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**Accelerated Development of VAccine beNefit-risk
Collaboration in Europe**

Grant Agreement n°115557

**D4.9 Work Package 4 White Paper:
methods for vaccine benefit-risk
monitoring, including vaccine
coverage, safety and effectiveness**

**WP4 – Methods for burden of disease, vaccination coverage, vaccine
safety and effectiveness, impact and benefit-risk**

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	D4.9 Work Package 4 White Paper; methods for vaccine benefit-risk monitoring, including vaccine coverage, safety and effectiveness	
	WP4. Methods for burden of disease, vaccination coverage, vaccine safety and effectiveness impact and benefit-risk monitoring	Version: V1.0 – Final
	Author(s): Kaat Bollaerts, John Weil and the WP4 task leads	Security: 2/19

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DEFINITIONS

- Participants of the ADVANCE Consortium are referred to herein according to the following codes:
 - **AEFI** Adverse events following immunization
 - **AGE** Acute Gastroenteritis
 - **AHP** Analytical Hierarchy process
 - **BCODE** Burden of disease of infectious diseases in Europe
 - **B/R** Benefit/Risk
 - **BRA** Benefit-Risk Assessment
 - **BRAT** Benefit-Risk Action Team
 - **DALY** disability adjusted life years
 - **DCE** Discrete choice experiment
 - **GP** general practice
 - **IBRR** Incremental Benefit Risk Ratio
 - **INHB** Incremental net health benefit
 - **NHB** Net Health Benefit
 - **NNV** Numbers needed to vaccinate
 - **MACBETH** Measuring Attractiveness by a Categorical Based Evaluation Technique
 - **MCDA** Multi-criteria decision analysis
 - **PAPRIKA** Potentially All Pairwise Rankings of all possible Alternatives
 - **SMAA** stochastic multi-criteria acceptability
 - **SMART** Simple Multi-Attribute Rating Technique
 - **VE** vaccine effectiveness
 - **YLD** years lived with disability
 - **EMC.** Erasmus Universitair Medisch Centrum Rotterdam (Netherlands) - Coordinator
 - **UNIBAS.** Universitaet Basel (Switzerland) - **Managing entity of the IMI JU funding**
 - **EMA.** European Medicines Agency (United Kingdom)
 - **ECDC.** European Centre for Disease Prevention and Control (Sweden)
 - **SURREY.** The University of Surrey (United Kingdom)
 - **P95.** P95 (Belgium)
 - **SYNAPSE.** Synapse Research Management Partners, S.L. (Spain)

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- **OU.** The Open University (United Kingdom)
- **LSHTM.** London School of Hygiene and Tropical Medicine (United Kingdom)
- **PEDIANET.** Società Servizi Telematici SRL (Italy)
- **KI.** Karolinska Institutet (Sweden)
- **ASLCR.** Azienda Sanitaria Locale della Provincia di Cremona (Italy)
- **AEMPS.** Agencia Española de Medicamentos y Productos Sanitarios (Spain)
- **AUH.** Aarhus Universitetshospital (Denmark)
- **UTA.** Tampereen Yliopisto (Finland)
- **WIV-ISP.** Institut Scientifique de Santé Publique (Belgium)
- **MHRA.** Medicines and Healthcare products Regulatory Agency (United Kingdom)
- **SSI.** Statens Serum Institut (Denmark)
- **RCGP.** Royal College of General Practitioners (United Kingdom)
- **RIVM.** Rijksinstituut voor Volksgezondheid en Milieu * National Institute for Public Health and the Environment (Netherlands)
- **GSK.** GlaxoSmithKline Biologicals, S.A. (Belgium) – EFPIA Coordinator
- **SP.** Sanofi Pasteur (France)
- **NOVARTIS.** Novartis Pharma AG (Switzerland)
- **SP MSD.** Sanofi Pasteur MSD (France)
- **CRX.** Crucell Holland BV (Netherlands)
- **PFIZER.** Pfizer Limited (United Kingdom)
- **TAKEDA.** Takeda Pharmaceuticals International GmbH (Switzerland)

- **Grant Agreement.** The agreement signed between the beneficiaries and the IMI JU for the undertaking of the ADVANCE project (115557).
- **Project.** The sum of all activities carried out in the framework of the Grant Agreement.
- **Work plan.** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.
- **Consortium.** The ADVANCE Consortium, comprising the above-mentioned legal entities.
- **Project Agreement.** Agreement concluded amongst ADVANCE participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

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1. INTRODUCTION

There is an increasing use of formal benefit-risk assessment (BRA) methods as an important healthcare decision-making tool, but BRA methodology for vaccines is still in its infancy. Until recently the focus in post-marketing research has predominantly been on vaccine safety, the risk component. Currently, BRAs are carried out at specific time points: after initial regulatory approval, and then later post-licensure if new safety concerns arise. The methods used are mainly qualitative, which also means they rely on expert judgment to evaluate the relative importance of benefits and risks. One area of need and development is the simultaneous post-licensure evaluation and monitoring of data on vaccine risks and benefits.

At the core of ADVANCE’s mission for many of its stakeholders is the concept of post-licensure near real-time benefit-risk (B/R) monitoring, which is understood to be ongoing continuous or periodic checks on key parameters (coverage, incidence of adverse events and of the preventable disease) to determine whether the actual B/R profile in the population is different from the expected one. Such monitoring could also generate a more formal analysis and assessment when signals indicate a safety issue has arisen. Monitoring should start as soon as a new vaccine is used in any given country, initially based on B/R information from the clinical development programme, and subsequently with accumulated post-marketing data.

The content of this white paper focuses on post-licensure BRA methodology carried out in Work Package 4 (WP4) of the IMI project *Accelerated development of vaccine benefit-risk collaboration in Europe* - ADVANCE. Its starting point is a simulated scenario in which a quantitative BRA for rotavirus vaccination in the UK is continuously monitored over time. An interactive dashboard has been developed for the simulation allows graphical display of the component data of the BRA.

We then consider the frameworks and methodological components of a BRA specifically as they relate to the dashboard inputs. As determination of coverage, benefits and safety of vaccination are some of the data needed to monitor B/R, we also include Web-based tools developed for extraction and evaluation of these data from healthcare databases in the recommendations.

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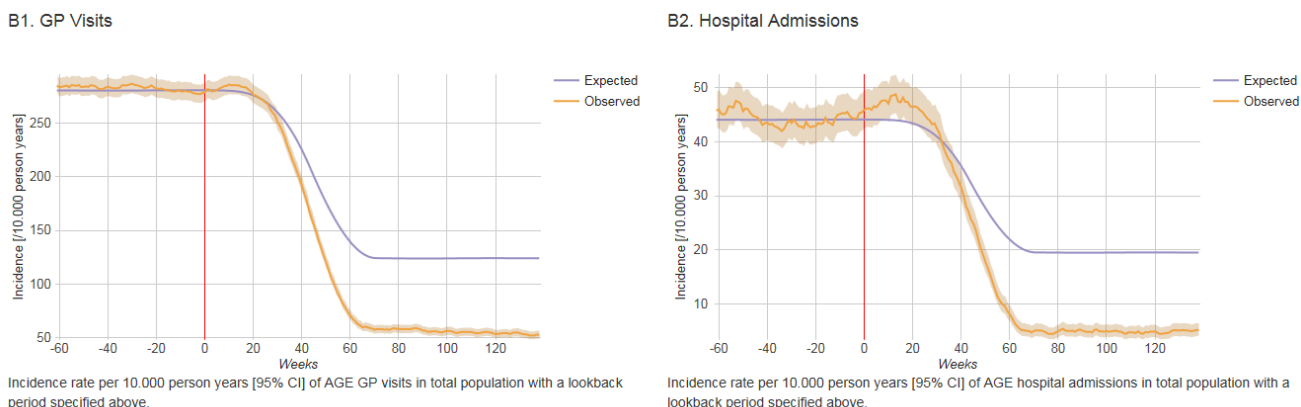
2. BENEFIT-RISK ASSESSMENT

We present here a summary description of the methods and the data simulation for the rotavirus vaccination example relevant to considerations on recommendations regarding the input data and methods. The full description is available in the final Deliverable 4.4 report.¹

The dashboard has input parameters for vaccine coverage, baseline (pre-vaccine) incidence of medically-attended rotavirus gastroenteritis, vaccine effectiveness, and baseline incidence of intussusception and vaccine risk for intussusception after each dose.²

The tool allows separate visualization of vaccine coverage, vaccine benefit and vaccine risk. [Figure 1](#) shows the incidence rates of medically-attended acute gastroenteritis (AGE) before and after rotavirus vaccination. To allow use of the most relevant time period for the baseline incidence data the length of the look-back period can be chosen by the end-user. Baseline incidence and vaccine effectiveness (VE) are also input variables. For simplicity, and as most of the vaccinated children received two doses, a conservative estimate of expected benefits is obtained ignoring the one-dose VE and the potential herd protection effects.

Figure 1: Incidence rates (per 10,000 person years) of acute gastroenteritis (AGE), total population



The tool can also combine the input parameters to display composite benefit risk. [Figure 2](#) shows the incremental net health benefit (INHB, left) and the incremental benefit risk ratio (IBRR, right) [95% CI]. The weights on the figure that are input parameters that the user can vary are explained in section 2.1.2.

¹ Tested methods for accelerated assessment of vaccination coverage, vaccine benefits, risks and benefit-risk of 28 Feb 2017 (pages 101-117).

² Table 8.1, page 104 of the D4.4 report.


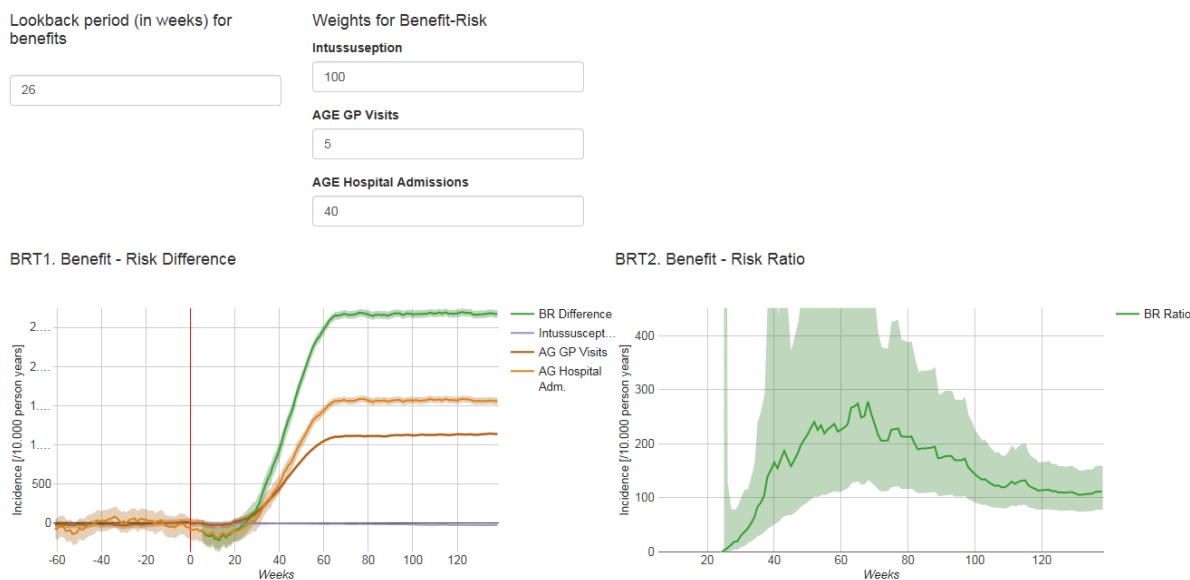
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Figure 2: Benefit-Risk of rotavirus vaccination, total population (observed benefits)



Rotavirus vaccine was an ideal scenario in that there were existing published data to use for the input simulations and coverage, benefits and risks were available from a single data source. In this example the benefit (reduced incidence of medically attended gastroenteritis) is available from a healthcare database and the database code does not need validation as AGE is generally considered to be accurately diagnosed in general practice, for which there is a known proportion that can be attributed to rotavirus without the need for laboratory confirmation. For other infectious diseases, this will be the exception rather than the rule. In this case, we recommend use of Public Health notifiable disease surveillance data when that is feasible.


The main recommendation of the white paper is the further use of this dashboard which is available at <http://apps.p-95.com/BRMonitor/>.

2.1 Frameworks for Benefit-Risk Assessment

Any BRA is a stepwise process, using structured approaches, divided into qualitative and quantitative frameworks.

2.1.1 Qualitative frameworks

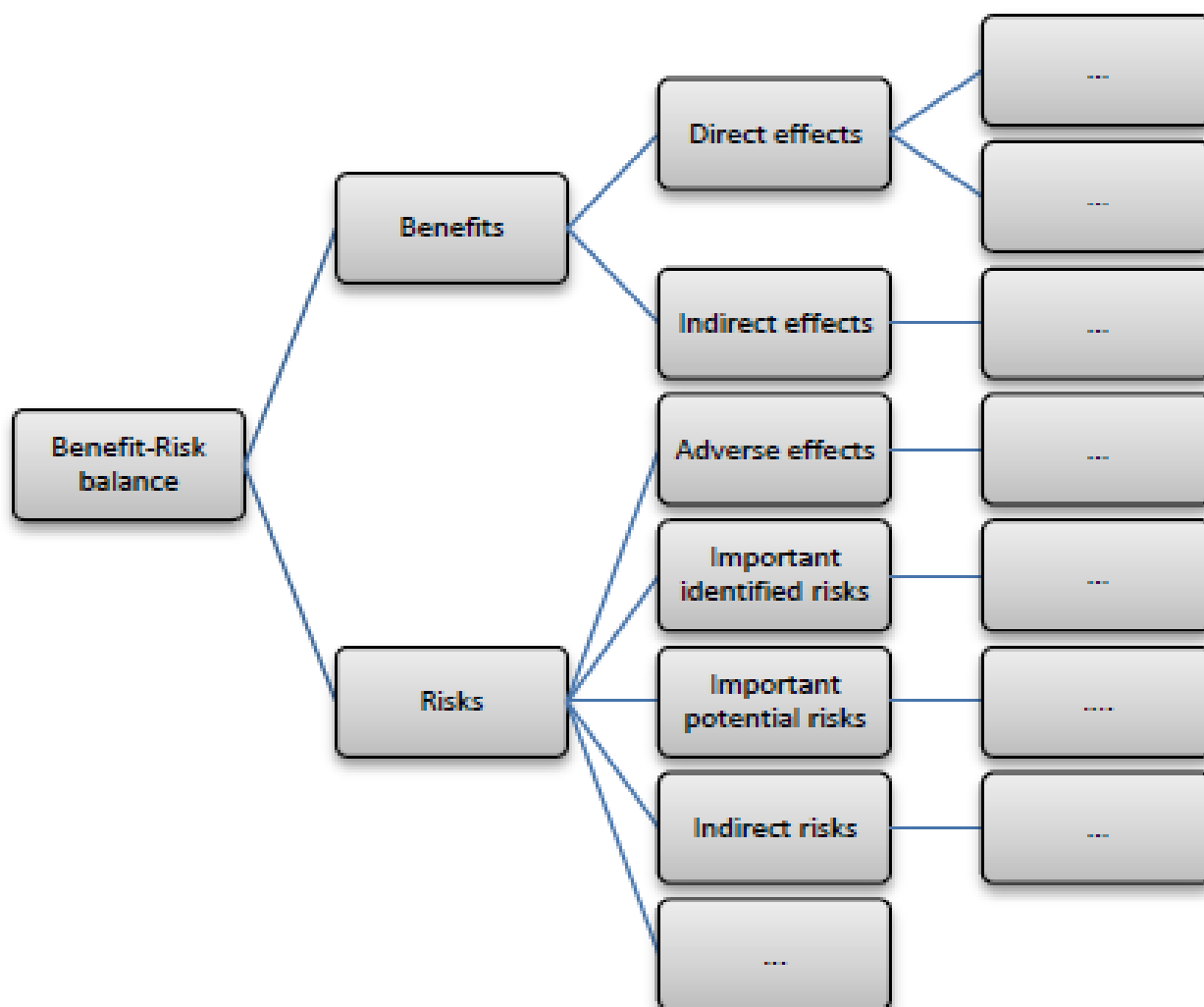
A BRA should always start with a structured qualitative assessment to ensure that all elements of the benefit-risk balance have been considered and rendered explicit, thereby improving transparency and communication in decision-making.

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The tools used for qualitative assessment are attribute trees followed by tabular summaries. The attribute tree is noteworthy given its ease of use and listing of the different benefits and risks. A generic example of an attribute tree for vaccines is shown below ([Figure 3](#)).

The tabular summaries then take as their starting columns the terminal branches of the attribute tree. Currently, Benefit Risk Action Team (BRAT) and PrOACT-URL are the most commonly used frameworks, either of which would generally be appropriate for vaccine BRAs. [Table 1](#) is a description of the PrOACT-URL framework adjusted for vaccines from the Deliverable 4.3 final report on appraisal of vaccine benefit-risk methodology.³

Figure 3: Attribute tree for qualitative benefit-risk assessment of vaccines



³ Deliverable 4.3 final report 04.11.2014 (page 25).

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In reality, descriptive frameworks for qualitative B/R assessment are generic stepwise instructions which follow good decision-making practice and we recommend them for this reason. A further recommendation is that it may not be necessary to complete a quantitative assessment if the data suggest this is not necessary to support decision making. Defining the decision problem, selecting criteria, and measuring performance can suffice.

In the simulated example for rotavirus there was one benefit and one risk. The value of using a framework such as BRAT or PrOACT-URL comes to the fore when there are multiple benefits or risks.


2.1.2 Quantitative B/R frameworks

Multiple methods that quantify benefits and risks of treatments are available. A review of existing benefit-risk metrics (Deliverable D4.3, 4.11.2014) covered 21 benefit-risk measures categorised as (1) numbers needed to treat and variants thereof, (2) benefit-risk measures based on differences in benefits and risks, and (3) benefit-risk measures based on ratios of benefits and risks. The composite benefit-risk measures Incremental Net Health Benefit (INHB) and IBRR were previously recommended by IMI PROTECT.⁴ Their simplicity makes them suitable for monitoring and we recommend both of them. NHB is the difference between the sum of the benefits and the sum of the risks of a treatment, with all outcomes expressed using the same metric. INHB is the difference between the NHB of the treatment of interest and the control or current standard of care treatment. We also recommend inclusion of numbers-needed-to-vaccinate (NNV) methods given their familiarity to clinicians and policymakers.

Multiple criteria decision analysis (MCDA) is included as it has become an important tool for quantitative BRA and it is sufficiently wide in scope that the dashboard can be defined as an application of MCDA methodology. A challenge for users of MCDA is that there are many MCDA methods available which makes the choice of MCDA method to use in any given context such as healthcare decisions quite complex. Belton and Stewart⁵ define MCDA as “an umbrella term to describe a collection of formal approaches, which seek to take explicit account of multiple criteria in helping individuals or groups explore decisions that matter.” This definition allows MCDA to be used to support decision making without the need for quantitative aggregation to a single number. For example, the attribute tree and effects tables in the qualitative BRA can be defined as a “partial” or qualitative MCDA.

⁴ <http://protectbenefitrisk.eu/documents/ShahruletalReviewofmethodologiesforbenefitandriskassessmentofmedicationMay2013.pdf>

⁵ Belton V, Stewart TJ. Multiple Criteria Decision Analysis: An Integrated Approach. Kluwer Academic Publishers, Massachusetts, 2002.

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For a “complete” quantitative MCDA the treatment effects e.g. results from clinical trials, are combined with explicit weights for stakeholders’ preferences between the treatment benefit and risk criteria. MCDA allows both benefits and risks to be split into multiple criteria. Overall weighted scores are calculated by multiplying the treatment effects by the weights and the result can be examined for uncertainty with sensitivity analyses.

MCDAs are often challenging to conduct because they require knowledge of various methods for modelling the clinical treatment value and eliciting stakeholder preferences to select the most appropriate for any given assessment. And then scores are needed for each branch of the value tree. In their review of BRA IMI PROTECT recommended further consideration and testing of MCDA and another variant of MCDA, the stochastic multi-criteria acceptability analysis (SMAA). For monitoring B/R of vaccines, we limit our recommendation to use of the qualitative components of MCDA.



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Table 1. Description of the PrOACT-URL framework

1. Problem	<p>To determine the nature of the problem, its context and frame the problem. This includes a description of the vaccine preventable disease epidemiology, the product, the indication(s) for use and the unmet medical need.</p> <p><i>Examples of vaccine related benefit-risk decision problems are: approval of a new vaccine, restriction of vaccinations, update of an existing benefit-risk assessment after safety signal, the decision by public health authorities to offer routine vaccination, to change the vaccination schedule and to launch a vaccination catch-up programme. For vaccines, it will be important to mention the target population, the vaccination schedule, the duration of vaccine exposure, the time period over which the benefits and risks will be measured, the perspective (individual or societal) and the decision maker (e.g. public health authority, regulators, candidate vaccine recipient).</i></p>
2. Objective	<p>To establish the objectives that indicate the overall purposes to be achieved (e.g. approval, restriction, update after safety signal) and identify criteria of benefits and risks that build the attribute tree.</p> <p><i>Criteria that might be relevant for vaccines are direct benefits, indirect benefits, (serious) adverse events, important identified risks, important potential risks and indirect risks. It is important to mention the relevant time window for observation.</i></p>
3. Alternatives	<p>To identify the options to be evaluated against the criteria.</p> <p><i>For vaccines, the alternatives include no vaccination, the use of an alternative vaccine, alternative use (age or risk group restrictions), the use of other preventive measures and other vaccination implementations.</i></p>
4. Consequences	<p>To describe how the options, perform on the different criteria (i.e. the magnitude of all effects, their desirability or severity, their incidence). To create the effects table.</p> <p><i>The information to be included in the effects table might come from clinical trials, epidemiological studies, database analyses and infectious disease models.</i></p>
5. Trade-offs	<p>To assess the balance between benefits and risks (i.e. clinical judgement and rationale).</p> <p><i>Depending on the benefit-risk decision to be taken, the preferences might be from candidate vaccine recipients, the general population, public health experts or patients.</i></p>
6. Uncertainty	<p>To assess the uncertainty associated with the effects (e.g. statistical uncertainty, bias and representativeness of the studies, correlates of protection). To consider uncertainty by conducting sensitivity analyses and scenario analyses on the model.</p>
7. Risk tolerance	<p>To evaluate the relative importance of the decision maker's risk attitude for this decision and how this affects the balance reported in 5.</p> <p><i>It is important to consider whether vaccination is recommended or mandated.</i></p>
8. Linked decisions	<p>Whether an alternative vaccine is available. Is this decision consistent with similar past decisions, and assess whether this decision could impact on future decisions?</p>

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2.1.3 Techniques for elicitation of weighting scores

The elicitation of value judgements for vaccines is challenging. Unlike drugs, vaccines are administered to healthy people, so the first problem is deciding who to ask for their judgement. For some vaccines (e.g. travellers vaccines), both the potential benefits and risks are borne by the same individual. Hence, preferences from candidate vaccine recipients are informative. For national immunization programmes that reduce disease transmission within the general population, one might argue that the general population and/or public health experts play an important role in generating these preferences, which may further depend on whether the vaccine is recommended or mandated. In addition, preference elicitation for vaccination might involve surrogate decision making, which is typically invoked when the care-receiver lacks decision-making capacity. For vaccines given to young children, the authority to make the vaccination decision on behalf of a child usually falls to the child’s parents and hence, parent’s preferences are informative. For vaccines given to adolescents (e.g. HPV vaccination), one might argue that the preferences of the adolescents, parents or both are informative. Finally, although patients suffering (or having suffered) from the vaccine preventable disease are typically not the ones being vaccinated, their preferences are informative as well because they are well placed to value the benefits of vaccination.

The second difficulty is deciding how to ask. Vaccines are primary preventive measures, implying that vaccine recipients are often never confronted with the disease against which they are protected, e.g. diphtheria, tetanus. This distorts the perceived benefits of vaccination. On the other hand, a very low risk tolerance exists because vaccines are generally given to healthy people, typically to young children, often as part of a vaccination recommendation or mandate. The risk perception is further influenced by the enhanced media attention for vaccine-related issues.

However, apart from the benefits of herd immunity the above difficulties are not unique to vaccines. We recommend searching for any methodological lessons from BRAs of preventive treatments, e.g. anti-hypertensive or cholesterol-lowering drugs.

The objective of weighting with scores is to capture stakeholders’ preferences between multiple criteria and bring the individual performance criteria on benefit and risk outcomes to a common value for comparison. In the Swing weighting method stakeholders are asked to decide on the most important outcome (based both on their preferences and on the frequency of the treatment outcome), which is then given a score of 100. Stakeholders are then asked to score the importance of other outcomes relative to the 100 for the most important outcome. In the demonstration example the scores for intussusception (IS), rotavirus gastroenteritis GP and hospital visits (RVGE GP and RVGE HOSP) were entered as simulated values with IS scored as 100, RVGE GP as 5 and RVGE HOSP as 40.

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For completeness, we mention that quantitative BRA can also elicit stakeholders' preference values for a treatment's effect on change in the performance on a criterion, e.g. an improvement in survival for an oncology treatment. For vaccines, the outcomes are binary (disease/no disease, adverse event/no adverse event) and this additional preference scoring is generally not required.


Eliciting scores remains in the domain of research with numerous methods cited: Swing – weighting; analytical hierarchy process (AHP); discrete choice experiment (DCE); Measuring Attractiveness by a Categorical Based Evaluation TecHnique (MACBETH) , Potentially All Pairwise RanKings of all possible Alternatives (PAPRIKA), Simple Multi-Attribute Rating Technique (SMART); SMARTER, SMART exploiting ranks; SMARTS, SMART with Swings, conjoint analysis) and different authors use different classifications of the methods. There are also diverse settings in which the methods can be applied: focus groups, MCDA decision-conference, and clinically-informed simulation approach or by different survey methods.

Thus, there is a need for more work to support the selection of appropriate weighting methods. Indeed, the literature on preference weights for evaluation of vaccines is limited to utility scores for specific infectious diseases intended to be used in an economic evaluation of the vaccine. The scarcity of appropriate utility weights for vaccine-preventable infectious diseases in children and a lack of standardization in their use (in economic assessments) limit the ability to accurately assess the (economic) benefits associated with interventions to prevent infectious diseases.

Eliciting stakeholder preferences is also resource intensive and subject to uncertainty if not done rigorously. In addition, for MCDA there are structural requirements, such as the criteria not having any mutual dependencies, which makes a quantitative MCDA with score elicitation incompatible with the ADVANCE mission for rapid evaluation.

We therefore recommend use of the weighting score fields on the dashboard only as an exploratory tool to understand the extent to which stakeholder values could influence the BRA. The value-neutral default would be to assign equal weights to health service encounters (a general practice consultation, a hospitalization) on either side of the risk benefit evaluation.

Disability adjusted life years (DALYs) can be used if a common unit of measurement is required, if DALYs are available for the outcome criteria. DALYs have been widely used to quantify the population-level health impact of disease or injury. DALYs are commonly and successfully used in the Global Burden of Disease project, to estimate the Burden of Disease of infectious diseases in Europe (BCoDE project funded by ECDC77) and to estimate the cost-effectiveness of vaccination programmes (guidelines World Health Organisation).

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ADVANCE tested the use of DALYs to estimate the burden of adverse events following immunization (AEFI). A framework was developed describing all steps involved, from criteria for selection of events, through retrieval of parameters and background incidence rates from the literature, to computation of the years lived with disability (YLD) measure, with estimation of uncertainty. A worked example estimated YLD for four adverse events following three childhood vaccines based on published background incidence rates and relative and absolute risks. The conclusion was that the methodology can be usefully applied to estimate the health burden of AEFIs, but that the availability of disability indices remains a challenge and that the interpretation of the findings must consider the quality and accuracy of the input data sources.

2.2 Conclusions and summary for B/R monitoring


To conclude, we recommend integrated post-marketing monitoring of risks, benefits, and coverage. A dashboard has been developed as a tool to achieve this in the ideal scenario when risks, benefits and coverage are all available from a healthcare database *and when the risk and anticipated benefit are also known*. Although not tested in ADVANCE we recommend consideration of use of Public Health infectious disease notification data when monitoring benefits is not appropriate using codes from a healthcare database. We also recommend the use of DALYs when available as a common measure for benefits and risks.

We further recommend that the resource intensity of the monitoring should be appropriate to the situation. A qualitative BRA will generally be sufficient and only on rare occasions of complex or marginal assessments, e.g. narcolepsy and pandemic influenza vaccination, will a quantitative BRA contribute to decision-making.

3. VACCINE COVERAGE

Of the three components for B/R evaluation typically available from healthcare databases vaccine coverage has the highest unused potential. As well as providing information on vaccine uptake, one measure of the success of new vaccination campaigns, it could also improve benefit risk assessment in the specific situation of the introduction of a new vaccine. Real-time analysis would be useful for seasonal and pandemic influenza vaccines, e.g. during the 2009 influenza pandemic manufacturers could provide little more than available distributed doses as the denominator for observed versus expected evaluation of serious adverse event reports, and this denominator data was not always available for a given country to accurately define reporting rates.

Collecting and assessing vaccination coverage data on an ongoing basis is part of vaccination programmes, but administrative methods used in Europe vary widely. Some quality issues in the coverage accuracy are evident when data reported through these methods are compared with seroprevalence studies or other surveys. However, more

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	WP4. Methods for burden of disease, vaccination coverage, vaccine safety and effectiveness impact and benefit-risk monitoring	Version: V1.0 – Final	
	Author(s): Kaat Bollaerts, John Weil and the WP4 task leads	Security:	17/19

important for rapid B/R monitoring for ADVANCE is the lag time before the coverage data is available which will be even longer for data at a European level collated from different national sources.

Some healthcare databases offer the possibility of near real-time monitoring of vaccine coverage. Public Health England used sentinel general practice (GP) level coverage data downloaded on a monthly basis to rapidly assess vaccine coverage of the meningococcal B immunisation programme, and weekly downloaded data to rapidly assess seasonal influenza vaccine coverage in eligible GP patient groups.


We recommend an evaluation of the possibility of the databases available in ADVANCE to provide near real-time vaccine coverage. The minimal requirements are that the vaccine is given in the healthcare setting covered by the database and that the data is refreshed at least monthly.

Populations captured in healthcare databases are dynamic, with members moving in and out of the population over time, due to switching between GPs or health insurance organisations for example. This leads to an underestimation of coverage as vaccines administered outside the follow-up period will not be recorded. ADVANCE (report D4.4) explored two methods—an inverse probability weighting based on comparing the observed follow-up with hypothetical complete follow-up and the cumulative distribution method based on applying the observed distribution of vaccination around a given age to all database subjects—to estimate vaccination coverage for dynamic populations and assess their performance with simulated data.

In the simulation both methods corrected coverage estimates for incomplete follow-up when incompleteness is not associated with coverage. If incompleteness is non-random with respect to vaccination then this can be adjusted as long as there is a third variable, C, that is related to coverage and incompleteness. We recommend evaluation of the methods using databases to determine whether they improve coverage estimates. These methods will be more applicable to cross checking coverage estimates from administrative data than to real time monitoring of vaccine coverage.

4. TOOLS TO MEASURE BENEFIT AND RISK OUTCOMES IN HEALTHCARE DATABASES

Included here are these web-based applications developed specifically for ADVANCE and one reference data set that we recommend as they are user ready and should prove useful beyond the current project. Full descriptions for each tool in the Deliverable 4.4 final report.

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4.1 CodeMapper: semi-automatic coding of case definitions

As use of different healthcare databases in the European Union requires extensive efforts in the harmonization of codes due to different vocabularies being used across countries a web application called CodeMapper was developed, which allows the mapping of case definitions to codes from different vocabularies while keeping a transparent record of the complete mapping process. CodeMapper builds upon coding vocabularies contained in the Metathesaurus of the Unified Medical Language System. The mapping approach consists of three phases. First, medical concepts are automatically identified in a free-text case definition. Second, the user revises the set of medical concepts by adding or removing concepts, or expanding them to related concepts that are more general or more specific. Finally, the selected concepts are projected to codes from the targeted coding vocabularies. The application was evaluated by comparing codes that were automatically generated from case definitions by applying CodeMapper’s concept identification and successive concept expansion, with reference codes that were manually created in a previous epidemiological study. The web application is available under <https://euadr.erasmusmc.nl/CodeMapper>.


4.2 Population differences between the ADVANCE databases

This project investigated differences in the population of the countries participating in ADVANCE, the source population in the databases with the relevant country population, and the differences between follow-up of the population on the databases. This allows an understanding of one potential source of heterogeneity and provides data to extrapolate the results beyond the data used to generate the results if needed. Data output is included in the Deliverable 4.4 final report⁶ and can be made available as reference data.

4.3 Impact of disease- and exposure-misclassification on estimations of vaccine effectiveness

Studies of vaccine effectiveness (VE) rely on accurate identification of vaccination and cases of vaccine-preventable disease. In practice, database codes and vaccination records often present inaccuracies, which can lead to biased effect estimates. Previous simulation studies assessing the impact of misclassification on VE assumed non-differential misclassification and did not account for exposure misclassification. We developed a web-application to assess the potential (joint) impact of disease- and exposure-misclassification when estimating VE using cohort, case-control, test-negative and case-coverage designs. The misclassification can be differential or non-differential. The impact of misclassification on the estimated VE is presented graphically. We demonstrated the application using simulated data on childhood seasonal influenza and pertussis vaccinations. Depending on

⁶ Deliverable 4 final report (pages 27-39)

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the scenario, the misclassification parameters had differing impacts. The impact of the misclassification parameters was found to be more noticeable than that of the different study designs. The web-application can be modified by users to evaluate the effect a specified misclassification bias would have on their own study results.

The simulation model was developed using the open-source statistics package, R 3.3.1.⁷ To allow modifications to the simulations for other parameter settings/diseases while maximizing user-friendliness, we encapsulated the source code of the simulation model in a web application created using the Shiny package.⁸ In the web application, the user can set all the necessary input parameters and the output files can be downloaded. The application is available to the ADVANCE consortium (with a user guide provided as supplementary file). <http://apps.p-95.com/VEMisclassification/> and <https://p95-tom.shinyapps.io/ShinyApp/>.

4.4 Validation of case-finding algorithms in healthcare research: analytical interrelations between validity indices

Validation of study outcomes is recognized as an important component of research using healthcare databases. Developing case-finding algorithms for study outcomes is recognized best practice as is validation of the case-finding algorithm. However, this is resource intensive. The typically evaluated validity indices of case-finding algorithms include sensitivity, specificity, positive and negative predictive values. These validity indices, as well as the observed and true disease prevalence are interrelated. For every combination of the observed prevalence and two other parameters, analytical expressions were derived to obtain the remaining three parameters. A web-application, developed using R and the Shiny package, calculates validity indices given user-defined values of the observed prevalence and any other two parameters, with the 95% uncertainty intervals of the derived parameters obtained through Monte Carlo simulation. The application also allows for uncertainty in the input parameters. This tool will be useful when two other parameters are available as a substitute for resource intensive validation studies and to derive estimates of the true prevalence for any combination of the observed prevalence and any two validity indices. The application is available to the ADVANCE consortium: <http://apps.p-95.com/Inter>.

⁷ R 3.3.1 is available from <https://cran.rstudio.com/>

⁸ Shiny package is available from <https://shiny.rstudio.com/>