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Accelerated Development of VAccine beNefit-risk Collaboration in Europe

IMI JU Grant Agreement nº115557

POC Study Protocol

Testing new approaches to monitoring benefit/risk with pertussis vaccines as test case: Incidence rates of pertussis and pertussis related outcomes of whole-cell pertussis and acellular pertussis vaccines in pre-school children

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

Disclaimer: *The study described in this protocol are conducted as part of the IMI ADVANCE project with the aim to test methodological aspects of the design, conduct and reporting of studies for vaccine benefit-risk monitoring activities.*

The protocol presented herein relates solely to the testing of these methodologies and is not intended to inform regulatory or clinical decisions on the benefits and risks of the exposures under investigation. Therefore any use of information from these studies should carry over this warning and be used accordingly.

V 1.3

Title	– Incidence rates of pertussis and pertussis related outcomes of whole-cell pertussis and acellular pertussis vaccines in pre-school children
Medicinal product	All available whole-cell pertussis- and acellular pertussis-containing vaccines
Product reference	Any acellular pertussis- and whole-cell pertussis-containing vaccines
Research question and objectives	The overall ADVANCE proof-of-concept (POC) question is to test the system for benefit-risk monitoring of vaccines in Europe. This will first be done by using test cases. For this POC, the following research question is used: "Has the initial benefit-risk profile in children prior to school-entry booster been maintained after the switch from whole-cell pertussis vaccines to acellular pertussis vaccines"? The objectives of this specific study that focuses on the benefits of pertussis vaccines are: 1. To assess the suitability of healthcare databases to estimate the incidence rates of pertussis following pertussis vaccination 2. To estimate the incidence rate of pertussis by age in infants and children up to school-entry or age 6 years – after any dose of primary or booster vaccine, dose-specific 3. To estimate the incidence of non-fatal pertussis-related complications leading to hospitalizations, i.e. febrile seizures and pneumonia in infants and children up to age 6 years 4. To assess the risk of death after diagnosis with pertussis in infants and children up to age 6 years For objectives 2-4, calendar month-specific incidence rates will be calculated using common standards and tools, this will also allow for time sequential analyses in methods development
Countries	Participating electronic health care databases from ADVANCE partners and associated partners in Denmark (Aarhus and national), UK (RCGP, THIN), Spain (IDIAP, FISABIO, BIFAP) and Italy (Pedianet, ASL Cremona), based on quality assessment (fingerprinting)
Authors	**Benefit POC Team**: Lisen Arnheim Dahlström, Toon Braeye, Maria de Ridder, Steffen Glismann, Silvia Peréz-Vilar, Fabian Alvarez, Susanne Hartwig, Ulrich Heininger, Tin Tin Htar Myint, Danielle Nijsten, Miriam Sturkenboom, Kaatje Bollaerts **Authors from POC Outline Document** (Parts of this study protocol have been copied from the POC Outline Document) **Main Authors**: Nicoline van der Maas, Kaat Bollaerts, Denis Macina, Miriam Sturkenboom, Vincent Bauchau **Reviewers**: Simon de Lusignan, Hanne Dorthe Emborg, Mendel Haag, Michael Greenberg, Ulrich Heininger, Alena Khromava, Piotr Kramarz, Xavier Kurz, Harshana Liyanage, Patrick Mahy, Laurence Pagnon, Tin Tin Htar Myint, Marianne van der Sande, John Weil, Eddy Ziani

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LIST OF ABBREVIATIONS

ADVANCE	Accelerated Development of VAccine beNefit-risk Collaboration in Europe
aP	acellular pertussis (vaccine)
ATC	Anatomical Therapeutic Chemical
CDM	Common Data Model
EMC	Erasmus Medical Center
IEC	independent ethics committee
ECDC	European Centre for Disease Control and Prevention
GP	general practitioner
ICD	International Classification of Diseases
IRB	institutional review board
POC	proof-of-concept
REB	research ethics board
RRE	remote research environment
WP	work package (i.e. WP5)
wP	whole-cell pertussis (vaccine)

1. RESPONSIBLE PARTIES

1.1. Main Author(s) of the Protocol

Name	***Institution***	***Role***	***Contribution***
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Toon Braeye			drafting statistical analysis in draftv0.1 150709
Lisen Arnheim Dahlström, Danielle Nijsten, Silvia Perez Villar			Review of v0.1.150709
Lisen Arnheim Dahlström			drafting of v0.2.150807
Miriam Sturkenboom			review, editing of v0.2.150807
Lisen Arnheim Dahlström, Maria de Ridder			Updating and editing according to SC comments and coordination team, new version v03.150907
Lisen Arnheim Dahlström, Stefan Glismann, Ulrich Heininger, Miriam Sturkenboom			revisions of v03.150907, resulting in v03.150915
SSI, BIFAP, SPMSD, Sanofi Pasteur and ECDC			Updating the protocol according to comments received from the consortium
Miriam Sturkenboom			Revisions of v1.2 definition of convulsions
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Germano Ferreira, Lampros Stergiopoulos	SURREY, P95	Section on POC evaluation	
Caitlin Dodd, Rosa Gini	EMC, ARS	Section on quality of database	In collaboration with WP 4

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1.3. Study Team

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- Maria de Ridder: EMC

VIROLOGISTS/PERTUSSIS VACCINE EXPERTS

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- Steffen Glismann: GSK
- Vana Spoulou: UOA
- Fabian Alvarez: SANOFI

ADDITIONAL MEMBERS

- Danielle Nijsten: RIVM
- Susanne Hartwig: SPMSD
- Tin Tin Htar Myint: PFIZER
- Leonoor Wijnans: EMC
- Marco Cavaleri: EMA

PROJECT MANAGER

- Silvia Pérez-Vilar: FISABIO & Erasmus MC

DATABASE LIAISONS/CUSTODIANS

Databases will be participating upon demonstration of data quality in the quality assessment module (fingerprinting) that will take place prior to start of the POC study. Custodians of contributing databases will be members of the study team.

Table 1: List of Database contacts who will be contacted for feasibility testing

Datasource	Contact
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2. ABSTRACT

Date of Protocol Abstract:
April 16 2016

Title: Incidence rates of pertussis and pertussis related outcomes of whole-cell pertussis and acellular pertussis vaccines in pre-school children

Observation Period: 1 January 1990 – 31 December 2015

Rationale and Background: The overall ADVANCE proof-of-concept (POC) objective is to test the system for benefit-risk monitoring of vaccines in Europe. This will first be done by using test cases. For this POC analysis, the following research question is used: "Has the initial benefit-risk profile in children prior to school-entry booster been maintained after the switch from whole-cell pertussis (wP) vaccines to acellular pertussis (aP) vaccines?"

This protocol aims to obtain the data on the benefits that will feed into the benefit-risk model.

Research Question and Objectives:

The objectives of this specific analysis that focuses on the benefits of pertussis vaccines are:

1. To assess the feasibility of healthcare databases to estimate the incidence rates of pertussis following pertussis vaccination
2. To estimate the incidence rate of diagnosed pertussis in infants and children up to school-entry or age 6 years – any case at, or between, any dose of primary or booster vaccine, dose-specific
3. To estimate the risk of non-fatal pertussis-related complications leading to hospitalizations, i.e. seizures and pneumonia in infants and children up to age 6 years
4. To assess the risk of deaths following pertussis in infants and children up to age 6 years
5. To calculate calendar month-specific incidence rates which will also allow for time sequential monitoring of effectiveness in the methods development

Design: The main design is a retrospective dynamic cohort analysis

The analysis will be conducted utilizing electronic health care data from ADVANCE partners in Denmark, UK, Netherlands, Spain and Italy.

Population: The source population for this analysis will comprise all children registered in any of the participating databases during the study period and for whom an adequate start and end of follow-up and date of birth can be defined.

The study population for analysis will comprise all children registered in any of the participating databases during the study period and for whom an adequate start and end of follow-up and date of birth can be defined. Children will be followed from birth until the end of study period (31-12-2015, the school-entry pertussis booster, transferring out of the database, death, reaching age 6 years: whichever is the earliest), children from the study population will enter the study cohort upon first dose of pertussis vaccine.

Variables:

Exposures of interest

All childhood pertussis vaccination schedules prior to the current scheduled age for school-entry booster if any, as defined by individual national/local immunization programs, or no later than 6 years of age

Outcomes

- Pertussis disease
- Complications of pertussis leading to hospitalization, i.e. pneumonia and seizures
- Death following pertussis

Data Sources:

- Electronic health care databases (record linkage, surveillance and GP-based databases) currently available in the ADVANCE consortium and eligible are located in Denmark, Spain, Italy, The Netherlands and UK. Short descriptions of databases and their full names will be included in this protocol upon final decisions of inclusions
- Informative data sources: European Centre for Disease Prevention and Control (ECDC) pertussis schedules in Europe and switch points of national ministries of health

Size: Total population (0-6 year of age) of all eligible ADVANCE databases

Data Analysis: Incidence rates of pertussis will be calculated by age in months, sex, country, calendar time (year and month) and wP/aP type and dose.

The risk of complications and death will be calculated within the 30 days after occurrence of pertussis disease in all subjects with a recorded diagnosis of pertussis. Risk will be stratified by age in months, sex, country, calendar time and wP/aP type and dose.

Informed Consent and Ethical Approval: The study will be conducted on the basis of secondary use of electronic healthcare records. Each database will apply local governance and privacy rules prior to aggregating and sharing anonymized data.

Milestones:

Draft protocol: July 31 2015

Submission to SC: August 6, 2015

Comments from SC: August 31, 2015

Submission for consortium review: September 2015

Finalized and cleared protocol: November 20 2015

Submission to Ethics Committee/Institutional Review Board: January 2016

Updated protocol after review: April 15, 2016

Final data extraction to CDM: June 15, 2016

Running scripts and submission to RRE: June 30, 2016

Data analysis: July 2016

Data interpretation and reporting: August 2016

Final report of study results: September 2016

3. AMENDMENTS AND UPDATES

Protocol amendments following IRB approval:

Table 2: Overview of Protocol Amendments and Updates

Number	***Date (DDMMMYY)***	***Section of the study protocol***	***Amendment or update***	***Reason***
1	160409		both	
2				
….				

4. MILESTONES

Table 3: Overview of Study Milestones

Draft protocol: July 31 2015

Submission to SC: August 6, 2015

Comments from SC: August 31, 2015

Submission for stakeholder consortium review: September 2015

Finalized and cleared protocol: November 20 September 30 2015

Submission to Ethics Committee/Institutional Review Board: January 2016

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Final data extraction to CDM: June 15, 2016

Running scripts and submission to RRE: June 30, 2016

Data analysis: July 2016

Data interpretation and reporting: August 2016

Final report of study results: September 2016

5. RATIONALE AND BACKGROUND [1]

The ADVANCE vision is to deliver "best evidence at the right time to support decision-making on vaccination in Europe". The mission is to establish a prototype of a sustainable and compelling system that rapidly provides best available scientific evidence on vaccination benefits and risks post-marketing for well-informed decisions. In light of this goal, the ADVANCE platform aims to provide evidence on the benefits and risks of vaccines to support decision-making by all stakeholders in a wide range of contexts. Examples of scenarios are the inclusion of a new vaccine in a vaccination program, and the occurrence of a new safety issue, e.g. when the benefits of the vaccine are questioned or when a new population is targeted (see Pertussis POC Outline).

The concept this POC analysis aims to demonstrate is as follows: in the event that an important decision regarding a health intervention is to be made, a benefit-risk assessment will be carried out. Upon a favorable benefit-risk assessment, the health intervention is implemented and the benefits and risks are monitored to investigate whether the benefit-risk balance is changing over time. The benefit-risk monitoring may focus primarily on the benefits and risks that could potentially modify the benefit-risk balance. If there is a strong indication that the benefit-risk has changed over time, a full re-assessment of the benefit-risk balance of the health intervention may be triggered using all accumulated evidence available at that point in time. To inform the benefit-risk assessment and monitoring, electronic health care databases available within Europe will be used.

To be able to prove this concept of benefit-risk monitoring in ADVANCE without waiting for the evidence to accumulate prospectively, we will start from a historical decision and simulate monitoring through a retrospective analysis. Pertussis vaccination, particularly comparing wP and aP vaccination, was chosen by the ADVANCE Steering Committee as the subject of the first POC study. Therefore, the starting point of the current POC analysis is the historical decision to switch from wP to aP vaccination in children in the pioneering countries.

PERTUSSIS DISEASE

Pertussis, also referred to as whooping cough, is a highly contagious respiratory disease caused by bacteria of the *Bordetella* genus, mainly *B. pertussis*, although other *Bordetella*-species also occur [1,2]. Pertussis is acquired through transmission of large respiratory droplets generated by coughing or sneezing from infected persons [3].

Transmission by the indirect route occurs extremely rarely if ever [4]. *B. pertussis* causes respiratory symptoms, along with systemic effects, presumably mediated by secreted toxins [4]. Infections range in clinical presentation from asymptomatic to severe. They are most severe, even life-threatening, in young infants before they are immunized [5]. It is less frequently severe in older children, adolescents, and adults.

[1] This section is obtained from the POC outline: https://www.dropbox.com/s/ioru753h9h8cy44/240315_POC%20pertussis%20outline_version%201.5_tobedistributed.docx?dl=0

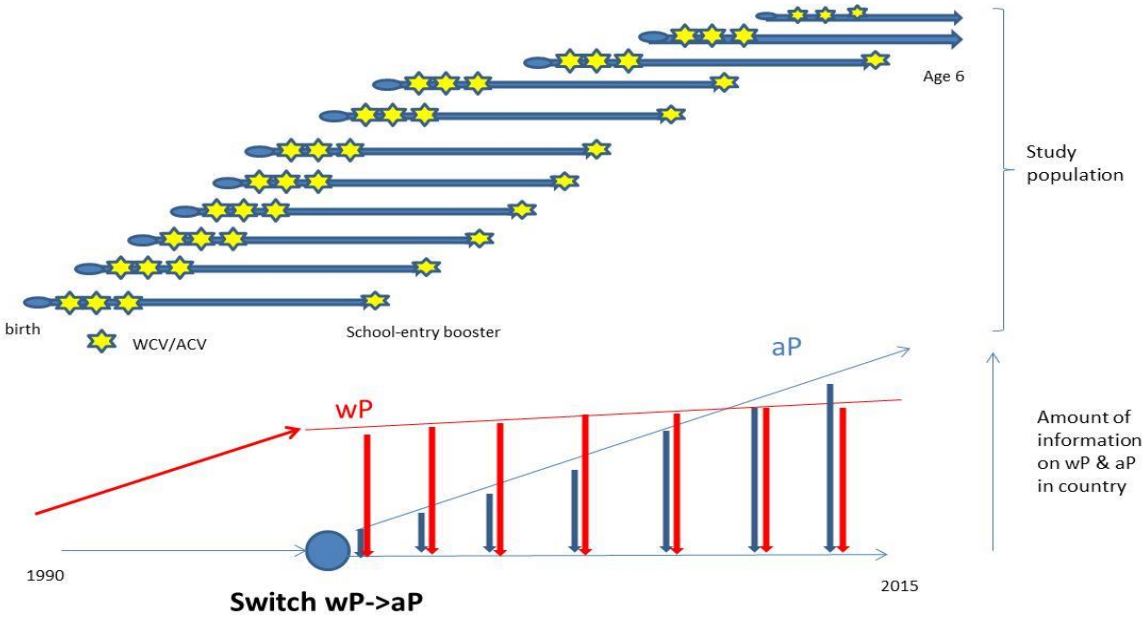

Figure 1: Graphic Representation of Time Axes/Horizons

For the study, a retrospective approach is taken (i.e. all benefits and risks to be measured have already occurred). For the decision analysis, benefits and risks will be compared between wP and aP. The evidence for wP vaccines has been accumulated mostly prior to the switch, with some data coming afterwards from the last vaccinated persons. Evidence from aP vaccines at the time of the switch comes mostly from clinical data and is complemented by post-marketing data after the switch. The arrows in Figure 1 show that the increasing amount of evidence on benefits and risks for wP and aP will be cumulatively assessed from the time of the switch. The upper part represents the time frame for the study subjects; these will be followed from start of the study period, one month after date of birth, or date of valid data in the database (whichever is the latest) until the end of study period (31-12-2015, the school-entry pertussis booster, transference out of the database, death, attainment of age 6 years: whichever is the earliest). Rates and risks of benefits and risks will be assessed by type and dose of aP or wP. Note: the primary vaccination series in infancy follows a '2+1' or '3+1' schedule, depending on country.

Typical clinical disease is characterized by three phases. After 7-28 days of incubation, the catarrhal phase (1-2 weeks) is largely nonspecific with coryza, eye redness, frequent coughing and sneezing. It is followed by a 1-6 week-long paroxysmal phase during which intense paroxysms of cough may lead to choking, emesis and the characteristic inspiratory whoop [3]. In very young infants, cough is often absent and apnea seems more characteristic of the disease [6]. Fever is rare in pertussis. The convalescent phase sees declining symptoms over widely variable duration [3].

Clinical criteria for the diagnosis of pertussis include a cough lasting at least two weeks and at least one of the following three: paroxysms of coughing, inspiratory 'whooping', and/or post-

tussive vomiting; or any person diagnosed as pertussis by a physician, or apnoeic episodes in infants.

Pertussis infection may be followed by common but usually self-limiting complications such as apnea, seizures, vomiting, gastroesophageal reflux, rib fracture, subconjunctival hemorrhages, epistaxis or syncope secondary to the paroxysms [4,5]. According to the Institute of Medicine report[2], apnea and respiratory arrest are the most common complication of pertussis followed by pneumonia and gastroesophageal reflux. Encephalopathy is a rare complication and occurs most often in younger patients. Other complications include seizures, ataxia, aphasia, blindness, deafness, subconjunctival haemorrhages, syncope, and rib fractures. Pertussis is most serious in infants less than 12 months of age, and the risk of death is highest among infants less than 6 months old.

TYPE OF PERTUSSIS VACCINES

Vaccines against pertussis were developed in the 1920s and have been used more widely since the 1940s [7]. The first vaccines were wP vaccines containing suspensions of killed *B. pertussis* organisms [4]. The production process varied between different wP vaccines, resulting in differences in antibody responses. Furthermore, due to the use of the whole bacterium, composition and thus immunogenicity, efficacy and reactogenicity of a specific wP vaccine could change over time, from lot to lot within one wP vaccine, and from one wP vaccine to another. Reactogenicity of the wP vaccine is probably due to their endotoxin lipopolysaccharide (LPS) content [8]. In an attempt to reduce reactogenicity, aP vaccines were developed. They were used for the first time in 1981 during mass vaccination campaigns in Japan [9], and more widely during and since the 1990s. aP vaccines contain purified secreted and surface components of *B. pertussis* which, based on animal models, are thought to play an important role in pathogenesis and induction of immunity [4]. Later on, several aP vaccines were manufactured, containing between one and five different pertussis components [2].

All aP vaccines contain at least a detoxified pertussis toxin (PT); the second antigen added in all formulations with two or more components is filamentous haemagglutinin (FHA); three-component vaccines contain also pertactin (PRN); finally, four- and five-component vaccines contain one or more fimbrial agglutinogens or fimbriae (FIM). Almost all aP vaccines are adjuvanted with aluminium salts and combined with diphtheria and tetanus toxoids, and possibly also additional vaccine valences such as inactivated poliovirus, *Haemophilus influenzae* type b and/or hepatitis B [4].

PERTUSSIS VACCINATION SCHEDULES IN EUROPE

Between 2004 and 2015 several countries switched from wP to aP vaccines for infants and children. All other countries in Europe switched to aP vaccines prior to 2006 (starting in the 1990s for some countries). As of March 2015, all countries except Poland use exclusively aP vaccines. In most cases, the switch to aP vaccines was conducted over a narrow age-cohort, while only in very few cases, such as Poland, the switch occurred, or is occurring progressively

[2] http://www.nap.edu/openbook.php?record_id=13164&page=529

over years. Different types of vaccines are being used. As part of the coverage pillar the way participating countries switched should be described.

Since the start of the introduction of pertussis vaccine in the 1940s, many countries have tended to adapt and customize the schedules of their vaccination programs, adding and removing doses, changing ages of primary and booster schedules, with or without catch-up campaigns, and transitioning from wP to aP vaccines for all doses, for one or more booster doses only, or not yet at all. As a result, pertussis vaccine schedules vary largely across Europe.

For detailed information on the schedules currently used in Europe, see Figure 2, and for more details see ECDC-website (http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx).

<table>
<tr><th>Schedule type</th><th colspan="4">First year of life</th><th>Second year of life</th><th>Third year of life</th><th>Preschool booster</th><th>Adolescent booster</th><th>Country</th></tr>
<tr><td rowspan="2">'2p+1'</td><td colspan="2">From 6 weeks to 6 months</td><td colspan="2">Around first birthday</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="2">P1</td><td colspan="2">P2</td><td>B1</td><td></td><td></td><td rowspan="2">B2</td><td>B3</td><td>F, IT, FI, NO, IS, SK</td></tr>
<tr><td colspan="4"></td><td></td><td></td><td></td><td></td><td>SE*, DK, RO, AT</td></tr>
<tr><td rowspan="4">'3p+1'</td><td rowspan="4">P1</td><td rowspan="4">P2</td><td rowspan="4">P3</td><td></td><td>B1</td><td></td><td>B2</td><td>B3</td><td>BE, BG, CZ, EE, DE, GR, HU, LI, LU,</td></tr>
<tr><td></td><td>B1</td><td></td><td>B2</td><td></td><td>HR, CY, LV, LI, MT, NL, PL, PT, SI, ES</td></tr>
<tr><td></td><td></td><td>B1</td><td></td><td></td><td>UK</td></tr>
<tr><td></td><td></td><td></td><td>B1</td><td>B2</td><td>IE</td></tr>
<tr><td>Vaccine combination generally used in EU/EEA</td><td colspan="4">• DTaP-IPV-HepB/Hib ('hexavalent')
• DTaP-IPV/Hib ('pentavalent')
• DTaP-IPV ('tetravalent')
• DTwP-IPV/Hib ('whole-cell pertussis combo')
• Hep B (used in conjunction with pentavalent)</td><td>• Hib-MenC combo</td><td>• DTaP-IPV
• TdaP
• Tdap-IPV
• Tdap</td><td>• Td
• Tdap
• Tdap-IPV</td><td></td></tr>
</table>

P=primary dose; B=booster dose

Figure 2: Recommended Pertussis Schedules from ECDC Report on Pertussis Vaccine Shortage (October 2015)

The World Health Organization (WHO) standards of childhood pertussis vaccination recommend a three-dose primary series administered between 6 weeks and 6 months of age, followed by a booster dose, preferably in the second year of life. As previously mentioned, various countries have adapted and customized their vaccination schedules according to their policy considerations. As of March 2015, 19 countries use a three-dose schedule for the primary series, either at 2-3-4 months of age (n=9) or 2-4-6 months of age (n=10). Most of these countries give a toddler booster dose towards the end of the first year of life (n=3) or during the second year of life (n=13). In one country this booster dose can be administered before or after the first birthday; two countries do not recommend any toddler booster dose. Seven countries administer a two-dose primary series at three and five months of age, followed by a booster for 12 month-olds. Only France has a two-dose schedule at two and four months of age followed by a booster at 11 months of age.

All countries, except Malta, recommend one (n=11), two (n=15) or three (n=4) further aP booster doses between two and 18 years of age.

Six countries recommend one or more aP booster doses for all adults and/or elderly. Two countries (United Kingdom and Ireland) only target pregnant women in their last trimester of pregnancy (since late 2012).

VACCINE BENEFITS

Efficacy

Although surveillance observations demonstrated that wP vaccines are efficacious, no formal prospective wP efficacy trials were initially conducted [2]. The main body of evidence of vaccine efficacy for both wP and aP vaccines stems from six trials conducted between 1990 and 1995, which compared a few wP vaccines, some of which are still in use today, to most of the currently used aP vaccines [10-15]. However, differences in the design of these studies and in the outcomes case definitions limit the comparability of the results across trials. For the wP vaccines, efficacy estimates ranged between 89% and 96%, except for the Connaught USA wP, for which an efficacy of 36%-48% was calculated [10,11]. Efficacy estimates for aP that were eventually introduced for broad vaccination programs ranged between 71%-85%

The impact on efficacy of the number of components in aP vaccines remains controversial. In addition, the follow up time in these studies was limited to about two years.

Impact of pertussis vaccination programs

It is recognized that the duration of protection with wP and aP vaccines is not as long as protection following natural infection with *B. pertussis*, although natural infection does not lead to life-long immunity. The waning of immunity following immunization with pertussis vaccines is well documented and such data must be included when a vaccination program impact is estimated.

At the ecological level of evidence, it is widely accepted that introduction of wP vaccines in broad childhood vaccination programs around the world has resulted in dramatic decreases in incidences of childhood pertussis. In the 1980s and 1990s (after large efficacy trials had been performed), aP vaccines were introduced and have now replaced wP vaccines mainly in western countries and Japan.

In the context of a steadily increasing reported incidence of pertussis since the 1980s, large pertussis outbreaks have been reported since 2009 in several developed countries using aP vaccines, for example in the US, the UK and Australia, despite relatively high childhood vaccine coverage [16-19]. Conversely, pertussis appears to be much better controlled in other countries like Sweden and France, which have also been using aP vaccines for more than 15 years. Some evidence also suggests that the resurgence of pertussis may not be limited to aP vaccine-using countries. The UK introduced aP vaccines in September 2004 with three doses in infants at 2,3,4 months of age, while the highest number of pertussis cases during the 2012 outbreak were reported outside the cohort of children vaccinated with aP vaccines (adolescents, adults and infants less than 3 months of age) [16]. The UK Department of Health introduced immunization of pregnant women to control the outbreak and to reduce the morbidity and mortality among infants too young to be immunized [16,20]. In several analyses of data

obtained in this context, Public Health England estimated that vaccinating pregnant women with an aP vaccine in the 3rd trimester of pregnancy had 90-93% effectiveness in protecting unvaccinated infants in the first 2 months of life against pertussis [21,22]. The outbreak of pertussis subsided in 2013, with incidence diminishing from more than 1600 cases at its peak in October 2012 to less than 250 cases per month on average in October through December 2013 [23]. Overall, in 2012 in the EU/EEA, ECDC reported incidence rates that varied between 0 and 0.05 per 100,000 in Malta and Hungary, respectively, to 85 per 100,000 in Norway. A notable increase in reported incidence was observed in 10 of 28 reporting countries, including the countries reporting the highest number of cases overall (i.e. the Netherlands, Denmark, the United Kingdom, Norway) [24]. The highest age-specific incidence of pertussis cases, hospitalizations and complications, is in infants 0 to 1 years of age, and mainly before 3 months of age in most countries (38.5 cases per 100,000 in 2011) [25]. Most young infants acquire pertussis from adults or adolescents in their own households, mainly parents (20-55%) and siblings (19-53%) [26]. In contrast, other countries such as Germany reported the highest age-specific incidence in adolescents [27], although there is variability by region with some also having the highest incidence in infants [28]. Furthermore, in 2012 in the EU, the most affected age group was those aged 5-14 years [24]. The improvements in surveillance methods, case-confirmation technology and the increased awareness of disease groups may have contributed to the increased detection of the milder forms of disease that more typically affect them.

Sizeable outbreaks have also been reported in wP vaccine-using countries such as Argentina, Chile and Uruguay in recent years [29,30]. The coverage with pertussis vaccines is an important factor for control of the disease, and drops in coverage have often resulted in rapid and large increases in disease incidence.

The re-introduction of pertussis childhood vaccination with aP vaccines in 1996 in Sweden following a 17-year gap in vaccination after the wP vaccines were abandoned in 1979, showed a large effect on the incidence of disease, demonstrating the effectiveness of aP vaccines in protection against childhood pertussis. Further ecological evidence of the effectiveness of aP vaccines was provided in the IMPACT surveillance network in Canada, with an 85% reduction in pertussis hospitalizations when the aP vaccines were introduced following the use of a poorly efficacious wP vaccine [31].

As evidenced in numerous publications, the recent resurgence and outbreaks likely result from the combined impact of multiple factors. These include enhanced awareness of disease, increased case reporting [32], rapidly increasing availability of more sensitive diagnostic tests (e.g. polymerase chain reaction) [33], and differences in vaccination schedules and coverage [34-38], while it is still a matter of controversy whether mutational evolution of circulating pertussis strains are causally related to aP vaccine use [39-42]. However, a central hypothesis analyzed to explain the current epidemiologic observations has been the potentially different immune response (Th1/Th2), and a differential waning and 'boostability' of the immunity elicited by aP compared to wP vaccines [43-51].

Effectiveness

Numerous observational studies have confirmed the immediate effectiveness of most wP and all aP vaccines used in large vaccination programs. Several studies have also investigated the duration of the protective effectiveness elicited by both wP and aP vaccines. After reviewing existing literature, Wendelboe et al. estimated that pertussis vaccination conferred protection for four to 12 years (duration of protection) with no great differences between wP and aP [52]. However, in light of the recent resurgence and outbreaks of pertussis observed in some countries, a number of observational studies have suggested a shorter long-term effectiveness of aP compared to wP. Some investigators assert that aP vaccines given to infants and young children provide shorter duration of protection than wP vaccines. However, it is important to highlight that none of the historical and recent evidence questions the immediate effectiveness of pertussis immunization in young children.

Furthermore studies in the 2010 California outbreak and in the 2012 Oregon outbreak confirmed that a full aP vaccination series elicited high levels of protection lasting until the age of the adolescent booster [43,53]. These latter findings are broadly considered as evidence that the current aP vaccines given to infants and young children do not prime recipients as well as wP vaccines did for future boosting, which is always done with aP vaccine.

Vaccine failure

Vaccine failure should be defined according to the CIOMS criteria [54]:

a) Confirmed Vaccination Failure

> The occurrence of the specific vaccine-preventable disease in a person who is appropriately and fully vaccinated, taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunization.

This definition requires clinical and laboratory confirmation (or epidemiological link to a confirmed case) that the actual disease is vaccine-preventable, i.e. that the pathogen (including, where appropriate, type, subtype, variant, etc.) and clinical manifestations are specifically targeted by the vaccine.

b) Suspected Vaccination Failure

> The occurrence of disease in an appropriately and fully vaccinated person, but the disease is not confirmed to be the specific vaccine-preventable disease, e.g. pneumococcal disease of unknown serotype in a fully vaccinated person.

c) Immunological Failure

> The failure of the vaccinee to develop the accepted marker of protective immune response.

This definition requires that there is an accepted correlate or marker for protection, and that the vaccinee has been tested/examined at an appropriate time interval after completion of immunization.

6. RESEARCH QUESTION AND OBJECTIVES

The overall ADVANCE POC question is to test the currently available system and its feasibility for benefit-risk monitoring of vaccines in Europe. This will first be done by the following research question: Has the initial benefit-risk profile in children prior to school-entry booster been maintained after the switch from wP to aP vaccines?

The objective of the work of the benefit pillar is to calculate incidence rates that will feed into the benefit/risk model (benefit-risk protocol).

The specific objectives of the benefit pillar are:

1. To assess the feasibility of healthcare databases to estimate the incidence rates of pertussis following pertussis vaccination
2. To estimate the incidence rate of diagnosed pertussis in infants and children up to school-entry or age 6 years – any case at, or between, any dose of primary or booster vaccine, by dose, type and calendartime (year/month)
3. To estimate the risk of non-fatal pertussis-related complications leading to hospitalizations, i.e. seizures and pneuomonia in infants and children up to age 6 years (these complications will be analyzed separately)
4. To assess the risk of death after diagnosis with pertussis in infants and children up to age 6 years
5. To calculate calendar month-specific incidence rates which will also allow for time sequential monitoring of effectiveness in methods development

Double counting of events leading to complications and death will be avoided by considering the worst outcome.

7. RESEARCH METHODS

The overall ADVANCE POC question is to test the currently available system for benefit-risk monitoring of vaccines in Europe. The system will be tested around the following B/R question: Has the initial benefit-risk profile in children prior to school-entry booster been maintained after the switch from wP to aP pertussis vaccines?

7.1. Process and methodology for system-testing

Although the system testing will occur largely outside of this study, it is summarised here, with details provided in annexes.

The system testing follows several steps which are visualized in the figure 3 and described in the following chronological order:

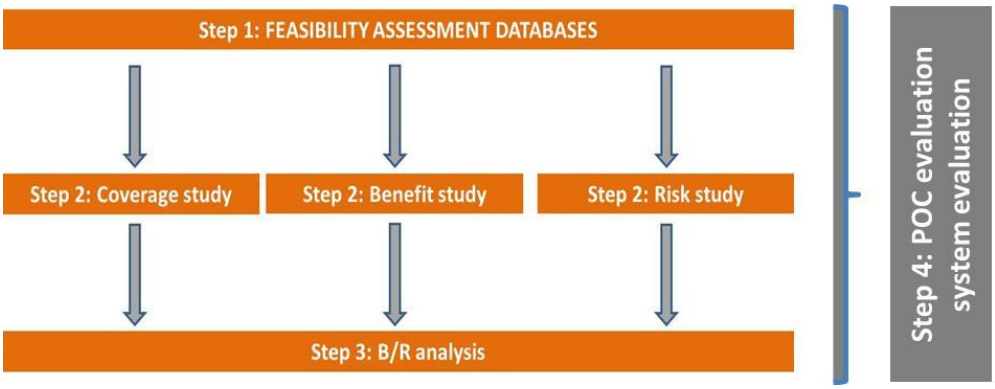

Figure 3 Visualization of the stepwise approach to the system testing

Step 1: Feasibility assessment of the databases: this step will assess whether the quality of the candidate database is sufficient inclusion in the study. The focus will be on what type of data are available in the databases and whether population, events, and exposure may be misclassified. This step is largely based on the so-called fingerprinting which has been described in deliverable D5.2. A summary of the components and methods is provided in appendix 1. A quality assessment summary will be created per database, with decisions whether the data-sources can or cannot participate in the different pillar studies (see below under 7.2). Responsibility of fingerprinting lies with the workpackage leaders.

Step 2: Estimation and delivery of the rates for coverage, benefits and risks, this is described in the different 'pillar' protocols in the databases that may generate adequate results according to the feasibility assessment. Responsibilities are with the study teams that have generated the protocols

Step 3: B/R analysis: integration of the incidence rates (generated from step 2) with the utilities to generate a B/R model, as described in the B/R analysis protocol, responsibility with the B/R study team

Step 4: Evaluation of the studies and the systems used. This is conducted by a POC evaluation team which is separated on purposes from the POC study teams. A description of the framework for the POC evaluation is attached in appendix 2.

The purpose of this protocol is to describe in detail the methods for the risk study in step 2.

7.2. Methods for estimations in the scientific question

7.2.1. Study design

A retrospective dynamic cohort analysis to estimate incidence rates of pertussis.

7.2.2. Setting

The analysis will be conducted in multiple population-based healthcare databases in various European countries. Each database will be analyzed separately, however pooling can done in the heterogeneity testing which is part of WP4.

7.2.3. Databases/Data Sources

The POC feasibility study will be conducted on data in electronic healthcare databases that reside with partners and associate partners of the ADVANCE consortium. Based on an assessment of the quality of information on exposure and outcomes, which will take place as part of the fingerprint process prior to study initiation for all the outcomes, the databases will be selected. The quality criteria for a database (i.e., inclusion criteria) are:

a) Vaccination data on pertussis vaccine available

b) At least one of the outcomes available; and

c) Data access and clearance of protocol possible within timelines of the POC feasibility study.

d) Comparison of the rate of events against country specific benchmarks

The list below provides an overview of potential databases, based on initial assessment of population sizes; this list will be updated with new associate partners in the consortium.

Based on the meta-data, fingerprint data, and discussions and information from the databases, parameters in table 5 will be collected and described. This will be the basis for a decision whether the databases will be eligible for the next step (estimation), eligibility may differ for the different POC protocols.

7.2.4. Source Population

The source population in each of the databases will be the pediatric population from birth to age six years or when receiving the booster dose at school entry that is registered in the participating databases.

7.2.5. Study Population Selection

The study population for analysis will comprise all children registered in any of the participating databases during the study period and for whom an adequate start and end of follow-up and date of birth can be defined. Children will be followed from birth until the end of study period (31-12-2015, the school-entry pertussis booster, transferring out of the database, death, reaching age 6 years: whichever is the earliest), children from the study population will enter the study cohort upon first dose of pertussis vaccine.

7.2.6. Study Period

The study period is from 01 January 1990 to 31 December 2015, and also be dependent on availability of data from specific databases.

7.2.7. Variables

All study variables will be obtained from the participating electronic health care databases. These will be transformed their local datasets into a pre-defined ADVANCE common data model (CDM) to allow for the running of common scripts across all the databases.

7.2.7.1. Exposure of Interest, Operationalization and Validation

EXPOSURE OF INTEREST

The exposure of interest in this study will be all types of pertussis-containing vaccines that were available during the study period and used in the participating study population in the participating countries.

Table 4 Databases from ADVANCE partners that will be approached for feasibility testing

Datasource Country_name	Coverage, Region	Type of data	Years covered	Size (N persons)	Outpatient diagnoses	Inpatient diagnoses	Vaccines general	Prescribed/ dispensed drugs
BE_network of sentinel GPs	National	Surveillance network (paper based)	Since 1979	Based on patient contacts	Some (surveillance of specific diseases)	Specific diseases	No	No
BE_Pedisurv	National	Pediatric surveillance network	Since 2002	National case based	Specific diseases	Specific diseases	no	No
DK_SSI	National	Record linkage	1996 - 2014	7.5 million	Yes (ICD-10)	Yes (ICD-10)	yes	yes
DK-AUH	Regional (Aarhus)	Record linkage	2004 - 2013	1.7 million	Yes (ICD-10)	Yes (ICD-10)	partial	yes
ES_BIFAP	National	GP	2002 - 2013	4.8 million	Yes (ICPC+free text)	yes (as text)	No (only influenza)	yes
ES_FISABIO	Regional (Valencia)	Record linkage	Since 2005	5 million	Yes (ICD-9)	Yes (ICD)	yes	yes
ES_IDIAP	Regional (Cataluña)	GP	Since 2005	5.8 million	Yes (ICD-9)	Yes	yes	yes
FI_HPVCHRT	Trial participants	HPV RCTs+ extension through record linkage	Prospective since 2007	Around 20,000	Yes (ICD-10)	Yes (ICD-10)	yes	yes
IT_ARS	Regional (Tuscany)	Record linkage			no	Yes (ICD-9)	Not yet	yes
IT_ASLCR	Regional (Cremona)	Record linkage	2002 - 2013	454,188	No	Yes (ICD9)	Yes	yes
IT_Arianna	Regional (Casserta)	GP + record linkage	Since 2000	1.1 million	ICD9	ICD9	Not yet	yes
IT_PEDIANET	Regional (Veneto)	Family pediatricians	2004 - 2014	77,021	Yes	Yes	yes	yes
NL_IPCI	National	GP linked to RIVM vaccine registries	1996 - 2014	1.8 million	Yes (ICPC)	Yes (from letters/ specialist)	no	yes
NL_RIVM	National	Case surveillance of infectious	?	16 million base population	Some (surveillance of specific	Specific diseases	no	No

		disease			diseases)			
SE_KI	National	Record linkage	1998 - 2010	9.4 million	Yes (ICD-10)	Yes (ICD-10)	partial	yes
UK_RCGP	National	GP	2003 - 2014	2.0 million	Yes (READ)	Yes (READ)	yes	yes
UK_THIN	National	GP	1996-2013	8.3 million	Yes (READ)	Yes (READ)	yes	yes

Table 5 Assessment sheet for the quality /feasibility of the database to participate in the POC studies

Quality of information				
META-DATA				
Category	**Data**	**Measure(s)**		**Origin of information**
Provenance of information	Sources for diagnoses (as codes or text) • primary care • outpatient specialist • hospital discharge • emergency admission • causes of death	per type yes/no	Certain missingness?	Data provenance questionnaire to databases
	Vaccinations • routine childhood • HPV • travel • influenza • voluntary Drugs • prescribed/dispensed primary by GP • prescribed/dispensed by specialist • prescribed/dispensed during hospitalization	per type yes/no	Certain missingness?	AIRR survey
	Diagnostic tests • primary care outpatient specialist during hospitalization	yes/no	Certain missingness? Results?	AIRR survey
POPULATION				
Size	Number of lives (at any point in time) in population	N		Population fingerprint
	Number of subjects active at 1/1/2015	N		Population fingerprint
Dates	Missing Birthdate (no valid date entry (to be supplied by database owner)	N	Percentage on total number of lives	Attrition diagrams DBs
	Birth dates (day of birth independent of month)	Frequency of each day of the month of the DOB (1-31)	Percentage on total number of lives	Vaccine fingerprint (R)
Observation Time & lag time	Origin for the start of follow-up • birth (start of follow-up = birth) • registration with database (start of follow-up > 1 month after date of birth)	N	Percentage of total	Jerboa Event fingerprint
	Origin for the end of follow-up • death (end of follow-up = date of death in event file) • exiting from database (end of follow-up < last data availability for practice	N Median (5^{th}, 95^{th} percentile of lag time from date of delivery till	Percentage of total	Jerboa Event fingerprint

		last data)		
Gender/age	Population age Distribution (Overall and by sex)* at 1/1/2015 (representativeness of population)	N	Compared to national statistics (see D5.2)	Population fingerprint
Per type of vaccination				
Vaccinations: BCG, DTaP, DTwP, polio, Hib, HPV, Seasonal Influenza	Granularity of vaccine exposure data • vaccine type • ATC code • brand	N	Percent of total (vaccinetype) for these levels	Vaccine fingerprint
	Recorded dose vs. Derived dose vs. sequence (all possible combinations)	Cross-tabulation		Vaccine fingerprint, R
	Vaccination records without dose	N		Vaccine fingerprint, R
	Coverage in birth cohorts at age ….	Estimated Coverage (per methodology as developed in ADVANCE)	Comparison against WHO data, VENICE and local information	Vaccine fingerprint, R
	Coverage by dose	histogram of doses		Vaccine fingerprint, R
Per database and event				
Events	Name of event			
	Availability of codes	List of available codes per data domain	Frequency of each code in input files	Event fingerprint, Jerboa
	List of components	Name and description of query		Event team
	Frequency of events as detected by each component algorithm	Table of frequency of possible combinations		Algorithm comparison module of Jerboa
	Frequency of event as detected according to chosen algorithm(s)	Frequency by year		Component analysis
	Chosen algorithm and reason			Component analysis
Validity	PPV of chosen algorithm(s)	%	confidence measure	Output of the validity workflow
	Sensitivity of chosen algorithm(s)	%	confidence measure	Output of the validity workflow
	Specificity of chosen algorithm(s)	%	confidence measure	Output of the validity workflow
	Procedure to obtain the above estimates			Output of the validity workflow
External benchmarks	Validation Studies	Summaries of previously conducted validation studies in the database		Event team & database experience
	Estimates of frequency of the	Available		Event team &

	event in the population represented by the database according to external data sources (e.g. literature)	estimates with source (and comments)		database experience

OPERATIONALIZATION

Vaccinations will be obtained from the databases by using names of vaccines and database specific codes. Brand names and Anatomical Therapeutic Chemical (ATC) codes have been obtained from the EMA Art 57 database in which companies need to list all products they have available in the EU, as well as from whocc.no(see Appendix 3)

Vaccines will be categorized as wP, aP or unknown.

EXPOSURE WINDOWS

Persontime of follow up in the cohort will vary depending on outcome and dose of vaccination (see Section for data analysis for details).

VALIDATION

Information on the quality of recording of vaccinations will be obtained from the ADVANCE fingerprint (quality assessment) data by comparing coverage estimates from the databases with WHO/national coverage rates in the same age range. Some databases may not be able to provide brand names of vaccines. The quality of this information will be assessed in the fingerprinting (see appendix 1).

7.2.7.2. Outcomes, Operationalization and Validation

The outcomes for this study are:

1 Pertussis

2 Most frequently reported non-fatal pertussis-related complications leading to hospitalizations: i.e. pneumonia and seizures/convulsions. These complications are analyzed separately from each other.

Note. It is not necessary for the B/R model to have all related complications. Pneumonia and seizures were chosen, as they are the most common complications reported.

3 Death after pertussis diagnosis

DEFINITIONS OF PERTUSSIS

Pertussis can be defined both clinically and by laboratory assessment as well with epidemiological criteria. This study will use the criteria for clinical and laboratory assessment. There are several definitions of pertussis that are commonly used. The type of assessment and definitions have also changed over time. The most current case definition was published in

2012 by the ECDC and is described below [55]. Other commonly used definitions are presented in Appendix 5.

Since the type of laboratory assessment for pertussis has changed over time, we will distinguish between clinical (diagnosis based) and laboratory based definitions:

1 *Clinical criteria* for the diagnosis of pertussis are:

a) Any person with a cough lasting at least two weeks and at least one of the following three: paroxysms of coughing, inspiratory 'whooping', post-tussive vomiting, or

b) Any person diagnosed as pertussis by a physician, or

c) Otherwise unexplained apnoeic episodes in infants

2 For *laboratory criteria* at least one of the following is needed for diagnosis:

a) Isolation of *B. pertussis* from a clinical specimen

b) Detection of *B. pertussis* nucleic acid in a clinical specimen

c) *B. pertussis*-specific antibody response

Serology results need to be interpreted according to vaccination status according to Guiso et al [56].

For this study a case can be classified as possible, probable or confirmed depending on which criteria the patient fulfills:

a) *Possible case* – any person meeting the recorded diagnosis

b) *Probable case* – any person meeting the recorded diagnosis and with an epidemiological link[3]

c) *Confirmed case* – any person meeting the recorded diagnosis and the recorded laboratory criteria

Note: this is not EU case definition

DEFINITIONS OF PERTUSSIS RELATED COMPLICATIONS

Definitions of non-fatal pertussis related complications to be included into the study are found in Appendix 6 and 7. Theses complications are convulsions and pneumonia.

Fatal complication of pertussis is defined as death within 30 days of a recorded pertussis diagnosis

[3] A person may be considered epidemiologically linked to a confirmed case if at least one case in the chain of transmission is laboratory-confirmed. In case of an outbreak of faeco-oral or airborne-transmitted infections, the chain of transmission does not necessarily need to be established to consider a case epidemiologically linked.

OPERATIONALIZATION: IDENTIFICATION OF OUTCOMES FROM DATABASES

ICD-9, ICD-10, READ and ICPC codes will be used to identify outcomes in the databases (Appendix 4). These codes will be identified from the event definition, using Codemapper (see appendix 1) and be discussed with the databases which will create algorithms. Where available, data on laboratory confirmation will also be used; laboratory-confirmed pertussis and unconfirmed diagnoses will be distinguished and rates calculated separately.

VALIDATION

Verification of the extracted codes and proxies for extraction of events will be done as part of the quality assessment and harmonization process (fingerprinting) prior to the start of the POC. Age, sex and calendar-year specific incidence rates will be benchmarked between databases and against external sources such as literature or other publicly available data. No medical chart validation will be carried out in this POC study, since this POC focuses on system testing.

7.2.7.3. Other Variables and Operationalizations

- Age when receiving pertussis dose and year of birth
- Sex
- Calendar time (month and year)
- Country
- Pertussis disease anytime prior to dose

7.2.8. Data Analysis

Data from participating databases will be transformed into a common data structure.

Follow-up time after study entry will be split up by age (month), year of birth, vaccination dose and prior pertussis disease in each of the databases, as follows:

- from first dose until two weeks after Dose 1
- from two weeks after Dose 1 to Dose 2
- from dose 2 to 2 weeks after Dose 2
- from two weeks after Dose 2 to Dose 3
- from dose 3 to 2 weeks after Dose 3
- from two weeks after Dose 3 to school-enter booster or age 6

Follow-up time is split in these windows to allow for studying occurrence of pertussis by dose assuming that it takes 4 weeks after dose 1 and then 2 weeks after the following doses to reach its effect. Categories between different doses may be combined for intention to treat analysis

Non-compliant children will contribute to the actual number of received doses not to the planned doses.

The risk of pertussis complications will be followed up to one month after the occurrence of each pertussis case and death will be followed up to three months after pertussis diagnosis in cases with diagnosed pertussis. Risks will be cumulative incidence rates.

7.2.8.1. Statistical Hypothesis

The purpose of this study is to test the currently available system for benefit-risk monitoring of vaccines in Europe by being able to provide incidence rates of pertussis and pertussis-related complications following pertussis-containing vaccines for use in a multi-criteria decision analysis (MCDA) model of benefits and risks of wP and aP vaccines and immunoglobulins. Since the focus is on system testing no formal hypothesis testing will be conducted.

7.2.8.2. Statistical Methods

The incidence rate of each event will be calculated using a dynamic cohort approach. When analyzing the incidence of pertussis, for each person in the cohort, follow-up time will be classified by calendar year, sex, age in months and the different risk window (see exposure section). This persontime will be the denominator for the incidence rate calculations. Incidence rates for the different outcomes will be calculated stratified by:

1. database
2. calendar year and month
3. age in categories
4. vaccination status by risk window stated above
5. pertussis prior to first dose

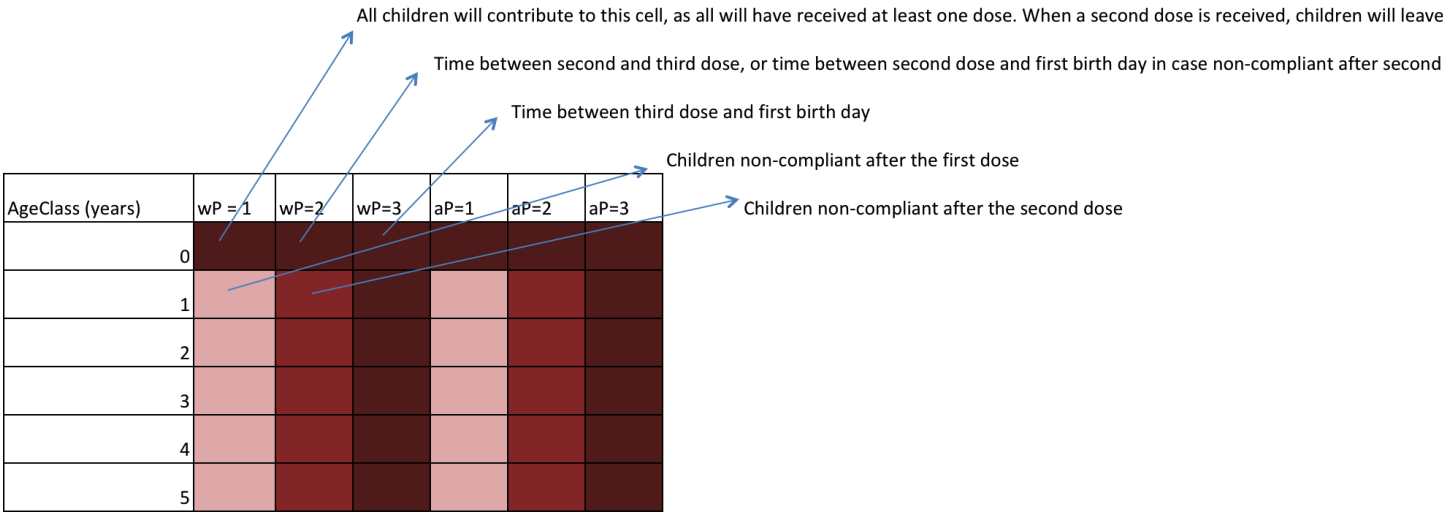

Figure 4: Distribution of PersonTime and Corresponding Events over Age Categories and Vaccination Status

Additional aggregation levels are calendar year and gender. As the analysis will be done per database, database is another aggregation level

Cases will be counted in the numerator for the rate calculation if the date of onset/occurrence falls into the specific window of that vaccine, and will be further stratified to count in the correct age and calendar year category at the date of onset.

Incidence rate of pertussis will be modelled as follows:

$$\text{Log}[\#\text{Events}/\text{PersonTime}] = \mu_{year} * 1_{YEAR=year} + \alpha_{age} * 1_{AGE=age\ category \in \{0,1,2,3,4,5\}} + \beta_{vac\ status,year} * 1_{STATUS=vac\ status \in \{,1wP,2wP,3wP,1aP,2aP,3aP\}}$$

Using the results from fitting this model, estimated incidence rates will be calculated by database, calendar year & month, age category and vaccination status.

For the analysis of risk of complications in pertussis cases we will calculate rates and risks (using Kaplan Meier analysis) within the period 30 days after onset of pertussis. For death this period is 3 months after diagnosis. The start of the period will be characterized by age, year and the number of pertussis vaccine dose and type.

Statistical Considerations:

The following potential difficulties in data management and analysis will need to be addressed:

- Direct comparison of wP and aP vaccines might be challenging since they have been used in different time periods when medical practices and recording of patient data has changed significantly. If it is not possible to determine which vaccine was received during the period when both types were used, the period of potential overlap will be excluded from analysis.
- For dose-specific analyses, it may be unclear in the databases whether a dose of vaccine is the first, second, third, or booster in a series. In subjects present from birth, this will be easier to determine.

7.2.9. Study Size

There is no target sample size for this study. The sample size is determined by the study population in the ADVANCE databases, which currently accumulates more than 34 million subjects and 314 million person-years. The actual size available to estimate incidence rates of pertussis after vaccination may diminish if databases do not have good quality data on the vaccinations, which is part of the study assessment.

7.2.10. Data Management

7.2.11. Data Processing

This section is taken directly from POC Outline document.

Processing of data from the different databases will be done in two steps as per ADVANCE policy:

Extraction of study specific de-identified data from the original databases into study specific common input files. This will be done according to the specifications in the POC study protocol. There is currently no common IT component supporting this, except from the tools that data processors use regularly on their local data.

Transformation of the study specific data into analytical datasets suitable for statistical analysis. This will be done according to the specifications in the POC study protocol with a common script.

7.2.11.1. Data Extraction

Following approval of the study protocols, data processors locally will be asked to extract study-specific data into a simple common data model (CDM). The data in this CDM could be used by the POC teams on coverage, safety and benefit. Before it can be used, the data will be harmonized and checked under quality control procedures; this will be done in the fingerprinting

7.2.11.2. Data Transformation

Data transformation is the step from having data locally in the CDM to creation of analytical datasets locally that can be shared for further analysis on the remote research environment (RRE). It is important that the analytical datasets are 'stripped' from variables that may create 'identification' issues, e.g. dates.

A central scripting approach will be used for the data transformation steps from CDM files to analytical datasets. This will be done by the statisticians in the POC study team, using R and SAS. The SAS and R scripts will be compared and serve as double-coded scripts for quality assurance.

As much as possible, scripts should be made as general modules so they can be re-used and varied with different parameters settings and shared amongst the statisticians.

7.2.12. Software and Hardware

Data analysis will be conducted by the statisticians on a remote research environment (RRE), called OCTOPUS. The RRE has R, SAS, and other programs.

The OCTOPUS RRE is a socio-technological framework that has already proven its value in various European Commission and European Medicines Agency funded projects. It stimulates geographically dispersed research groups to collaborate and has resulted in consortia that were engaged in all the phases of drug safety research.

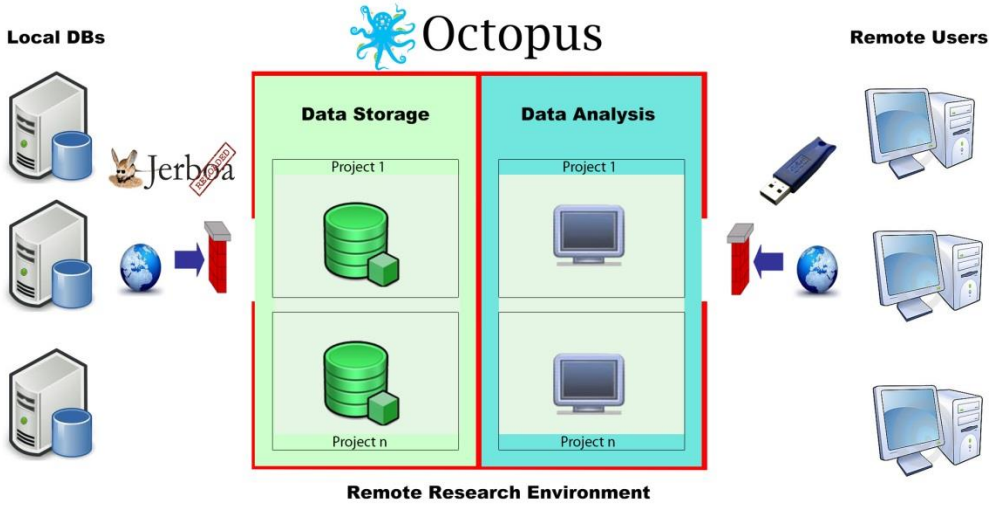

Figure 5: Schematic Representation of the OCTOPUS Remote Research Environment

OCTOPUS ARCHITECTURE

Octopus is hosted on an application server (Windows Server 2008R2) located in the data center of the Erasmus Medical Center (EMC) in the Netherlands. The data center is a Tier level III data center which means it has multiple independent distribution paths serving the IT equipment and has an expected availability of 99.9%. The server is secured by the EMC firewall and will not have any direct connections to the LAN of the hosting institute. Access to application server is only allowed from a restricted set of IP addresses using two-factor authentication with a password and token. The infrastructure is monitored by the Erasmus MC Computer Emergency Response Team (CERT).

Procedures have been developed to ensure data protection and secure file transfer from and to the collaborating partners. The following paragraphs describe these procedures in more detail.

DATA SECURITY PROCEDURE

For the OCTOPUS infrastructure many policies for data security have been put in place, for example:

- To acquire access to the RRE, each user has to fill in a request form and sign a confidentiality agreement. WP5 leaders (or Steering Committee) need to formally approve each request.
- Users will only have access to the RRE using a remote desktop session.
- Authentication of users consists of two factors: in addition to the basic authentication procedure (with username and password), an authentication with a personal token is performed (SafeNet eToken Pro, www.safenet-inc.com).
- All log on/log off operations are automatically logged (registered) by the RRE.

- The authentication of users is performed by asking, at each login attempt, the username and password (i.e. saved credentials are not allowed).
- Users only gain access to folders/files that are part of the project in which they collaborate. The system administrators can grant permissions to users based on their role in the project.
- Users will not have access to the control panel, internet, and administrative tools.
- Any attempt to copy and paste files between the remote session and local PCs of partners will be disabled.
- All devices on local PCs of partners (i.e. printers, storage...) will be disabled in the remote session.
- A complete log of all requests for files and copies of these files sent outside the RRE will be kept and can be inspected upon request.
- A screensaver will be activated on the remote desktop if the user is not active for a predefined time interval.

Any misconduct or violation of RRE security principles will be notified to the data manager and project manager immediately. Standard operating procedures for access and file transfer rights will be developed within the consortium.

DATA TRANSFER PROCEDURE

The procedure is illustrated in Figure 6. The user will upload new data, e.g. Jerboa encrypted file, to a personal upload directory using the secure sftp protocol in FileZilla (step 1,2), and after approval, the administrator will decrypt the file and will import the data in the data folder of the project (step 3). The administrator will confirm the dataset preparation and the user can view and work on the data using the token (step 4,5). To avoid data manipulation the data folder is read-only for all users. Upload of other files, e.g. SAS scripts, will follow the same procedure.

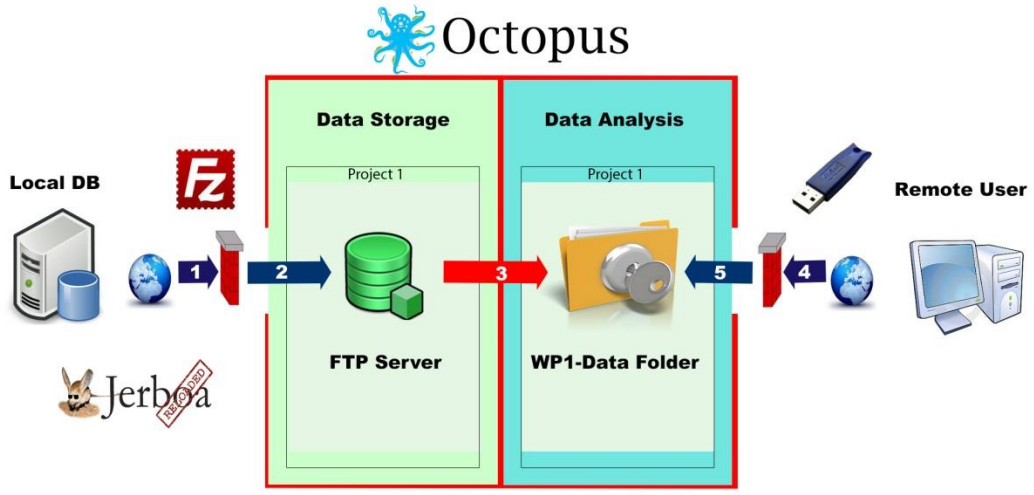

Figure 6: Upload of Data to OCTOPUS

To download results from the RRE (see Figure 7), e.g. a PowerPoint presentation, the user has to login to the RRE (step 1) and place these files in a personal export directory (step 2). In order to receive those files, a request must be sent to the RRE system administrator having the corresponding WP leader in carbon copy (cc). The system administrator will verify that the files do not contain any restricted data, and then will put the files in the download directory of the user (step 3). Subsequently, the user can download the files from the server using the FileZilla sftp client (step 4,5).

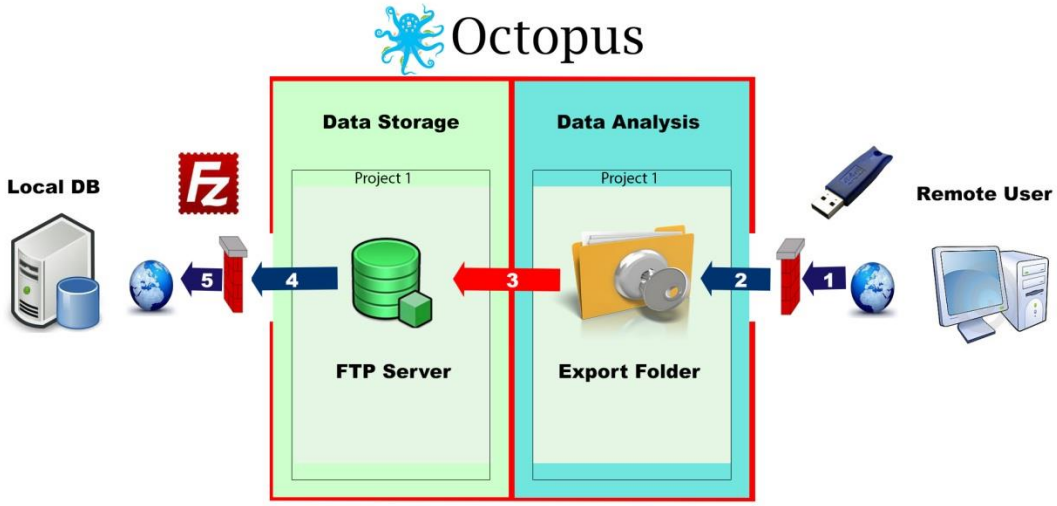

Figure 7: Download of Data from the RRE

DATA ANALYSIS PROCEDURE

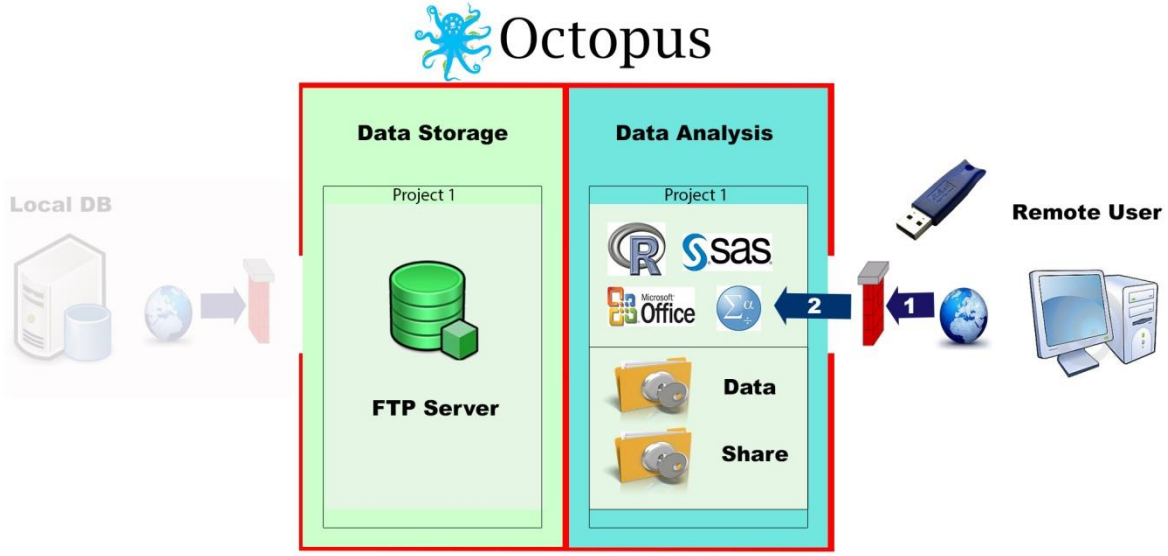

Figure 8: Data Analysis in the RRE

Data analysis will be done inside the RRE, i.e. the user logins in the server (step 1) and has access to a number of analysis and word processing tools (step 2). All users in the project or

WP have access to the data folders (read only) or can share files with others using their personal Share. In the Share, only the owner has write-access; all others only have read permissions. The folder structures can easily be customized to address specific project needs.

7.2.13. Quality Control

7.2.13.1. Record Retention

Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced will be retained for a period of 5 years in accordance with Good Participatory Practice (GPP) guidelines. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement between study partners. It is the responsibility of the principal investigator to inform the other investigators/institutions as to when these documents no longer need to be retained.

These principles of record retention will also be applied to the storage of laboratory samples, if applicable, providing that the integrity of the stored sample permits testing.

Study records or documents may also include the analysis files, syntaxes (usually stored at the site of the database), and questionnaires.

7.2.14. Limitations of the Research Methods

As this is the first POC in the ADVANCE consortium, there are several methodological limitations that will be addressed when evaluating the system and interpreting results. The major concerns are addressed in this section.

1. **Change over time for pertussis definitions**. Pertussis definitions have changed over time; it will not be possible to identify which definition has been used when by the health care professionals that were creating the electronic health care data we will be using. However, all rates will be stratified by year of birth and age, and therefore will approximate this time aspect. Since aP has replaced wP over time, the definitions will be different between wP time and aP time, although they will be extracted using the same codes. Misclassification may differ between the periods. The impact of that will be studied in WP 4.
2. **The same case definition is not used by the different countries participating with data.** Data and comparisons between wP and aP will be analyzed as far as possible per database/country in both wP and aP to overcome this limitation.
3. **Case definition through diagnostic codes**. Using mainly diagnostic codes for case identification is a limitation as it cannot be assured if the case has been confirmed or not. Laboratory confirmation will be used whenever this data is available. Low substantial misclassification is expected based on the diagnosis codes only; the positive predictive value of a diagnosis code for pertussis will be assessed where possible if laboratory confirmation or surveillance data are available, and using different types of components in the fingerprint process

4. **Reporting systems-behavior to the surveillance or database** (passive or active); i.e. active case detection will yield to higher incidence
5. **Data on wP vaccination may not be available in all databases**. Should data on wP not be available, other sources will be considered such as literature or, if available, clinical trial data. Data from literature may not be comparable with the data collected from the databases, which may influence the interpretations of the results.
6. **Diagnostic bias due to change of pertussis awareness over time**. Since there has been publicity on pertussis, the change of having a diagnosis has increased. Patterns will be calendar time specific. Since publicity was higher in later years, this will impact aP in particular.
7. **Few cases of pertussis in each database, not allowing for country-specific analysis**. The study aims to test a system. If there are too few cases in the database, it will provide information on how much one database may be able to contribute, which is part of the system testing.
8. **The type of data provided will influence the incidence**. If pertussis is more commonly reported in general practitioner (GP) databases, and this data cannot be provided by one database/country, there will be an underestimation of pertussis incidence. The rates will be compared between claims databases and GP medical record databases to investigate differences if they are available in one country.
9. **The current methodology will not account for differences in vaccination schedules.** Different countries use different vaccines and schedules that may have changed over time. ATC codes will identify which types of vaccines were used; this will allow stratification on vaccine types. Further, benefits will not be evaluated on a schedule level but on a dose level, as each case is followed after each dose given.
10. **In some cases it will not be possible to confirm that death really is associated with pertussis diagnosis**. Some databases will be able to provide information on cause of death. For those that will not, follow-up time will be allowed up to three months after pertussis diagnosis to narrow the risk for misclassification.
11. **The current methodology will not consider/analyze benefits of the vaccines by brand.** However, the feasibility of doing so will be carried out by WP5, in the fingerprinting exercise.

7.2.15. Advisory Committee

The ADVANCE Scientific Advisory Board

7.3. Use of the data generated in this study

The data generated in this study will be used into a B/R model, as describe in the B/R analysis protocol. The data will also be used for further test of statistical methods within the ADVANCE WP4 working groups.

7.3.1. Benefit/risk analysis

This POC study will yield incidence rates (during exposure window and after exposure window) which will be used in the B/R analysis.

Table 6: Evidence Required from the Databases for Benefit Outcomes to Build the Effects. Table by Country, and by Year of Birth*.

	Incidence in risk period after wP/aP vaccination							
		Dose 1[a]		Dose 2[b]		Dose 3[c]	
*Outcome ** *	*Vaccine type (wP or aP)*	*Inc*	*95% CI*	*Inc*	*95% CI*	*Inc*	*95% CI*
Pertussis disease							
Pneumonia after pertussis[d]							
Seizures after pertussis[d]							
Death after pertussis[e]							

* Number of doses till pre-school booster/six years of age. Number of doses might depend on the country and year of birth. This information will be provided by the Coverage study team.
** For case definitions, see Benefit protocol
a Pertussis from 2 weeks after Dose 1 until 2 weeks after Dose 2
b Pertussis from 2 weeks after Dose 2 until 2 weeks after Dose 3
c Pertussis from 2 weeks after Dose 3 until school-enter booster/age 6
d Complications until 1 month after onset pertussis disease
e Death until 3 months after onset pertussis disease

In addition the relative risk estimate from the SCCS will be used as described in the analysis

7.3.2 Re-use of data from the POC study for methods development

The table below details how the data generated in the feasibility step and the scientific step will be re-used /produce in the methods development proposals.

	Data from fingerprint for these protocols	**Data from Rate and risk estimations in POC**
Methods development topics research topic		
Burden of adverse event	Disease rates of events, quality of databases	Disease rates of events
Effectiveness	Rates of disease, PPV, quality of databases	Differentiality
Monitoring of B/R	Lag times to get data	Monthly rates of events, coverage, outcomes
Heterogeneity	Population, event, vaccine misclassification	None
Ontology	Vaccine	Will provide information to POC

Coverage	Vaccine & dates distributions	Will provide information to POC
Codemapper	Event	Will be used in POC

8. PROTECTION OF HUMAN SUBJECTS

8.1. Regulatory and Ethical Compliance

"This study is non-interventional, based on secondary use of data. Therefore the reporting of suspected adverse reactions in the form of individual case safety reports (ICSRs) is not required. Reports of adverse events/reactions should be summarised as part of any interim analysis and in the final study report unless the protocol provides differently.

This study is not considered as a PASS nor PAES by EMA

The study protocol and study report will be posted on EU-PAS register.

While the study is being conducted, the MAH shall monitor the data generated and consider its implications for the risk-benefit balance of the medicinal product concerned. Any new information which might influence the evaluation of this risk-benefit balance shall be communicated to the competent authorities of Member States in which the medicinal product has been authorised. The channel for communicating this information is the notification of an Emerging Safety Issue."

8.2. Informed Consent

No informed consent is necessary as this a retrospective study using de-identified/anonymized data for secondary purposes.

8.3. Responsibilities of the Investigator and IRB/IEC/REB

The protocol and waiver of informed consent must be reviewed and approved by a properly constituted institutional review board/independent ethics committee/research ethics board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol has been approved by the IRB/IEC/REB and waiver of informed consent must be given to the principal investigator before study initiation.

8.4. Protocol Adherence

Investigators will apply due diligence to avoid protocol deviations. If the investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by all partners involved and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the Study Report. Specifically, observational reportable Protocol Deviations are those Protocol Deviations which directly or indirectly have a significant impact on any 1 or more of the following:

1. Subject's rights, safety, or well-being

2. Data integrity, i.e. completeness, accuracy, and reliability of safety, efficacy, and immunogenicity outcomes of the clinical study, and
3. Regulatory compliance.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

Not relevant for POC benefit study.

10. PLANS FOR DISSEMINATING AND COMMUNICATING RESULTS

10.1. Registration in Public Database(s)

Principal investigator assures that the key design elements of this protocol will be posted in a publicly accessible database where applicable and in compliance with current regulations.

Principal investigator also assures that key results of this study will be posted in a publicly accessible database within the required time-frame from completion of the data collection where applicable and in compliance with current regulations.

10.2. Publications

Further to legislated data disclosure, the results of this study will be published as scientific papers in peer-reviewed journals. Preparation of such manuscripts will be prepared independently by the investigators and in accordance with the current guidelines of STrengthening the Reporting of OBservational studies in Epidemiology (STROBE). The ADVANCE Steering Committee will be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.

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APPENDIX 1: FEASIBILITY TESTING (FINGERPRINTING)

Step 1: feasibility assessment of databases

The concept of bringing data together within and across countries with the purpose of addressing vaccine benefit/risk questions in a collaborative and integrated approach can be addressed in several ways with respect to:

1) Standardization of protocols to conduct studies on multiple data sources
2) Local data extraction
3) Transformation of the data into analytical datasets
4) Pooled analyses of data

In ADVANCE steps 1, 3 and 4 are harmonized and centrally coordinated.

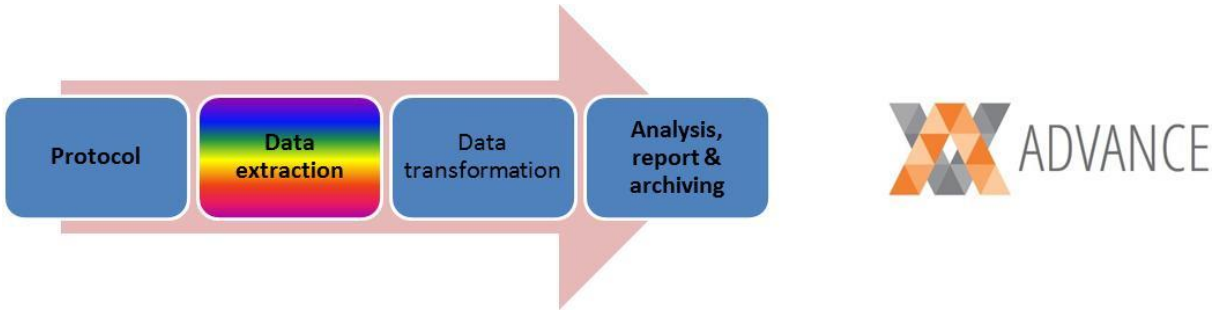


Figure 9 : Distributed collaborative information generation workflow, with common protocol, standardized transformation and shared analyses while data extraction and original data remain local.

Step 2 cannot be harmonized for the following reasons:

1) Different structures of health care systems across EU member states
2) Different types of databases within a country and across EU member states (i.e. health care databases, claims databases, inpatient databases, surveillance networks, laboratory data, microbiology data, vaccination registries, medical record databases), if possible all these databases will be fingerprinted
3) Different content of similar types of databases across EU member states
4) Different coding/terminologies and language of similar information between databases in different EU member states

To gain insight into the underlying determinants and mechanisms of data generation, and to address these differences in a consistent and informed way, such that we can actually use the data for the purpose of vaccine benefit/risk monitoring we will use the following approaches:

1) Use of local source data knowledge: Full involvement of the database custodian in data extraction processes and interpretation of the data to appreciate differences, and filling out the survey on the database characteristics (AIRR survey) as well as database experience forms

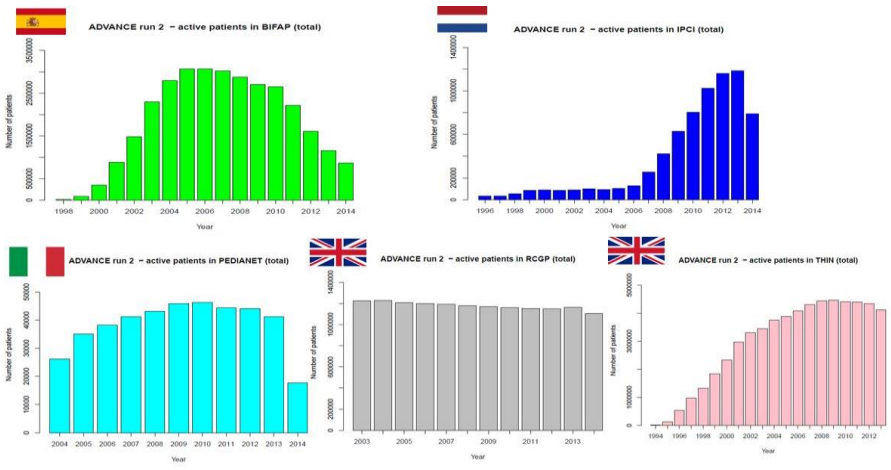
2) Semantic harmonization: mapping of terminologies and variables for population, events (outcomes and covariates), vaccines and drugs & creation of ontologies and mappings of codes and terms to allow for specific data to be integrated into a common data model
3) Fingerprinting: (i.e characterizing) of what data is actually available in the databases by real data extraction (transparency)
    a. Stepwise conversion of specific required study data into a simple common data model
    b. Describing the data quantitatively using a common script and visualization
    c. Iterative harmonization and verification of data extraction steps under item 2 across the databases
    d. Benchmarking of data extracted against available external sources of information.
4) Knowledge & information management: Reporting of generated evidence and knowledge and making it available and accessible

In the fingerprinting task which informs the feasibility assessment, we describe the databases based on the data that are locally extracted into the ADVANCE common data model. Database custodians will have to transform their local data into these common input files. These input files will be processed locally by a common tool that is either R, Jerboa or SAS and these scripts will generate aggregated fingerprinting data that will allow us to assess the quality of the database for specific vaccines/events. The fingerprinting is not the responsibility of the POC PI but of the WP 5 leaders.

Population fingerprint

Based on the common input files that have been agreed in ADVANCE, Jerboa generates standard statistics for the population per gender, calendar year and age group.

Outputs of this fingerprint allow for assessment of the representativeness of the population and many other features. An example from the D5.2 is provided below.



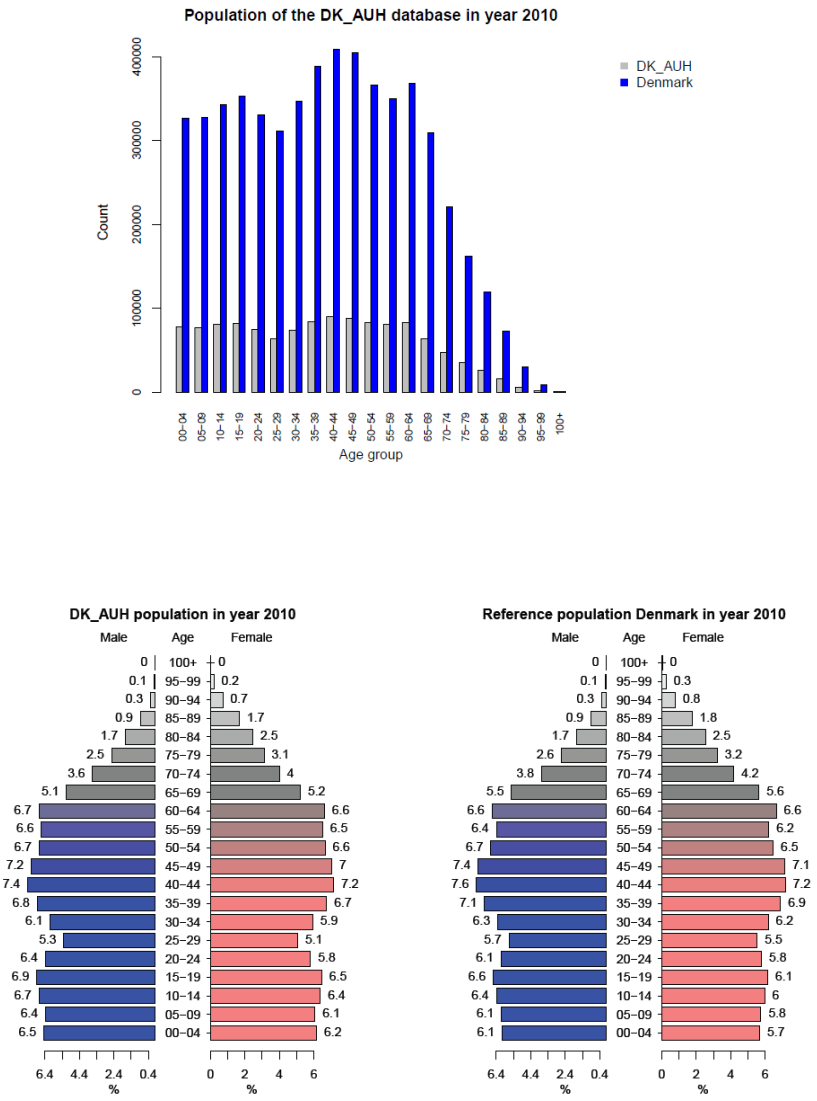


Figure 10: Example of population fingerprint output

Event fingerprinting

The overall aim of the event fingerprinting workflow (or also called data derivation workflow) is to obtain for each data source the best algorithm to extract an event/condition, and document this in a structured fashion. The full data extraction algorithm is a logical combination (AND, OR, or AND NOT) of components that could contain for example the following information:

- a diagnosis, recorded in a primary, secondary, inpatient care or other settings
- diagnostic evidence, for example laboratory measurements

- utilization of healthcare services specifically indicated to diagnose or treat that condition, such as a drug, a diagnostic test, a procedure or other health service

For instance, for some data sources a diagnostic code could be available for pertussis. In other data sources, results from blood tests may be available or surveillance data. In Figure 5 a high level graphical representation of the workflow is presented. In short the following questions are answered in each of the steps:

- Definition: How do we define the specific condition and its context?

- Collect experience: collection of how these conditions have been collected in the past. How can we leverage the valuable domain knowledge of the data custodians?

- Literature Search: what is the incidence/prevalence of this conditions in the countries of interest, this information will serve as an external benchmark to see whether the data retrieved have external validity

- Terminology Mapping: How can we translate the case definition into different terminology systems?

- Component algorithms: collection of information on how each database extracts the data which algorithms are used? Which is the list of unique component algorithms that each database should be invited to extract?

- Results Analysis: comparison of incidence rates between databases and with literature, and if possible component analysis, what is the influence of certain components on the incidence/prevalence?

- Final Decision: what is the best algorithm for each database, and archive this?

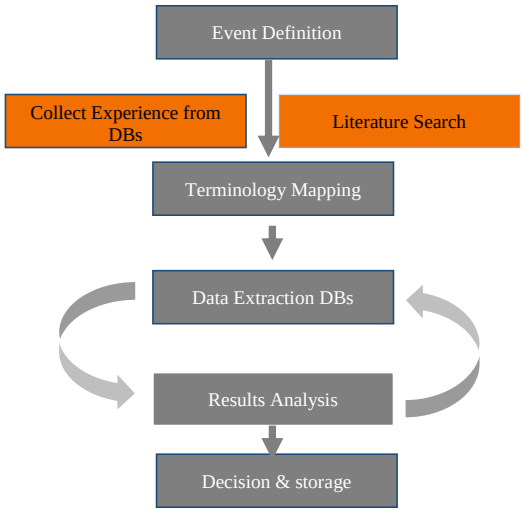


Figure 11: Workflow fingerprinting of events and component analysis

The event fingerprinting is led by an event team comprising the event team leader, the person who defined the event, the PIs of the study teams that need the event and the CODEMAPPER developer.

Event definition forms

Event definition forms are filled for each event. These forms contain the following information:

- Event definition & validity classifications
- Synonyms / lay terms used
- Laboratory tests done specific for event
- Diagnostic tests done specific for event
- Drugs used specific for event treatment
- Procedures used specific for event treatment
- References
- Codes (ICD-9 codes, or ICD 10 codes)

Event routing questionnaire

A survey will be launched to physicians to understand the pattern of care for each of these events of interest. This will inform us which components are important in algorithm constructions.

Database experience sheet

Data base experts will be asked to fill an excel sheet that will provide information on how they have extracted the events in the past. The following information is collected:

- experience with extraction of this event: yes/no/other
- Extraction algorithms used (ie was a logic applied in terms of at least two codes, prescription)
- Was validation performed?

- Do you have papers on the validation of this event in your database

Literature

In order to validate the extractions against an external benchmark, literature on the incidence of the event will be searched by the eventteam for the country of interest and if this is absent from other countries. For ADVANCE we will need to search of Spain, Italy, Netherlands, UK, Sweden, Finland and Denmark.

Terminology mapping

Terminology mapping is done with the ADVANCE Codemapper . The ADVANCE Codemapper is mapping the codes of different coding systems to concepts and terminology found in the clinical definition forms according to the flow described in figure 5.

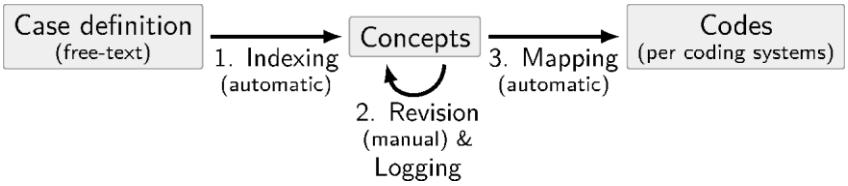


Figure 12: workflow of the ADVANCE Codemapper

The workflow of CodeMapper has three phases as shown in figure 6 which comprise multiple components. It start from the case definition forms that are copied in the Codemapper. The Codemapper calls the Peregrine text indexing engine to identify medical concepts in the case definition. These are highlighted in the copied text. Concepts that belong to the semantic group of disorders in UMLS are pre-selected. After this automated selection the user can walk up and down the ontology to select further specify individually which concepts should be additionally included/excluded for further processing. Second, these concepts are related to concepts of the Unified Medical Language System (UMLS). The UMLS is then used to automatically retrieve codes that correspond to the selected UMLS concepts in a set of user defined coding systems. The concepts are displayed in a table alongside the associated codes in each coding system. Third, the user can revise codes of the mapping by applying concept-level operations. The user can add concepts, remove concepts, and retrieve more general or more specific concepts according to the hierarchical information in the UMLS . The set of targeted coding systems can be changed on-the-fly. After every operation, the code sets associated with the concepts are automatically updated. Feedback about the mapping is captured in comments that can be attached to the concepts.

Every operation is recorded in a history for later traceability. When saving her or his work, the user has a machine generated to summary of the modifications. The summary is added to the history. The mapping, comprised of the concepts and code sets is stored online together with the case definition, the initial mapping and history. All data can be downloaded as an Excel document to support incorporation into extraction scripts.

Availability: The CodeMapper application is freely available for non-commercial projects at https://euadr.erasmusmc.nl/CoMap.

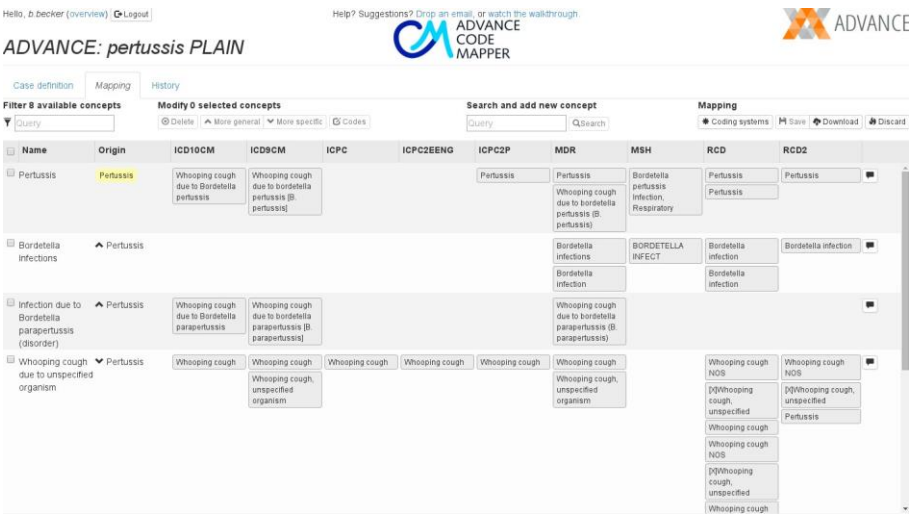


Figure 13: Screen-shot of the CodeMapper application

Extraction of outcomes

The Codemapper lists will be sent to the databases who will be requested to extract the events and transform them in the common data model format. Codemapper will provide only disease codes, thus database experience should be used to define alternative algorithms. (e.g. using drugs as proxy, or using a combination of codes and drugs.

The case definition comprises information on the drugs and procedures that are used for the event. The event teams will collate the experience from the databases, the codes and drugs/procedures in the case definitions to suggest recommended 'component' algorithms is created (combination of disease codes, text, procedures/measurements and drugs) , and each database is invited to extract as many components as apply.

Local database contacts provide feedback on component algorithms and/or propose new ones. The final list of components results from an iterative process of refinement involving local experts and the data derivation leader.

Databases are making available different component algorithms per event.

Database experts extract the component algorithms and run the Algorithm Comparison Module of Jerboa. The result is a dataset of aggregated data which must be uploaded on the Remote Research Environment.

Extraction of codes for the POC have a time priority over the WP 4 events

Results analysis

For all events the following statistics will be calculated

1) age specific incidence rates and standardized incidence rates. These data will be compared
    a. Across databases
    b. Against the literature
2) Overview of code counts (e.g. ICD 9 codes, READ codes)

Data needs to be submitted to RRE by the databases and the data will be post-processed and produce graphics that can be used for discussion.

All the information will be uploaded to the ADVANCE sharepoint

Component analysis

Different algorithms using specific components will be compared and analyzed. Conclusive decision will be taken on algorithms to be used for final extractions

Using the Analysis Tool developed within the EMIF project, local experts are allowed to test the extracted component algorithms in different logical combinations using Boolean operators (AND, OR, AND NOT) in order to build more complex extraction strategies, referred to as *composite algorithms (e.g. ≥1 primary care diagnosis AND ≥1 test result positive)*.

The event team leader makes a proposal for each database. Local experts choose the composite algorithm that they recommend for the identification of the event in their data source, following or challenging the recommendation of the event team leader. Each recommended composite algorithm is stored together with a comment of a data source expert explaining its choice.

An estimate of the sensitivity and PPV is also provided based on previous validation studies, local expert's expectations, information from other data sources and procedures developed in WP4.

Archiving of final algorithms and fingerprint results

Each database will submit the final algorithm that was used both in code as well as in narrative (pseudo code). All this information will be stored in the Codemapper/Sharepoint.

Vaccine fingerprinting

Initial discussions with the databases showed that most databases will have information on the vaccinetype and the ATC code or at least part of it. In the Anatomical Therapeutic Chemical (ATC)[4] classification system, the active substances are divided into different groups according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. Vaccines are coded in different Anatomical groups although the majority are part of the therapeutic subgroup J07.

The divisions are made between bacterial (J07A), viral (J07B), bacterial & viral (J07C), other vaccines (J07D) and cancer vaccines (in L03). Bacterial vaccines are divided in 14 subgroups, viral vaccines are divided in 13 subgroups, grouping is based on the vaccine preventable disease. Within the groupings the most detailed level finishes with the type of antigen.

J07BB **Influenza vaccines**

ATC code	Name
J07BB01	influenza, inactivated, whole virus
J07BB02	influenza, inactivated, split virus or surface antigen
J07BB03	influenza, live attenuated

Figure 14: Most detailed ATC codes for vaccines

[4] http://www.whocc.no/atc_ddd_index/

For future benefit risk analyses we may need additional information on the vaccines (e.g. valence, excipients). This information needs to be retrieved from other sources, therefore we will need a vaccine ontology that can provide additional information on the vaccines which may be useful for analysis as well as to enable the fingerprinting across multiple databases.

Analysis of vaccination fingerprint

The vaccine fingerprint will be described by using vaccination coverage estimates as well as the number of doses per person. To fingerprint the datasources in terms of vaccine coverage /uptake data we will:

Estimate coverage by age, gender, calendar year of the following vaccinations and compare these to the monitoring data from WHO[5], the ECDC funded VENICE II consortium[6] and available national statistics: Bacille Calmette-Guérin (BCG) vaccine, the third dose of diphtheria and tetanus toxoid and pertussis vaccine (DTP3), the third dose of polio vaccine — either oral polio vaccine or inactivated polio vaccine, the first dose diphtheria and tetanus toxoid and pertussis vaccine (DTP1) and the third dose of haemophilus influenza type b (Hib3), seasonal Influenza (compared to VENICE)[7] and the first dose and third dose of human papillomavirus vaccinations (HPV)[8]. These vaccines are also reported to WHO and provide for benchmark

Assess timing of childhood immunizations in databases (by age) and compare these with local recommended schedule.

For vaccination fingerprint we will look at describing coverage at 12, 24, 48 and 120 months (BCG, DTP, polio, Hib), and a cumulative approach (Kaplan Meier) for birth cohorts. For HPV, we will assess coverage at age 16. For seasonal influenza vaccination, we will assess coverage by year of age. Timing of vaccinations will be described by plots for age of vaccination by type and dose of vaccine and this will be compared with the information in the vaccine schedules.

[5] http://www.who.int/immunization/en/
[6] http://venice.cineca.org/the_project.html
[7] VENICE II: Go on combining our efforts towards a European common vaccination policy! F D'Ancona on behalf of VENICE II group. Eurosurveillance, 2009, vol. 14 n.12: Seasonal influenza immunisation in Europe. Overview of recommendations and vaccination coverage for three seasons: pre-pandemic (2008/09), pandemic (2009/10) and post-pandemic (2010/11). J Mereckiene, S Cotter, A Nicoll, P Lopalco, T Noori, J T Weber, F D'Ancona, D Lévy-Bruhl, L Dematte, C Giambi, P Valentiner-Branth, I Stankiewicz, E Appelgren, D O'Flanagan, the VENICE project gatekeepers group. Eurosurveillance, 19 (16) 2014.
[8] Health technology assessments on human papillomavirus vaccinations in Europe: a survey from Venice network, Frédérique Dorléans, Daniel Lévy-Bruhl, Cristina Giambi, Fortunato D'Ancona, Giuseppe La Torre, Suzanne Cotter, Jolita Mereckiene, Pawel Stefanoff, Eva Appelgren and the Vaccine European New Integrated Collaboration Effort (VENICE II) project gatekeepers, Italian Journal of Public Health, Volume 9, N. 1 (2012)

APPENDIX 2: POC EVALUATION (SYSTEM TESTING FRAMEWORK)

Methods for the evaluation of the system: POC Evaluation Framework

The POC evaluation will be conducted by the POC evaluation team which is independent from the study teams. The team is coordinated by prof. L Stergioulos (SURREY) and dr. G Ferreira (P-95)

Purpose of the POC evaluation: POC evaluation focuses on combining, analysing and reporting on the performance and knowledge generated during the performance of the POC experiments, to inform the reliability and sustainability of a post-ADVANCE platform, as defined in the Vision and Mission. Conceptually, POC evaluation aims to evaluate the "whole system", including the technology, the framework, and the process used in the POC to perform vaccine B/R assessment.

The POC evaluation is therefore based on a systematic assessment whether the concept designed and tested through conducting the POC is *acceptable and good enough to be recommended for "release into production"* in the ultimate ADVANCE blueprint. Thus, the focus will be on whether ADVANCE adds value in terms of: *(1) Speed to obtain results; (2) Fostering productive collaboration; (3) Enabling good science*.

OBJECTIVES:

1. **Feasibility and effectiveness:** Demonstrate that the selected POC cases can be implemented (more) effectively using the ADVANCE Framework
   "assess the level of attainment of the ADVANCE mission (and vision) statements, through collecting, analysing and reporting on the outputs of the POCs"
   Questions to be answered by the evaluation:
   I: Is it doable?
   Are *the basic conditions and processes* sufficient/enabling for ADVANCE to operate?
   II: Is the output meaningful?
   Is *the evidence produced* meaningful for the purpose of B/R decision making?
   III: Adds-value, cost-effective?
   Is the value/cost ratio in maintaining and performing a study improved *(i.e. greater cost effectiveness),* as perceived by the partners in the collaboration?
2. **Scaling:** Derive general guidelines to guide the implementation of the evidence creation process for any Research Question (RQ) in the future (i.e.: developing the Blueprint: how to design and conduct any vaccine B/R study based on the ADVANCE Framework**)**

   Questions to be answered by the evaluation:

   IV: Is it generalizable and scalable?
   Can ADVANCE be used and perform equally when addressing other B/R questions in other vaccines, and disease areas?

In a nutshell, the ADVANCE Evaluation Framework offers quality indicators, methods, and a timeplan. It spans five evaluation areas, which follow loosely the POC work progression * (i.e. concurrent with the POC timeplan), a number of dimensions with the corresponding sets of indicators and related datasets, and the methods with which these will be measured **:

AREA 1: ADVANCE Process performance and IT infrastructure

The *Process & IT evaluation* covers both **Technical infrastructure** and **Process Workflows** at the same time, and follows the *4 stages* of the overall process: protocol writing, data extraction, transformation, analysis.

Evaluating the Research protocol formation process. The ultimate goal of a process evaluation is to illuminate the pathways linking what starts as a Research Question (theoretical/scientific protocol), and its underlying causal assumptions, to the outcomes produced. In order to achieve this, it is necessary to understand:

- The implementation, both in terms of how the RQ was implemented (new or "tech-enhanced/ IT-enabled" protocol) and the quality of what was delivered;
- the mechanisms of impact linking RQ implementation activities to outcomes;
- how the context in which the RQ is investigated (e.g. external factors) affects both what is implemented and how outcomes are achieved.

For this, the **ISO/IEC 15504 (SPICE)** standard can be followed, which is a framework for the process assessment that defines a **process dimension** and a **capability dimension**.

Evaluating the IT infrastructure. The evaluation measures are built on provisions included in the ISO/IEC 25010 System and Software Product Quality standard (part of ISO/IEC 25000 - SQuaRE). This standard defines internal metrics (static, do not rely on software execution) and external metrics (applicable to running software). It comprises 8 quality characteristics:

IT infrastructure metrics: a. User satisfaction; b. Processing capacity and speed; c. Flexibility; d. Resources and effort; e. CPU times for analyses, loading; f. Failure rates, errors, black outs, off line time; g. Gaps in IT tools and functionality (e.g. document review platform, archiving and version control)

A1 Evaluation dimensions: Time, Cost, Data Access, IT infrastructure, Data sharing, Privacy and ethics, Data processing, Data protection, Data privacy, Qualified study personnel, Accessibility of data (study results and resources)

AREA 2: Scientific validity and innovation

This area covers **Data sources**; **Methods;** and **Innovation potential.**

Approach: Consultation with Experts, Scientific advisory committee

Flexibility/adaptability: how flexible to address the new guidance and requirements WP3 use cases, flu guidance, new vaccines.

Scientific validity: SAB review and feed-back

- Quality of research questions
- Early scientific input in the formulation of relevant B/R framework prior to the protocol development

Innovation aspects:

What has been done that was not already done before?

What has been developed that would not be possible to do without ADVANCE?

What was developed in the POC that can become a tool or asset in the real world?

What was not tested in the POC, but should had been?

Is there potential to implement or support continuous B/R monitoring

A2 Evaluation dimensions: Science / Scientific quality, Data access, Flexibility / generalizeability, Scientific validity, Documentation, Reproducability, Innovation (multiple aspects)

AREA 3: Quality standards, regulatory compliance and legal robustness

Compliance: with legislation, standards, approvals to run the study

Quality of process, data management, data integrity, privacy and security, validation of the writing, validation of the programming, number of amendments to the protocols, number of errors

A3 Evaluation dimensions: Compliance, Ethics, Quality, Quality control, Confidentiality, Data protection, Privacy

AREA 4: Stakeholder satisfaction

Does the POC answer the needs of the different stakeholders and perspectives in terms of decision B/R focus, and the satisfaction and added value of working collaboratively?

Acceptability of study team, study proposal, workflow and report by stakeholders (stakeholder feedback survey), including decision process.

Before and after survey: Needs satisfied

Transparency as perceived by all stakeholders: What information can be made public (protocol, authors), how much time after it was done, is the information understandable, the decision-making processes (minutes, agendas), whose interests are involved / who benefits.

A4 Evaluation dimensions: Acceptability, Transparency, Satisfaction, Public trust

AREA 5: Code of conduct and Collaboration

This area covers the **Code of conduct, Collaboration** and **Rules of governance.**

An important aspect of the evaluation will be the **European network** (regulators and standards organisations, as well as industry) and the enablement/facilitation or strengthening of cross-

discipline/cross-sector international collaboration – including sustainable collaboration, and collaboration opportunities.

Before and after survey: Perceived added value of collaboration

A5 Evaluation dimensions: Satisfaction, Interoperability, Network building, Trust

Methods of data collection for the evaluation activities include:

- Surveys, collecting mass feedback from users and stakeholders
- Review and analysis of meeting minutes
- Interviews with experts and stakeholders
- Quantitative data analysis of existing data sets

A detailed description of the specific methods to be used for each dimension/indicator is provided in the *ADVANCE Evaluation Indicators* table**.

**The evaluation process should be as observational as possible (non-interventional) and PIs and study teams should operate as per process rather than towards fulfilling the indicators requirements.*
***A detailed description of all the **indicators, together with specific methods and requirements**, is provided in a separate spreadsheet document (ADVANCE Evaluation Indicators)*

APPENDIX 3: PERTUSSIS VACCINES

ATC code	ATC name	Whole cell or a-cell
J07AJ52	Pertussis, purified antigen, combinations with toxoids	aP
J07CA02	Diphtheria-pertussis-poliomyelitis-tetanus	aP
J07CA06	Diphtheria-hemophilus influenzae B-pertussis-poliomyelitis-tetanus	aP
J07CA09	Diphtheria-hemophilus influenzae B-pertussis-poliomyelitis-tetanus-hepatitis B	aP
J07AG52	Hemophilus influenzae B, combinations with pertussis and toxoids	aP
J07CA05	Diphtheria-hepatitis B-pertussis-tetanus	wP
J07AJ01	Pertussis	wP
J07AJ02	Pertussis	aP
J07AJ51	Pertussis	wP
J07CA11	Diphtheria-Hemophilus influenzae B-pertussis-tetanus-hepatitis B	?
J07CA12	Diphtheria-pertussis-poliomyelitis-tetanus-hepatitis B	?
J07CA13	Diphtheria-hemophilus influenzae B-pertussis-tetanus-hepatitis B-meningococcus A + C	?
J07AG	Hemophilus influenzae B, combinations with pertussis and toxoids	wP

APPENDIX 4: PERTUSSIS DATABASE codes

CASE DEFINITION		
pertussis PLAIN	*(Mapping created with ADVANCE Code Mapper)*	
CODING SYSTEMS	***CODE***	***NAME IN CODING SYSTEM***
ICD10CM	A37.0	Whooping cough due to Bordetella pertussis
ICD10CM	A37	Whooping cough
ICD10CM	A37.00	Whooping cough due to Bordetella pertussis without pneumonia
ICD10CM	A37.01	Whooping cough due to Bordetella pertussis with pneumonia
ICD9CM,	033.0	Whooping cough due to bordetella pertussis [B. pertussis],
ICD9CM	33	Whooping cough
ICD9CM	033.9	Whooping cough, unspecified organism
ICD9CM	484.3	Pneumonia in whooping cough
ICPC2P	R71001	Pertussis
ICPC2P	R71002	Whooping cough
RCD	XE0Qw	Pertussis
RCD	A33z.	Whooping cough NOS
RCD	Ayu3A	[X]Whooping cough, unspecified, Whooping cough due to unspecified organism, C0043168, Expanded more specific than Pertussis, Pertussis
RCD	XE0Qw	Whooping cough
RCD	H243.	Pertussis pneumonia
RCD	Ayu39	[X]Whoop cgh/oth Bordetela spc
MDR	10034738	Pertussis
MDR	10047976	Whooping cough due to bordetella pertussis (B. pertussis)
MDR	10006024	Bordetella infections
MDR	10052307	Bordetella infection
MDR	10047974	Whooping cough
MDR	10035713	Pneumonia in whooping cough
MSH	D014917	Bordetella pertussis Infection, Respiratory
MSH	D001885	BORDETELLA INFECT

APPENDIX 5: ADDITIONAL DEFINITIONS OF PERTUSSIS COMMONLY USED

Organization/ Country, Year	Clinical Criteria	Laboratory and Epidemiologic Criteria	Comment
WHO, 2000	A case diagnosed as pertussis by a physician, or a person with a cough lasting ≥2 weeks with ≥1 of the following symptoms: • paroxysms (ie, fits) of coughing • inspiratory "whooping" • posttussive vomiting (ie, vomiting immediately after coughing) without other apparent cause	Isolation of *B. pertussis*, or detection of genomic sequences by PCR, or positive paired serology	Case classification: **clinical case:** a case that meets the clinical case definition, but is not laboratory confirmed. **laboratory-confirmed case:** a case that meets the clinical case definition and is laboratory confirmed.
CSTE/CDC, 2010	A cough illness lasting ≥2 weeks with 1 of the following: paroxysms of coughing, inspiratory "whoop," or posttussive vomiting, without other apparent cause (as reported by a health professional)	Isolation of *B. pertussis* from clinical specimen PCR positive for pertussis	Case classification: **probable:** in the absence of a more likely diagnosis, a cough illness lasting ≥2 weeks, with ≥1 of the following symptoms: • paroxysms of coughing or • inspiratory "whoop" or • posttussive vomiting and • absence of laboratory confirmation, and • no epidemiologic linkage to a laboratory-confirmed case of pertussis **confirmed:** acute cough illness of any duration, with isolation of *B. pertussis* from a clinical specimen, or cough illness lasting ≥2 weeks, with ≥1 of the following symptoms: • paroxysms of coughing or • inspiratory "whoop" or • posttussive vomiting and ≥1 of the following: • PCR positive for pertussis or • contact with a laboratory-confirmed case of pertussis
France, 2009	Patient coughing ≥14 days with 1 or more of the following: • whoop • vomiting • cyanosis • apnea	Patient coughing ≥14 days with: • positive PCR/culture • >100 IU/mL of anti-PT antibodies >3 year from vaccination or 100% change in the antibody titer between 2 serologies at 1-month interval	**Epidemiologically confirmed:** patient coughing ≥7 days and in contact in the past 20 days with a biologically confirmed case
Canada, 2009	**Suspect case:** one or more of the following, with no other known cause: • paroxysmal cough of any duration • cough with inspiratory "whoop" • cough ending in vomiting or gagging, or associated with apnea **Probable case:** cough lasting 2 weeks or longer in the absence of appropriate laboratory tests and not epidemiologically linked to a laboratory – confirmed case **AND** ≥1 of the following, with no other known cause: • Paroxysmal cough of any duration • Cough with inspiratory "whoop" • Cough ending in vomiting or gagging, or associated with apnea	**Confirmed case:** laboratory confirmation of infection: • isolation of *B. pertussis* from an appropriate clinical specimen or • detection of *B. pertussis* DNA from an appropriate clinical specimen and • ≥1 of the following: - cough lasting ≥2 weeks - paroxysmal cough of any duration - cough with inspiratory "whoop" - cough ending with vomiting or gagging, or associated with apnea or • epidemiologic link to a laboratory-confirmed case and ≥1 of the following for which there is no other known cause: - paroxysmal cough of any duration - cough with inspiratory "whoop" - cough ending in vomiting or gagging, or associated with apnea	
Massachusetts, 2009	1989–1992: ≥1 week with paroxysms or posttussive vomiting From 1993: cough ≥2 weeks with 1 of the following: paroxysms, whoop, or posttussive vomiting (CDC definition)	**Bacteriologic cases:** positive culture (or + DFA until 1992), PCR added 2004 **Serologic case:** positive single-serum anti-pertussis toxin antibody (persons ≥11 years only) + clinical case definition **Epidemiologically linked case:** contact with a laboratory confirmed case + clinical case definition	
EU, 2008	Cough ≥2 weeks with ≥1 of the following: • paroxysms • inspiratory "whooping" • posttussive vomiting or any person diagnosed as pertussis by a physician or apnea episodes in infants	Isolation of *B. pertussis* Nucleic acids of *B. pertussis* *B. pertussis*-specific antibody response Epidemiologic link by human-to-human transmission	**Possible case:** any person with clinical criteria **Probable case:** person with clinical criteria and epidemiologic link **Confirmed case:** person meeting the clinical and laboratory criteria

Taken from Cherry et al, Clinical definitions of pertussis: Summary of a Global Pertussis Initiative roundtable meeting, February 2011. Clin Infect Dis 2012;54:1756-64

APPENDIX 6: CASE DEFINITIONS FOR PERTUSSIS-RELATED COMPLICATIONS

Generalized convulsions1. EVENT DEFINITION AND VALIDITY CLASSIFICATIONS

1.1. **Case Definition**

(ICD-9: 780.39 and ICD-10: R56.9 Read codes if applicable can be included in a table as there are many.

1.1.1 *Case Classification for Febrile Seizure*

For the case definition we will use the Brighton Collaboration definition on generalized convulsions. As in

Bonhoeffer J(1), Menkes J, Gold MS, de Souza-Brito G, Fisher MC, Halsey N, Vermeer P; Brighton Collaboration Seizure Working Group. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine. 2004 Jan 26;22(5-6):557-62

PNEUMONIA

DIAGNOSTIC CODES

A first-listed discharge diagnosis of pneumonia (ICD-9: 480.xx–486.xx or 487.0)

Pneumonia codes were ICD-9 480–486 and ICD-10 J12–18.

ICD-10: (J12–J18): J12 (viral pneumonia), J13 (pneumonia due to Streptococcus pneumoniae), J14 (pneumonia due to Haemophilus influenzae), J15 (bacterial pneumonia), J16 (pneumonia due to other infectious organisms), J17 (pneumonia in diseases classified elsewhere), and J18 (pneumonia, unspecified organism)

CASE DEFINITION

A new infiltrate on a chest radiograph together with two or more clinical symptoms (dyspnoea, cough, sputum production, chest pain, and/or body temperature > 38°C or < 36.1°C) and/or WBC > 109 cells/L) or plasma CRP > 30 mg/L) [26]. Severe pneumonia was defined as pneumonia with a CURB-65 score ≥ 2.

Community acquired pneumonia was defined as: (1) the presence of symptoms consistent with acute lower respiratory tract infection (at least one of increasing breathlessness, cough, sputum orfever); and (2) the presence of a new infiltrate on the chest radiograph.

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