coverage, benefits and risks could be generated in each of the seven databases, and a B/R analysis could be conducted and are available in the public full report (d5.6) at the ADVANCE website (www.advance-vaccines.eu) (see also direct link https://goo.gl/Cenaco). Below we just summarize the characteristics of the data sources that were included in the studies.

Table 1: Summary of the characteristics of databases that completed the eligibility assessment and were selected for inclusion in the POC-1 study.

	DK-SSI	DK-AUH	ES-BIFAP	ES-SIDIAP	UK-THIN	UK RCGP	IT-Pedianet*
Type of database	National record linkage	Regional record linkage	National sample GP	Regional GP	National sample GP	National sample GP	Regional sample family paediatricians (FP)
Type of Events captured	Hospital based only	Hospital based only	GP & reported hosp.	GP & hospital linkage for a subset	GP & reported hosp.	GP & reported hosp.	FP & reported hosp.
Age range covered	All	All	All	All	All	All	0-14 years born in 2006 or 2007*

	DK-SSI	DK-AUH	ES-BIFAP	ES-SIDIAP	UK-THIN	UK RCGP	IT-Pedianet*
Calendar years with event information	1995-2014	1976-2015	2003-2014	2005-2015	1985-2015	1989-2016	2006-2015
Accuracy of birth dates	Exact day & month & year	Exact day & month & year	Exact day & month & year	Exact month & year, day rounded to first	Rounded month (7) and rounded day (1), for children only rounded day and exact month/year	Exact month & year, day rounded to first	Exact month & year, day rounded to 15th
Total population captured	7,152,032	2,563,188	7,541,864	6,109,234	11,696,261	2,678,749	9,708
Percentage registered in DB within one month after birth	16% $	63%	4%		3%	2%	64%
Vaccines extracted for fingerprint	Pertussis containing vaccines. Most frequent quadrivalent and pentavalent N=4,112,070	Pertussis, HPV, HIB, Influenza, Polio	Pertussis containing vaccines. Most frequent pentavalent /heptavalent n=1,941,728	All vaccines N=22,412,697 2,846,877 pertussis containing	Pertussis containing, no type available just antigens	Pertussis containing vaccines. Most frequent quadrivalent and pentavalent N=1,905,628	Pertussis containing vaccines N=36,124
wP information	Yes, limited 2.1% of pertussis containing vaccines	Unclear	Yes only 1.7% of all pertussis containing vaccines	No	Yes, 64% of all pertussis containing vaccines	Yes, 47.7% of all pertussis containing vaccines	No

	DK-SSI	DK-AUH	ES-BIFAP	ES-SIDIAP	UK-THIN	UK RCGP	IT-Pedianet*
Events extracted	No persistent crying	No persistent crying	All	No persistent crying	All	All	All
Modality for event extractions	ICD10-Danish version codes	ICD9 and ICD10 codes	ICD9 and ICPC codes and text	ICD10 codes	READ2 codes	READ and CTV3 codes	ICD9 codes & text

*In the Pedianet database the number is small since only children born in 2006 or 2007 were included (those who provided informed consent for linkage with vaccine registry) with their data from 2006/2007 till 2015. $ In SSI children are usually registered from birth, but for fingerprinting data are used from 1996, so many people start follow-up after birth.

Table 2: Attrition table for the databases in the three pillars

Verifications	SSI (Denmark)	AUH (Denmark)	THIN (UK)	RCGP (UK)	BIFAP (Spain)	SIDIAP (Spain)	PEDIANET[1] (Italy)	Total
Number of persons originally in the full population file (all ages; including adults)	7,512,032	1,725,165	11,696,261	2,678,749	7,541,864	7,096,695	9,708	38,260,474
Remaining population risk pillar (no requirement to be registered before one month of age)								
Number of children (0-5 years) included in the final risk cohort (aP or wP)[2]	1,215,124	271,949	1,735,910	387,003	568,400	872,580	9,079	5,060,045
Remaining population coverage and benefit pillars (registered before 1 month of age)								
Number of children (0-5 years) included in the final coverage cohort[3]	1,218,555	188,335	423,393	698,644	1,467,595	515,236	9,708	4,521,466
Number of children (0-5 years) included in the final benefit cohort[4]	1,004,854	143,399	770,849#	204,370	288,476	519,330	7,695	2,938,973

[1]PEDIANET included only children 0-14 years of age; [2]reduction due to exclusion of all persons who did not have age 0-5 years during study period. [3]children were excluded if registered later than one month after birth as were those with an inconsistent vaccination history or without one day of follow-up between dose 1 and booster; [4]In THIN the benefit cohort is larger than the coverage cohort since most children entered the database between 1 and 3 months of age.

Conclusions

Overall, the primary objective of this first POC, i.e., to test a system to generate evidence on the benefits and risks of vaccines, was achieved. The generation of evidence using a 'known test case' was successful. Four stages were distinguished: protocol, data extraction, data transformation and reporting. Each of these stages had its own workflow and obstacles, which was to be expected since we were trying to innovate and/or create/test something new while working with a large group of people with different backgrounds and perspectives.

The protocol development and data transformation phases required the most time but these phases could be much shorter in future studies since the processes, tools and human capacity are now in place. The full discussion of the system testing features that worked well, those that did not work as well and a summary of the key indicators of success are presented in Section **Error! Reference source not found.** of this report (discussion on system testing), scientific discussions about the pillars are presented after the pillar results.

One of the major accomplishments of this POC was the transparent multi-stakeholder collaboration and capacity building. The POC studies were executed by four different study teams and included 68 epidemiologists, vaccinologists, medical doctors, computer programmers and 10 statisticians. All ADVANCE partners/stakeholders were active participants with roles and responsibilities shared in an open and synergistic manner. All participants worked according to the ADVANCE code of conduct, with full transparency of conflicts of interest (providing declaration of interests) competencies (providing curriculum vitae) and input (all contributions by stakeholders toward the protocols, statistical analysis plans and report development were tracked). This represents a true multi-stakeholder, public-private collaboration with public and private partners in study teams sharing responsibilities.

We conclude that this POC study was successful and promising for the ADVANCE concept and that future POC studies should aim at reducing the delay from the time the research question is generated to data access and results being available as well as on near real time monitoring. This POC-1 will be evaluated by the POC evaluation team that will report in D5.8 and all lessons will be included in the white paper that will lead to the ADVANCE blueprint (D5.9). All will be publicly available on the ADVANCE website

Summary of the proof-of-concept objectives and their achievement

POC-1 objective	***POC-1 achievement (pertussis test case)***

POC-1 objective	***POC-1 achievement (pertussis test case)***
Establish the feasibility of continuously updating the information on the B/R of a vaccine from the first day after a vaccine is marketed.	In this POC we assessed the change of B/R of a vaccine, after a switch to a 'new' vaccine, retrospectively. Prospective monitoring was not possible but will be done in POC1.2.
Assess IMI ADVANCE platform for data availability on a routinely-used vaccine in established vaccination programmes covering different populations and different schedules across countries.	Data were partially available from eight countries, but only four countries (DK, ES, IT, UK), covering different populations and vaccination schedules, contributed successfully to the full POC. This POC only looked at children.
To test and assess the level of collaboration between different stakeholders in collecting and integrating evidence on the benefits and risks of vaccines.	Diverse study teams (in line with the ADVANCE code of conduct), involving 68 persons showed extensive, open collaboration in generating evidence on the benefits and risks of vaccines.
To assess the methods for evidence generation on safety, benefits, preferences and vaccination coverage, using a near real-time scenario.	Distributed methods of data generation were applied to generate data on safety, benefits, coverage and benefit-risks of pertussis containing vaccines. Several new tools and new methods (especially for coverage estimations, and benefit-risk integration) were used.
To evaluate the acceptability of the results by stakeholders for decision making on B/R.	The POC evaluation is ongoing and will be completed after this report is published.