

IMI1 Final Project Report Public Summary

Project Acronym: ADVANCE

Project Title: Accelerated Development of
VAccine beNefit-risk Collaboration in Europe

Grant Agreement: 115557

Project Duration: 01/10/2013 – 31/03/2019

1. Executive summary

1.1. Project rationale and overall objectives of the project

The ADVANCE vision is to deliver “best evidence at the right time to support decision-making on vaccination in Europe” for health care professionals, regulators, public health organizations and parents. Within the ADVANCE project we built and tested an ecosystem that would provide robust scientific evidence on vaccination coverage, benefits and risks.

1.2. Overall deliverables of the project

To achieve the overall objectives set out at the start, ADVANCE implemented an efficient collaborative approach for public-private interaction through a scientific programme aimed at:

1. Establishing best practice rules for interaction between public-public and public-private stakeholders for best practice conduct of studies on the benefit-risk of vaccines (WP1).
2. Mapping and promotion of synergies with other relevant research and training initiatives to maximize utilization of foreground and identification of gaps for program strengthening (WP2).
3. Profiling of data sources that will yield rapid access to burden of disease, vaccine coverage, and benefits and risks of vaccines (WP3).
4. Adaptation and development of new methods for monitoring of vaccine benefits, risks and their integrated analysis (WP4).
5. Testing and implementation of the best practice guidance, data sources, and methods through different proof of concept studies on real world data throughout Europe (WP5)
6. Describing a Blueprint of a sustainable system that could be implemented post-project (WP7)

The design of the project was that innovations and developments would be made in work packages 1 (best practice), 3 (data source identification), and 4 (methods) during year 1-3, which would be tested on real data in several proof of concept studies in work package 5. Work package 7 would take the key outputs from the work packages plus white papers, assess acceptability outside of the consortium, assess sustainability and write the Blueprint of the future system. Work packages 2 (synergies with other projects) and 6 (management coordination) were support packages, running across the entire period.

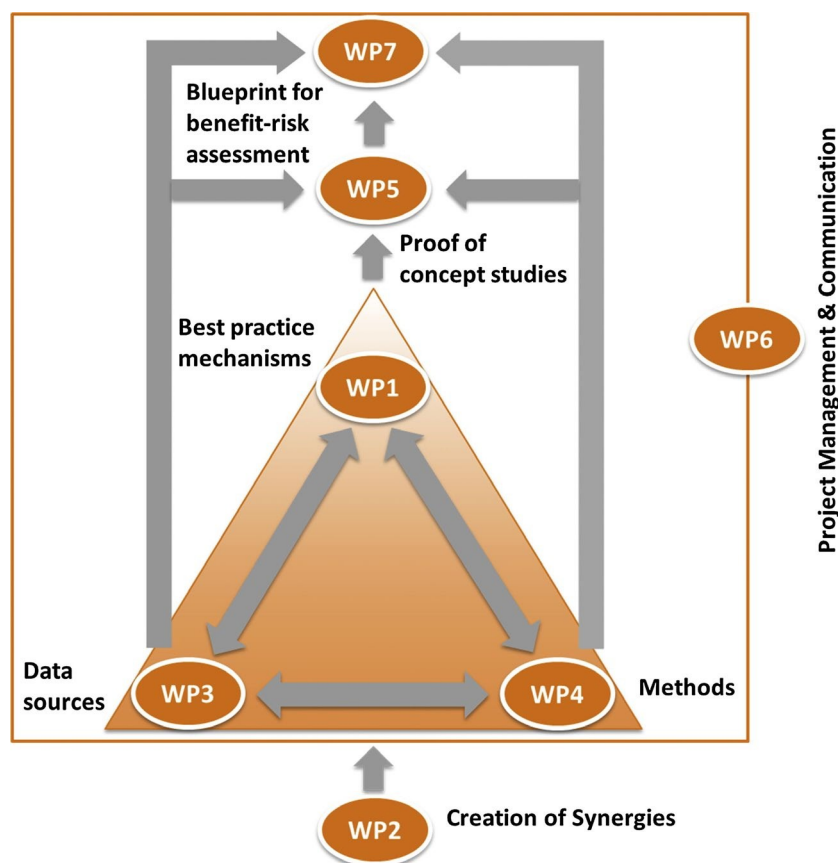


Figure 1: Structure of the ADVANCE workplan

1.3. Summary of progress versus plan since last period

The entire workplan has been finalized. A no-cost extension was requested during the last reporting period because of a change in roles and coordinator ship, which led to delays especially in WP5. In the past reporting period, including the extension, all outstanding work (15 deliverables) have been delivered. For WP1 this meant the deliverable on communication strategies, as well as publications. Moreover, an extra report on public-private collaborations was created based on a workshop organized by EMA. WP2 delivered the final deliverable and organized collaborations with several organizations/projects of relevance, namely the EU Joint Action for Vaccines, the IMI-funded DRIVE consortium and LifetechBrussels. Work package 3 had delivered all its work in the prior reporting period as planned, and worked on publications related to privacy in the last reporting period. Work package 4 had finished the deliverables but spent the time in the last reporting period to create publications on the work that was done. Much work was done in WP5 during the last reporting period, which aimed to test the methods, guidance and data sources from WP1, 3 and 4. The evaluation of the first proof of concept studies and their publications plus the second round of proof of concept studies were conducted and reported. All proof of concept studies showed the ability of the ADVANCE system to generate robust evidence on vaccine coverage, benefits and risks, using data from more than 44 million people in 9 data sources. WP7 created its key deliverable the ADVANCE Blueprint, this was based on the white papers of each work package, advice from the implementability advisory board and underwent wide public consultation. Moreover, WP7 conducted all the work to create the

sustainability solution for ADVANCE, a non-for-profit international association called Vaccine monitoring Collaboration for Europe (VAC4EU). WP6 organized the project management, final ADVANCE workshop and the conclusion of the project. All public deliverables are available on the ADVANCE website.

1.4. Significant achievements since last report

WP1 – Best practice for benefit-risk monitoring of vaccines

During the last reporting period all remaining work was concluded, which was the D1.12: communication strategies for benefits and risks of vaccines, in a public private partnership.

In addition, an extra report was written, based on a workshop with around 70 senior experts in vaccine benefit-risk monitoring. This workshop was organized by WP1 at EMA. This report is available on the ADVANCE website and is called: “Public-private collaborations and partnerships for vaccine benefit-risk monitoring in Europe: the ADVANCE framework and governance principles”.

Moreover the ‘Guidance for the governance of public-private collaborations in vaccine post-marketing settings in Europe’ was presented to the ESCAIDE meeting, Malta, 21 Nov 2018 and is now published in Vaccine (Torcel-Pagnon L, Bauchau V, Mahy P, Tin Tin Htar M, van der Sande M, Mahé C, Krause TG,

Charrat A, Simondon F, Kurz X; ADVANCE Consortium. Guidance for the governance of public-private collaborations in vaccine post-marketing settings in Europe. *Vaccine*. 2019 May 31;37(25):3278-3289).

The governance model for public-private collaborations in vaccine post-marketing settings has been applied into the proposed governance model for IMI-DRIVE and the new VAC4EU organisation.

WP2 – Creation of synergies for benefit-risk monitoring in Europe

Creation of synergies was important and WP2 undertook a systematic approach to looking for these. In the last reporting period the D.2.4: Final report on landscape analysis, synergies, added value of ADVANCE and future opportunities was submitted to IMI.

In addition, in the last reporting period synergies were established with: (1) the European Joint Action for Vaccines (Memorandum of Understanding) resulting in an agreement that the EU JAV may use ADVANCE programs to estimate coverage, and that we will collaborate in exchanging information, crosslinking and other synergies ; (2) LifetechBrussels (for work on sustainability of ADVANCE and business plan of the Vaccine monitoring Collaboration for Europe), LifetechBrussels provided the business plan template and the cost book; (3) the DRIVE consortium uses many ADVANCE outputs: the governance, models of distributed analyses and has asked whether VAC4EU will participate in DRIVE, with the DRIVE consortium we held several meeting and the project leaders attended the final event as speakers.

WP3 – Data sources for rapid and integrated benefit-risk monitoring

The last deliverable was submitted in March 2017 as planned. In the last reporting period, 2 publications were created.

- Harshana Liyanage, Lieke van der Aa, Charlotte Switzer, Filipa Ferreira, Patrick Mahy, Miriam Sturkenboom, Alena Khromava, Simon de Lusignan. **Data partners suitable for vaccine benefit-risk studies in Europe: ADVANCE International Research Readiness (AIRR) survey results**. Not yet published.
- Lieke Maria van der A, Charlotte Switzer, Harshana Liyanage, Miriam Sturkenboom, Patrick Mahy, Alena Khromava, Simon de Lusignan. **Data privacy considerations for vaccine collaborative studies and the impact of the GDPR**. Not yet published.

WP 4 - Methods for burden of disease, vaccination coverage, vaccine safety & effectiveness, impact and benefit-risk monitoring

There were no WP4 deliverables to be submitted during the last reporting period. However, efforts were made to further disseminate the work through the writing of publications and conference attendance, as listed below.

Publications

- Bollaerts K, Rekkas A, De Smedt T, Dodd C, Andrews N, Gini R. Analytical interrelations between



validity indices for validation of case-finding algorithms in healthcare data research: a contribution from the ADVANCE project. Submitted.

- Braeye T, V. B, Sturkenboom M, Emborg H-D, Garcia AL, Huerta C, et al. Estimation of vaccination coverage from electronic healthcare records; methods performance evaluation – A contribution of the ADVANCE-project. PLoS One. 2019 Sep 18;14(9):e0222296.
- De Smedt T, Merrall E, Macina D, Perez-Vilar S, Andrews N, Bollaerts K. Bias due to differential and non-differential disease- and exposure misclassification in studies of vaccine effectiveness. PLoS One. 2018;13(6):e0199180.
- Bollaerts K, De Smedt T, Donegan K, Titievsky L, Bauchau V. Benefit-Risk Monitoring of Vaccines Using an Interactive Dashboard: A Methodological Proposal from the ADVANCE Project. Drug Saf. 2018;41(8):775-86.
- McDonald SA, Nijsten D, Bollaerts K, Bauwens J, Praet N, van der Sande M, Bauchau V, de Smedt T, Sturkenboom M, Hahné S. Methodology for computing the burden of disease of adverse events following immunization. Pharmacoepidemiol Drug Saf. 2018 Jul;27(7):724-730.

Based on the work in WP4, one PhD thesis was presented and defended:

- Becker, B.F.H. (2019, January 8). Vaccine semantics: Automatic methods for recognizing, representing, and reasoning about vaccine-related information. Erasmus University Rotterdam. Retrieved from <http://hdl.handle.net/1765/111218>

WP5 – Proof-of-concept studies of a framework to perform vaccine benefit-risk monitoring

WP5 was charged with the characterization of electronic health record datasources, to assess whether they are fit for purpose and to conduct proof of concept studies. In the last reporting period a lot of work was conducted with key achievements.

- To address the differences in coding of vaccines across EU health databases and facilitate extraction, a vaccine ontology was created called VaccO. This was described in the deliverable **D5.5 “Ontology for the Integration and Extraction of Vaccine-related Information in Europe: a proof of concept”** which is publicly available. VaccO web applications were created that are a demonstration of the algorithms described in the manuscript “Alignment of vaccine codes using the ADVANCE VaccO ontology”. The web applications allow 1) the analysis of individual vaccine descriptors, 2) the selection of vaccine codes based on their defining properties and 3) the alignment of any pair of user-provided vaccine coding systems. These web applications are accessible from the VAC4EU website.
- Detailed database characterization (fingerprinting) based on actual data-analysis in a distributed manner was completed on 26 events of interest (safety events, vaccine preventable diseases) and 4 vaccines, based on 10 electronic health care databases covering more than 44 million subjects in the EU.

Since electronic health care data sources are collected for routine care or administrative purposes, they may not always be suitable for the generation of evidence. Moreover, the structure and semantics differ between data sources. Before evidence can be trusted by stakeholders it is important to assess whether the data is fit for purpose. ADVANCE used a distributed network where original stay local and only aggregated output (sometimes at individual level), which is the result of common analytics is shared. The results of this process of and the results of the database

characterization are described in **D5.4 “Final fingerprinting of the participating health care databases”**, which is publicly available from the ADVANCE website

The POC1.2 focusing on near real time monitoring was approved conducted and delivered as **D5.7 “Proof-of-Concept studies Phase 1: Results on near real-time monitoring”** during the last reporting period. 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. Data collection delays were calculated and an interactive web application facilitating the visual monitoring of vaccination coverage, benefits and risks was developed. Nine databases from four countries (Denmark: SSI and AUH; Italy: ARS, ATSVS and PEDIANET; Spain: BIFAP and SIDIAP; UK: THIN and RCGP RSC) participated in the qualitative feasibility assessment. Five databases (SSI, ARS, ATSVS, SIDIAP, RCGP RSC) provided baseline data for the cohort study. Three databases (SSI, ATSVS and RCGP RSC) also participated in the NRT monitoring, providing data

extractions on an almost weekly basis for 374,161 (SSI), 2,492 (ATSVP) and 6,362 (RCGP RSC) children. For vaccination events, the median data latency (time between event date and data release date) were 2 (SSI), 1 (ATSVP) and 2 (RCGP RSC) weeks. For the benefit and risk events, the median latencies were 2 (SSI), 16 (ATSVP) and 1 (RCGP RSC) weeks. It was concluded that several European eHR databases successfully demonstrated the feasibility of providing data for weekly NRT monitoring, with short data latencies during three months.

- The deliverable **D5.8 “Evaluation of the POC-1 studies”** was written and delivered.
- The second proof of concept study was designed after several rounds of consultations to investigate whether data sources are able to conduct brand specific analyses. The proof of concept protocol was created after partner consultation on the perceived needs for testing. The protocol was registered in the EU PAS register and delivered in the **D5.10 “Research plan for POC-2”**
- A key achievement was the conduct and execution of the POC-2, which started in January 2019. The methods and results are delivered in D5.11

The system and the results of the POC-1 were written up in 10 papers which will be published as an open access supplement in Vaccine.

- 1) Sturkenboom M, Bahri P, Chiucchiuini A, Grove Krause T, Hahné S, Khromava A, Kokki M, Kramarz P, Kurz X, Larson HJ, de Lusignan S, Mahy P, Torcel-Pagnon L, Titievsky L, Bauchau V; ADVANCE consortium. Why we need more collaboration in Europe to enhance post-marketing surveillance of vaccines. Vaccine. 2019 Oct 31. pii: S0264-410X(19)31002-3.
- 2) M. Sturkenboom, L. van der Aa, K. Bollaerts, H.D. Emborg, G. Ferreira, R. Gino, et al. The ADVANCE distributed network system for evidence generation on vaccines coverage, benefits and risks based on electronic health care data Vaccine (2020) Submitted to Vaccine
- 3) Sturkenboom M, Braeye T, van der Aa L, Danieli G, Dodd C, Duarte-Salles T, Emborg HD, Gheorghe M, Kahlert J, Gini R, Huerta C, Martín-Merino E, McGee C, de Lusignan S, Picelli G, Roberto G, Tramontan L, Villa M, Weibel D, Titievsky L. ADVANCE database characterisation and fit for purpose assessment for multi-country studies on the coverage, benefits and risks of pertussis vaccinations. Vaccine. 2020 Feb 12. pii: S0264-410X(20)30153-5.
- 4) Emborg HD, Kahlert J, Braeye T, Bauwens J, Bollaerts K, Danieli G, Duarte-Salles T, Glismann S, Huerta C, de Lusignan S, Martin E, McGee C, Correa A, Tramontan L, Weibel D, Sturkenboom M. ADVANCE system testing: Can coverage of pertussis vaccination be estimated in European countries using electronic healthcare databases: An example. Vaccine. 2019 Oct 31. pii: S0264-410X(19)30930-2.
- 5) Tin Tin Htar M, de Ridder M, Braeye T, Correa A, McGee C, de Lusignan S, Duarte-Salles T, Huerta C, Martín-Merino E, Tramontan L, Danieli G, Picelli G, van der Maas N, Berencsi K, Arnheim-Dahlström L, Heininger U, Emborg HD, Weibel D, Bollaerts K, Sturkenboom M. Advance system testing: Vaccine benefit studies using multi-country electronic health data - The example of pertussis vaccination. Vaccine. 2019 Oct 31. pii: S0264-410X(19)31167-3.
- 6) Weibel D, Dodd C, Mahaux O, Haguinet F, De Smedt T, Duarte-Salles T, Picelli G, Tramontan L, Danieli G, Correa A, McGee C, Martín-Merino E, Huerta C, Berencsi K, Emborg HD, Bollaerts K, Bauchau V, Titievsky L, Sturkenboom M. ADVANCE system testing: Can safety studies be conducted using electronic healthcare data? An example using pertussis vaccination. Vaccine.

2019 Oct 31. pii: S0264-410X(19)30802-3.

- 7) Bollaerts K, Ledent E, de Smedt T, Weibel D, Emborg HD, Danieli G, Duarte-Salles T, Huerta C, Martín-Merino E, Picelli G, Tramontan L, Sturkenboom M, Bauchau V. ADVANCE system testing: Benefit-risk analysis of a marketed vaccine using multi-criteria decision analysis and individual-level state transition modelling. *Vaccine*. 2019 Oct 31. pii: S0264-410X(19)31243-5.
- 8) Gini R, Dodd CN, Bollaerts K, Bartolini C, Roberto G, Huerta-Alvarez C, Martín-Merino E, Duarte-Salles T, Picelli G, Tramontan L, Danieli G, Correa A, McGee C, Becker BFH, Switzer C, Gandhi-Banga S, Bauwens J, van der Maas NAT, Spiteri G, Sdonà E, Weibel D, Sturkenboom M. Quantifying outcomemisclassification in multi-database studies: The case study of pertussis in the ADVANCE project. *Vaccine*. 2019 Oct 31. pii: S0264-410X(19)30936-3.
- 9) Dodd C, Weibel D, de Ridder M, Mahaux O, Haguinet O, de Smedt T, de Lusignan S, McGee C, Duarte-Salles T, Emborgh HD, Huerta C, Martín-Merino E, Picelli G, Berencsi K, Daniel G, Sturkenboom M. ADVANCE system testing: estimating the incidence of adverse events following pertussis vaccination in healthcare databases with incomplete exposure data. *Vaccine* submitted
- 10) Bollaerts K, de Smedt T, McGee C, Emborg HD, Villa M, Alexandridou M, Duarte-Salles T, Gini R, Bartolini C, de Lusignan S, Tin Tin Htar M, Titievsky L, Sturkenboom M, Bauchau V. ADVANCE: Towards near real-time monitoring of vaccination coverage, benefits and risks using European electronic health record databases. *Vaccine*. 2019 Oct 31. pii: S0264-410X(19)31051-5.

In addition, other manuscripts based on the database characterization listed in D5.4 are being submitted.

WP6 – Project management and communication

- Significant management efforts were devoted to develop and closely monitor a work plan to ensure timely finalization of all project deliverables, considering the dependencies between workstreams and deliverables.
- The Steering Committee held a Bootcamp in January 2018 in Leuven to discuss about the sustainability scenarios, including challenging topics such as the governance and the role of industry in the future of ADVANCE, the form of the new entity, potential revenue streams, etc. The meeting was facilitated by an external expert (former IMI executive director)
- A fourth and fifth amendment of the DoW have been submitted to update all necessary adjustments in the work plan and changes at the operational and management level, including the request for 6 months extension.
- The final ADVANCE event was held on March 6th 2019, and gathered more than 100 international vaccine and health data experts from at least 12 countries at the Royal Academy of Science in Brussels, Belgium.
- A podcast was later on recorded to illustrate the outcomes of ADVANCE and the launch of VAC4EU.

WP7 – Implementability and sustainability

Work Package 7 had its key deliverable created in the last reporting period: The Blueprint. In order to achieve this several activities were conducted:

- Multiple meetings of external expert Review Panels to review key deliverables of the other technical Work Packages of the project. The Review Panels further constituted the full Implementability Advisory Board
- Implementability Advisory Board face-to-face meeting
- Drafting of the Blueprint of a framework to rapidly provide scientific evidence on post-marketing vaccination benefits and risks for informed decisions
- Consultation of the Blueprint with: (a) ECDC Advisory Forum; (b) ADVANCE project Steering Committee; (c) ADVANCE project General Assembly;
- Public consultation of the draft Blueprint on ECDC web portal
- Addressing comments and suggestions from all the consultation phases and preparation of the final Blueprint
- Providing input into the interactive display of the Blueprint online

Work Package 7 has also defined indicators to measure the ADVANCE Project's added value for public health and provided feedback to the Project's Steering Committee from public health organizations not directly represented in the project. Finally, Work Package 7 has prepared, at the initial phase of the project, the discussion paper on sustainability of the project outcomes beyond the duration of ADVANCE. Sustainability efforts were increased in the last reporting period, based on the endorsement of the Steering Committee and the consortium to explore the organization of a hub (one of the



sustainability models identified in the discussion paper). Within the last reporting period, the Vaccine monitoring Collaboration for Europe (VAC4EU) was designed, the Articles of Association, the website (<https://vac4eu.org>) was created and the business plan was written.

1.5. Scientific and technical results/foregrounds of the project

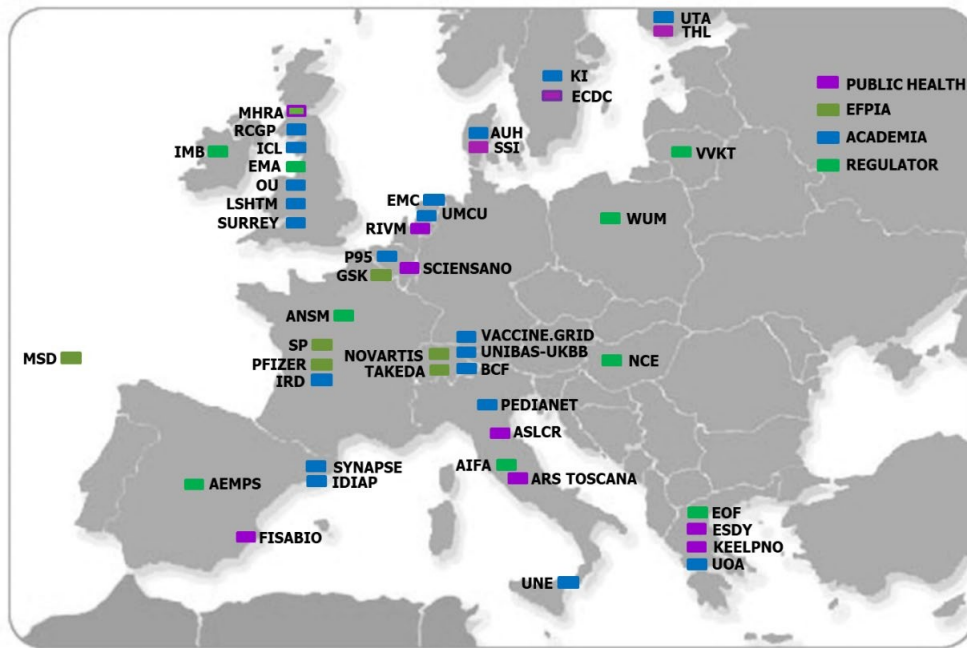
ADVANCE has brought together scientists from all major stakeholders interested in post-licensure monitoring of the coverage, benefits and risks of vaccines. The ADVANCE consortium established a public-private collaboration (PPC) to enable rapid and comprehensive development of post-marketing vaccine evidence generation which was not possible in Europe before the project was initiated. Regulators such as the European Medicines Agency (EMA), public health institutes including the European Centre for Disease Control & Prevention (ECDC), numerous vaccine manufacturers and many of Europe's leading academic institutions collaborated to create best practice guidance, methods, tools and capacity to generate rapid evidence on vaccines from existing healthcare data. The ADVANCE consortium has demonstrated that the enormous resource of existing and fragmented European real-world healthcare data can be used to generate actionable evidence on vaccine coverage, benefits and risks for drug regulatory agencies, public health agencies, vaccine manufacturers, health care professionals, and patients.

How did we ADVANCE?

During the project's lifetime, the ADVANCE consortium developed and tested procedures, methods, and workflows to ensure readiness for rapid generation of evidence on coverage, benefits and risks of vaccines. ADVANCE's outputs and tools are publicly available at www.vac4eu.org. These include:

Environment & governance readiness

- Engagement of 47 partners across 19 European countries: 16 academic/public research institutions; 10 public health organisations; 9 national drug regulatory agencies, including the EMA and ECDC; 7 vaccine manufacturers; 3 small medium enterprises (SMEs); and 2 charities.



- Development of best practices (code of conduct) and governance for collaborative vaccine studies.

Methods readiness

- Overview of existing and novel methods for estimation of vaccine coverage, benefits and risks estimation
- Online tools supporting generation of evidence:
 - Codemapper: maps outcome definitions into diagnostic codes across a range of vocabularies
 - VaccO: a vaccine ontology
 - Interrelation tool: estimation of outcome validity measures
 - Vaccine effectiveness misclassification tool
 - Near-real time Benefit-risk monitoring: interactive dashboard for visualising vaccine coverage, benefits, risks and composite B/R measures.

Data source readiness

- Online data source catalogue listing the characteristics of 30 electronic healthcare databases in Europe
- A simple common data model for multi-database studies
- Detailed processes and workflows to assess whether data sources are fit for purpose
 - Data characterisation of 19 data sources in 8 countries
 - Age, calendar-year, and gender-specific incidence rates for 25 events of interest
 - Vaccine coverage estimates by birth cohort, calendar-year, age and target groups
- Near real time monitoring of vaccine coverage, benefits and risks

Study readiness

- Best practice guidance implemented and tested in multi-database studies
- Templates for study outlines, protocols, declarations of interest, statistical analysis plans, and

reports

- SAS and R syntax/programs to transform raw healthcare data into required evidence
- Operational platforms for the transfer, sharing, and pooling of data

Implementation plan

- Blueprint describing how to use the ADVANCE systems for monitoring vaccine coverage, benefits and risks in Europe; created by the ECDC, that has undergone public consultation.

To implement its vision and enable actionable and rapid evidence-generation on the effects of vaccines in a collaborative manner, the consortium has decided to create a multi-stakeholder scientific community and an operational study network, which will have an official status as a legal entity with the following principles:

- **VAC4EU** will be a not-for profit legal entity (international association), with institutional membership (study network).
- **VAC4EU** will maintain and support an open community of scientists.
- **VAC4EU** will support provide access to a well characterised public study network, which can provide data access and perform studies for different external requesters (e.g. vaccine manufacturers, European Commission, regulators, public health institutes) or internally.
- **VAC4EU** will have a Multi-stakeholder Advisory Forum (with major EU organisations) as well as independent scientific and audit committees for oversight.

The consortium has delivered 50 deliverables, after the first year it was decided to make all deliverables publicly available. In addition, tools (open source) and templates are publicly available. The project has resulted in contributions to at least 4 PhD theses and resulted in 26 scientific publications. It has set the stage for the collaborative and sustainable approach toward vaccine benefit and risk monitoring.

1.6. Potential impact and main dissemination activities and exploitation of results

The stated aim of the ADVANCE project is to “help health professionals, regulatory agencies, public health institutions, vaccine manufacturers and the general public make more informed decisions on benefits and risks of marketed vaccines. It will do this by creating a framework and tools to rapidly deliver reliable data on vaccine benefits and risk”.

As described in section 1.4 ADVANCE has created and tested readiness of methods, people and data to rapidly generate robust evidence on vaccine coverage, benefits and risks from ‘Big’ health data. The final goal of the project was to deliver a Blueprint for future implementation of the system.

All of the methods, tools and templates (see section 1.4) that were created as foreground were described and listed in the Blueprint. The Blueprint document contains two substantial chapters. The first one is intended to form a manual (“cook book”) for real-life future use of the framework: steps to take, tools to use, links to existing applications and sources – those developed by ADVANCE as well as

others. The second contains a discussion on the possible future of the framework – its sustainability after the ADVANCE project has ended.

The Blueprint defines a framework, within which a range of systems can be implemented according to need. The Blueprint includes a clear description of components, dependencies, workflows, stakeholder involvements and roles, access to the platform/tools developed and tested as part of the project, the entity (entities) in charge of running the platform/tools, and options for financing to ensure sustainability of the proposed solution.

The framework described should optimally be characterised by, among others: (1) accessibility, (2) acceptability, (3) adaptability, (4) effectiveness, (5) interoperability, (6) reliability, (7) resilience, (8) scalability, (9) simplicity, (10) transparency and (11) sustainability.

In the context of the Blueprint this translated into the following key characteristics, i.e. the framework should have:

- operational IT platform;
- stable operational and managerial organisational structure and tools;
- dedicated trained staff, available centrally and locally;
- well-defined and tested processes and rules of interactions between stakeholders;
- template documents for each step during evidence generation;
- secured base funding;
- mechanisms to ensure data access;
- mechanisms to ensure sufficient data quality, comparability across different sources and continuous validation of data sources; and
- data security and privacy assured as per General Data Protection Regulation (GDPR).

The scientific area covered by the Blueprint – vaccination coverage, benefit, risk and benefit-risk assessment conducted throughout the life cycle of vaccines – is quite specific, due to several factors: the benefits and risks of vaccines are perceived and weighed differently, as they are often offered prophylactically to healthy individuals, e.g. as part of the national childhood vaccination programmes. Vaccinations thus have major public health implications and, in addition, get a lot of media attention. Hence, the tolerance for risk, even if it is an easily treated adverse event, is very low, as current debate in several EU Member States demonstrates. Lack of public confidence in vaccine benefit/risk may lead to poor coverage, and to outbreaks of vaccine preventable diseases.

Stakeholders working in the vaccine area therefore need to monitor relevant data continuously and need to have data easily available for quick decision making and risk management. Other specificities of scientific studies of vaccines include large vaccinated populations, indirect effects of vaccination, multiple stakeholders involved in decisions on vaccination and the differences in time scales over which risks and benefits of vaccination are observed e.g. benefits of HPV and hepatitis B vaccines may not show up until decades after vaccination.

In the ADVANCE concept, evidence on vaccine coverage, benefits, and risks may be generated faster through secondary use of existing health care data in Europe. This follows from the realisation that benefit-risk information on a particular vaccine is often needed rapidly, leaving little or no time for specific primary data collection (even if the delay in updating of available databases may in some instances be a limiting factor). This concept was tested by ADVANCE partners who have access to data sources including general practice databases, claims databases, vaccine registries, vaccine trial cohorts and disease surveillance data.

The Blueprint describes how to use the platform in eleven steps, from activation of the platform to dissemination of results. For several of these steps, the tool or activity to be applied will vary with the actual study question asked. For these steps four different scenarios are used, making it possible for the user to follow one scenario (for example a study of vaccine safety) through the various steps.

The chapter on sustainability describes four different potential models of sustainability, from a loosely connected network of experts and databases, which is activated only when there is a specific question to be studied, to a permanent structure with a small secretariat and a governance structure, which is agreed in advance, independent of any specific study. The last of these models is discussed in some details and has been the reason for VAC4EU creation. The IMI funding ended March 2019, but the ADVANCE legacy is now continued in a different shape in VAC4EU.

VAC4EU as exploitation of the ADVANCE results

European collaboration to monitor the coverage, benefits and risks of vaccine to provide rapid and robust evidence to citizens and decision makers is an essential contribution for keeping up vaccine confidence. The European Parliament and Council have requested such evidence in the Council recommendations.

There are clear benefits of EU wide collaboration

Member States (MS) have their national program for vaccination programme monitoring and the National Regulatory Agencies (NRA) monitor benefits and risks of vaccine products. Beyond these national programs there are benefits for an EU collaborative approach:

- 1) ability to estimate coverage, effectiveness and safety of different vaccine products and schedules within and across member states;
- 2) increased power to monitor rare safety events;
- 3) combining expertise and capacity to run studies more efficiently across member states; and
- 4) use comparable near real time monitoring systems within and across member states to have most up to date information on vaccines.

What is VAC4EU?

VAC4EU will be a non-for-profit international association under the Belgian law. VAC4EU aims to enable robust and timely evidence-generation on the effects of vaccines in a collaborative manner primarily by re-using existing health data. VAC4EU members are research organizations and public health institutes that can generate evidence on vaccines using standard procedures in a study network.



VAC4EU governance relies on 2 key bodies:

1. The General Assembly of members (public health organizations and research organizations providing expertise and/or data).
2. An Executive Board elected by the General Assembly, whose task is to steer and monitor the VAC4EU organization.

VAC4EU can consult two independent bodies that are installed by, but not governed by VAC4EU

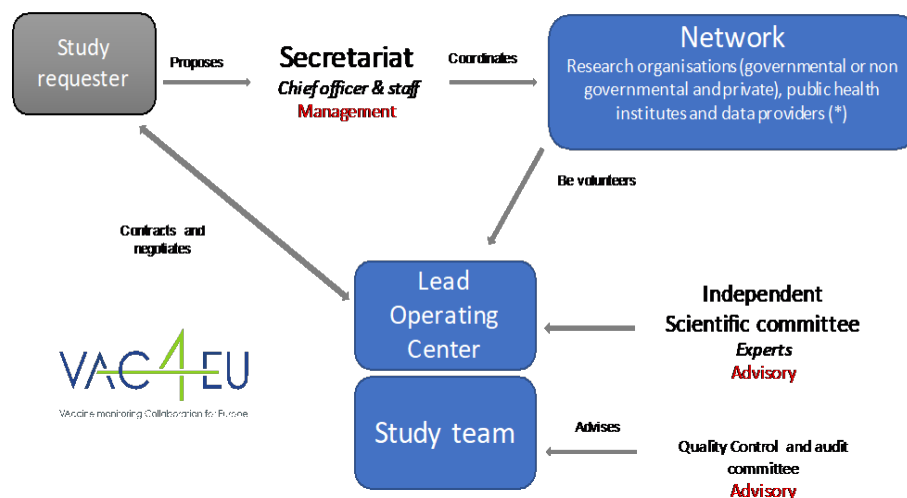
1. A community of scientists for open debates about methods, science and vaccines
2. A Multi-stakeholder Advisory Forum (MAF), to be consulted by the Executive Board for EU strategies

The VAC4EU secretariat will administer the VAC4EU organization.

How does VAC4EU operate?

- In VAC4EU membership is open to qualified research organizations (not publicly listed) and public health institutes.
- Vaccine Manufacturers, National Regulatory Agencies and European Agencies cannot be a member of VAC4EU but can be consulted for strategy assessment through the MAF.
- Vaccine Manufacturers, National Regulatory Agencies and European Agencies and others may request or tender studies to be conducted through VAC4EU, according to Best Practice, methods and processes created in ADVANCE.
- The VAC4EU secretariat facilitates interactions between study requesters and the study network.
- The VAC4EU study network creates a study team and a lead operating centre, which will contract with the study requester and the collaborating organizations.

Study governance



VAC4EU will leverage the trust that has been built during the ADVANCE project and other FP-7 funder projects. Letters of interest have so far been received from 18 organizations, having access to data on more than 120 million subjects.

1.7 Lessons learned and further opportunities for research

The IMI Call which ultimately led to the ADVANCE project was one of the actions proposed to address the gaps in post-marketing surveillance of vaccines observed during the H1N1 pandemic campaign. The need to improve interaction and collaboration across all stakeholders was one of the major challenges. This could only be tackled by joining all main stakeholders in the same project. In this case this meant that Vaccine Manufacturers, Regulatory Agencies and Public Health Institutes should agree to a joint effort. This was a very challenging task given the various sensitivities. It was achieved ultimately in ADVANCE but it definitely could not have been possible without a clear and established framework for research-oriented collaborations such as IMI.

Over the entire project we have maintained an open forum where all stakeholders were able to clarify their needs, express their concerns, and educate the others about their own constraints (such as specific regulations, standards, transparency level...). The so-called proof-of-concept studies have been delivered by study teams where members were mixed from various stakeholders, and this was a unique opportunity. This approach was formalized in a Code of Conduct (later published). Similarly, the multiple discussion on governance have led to a set of definitions of the roles and a systematic approach to describe the governance structure for any project. This was already used for VAC4EU, the platform designed to succeed to ADVANCE in a sustainable mode.

The extent of the diversity of stakeholders was very large in ADVANCE. Bringing together the expertise, background and knowledge of the various stakeholders was a major benefit. We could also observe

some unexpected disadvantages of PPPs, such as the potentially increased complexity and administrative burden due to the need to satisfy the various mandates and obligations of the different stakeholders. Vaccine Manufacturers (or EFPIA/MAHs in general) may have to observe stricter obligations than others, for example in terms of time-consuming and resource-intensive traceability and documentation processes.

The benefits we have seen and some of the challenges have been extensively discussed. Concerns about scientific integrity and independence due to potential or real conflicts of interest when public authorities and vaccine MAHs collaborate could also have a negative impact on public trust. Therefore, our main recommendation is that:

- PPC should only be envisaged if the anticipated advantages of the collaboration outweigh the expected disadvantages for all the stakeholders involved; and
- the governance model should be as simple as possible, transparent, acceptable to all partners, and appropriately-sized to ensure efficiency. The roles and responsibilities and decision-making rules should be agreed between the partner organizations and explicitly described.

As explained above, the ADVANCE project has produced and published a guidance on governance models for PPP projects where these recommendations are detailed. This guidance also provides a framework to ensure that any proposed governance is clear, explicit, as well as visually recognizable.

ADVANCE was designed from the start as a first step to a sustainable follow-up. The project has concluded with a sustainability plan which is now being implemented as a new platform, under the name of VAC4EU. This platform will be a non-profit association, which will function in effect as service provider. For various reasons, this will no longer function as a PPP - for example, Vaccine Manufacturers (EFPIA) can be customers but cannot be members. Other more inclusive options have been debated within the project but could not be selected. For example, innovative approaches such as a match-making service was proposed. This could well be an interesting subject for further research, along with other options such as more open data. Management of conflict of interest was another related hot debate which could not really conclude. One innovative approach was proposed in the Code of Conduct, which suggests to increase diversity across all stakeholders to cancel out the possibly diverging interest, under a clear framework of guiding principles. This proposition is clearly still met with resistance (including within VAC4EU) and further elaboration and testing may also be a very relevant and valuable topic for further research.