D1.1 Multi Stakeholder Influenza Vaccine Effectiveness Research Agenda

777363– DRIVE
Development of Robust and Innovative Vaccine Effectiveness

WP1 – Development of a governance model for joint influenza vaccine effectiveness studies in Europe

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The aim of the DRIVE project is to develop robust evidence on brand-specific influenza vaccine effectiveness (BSIVE) in Europe. This research agenda has been developed to identify areas where increased knowledge could support decision making for regulatory purposes and for public health programs. The agenda will be shared externally to solicit input that will be discussed with relevant stakeholders at the DRIVE Forum in Rome in September 2018. It will be updated annually to monitor research advances and possible new areas to investigate.

Aspects that could be researched to improve the robustness of estimates of influenza vaccine effectiveness have been delineated in terms of needs for evidence, in terms of data and methods, and in terms of governance. The needs for evidence are described according to the regulatory framework and discussed according to time, place and people. Robustness is described with the objective of improving grading of observational studies on IVE and BSIVE. The needs for data are described for exposure and outcome. A list of possible methodological investigations is proposed.

The section on governance discusses regulatory aspects of IVE and BSIVE, and the context of European collaborations in a post-authorization setting. It is proposed to develop key indicators for governance evaluation, explore the usefulness of existing standards to assess scientific independence and transparency of collaborative research, and evaluate the perception of public-private partnerships (PPPs).
## Contents

Document History ............................................................................................................................................... 2
Publishable Summary ........................................................................................................................................ 3
Background .................................................................................................................................................... 5
1. Research needs ........................................................................................................................................... 6
   1.1 Systematic analysis of the evidence needed ......................................................................................... 6
      1.1.1 Specificities of Brand Specific Influenza Vaccine effectiveness .................................................... 6
      1.1.2 Evidence needed ............................................................................................................................... 6
      1.1.3 Needs for evidence in terms of time, place and people ................................................................. 8
   1.2 Robustness and its operationality .......................................................................................................... 9
2. Data ............................................................................................................................................................ 11
   2.1 Case definition ...................................................................................................................................... 11
      2.1.1. Clinical case definitions ............................................................................................................... 11
      2.1.2. Laboratory-confirmed influenza .................................................................................................... 12
      2.1.2. Non-specific endpoints .................................................................................................................. 13
   2.2. Exposure ........................................................................................................................................... 13
      2.2.1. Influenza vaccination exposure ..................................................................................................... 13
      2.2.2. Brand data collection .................................................................................................................... 13
3. Methods ................................................................................................................................................... 14
   3.1 Study design specific ............................................................................................................................ 14
      3.1.1 Participatory epidemiology ........................................................................................................... 14
      3.1.2 Best control sampling methods for TND studies .......................................................................... 15
      3.1.3 Screening method .......................................................................................................................... 15
      3.1.4 Propensity score method .............................................................................................................. 16
      3.1.5 Adjustment and confounding ....................................................................................................... 16
      3.1.5.2 Effect of previous influenza infection ...................................................................................... 17
   3.2 Pooled analysis ................................................................................................................................... 18
      3.2.1 Pooled analysis: one stage vs two stage approach ..................................................................... 18
      3.2.2 Methods for pooling across seasons ........................................................................................... 19
      3.2.3 Adaptive design ............................................................................................................................ 19
4. Governance ............................................................................................................................................... 19
   4.1 Building a European environment for IVE studies ............................................................................. 19
   4.2 Perception of PPPs and scientific independence .............................................................................. 21
5. Implementation and monitoring .............................................................................................................. 22
   5.1 Liaising with other programmes ......................................................................................................... 22
   5.2 Timelines ............................................................................................................................................ 22
   5.3 Updates ............................................................................................................................................... 22
6. Conclusion ................................................................................................................................................. 23
Background

The objective of the DRIVE Work Package 1 (WP1) is to support consensus building around the governance of the DRIVE platform among the different stakeholders, allowing and encouraging them to participate. The work has been organized into three tasks:

1.1. To set up a multi-stakeholder IVE agenda.
1.2. To fine-tune the governance of the platform, ensuring at the same time active stakeholder engagement.
1.3. To propose a generic development plan for influenza vaccine effectiveness (IVE), which would benefit from the established infrastructure.

The results of task 1.1 are presented here. Its objective is to identify a common research agenda for the different stakeholders at EU/EEA and national level, i.e. ECDC, EMA, national public health institutes (NPHIs), supranational bodies such as WHO, national regulatory agencies (NRAs), Health Technologies Assessment and recommendation bodies, vaccine manufacturers, health care professionals (HCPs), patients and academia. The research agenda has two complementary aspects:

The first aspect is related to the **needs for evidence** on IVE that are still not available in Europe. Specifically, in the context of IVE, national-level studies and established networks provide IVE estimates but do not currently address the regulatory needs for brand-specific IVE. Sharing and establishing the needs for evidence for IVE and BSIVE in the classical terms of time (annual periodicity?, real time?), place (are estimates in each country, each year needed?) and people (which population groups?) at a European level would support optimal use of resources and encourage sharing of efforts. DRIVE’s focus on the regulatory field is related to the need to explore how recent EMA guidelines on estimates of influenza vaccines effectiveness can be implemented.

The second aspect is related to increasing the **robustness** of evidence provided from observational studies. Robustness is related to the quality of the data, aiming at reducing uncertainties, allowing the use of simpler methods and analyses, and minimizing the risk of bias. Other key components of robustness include sample size, methods used for data collection, management and analyses, and reporting. ;

Although these two previous aspects are at the cornerstone of scientific evaluation of the robustness of estimates, they are not the only ones, and a third section of the research agenda will also explore the robustness of the governance of projects and studies. This aspect is critical, ranging from studies initiation (decision to initiate a study, ways of funding...) to study conduct (preparation, implementation, analysis and communication) and to the management of the evidence generated.

These three main aspects of robustness are interrelated: as examples, the better the data, the easier the methods to analyze and interpret results; the higher the sample size requirement, the greater the need for collaborative studies and good governance. These aspects have also in common than they can be explored by referring to general and specific guidelines and principles and their related codes of conduct. It is planned to perform a systematic analysis of various guidelines and codes of conduct addressing these. This might impact study conduct and governance and generate ideas for improvement of guidelines and codes. Increased robustness should also contribute to the acceptance of the results and decisions based on the results, from different stakeholders’ perspectives, including public health authorities and the general public. However, increased robustness should not come at the cost of disproportionately more complex and expensive studies. To this end, maintenance of feasibility and sustainability and avoidance of complexity and futile management will be an identified research topic on the agenda.

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The research agenda will thus identify needs for evidence and areas of further research on IVE and BSIVE and ways to increase robustness of IVE/BSIVE estimates. The three aspects outlined above (on data, methods, governance) are presented in chapters 2, 3 and 4, after an introductory section on the need for evidence. A 5th section will discuss implementation and monitoring of the research agenda. The agenda will highlight evidence available for action, gaps and priorities, synergies and complementarities, and express the needs and expectations from different stakeholders. Some aspects will be developed outside DRIVE, others within.

1. Research needs

1.1 Systematic analysis of the evidence needed

1.1.1 Specificities of Brand Specific Influenza Vaccine effectiveness

There are important regulatory aspects related to the estimation of Brand Specific Influenza Vaccine Effectiveness (BSIVE), compared to Influenza Vaccine Effectiveness in general (IVE).

From a regulatory perspective, results of effectiveness studies by brand contribute important information to the overall clinical evidence available for each individual influenza vaccine.

There are procedural obligations of the manufacturers related to their products’ licenses and submission of relevant benefit/risk data as per new European Medicines Agency (EMA) Guidelines on Influenza Vaccines. The generation of such data also has an added value for public health at the EU level.

There is a need for broader scientific discussion with EMA and relevant regulatory authorities on understanding influenza vaccine effectiveness as well as on the feasibility of and experience with the implementation of the guidance.

- Establish how IVE and BSIVE studies could best answer both public health and regulatory needs.

1.1.2 Evidence needed

Evidence needed is best expressed as dummy tables or a minimum set of results that would satisfy the needs of the different stakeholders. It is described in Table 1 below for a given brand:

Table 1: estimates of vaccine effectiveness (VE) of brand specific influenza vaccination against specific outcome (laboratory confirmed influenza/influenza type X/influenza subtype (lineage) X) for a cohort study.

<table>
<thead>
<tr>
<th>Age</th>
<th>Cases not vaccinated (n)</th>
<th>Cases vaccinated (brand specific)</th>
<th>Population not vaccinated (N)</th>
<th>Follow-up not vaccinated (person years)</th>
<th>Population vaccinated (N)</th>
<th>Follow-up vaccinated (person years)</th>
<th>Crude VE (%) and 95% CI</th>
<th>Adjusted VE (%) and 95% CI</th>
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For a given brand, estimates of vaccine effectiveness are stratified by age and virus subtypes, which are potential effect modifiers. They are provided as of interest for regulatory purposes, as well as for public health purposes. Other factors are accounted for in the adjustment estimates. Analyses performed to produce these tables and description of adjustment and stratification are described in WP4 deliverable 4.4, and research activities identified for such analyses will be described in the research agenda chapter 3 on methods, below.

- Evaluate the completeness of these dummy tables in terms of evidence needed for decision making
1.1.3 Needs for evidence in terms of time, place and people

**Time.** IVE estimates are needed each year, preferably including early, mid-season or even real-time estimates to guide additional public health actions (antivirals etc.) in a timely way and to explore the potential effect of waning immunity. For regulatory purposes, robust end-of-season estimates (or even pooled data over several years) are thought to be the most relevant. The choice of when to release overall and brand-specific IVE results may also impact the uptake of influenza vaccines in either a positive or negative way. For example, when trivalent vaccines are being used which do not cover the circulating B-virus (as during the season 2017-18, B/Yamagata, in many countries), IVE results which convey the message that even TIV may have cross-protective effects are useful to counterbalance the negative message of the mismatch.

- Identify the best timing of releasing IVE results to answer public health and regulatory needs

**Place.** Patterns of virus circulation and the use of influenza vaccines differ between countries. Currently, many European countries conduct IVE studies at country level, often as part of an existing network. However, WHO does not recommend that IVE studies be necessarily conducted by every country with an influenza vaccination programme, noting that the results from existing studies should be applicable more widely. This is comparable to randomised controlled trials (RCTs), where replicating findings in each country is generally not needed. Indeed, some countries with the capacity for IVE studies have chosen not to conduct them, instead relying on information produced by others.

For brand-specificity, countries or regions that use a given vaccine are of particular relevance and should be prioritized for support. On the other hand, once reliable estimates for a given vaccine are available from a country or region, replication of estimates in other countries should be justified. As an example, do IVE estimates for the live-attenuated influenza vaccine (LAIV) in Finland satisfy evidence needs for the EU? Input from EMA VWP will be sought in the spirit of “investigations plans” such as Paediatric Investigation Plans (PIP) with the aim of orienting efforts toward vaccines or populations where evidence is lacking. There is also a need to align with WHO on their new definitions on geographic divisions of influenza surveillance in Europe and to take into consideration the different purposes IVE data are used for (post-licensure purposes, Cost Effectiveness Analyses for tenders, or for vaccine programme development in general, individual target group preference in recommendations, etc.)

- Identify the optimal structure and size of a study network in Europe for the IVE results to be generalizable and to have adequate brand coverage.

**People.** Most of the IVE estimates are currently derived from the elderly adult population. However, influenza infections are common in children who also shed viruses for a long time and often have many close social contacts. Very young children are vulnerable to a severe disease and hospitalization. Thus, vaccinating children may be an effective measure to prevent the disease in the population through indirect (herd) immunity. Similarly, health care workers treating infected patients have a high infection pressure, and after getting infected, they may effectively transmit the disease to persons vulnerable to severe disease in close treatment contacts. Pregnant women are recognized as a primary group for influenza vaccination by WHO, as they are vulnerable to severe disease, and vaccination may prevent both harm during the pregnancy and the transmission of the disease to the new-born child. Yet, vaccine coverage among pregnant women is low\(^2\) and there is a lack of specific estimates, and further work has been expected. Specific information on vaccine effectiveness in groups with chronic conditions, e.g. according to their nature and severity, could motivate vaccination in the groups who most need it.

- Identify specific populations who need specific estimates of IVE, BSIVE

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Conclusion. The three aspects of time, place and people are interdependent, and the prioritization of IVE studies should consider these aspects simultaneously. The current trend of secondary use of healthcare data collected for other purposes might suggest that every analysis is possible and easy to run. However, this exercise of identifying evidence gaps and planning which estimates are needed and in which populations is still very important to perform. A European vision to achieve this exercise is needed, and an active role of European agencies such as EMA and ECDC is expected on providing or commenting on a plan of needs over time.

1.2 Robustness and its operationality

The GRADE approach (Grades of Recommendation, Assessment, Development and Evaluation) is a way to assess the robustness of available evidence. It might be further developed by merging with other initiatives such as ISPOR-ISPE good practices for Real World Data about registration and replicability, which identified seven topics. Specific efforts have been developed for vaccines, such as by RKI and PRECEPT work and by WHO. A recent report by WHO also contributes specifically on this aspect using STROBE. Taken together, with the strengthening of practices such as IEA, ISPE, ENCePP, these standards are likely to further improve the robustness of estimates. However, would studies following all these standards and practices be upgraded in the GRADE system to levels closer to good clinical trials? Is this achievable, and how?

- Identify innovative approaches of study preparation, conduct and analyses that would allow the upgrading of estimates on IVE and BSIVE in GRADE.

Much is to be learned from these systematic approaches to assess evidence quality for public health decision making; however DRIVE specificity on the principle for collaborative projects needs extension of assessment of robustness to governance factors. It is expected that further investigation of the concept of robustness can provide insight on governance models, and help to provide rationality for such models, as well as for study conduct. Complementary aspects of robustness, such as avoidance (e.g. CoI) and resistance (CoI, biases etc) can be delineated in governance models of studies and projects.

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6 Evaluation of Influenza vaccine effectiveness, a guide to the design and interpretation of observational studies , WHO 2017.
• Which aspects of a governance structure contribute to avoidance of risks, and which aspects contribute to resistance to risks?

These aspects will be part of section 4 on Governance, below.

Improving the grading of evidence on IVE and BSIVE from observational studies, on the three aspects of data, methods, and governance can be supported by a mapping of the different reasons for vaccinations to fail to protect against disease. Table 1 is extracted from a piece of work by Fine and Zell7.

An adaptation and extension of the list from this table to IVE and BSIVE would help to delineate the different aspects or 'components' of vaccine effectiveness estimates based on the different factors identified.

These components, which can group several factors, could be linked to their primary concerned stakeholder. This link between a factor or a group of factors, and the relevant primary stakeholder responsible for this factor, should support the rationale for collaboration within a network: for example, assessing the quality of the vaccine in terms of antigen content is the responsibility of the MAH, from production to some point of the cold chain, supported by external monitoring by authorities. But assessing or forecasting antigen match to circulating influenza viruses is not the MAH’s responsibility, rather that of WHO networks. Assessing primary responsibilities would support the rationale for collaborations and perception of collaborations providing independent and unbiased results. This will support the principle of complementarity in collaborations. Too often, collaborations are based or justified on the principle of adding manpower with similar expertise. This might be relevant in some areas, but needs to be carefully assessed in vaccine effectiveness or observational studies in general, as it also conveys a risk, or the perception of a risk of influence. Inversely, delineation of complementarity could be a strong basis for communication of the rationale for collaboration. These aspects will be further developed in the governance section.

• Map different factors, influencing IVE and BSIVE in the domain of data, methods and governance;

• Identify responsible stakeholder for the identified risk factors or group of risk factors (components of effectiveness);

The mapping of factors and responsible stakeholders will be tabulated as a 2 dimensional table. Factors for vaccine failure will be adapted to IVE and BSIVE and presented in lines in the table. A column will be identified for each stakeholder. For a given factor, the level of responsibility will be

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indicated for each stakeholder. Together with the table on evidence needs, this second table will frame the research agenda.

It is acknowledged that the present description of needs for evidence focuses on direct effects of vaccines, in line with the regulatory aspects underlying DRIVE objectives. However, the evaluation of needs for evidence could be extended to indirect effects (i.e. herd immunity, such as prevention of disease in the elderly as a consequence of reduced transmission by vaccinating those close by, i.e. health care workers and children) of influenza vaccines and impact of influenza vaccination programmes, as generically discussed by Hanquet et al. 2013. Such extension could bring value to the public health dimension of influenza vaccines, with shared benefits from the research agenda.

2. Data

2.1 Case definition

2.1.1. Clinical case definitions

Clinical case definitions are used in IVE studies to identify those subjects that should be tested for influenza. Therefore, the choice of case definition can greatly influence laboratory testing yield.

Influenza-like illness (ILI) and severe acute respiratory infection (SARI) are frequently used definitions of clinical outcome. Definitions differ. For example, while WHO ILI and SARI definitions require a measured temperature of $\geq 38^\circ C$, EU ILI and SARI case definitions do not require it.

While there has been some research looking at the performance of the different case definitions, it may be of interest to conduct further research into this subject. Using a case definition with high specificity may increase the yield of laboratory testing, and increase the number of influenza cases to be included for IVE analysis. Within DRIVE, it may be possible to include an objective to look at the performance of the case definitions, although it will depend on how the data is collected and the possibility to apply different case definitions to the same subjects.

- Identify optimal clinical case definitions to identify subjects for influenza testing in IVE studies

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8 Hanquet G1, Valenciano M, Simondon F, Moren A. Vaccine effects and impact of vaccination programmes in post-licensure studies. Vaccine. 2013 Nov 19;31(48):5634-42
2.1.2. Laboratory-confirmed influenza

The WHO recommends the use of laboratory-confirmed outcomes as opposed to non-specific (syndromic) outcomes. The decision to assess potential study subjects for laboratory-confirmed influenza virus infection should be based on pre-specified protocol guidelines, in order to avoid systematic misclassification of study subjects, which may arise in cases where clinicians choose freely whom to test. Whenever possible, study protocols should specify the symptoms, duration of illness, and other eligibility criteria for attempting to enrol and test patients for influenza (in studies based on administrative databases this cannot be done). According to the Committee for Medicinal Products for Human Use Guideline on Influenza Vaccines, Non-clinical and Clinical Module, cases should meet the EU ILI and influenza case definitions.

Available laboratory tests to confirm influenza can be grouped into direct or indirect diagnostic tests. Direct diagnostic tests to identify influenza viruses include viral culture; Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR); Rapid Influenza Diagnostic tests (RIDTs) and the detection of viral proteins by immunofluorescence; using direct fluorescent antibody (DFA) testing, also known as the immunofluorescent antibody test (IFA); or enzyme immunoassay (EIA). Indirect diagnostic tests include the serological evidence of infection on paired blood samples.

Direct tests are performed on nasal or throat swabs, nasopharyngeal aspirates or bronchoalveolar washes. Not all specimen types yield equivalent results: nasopharyngeal specimens have higher yield than nasal or throat swab specimens. Moreover, combining nasal and throat swabs in the same specimen increases influenza viruses detection compared with either specimen type alone. Since the average duration of virus shedding in infected persons is around five days, and highest around the time of illness onset, the sample has to be collected within seven days after illness onset to reduce the likelihood of a false negative test result (otherwise sensitivity would be harmed). Sensitivity may be further improved by choosing non-cases from swabs testing positive for another respiratory virus, to ensure that the sample is of sufficient quality to detect the virus (alternatively, reference/housekeeping genes could be co-detected).

The approach based on virologically-confirmed human influenza cases has the disadvantage that virus shedding in infected persons typically lasts only a week and has often diminished or ended by the time of sampling. In addition, infections may cause only mild illness, leading to cases possibly remaining undetected. Studies based on the serological evidence of infection have a wider window of detection. However, data need to be interpreted with caution due to cross-reactivity of antibodies among and within virus subtypes, and sensitivity decreases when used to detect antibodies against novel influenza subtypes.

In order to avoid biases and confounding, IVE studies require the identification of viruses by means of sufficiently sensitive and specific laboratory techniques, so that detailed relevant biological information about the causative agent is provided. Therefore, viral detection should use the most up-to-date diagnostic tools.

Innovative study designs should be planned with the aim to investigate the value of other methods of influenza virus detection, such as RIDTs, which have become available in recent years to detect influenza virus antigens or viral enzyme activity and which can be conveniently used at the point-of-care in a routine clinical setting. Currently, RIDTs are unable to distinguish between influenza A subtypes or, for some tests, between influenza types A and B, and are less sensitive and also considerably less specific than RT-PCR. For these reasons, in order to avoid disease

misclassification, the use of rapid influenza diagnostic tests for obtaining laboratory-confirmed outcomes should be limited. More research is needed in order to develop RIDTs with higher sensitivity and specificity and enhance the accuracy of clinical diagnoses.

- Identify innovative diagnostic tests with high sensitivity and specificity in order to enhance the accuracy of clinical diagnoses.

2.1.2. Non-specific endpoints

Influenza vaccines may have broader benefits beyond the prevention of the disease. There is indirect epidemiologic evidence that influenza contributes to all-cause mortality and to cardiac, stroke and respiratory hospitalisations. Many studies show increases in rates of hospitalisation for acute myocardial infarction (AMI) and cardiovascular and all-cause death during the influenza season. Evidence from observational studies is increasing, with numerous cohort and case-control studies showing influenza vaccination is protective against AMI, cardiac death and stroke. Such end-points may be captured through health databases using hospital discharge codes and linkage with vaccination registries.

- Estimate the indirect influenza morbidity and mortality (especially in elderly and at risk populations) and the preventable fraction with influenza vaccines as part of the IVE.

2.2. Exposure

2.2.1. Influenza vaccination exposure

It is common in IVE studies to define vaccination exposure not from the moment the vaccine is administered, but after a period of 14 days has elapsed since vaccination. During this 14 days window, subjects are considered for analysis purposes as “partially vaccinated”, and are either analysed separately or completely excluded from the analysis. Further research is warranted to establish the best approach, and maybe even explore the effect of shorter window periods (e.g. 7 days) on IVE. This could be addressed by conducting sensitivity analyses exploring the effect on IVE of different options.

- Explore the effect of different vaccination exposure windows on IVE estimates
- Identify optimal window period after vaccination to consider a subject vaccinated

2.2.2. Brand data collection

DRIVE aims to estimate brand-specific IVE, for which reliable information on the brand administered to each subject needs to be obtained. Within DRIVE WP2, there is a specific task (T2.2) that will


produce guidelines for vaccine brand identification, starting first with the mapping of the resources available in Europe for this purpose.

- Identify best methods to obtain reliable vaccine brand data

3. Methods

3.1 Study design specifics

3.1.1 Participatory epidemiology

There is an increasing trend of participatory sciences in various fields of science. Participatory sciences can be defined as the production of knowledge with the active and deliberate contribution of non-professional scientists, either individuals or groups. Participatory approaches are of interest to better assess exposure and outcome.

Exposure

Several immunization information systems exist with clear involvement of vaccines, such as MesVaccins.net in France, the electronic vaccination card that can be validated by health care providers (MesVaccins.net), and CANImmunize in Canada. Ongoing work by ECDC on Immunization Information Systems Guidance on IIS, to be released in 2018, supports the participation of vaccines.

Outcome

In Europe, Influenzanet is the largest online platform for participatory disease surveillance. Influenzanet is a "system to monitor the activity of influenza-like-illness (ILI) with the aid of volunteers via the internet"\(^{20}\). It was launched in 2003 in the Netherlands and Belgium, and over the past 15 years it was expanded to include 10 European countries (Figure 1)\(^{21}\). Participation is open to anyone residing in the countries where Influenzanet is implemented; in the 2015-2016 season there were over 36,000 participants. Data are collected on various medical, geographic and behavioural questions at registration, after which participants receive weekly reminders to report any symptoms. Cases are identified using the ECDC ILI case definition.

Participatory approaches allow the capture of ILI cases that do not seek medical care and close to real-time IVE estimates against ILI. A pilot study has shown the methodological feasibility of obtaining self-swabs of Influenzanet participants with ILI.

- Explore possibilities of implementing self-sampling at a sufficiently large scale to enable the calculation of VE against virologically-confirmed influenza;
- Determine which specific population could best host this participative approach


3.1.2 Best control sampling methods for TND studies

The test-negative design is the most frequently used design to estimate IVE. The design controls for selection bias due to health-care seeking behaviour by restricting the source population to patients who seek medical care for a respiratory illness. Participants are selected among individuals who seek care for disease syndromes such as acute respiratory illness (ARI) or influenza-like illness (ILI), who are subsequently subjected to confirmatory testing\textsuperscript{22}. Subjects that test positive for influenza become the cases, while the subjects who test negative become the controls. The cases are then chosen among the test positives, and the controls among the test negatives. Since it is normally not feasible to test all subjects with ILI/ARI for influenza, a selection needs to be made. This selection may vary per study and study site, with the selection left to the physician in some instances, while systematic sampling may be implemented in others.

- Explore the effect of different sampling techniques used on IVE
- Identify best sampling technique which minimizes selection bias while being operationally feasible

3.1.3 Screening method

The screening method is also referred to as the case-coverage method with external coverage cohort. This method uses data on the exposure prevalence in cases and in the coverage cohort, from which the cases originate\textsuperscript{23}. The unadjusted VE is obtained as

\[
\hat{VE}_{SCREEN} = 1 - \hat{OR}_{SCREEN} = 1 - \frac{\hat{p}_d / (1 - \hat{p}_d)}{\hat{X} / (1 - \hat{X})}
\]

with the odds ratio \(\hat{OR}_{SCREEN}\) derived from the exposure prevalence among the cases \(\hat{p}_d\) and the, often externally-derived, estimate of the vaccine coverage in the coverage cohort \(\hat{X}\).

Both estimates \(\hat{p}_d\) and \(\hat{X}\) are often available from routine surveillance, making the case-coverage method an inexpensive and ready-to-use method that might be useful in providing early effectiveness estimates or to monitor changes in effectiveness over time. Control for confounding is possible using stratified analysis, provided that the confounders are similarly measured for the cases and the coverage cohort. The method does not allow for uncertainty in the expected odds of exposure in the coverage cohort. This is immaterial when the coverage cohort is large, the major issue being the possible bias if cases are drawn from a population with a different vaccination profile from that of the coverage cohort. The method has been used to monitor IVE among the elderly in Germany\textsuperscript{24,25}.

- Could screening methods be used reliably to estimate BSIVE?

3.1.4 Propensity score method

The propensity score method removes confounding caused by the observed covariates, by balancing baseline covariates values between vaccinated and unvaccinated subjects. This is achieved by assigning each subject a so-called 'propensity score.' The propensity score is most often estimated using a logistic regression model, in which vaccination status is regressed on confounders. The propensity score is then the predicted probability of being vaccinated. VE estimates are obtained by adjusting for the propensity score as a linear or categorical variable or by matching subjects with similar propensity scores.

Propensity score adjustment is often used in pharmacoepidemiological studies and it seems to be a valuable method worth consideration in influenza vaccine effectiveness research. Estimates originating from cohort studies are prone to confounding bias, which is difficult to control for because differences in infection pressure or healthcare seeking behaviour can hardly be measured directly. Therefore, in the presence of routine healthcare register data, high-dimensional propensity score adjustment might be a solution.

However, the validity of this approach in infectious diseases epidemiology must be investigated. One of the fundamental assumptions on which the propensity score definition is based is the Stable Unit Treatment Value Assumption. As the (influenza) outcome of one study subject could be affected by the treatment (vaccination) assignment of the other subjects, this assumption does not hold in settings with coverage levels close to or above the herd immunity threshold. Additionally, the propensity score approach only leads to unbiased estimates when absolutely all confounders are included in the model. The presence and effect of unobserved confounders might violate the statement of strongly ignorable treatment assignment. How these issues influence the applicability of propensity score adjustment in studies estimating influenza vaccine effectiveness must be further examined.

- Explore the applicability of using propensity scores for IVE and BSIVE

3.1.5 Adjustment and confounding

Observational influenza vaccine effectiveness studies are prone to several sources of confounding, effect modification, and other types of bias. Understanding these and taking them into account in statistical analyses is essential for obtaining accurate vaccine effectiveness results. Within DRIVE, D2.2 (Systematic review of the sources of confounding, bias and strategies to manage their impact in influenza vaccine effectiveness studies) will provide the current evidence on bias and confounders, while D4.1 (Methodological guidelines for IVE studies) will provide guidance on how to account for bias, confounding, and effect modification in the study design and analysis.

We discuss here bias and confounders that we believe warrant further research.

3.1.5.1 Effect of previous influenza vaccination

Studies have found both positive and negative interference of repeated influenza vaccination on IVE, and this may differ by season. The antigenic distance hypothesis proposes that negative interference may occur if the consecutive vaccines are antigenically similar, and antibodies produced in the past season may neutralize vaccine antigens of the subsequent year’s vaccine before it can...
trigger a full immune response. Conversely, positive interference may occur when the antigenic distance between consecutive vaccines is larger, and pre-existing antibodies can cross-react with the new vaccine’s antigens, thereby boosting the response to the vaccine. IVE may be influenced by vaccination patterns over at least several seasons. Also, under the assumption that antibodies produced in the past seasons persist, as well as those from natural disease, the comparative group of non-vaccinated are not fully naive subjects. This is likely to underestimate true vaccine effectiveness.

- **Gain further understanding in the role of the effect of previous vaccination on IVE and BSIVE through specifically designed studies**

### 3.1.5.2 Effect of previous influenza infection

Prior influenza infection can influence the choice to receive influenza vaccine in the current year and can lead to a degree of existing immunity against influenza. This can lower the VE estimate in the current year. For example, Saito et al. found a profound protective effect of medically attended influenza A infection in the prior season. Little research has been done on the interplay between prior influenza infection and prior vaccination and its effect on IVE.

- **Gain further understanding in the role of the effect of previous influenza infection on IVE and BSIVE through specifically designed studies**

### 3.1.5.3 Virus drift

*Antigenic drift* refers to the accumulation of mutations within the antibody-binding sites in the glycoproteins on the viral surface, hemagglutinin and neuraminidase, or both, as a consequence of which the antibodies’ binding may be hampered. VE estimates may potentially change over time if the circulating influenza virus, initially well-matched with the vaccine, drifts away from the strains included in the vaccine.

- **Investigate the effect of virus drift on IVE during the season**

### 3.1.5.4 Indirect protection

Indirect protection, also called herd immunity or herd protection, is the resistance of a group to invasiveness and spread of an infectious agent, based on the resistance to infection of a high proportion of individual members of the group and resulting in decreased probability of a susceptible person coming into contact with an infected person.

In the case of influenza, children are responsible for much of the transmission. Studies in areas where influenza vaccination programs for school children are in place suggest disease burden was reduced in the broader population.

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Pebody RG, Green HK, Andrews N, Boddington NL, Zhao H, Yonova I, et al. Uptake and impact of vaccinating school age children...
Herd immunity should prevent exposure to influenza virus to the same degree in vaccinated and non-vaccinated people, therefore it should not affect VE.

- **Explore the role of herd immunity in adults and the elderly derived from child influenza vaccination programmes**
- **Explore if herd immunity has no effect on IVE and BSIVE estimates**

### 3.1.5.5 Brand-specific confounding by indication

Brand-specific IVE studies will be pooled from settings in multiple countries. Vaccine type recommendations may differ between countries. For example, country 1 may use non-adjuvanted trivalent vaccine for all adults, whereas country 2 may prescribe adjuvanted trivalent vaccine to a specific risk group and non-adjuvanted to the rest of the population. This may result in potentially important differences between the exposed groups that affect the pooled VE estimate. Knowledge of vaccine recommendations (see also WP2.2 and WP3.1) or prescription practices across settings is necessary.

- **Explore how to best control for brand-specific confounding by indication in the pooled analysis, and the effect of the confounding as a source of between-studies heterogeneity.**

### 3.1.5.6 Statins

Recent studies suggest statins may impair the antibody response and thereby reduce vaccine-induced protection. Studies have shown reduced immune response to influenza vaccine, reduced VE to medically attended acute respiratory infection, and reduced IVE to some (but not all) influenza types/subtypes\(^{35}\). On the other hand, statins have been suggested to have a protective effect against infections\(^{36}\).

- **Explore the effect of statins on IVE further**

### 3.2 Pooled analysis

#### 3.2.1 Pooled analysis: one stage vs two stage approach

There are two statistical approaches for pooling data: a one-stage or a two-stage pooling approach. The two-stage approach refers to the classic meta-analytical approach, also called aggregated data meta-analysis (AD-MA). In this approach, the patient-level or minimally aggregated data from each study are analysed separately in order to obtain the effect estimates of interest (here vaccine effectiveness) and the corresponding confidence intervals (CIs). Then, in the second step, the effect estimates are combined by an appropriate meta-analysis model to obtain the meta-analytical (pooled) estimates against influenza during a season with circulation of drifted influenza A and B strains, England, 2014/15. Eurosurveillance. 2015;20(39).


estimate. The one-stage pooling approach analyses all the combined patient-level or minimally aggregated data from the different data sources in a single step. This approach is also called the individual participant data meta-analysis (IPD-MA).

The objective of DRIVE is to estimate brand-specific influenza vaccine effectiveness in Europe by combining data from different study sites. Some site-specific studies will adopt the test-negative case-control study design while others will use a cohort design. These different study designs imply that different data will be collected and that different statistical analyses are needed to analyse these data (i.e. logistic or conditional logistic regression for case-control versus Poisson or Cox regression for cohort studies). Given the statistical equivalence of AD-MA and IPD-MA and given the additional complexity or even impossibility of performing IPD-MA when data are collected using different study designs, the AD-MA is the preferred method for combining data from different study sites.

- Compare if possible the IVE results obtained applying both pooling methods

### 3.2.2 Methods for pooling across seasons

To reach enough sample size for BSIVE, pooling of annual BSIVE across seasons may be called for, keeping in mind the different epidemiology of influenza between seasons.

- Explore and define methods for pooling BSIVE estimates across seasons, taking into account seasonal difference in vaccine composition and strain circulation.

### 3.2.3 Adaptive design

An adaptive design refers to a process in which earlier findings influence later stages of the process. Adaptive designs help researchers to reduce the overall amount of collected data needed for the analysis. This approach is usually followed in clinical trials and its validation and relevance in observational studies for influenza vaccine effectiveness estimation could be explored.

- Could this type of design be adapted to a pooled analysis of BSIVE from different sites over time, as a way of accumulating required sample size for a specific brand?
- Could this design allow yearly monitoring of possible lack of effectiveness, thus providing reassuring information until required sample size is available?

### 4. Governance

#### 4.1 Building a European environment for IVE studies

In the new Guideline on Influenza Vaccines dated Feb 2017, EMA stated that, from a regulatory perspective, there is a need to generate brand-specific VE data to contribute important information to the overall clinical evidence available for each influenza vaccine, especially new vaccines. Marketing Authorisation Holders are therefore requested to replace the annual clinical immunogenicity trials for influenza vaccines (due to the absence of clear correlates of protection) by strengthening sustainable surveillance and monitoring of vaccine performance that will provide product-specific (type/brand) influenza vaccine effectiveness data. To reach this goal, MAHs are encouraged to liaise with
organisations/institutions/public health authorities who have experience in VE measurement and who have implemented a functioning infrastructure to conduct multicentre studies. This need has been reflected in topic 6 of the IMI call 9, which offers a well-known and recognized structure for public and private interactions and funds from the European Commission for public contribution.

- **What are the legal bases for the different stakeholder missions and what are the possible overlaps between missions?**
- **Is a PPP necessary in order to build a BSIVE platform in Europe?**

Since the 2009 pandemic influenza crisis, collaborations between European stakeholders, including public and private interactions, are at the centre of discussions on how to monitor vaccines and vaccination programmes in post-marketing settings. Indeed, public and private stakeholders have a broad range of missions: PHIs are responsible for monitoring their vaccination programmes, RAs are responsible for evaluating the quality, safety and efficacy of vaccines marketed in their territory, and MAHs are responsible for monitoring the benefit/risk of their vaccines. Expertise and resources could be more efficiently mobilised through public-private collaborations with the common objective to provide robust benefit/risk results, and improve public trust in vaccines and vaccination programmes.

In 2013, an IMI project called ADVANCE (Accelerated Development of VAccine beNefit-risk Collaboration in Europe) was initiated with the aim of establishing an efficient and trusted framework for collecting robust post-marketing data to support decision making in Europe. Because the ADVANCE consortium comprised key stakeholders in vaccines (national public health institutes (PHIs); European Centre for Disease and Control (ECDC); European Medicines Agency (EMA); national health regulatory authorities (RAs); research institutes; contract research organisations (CROs); small and medium enterprises (SMEs); and vaccine marketing authorisation holders (MAHs)), it presented a unique forum to establish common rules for future public-private collaborations. After 4 years of collaborations and external consultations, ADVANCE produced guidance at the end of 2017 with a set of governance proposals (functions, core principles and a generic model) and recommendations to support stakeholders willing and able to develop European public-private collaborations in vaccine post-marketing settings. The ADVANCE Governance guidance can be seen as a “cook book” and a tool allowing researchers to develop their own public-private governance, fitting with their project specifics.

ECDC, as part of the work package 7 of ADVANCE, and independently from other ADVANCE Work packages, is developing a “blueprint” with the aim of providing a clear action plan for real-world implementation of the ADVANCE outputs and identification of potential sustainability models. As part of the scene, ECDC and EMA made a joint proposal in 2017 to the EC about their view and potential model for the conduct of vaccines post marketing studies needed at the European level for 2021. The EC recently recognised the need to create a sustainable and multi-stakeholder platform for EU post-authorisation studies monitoring the safety, effectiveness, and impact of vaccination;

- **What are possible efficient and sustainable European platforms to support the monitoring of the safety, effectiveness and impact of vaccination?**

The ADVANCE Governance guideline was used by the DRIVE consortium to initiate a platform to conduct influenza brand-specific vaccine effectiveness studies, balanced with the concern raised by the public health institutes and ECDC asking for scientific integrity in the conduct of the studies.

As part of the 5 year project, DRIVE is willing to operationalize the initial model (real life testing with the conduct of studies) and evaluate the governance in terms of efficiency, transparency, and acceptability, with the potential involvement of additional public health institutes/organisations in the data generation platform.
• **How efficient is the DRIVE governance platform in generating evidence that will allow the different public and private stakeholders to collectively fulfil their respective missions and obligations regarding seasonal influenza vaccines effectiveness in Europe?**

• **What is the fit of existing IVE collaborations with ECDC blueprint?**

An Internet search of available governance guidelines on health public private collaborations revealed that governance evaluation materials are often very complex as they address large organisations (WHO, GAVI, NEG) and so cannot be used as such for collaborative projects.

• **What are the key indicators to evaluate the governance of collaborative platforms?**

DRIVE is planning to develop specific governance indicators and test them through the 5 year projects, with the final objective to reach an acceptable governance platform that allows collective generation of yearly brand-specific influenza vaccine effectiveness data to fulfil EMA requirements and enhance monitoring of influenza vaccines performance by public health institutes.

• **Is the DRIVE governance understandable and transparent for external stakeholders? What are perceived as added values or risks? Are the outputs valuable?**

• Are the governance indicators developed within DRIVE generalizable to other collaborations on IVE and BSIVE?

### 4.2 Perception of PPPs and scientific independence

Practices and attitudes towards PPPs differ in the European public health field, and concerns over their scientific independence have been put forth. Clear evidence-based and comprehensive guidelines on how to evaluate the scientific independence, integrity and transparency of studies in the presence of diverse governance and funding models are lacking. This also has some implications on how to communicate study results.

• **Establish a structured way to assess scientific independence, integrity and transparency in observational studies.**

• **Identify ways to communicate the findings of such assessments.**

• **Investigate the perception of PPPs in various countries.**

For studies from DRIVE WP7, systematic analysis of study protocols (ECDC generic protocol, study sites protocols with respect to guidelines and codes of conduct: with reference to ENCePP revision 4 of the Code of Conduct, and the Advance code of conduct:

• **Conduct a systematic analysis of compliance of DRIVE project, ECDC protocols and studies from DRIVE WP7 to relevant guidelines on scientific independence and transparency**

• **Develop a tool for systematic analysis of compliance or projects and studies to relevant guidelines**

A specific aspect of governance at both the levels of studies and the project is about scientific publications. Systematic reference to established standards in 4.3.1 and 4.3.2 can be extended to the
guidelines for authorship from the International Committee of Medical Journal Editors\textsuperscript{37}. These guidelines imply that co-authorship induces co-responsibility of the interpretation and integrity of the results. The underlying concept is to work under the principle of consensus: in the end, everybody agrees and aligns on the interpretation of the study, or declines authorship. This situation, should it occur, does not support transparency, and declining authorship is a strong individual decision. However, a more general approach, probably of specific interest for PPPs, would be to accept a non-consensus mode. Ways have to be found to achieve the balance between the additional information provided by non-consensus mode, and the possible risk of losing the chance of publication, or how results could still be of value for decision making.

- \textit{Identify ways of communicating results when complete consensus is not established between authors.}

\section*{5. Implementation and monitoring}

This initial research agenda presents specific topics summarized in research questions. These research questions can be focused or broad, and the list updated; some questions can be best worked out as scientific reviews to be published.

\subsection*{5.1 Liaising with other programmes}

This agenda will take into account activities developed by concurrent programmes such as I-MOVE, ECDC’s work on IIS and IVE generic protocols, ENCePP & ADVANCE. The initial version of the agenda will be shared with relevant external stakeholders (e.g. ECDC, I-MOVE scientific committee, EMA Vaccines Working Party).

\subsection*{5.2 Timelines}

The common research agenda will be deliverable 1.1 (M10 April 2018). It will be presented, discussed and refined during a dedicated workshop open to external stakeholders in September 2018 during the DRIVE Forum.

Input from the external consultation will be incorporated in the research agenda by the core group for the second version in the first trimester of 2019 and every year to the end of the DRIVE project.

\subsection*{5.3 Updates}

The research agenda will be updated every year for new identified topics, for answers to specific aspects, while trying to propose it as a common tool for improvement of robustness of IVE and BSIVE that could be used externally.

Through external consultations and discussions around the Research Agenda, DRIVE will identify programmes /stakeholders, map and update existing works/initiatives, and decide DRIVE contributions and potential collaborations.

\textsuperscript{37} http://www.icmje.org/
6. Conclusion

This research agenda proposal is focused on Influenza vaccines effectiveness and brand specific influenza vaccine effectiveness. However, the structure and many aspects are likely to apply to other vaccines as well, and to the safety aspects of vaccines. The recent EU commission position on vaccination policies acknowledged the need for a sustainable and multi-stakeholder platform for EU post-authorisation studies monitoring the safety, effectiveness, and impact of vaccination. In this respect, it is suggested that such a platform should also consider, identify, prioritize and plan the related research needed for efficient monitoring. It is hoped that this research agenda proposal can be further developed and maintained in such wider environment.