D7.1.3 Core protocol for type/brand-specific influenza vaccine effectiveness studies – Test-negative design

777363 – DRIVE

Development of Robust and Innovative Vaccine Effectiveness

WP7 – Influenza Vaccine

Effectiveness Studies

Lead contributor	Stefania Bellino (ISS), Anke Stuurman (P95), Jorne Biccler (P95), Antonio Carmona Serrano (FISABIO), Alexandre Descamps (INSERM)
Other contributors	Caterina Rizzo (OPBG), Kaatje Bollaerts (P95), Margarita Riera (P95), Simon de Lusignan (University of Oxford), Uy Hoang (University of Oxford), Harshana Liyanage (University of Oxford), Christine Pereira (INSERM), Cintia Muñoz-Quiles (FISABIO), Ornella Punzo (ISS)

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Document History

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V3.6	29 JUL 2021	Final version implementing EFPIA and ISC comments

List of abbreviations

DRIVE	Development of Robust and Innovative Vaccine Effectiveness
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
ENCePP	European Network of Centres for Pharmacoepidemiology & Pharmacovigilance
EU	European Union
GEP	Good Epidemiological Practice
GP	General Practitioner
ICD	International Classification of Diseases
IMI	Innovative Medicines Initiative
ILI	Influenza-like illness
IVE	Influenza vaccine effectiveness
OR	Odds ratio
RT-PCR	Real-Time Polymerase Chain Reaction
SARI	Severe Acute Respiratory Infection
TND	Test-negative design
VC	Vaccination coverage
VE	Vaccine effectiveness
WHO	World Health Organization

Preface

The Innovative Medicines Initiative (IMI) project Development of Robust and Innovative Vaccine Effectiveness (DRIVE) aims to create a European platform for studying brand-specific influenza vaccine effectiveness (IVE) and to develop a governance model for scientifically robust, independent and transparent implementation of IVE studies in a public-private partnership.

In DRIVE, data from several independently operating national or regional study sites will be analysed jointly to obtain sufficient geographical coverage and sample size for brand-specific IVE estimates. DRIVE recognizes the value of current study networks and strives to include secondary data from existing studies and initiatives. This is expected to foster European cooperation and maximize the sustainability of the pooled IVE studies.

In **2017/18,** a pilot study was performed to test the different operational aspects of the DRIVE project, including the IT infrastructure, the DRIVE governance for conducting IVE studies and to streamline key processes such as data collection, statistical analyses and dissemination of study results. In the pilot study, there were four test-negative design studies (TND) and one register-based cohort study. The DRIVE network is continuously expanding. The **2018/19** season was based on a multi-centre study with data available from five primary care based TND studies, six hospital based TND studies, one register-based cohort and two clinical cohorts (in pregnant women and their young infants and in healthcare workers) Publication of 2018/19 results in Vaccine can be found here. For the **2019/20**, the DRIVE network included 13 TND studies and one register-based cohort study. Publication of 2019/20 results in Vaccine can be found here.

During the **2020/21** season, a total of 13 TND studies and the Finnish register-based cohort provided data to DRIVE. However, influenza viruses circulated below the epidemic threshold, which is to a large extent likely attributable to non-pharmacological measures taken against person-to-person transmission of respiratory infections as SARS-CoV-2.

The TND Generic protocol was amended in June 2020 (D7.1.2) to include an objective on the assessment of the impact of SARS-CoV-2 on influenza VE. Due to lack of influenza circulation in 2020/21, this could not be evaluated. However, the objective has been kept in this protocol update and study sites investigating influenza VE will need to collect epidemiological data on COVID-19. On the other hand, the objective comparing clinical presentation of COVID-19 versus influenza was removed.

This amended generic protocol (June 2021, D7.1.3) has been updated to reflect the experience of the previous DRIVE studies; and is intended to be adapted to the local procedures at each individual study site since season 2021/22 onwards. Its aim is to achieve maximum harmonization between the different sites while respecting their different backgrounds. Experience from the studies, together with the completion of other, interconnected DRIVE tasks, will inform the subsequent versions of the protocol.

Moreover, the amendment reflects the impact of COVID-19 on IVE estimation for the 2020/21 and potentially beyond. Influenza and Coronavirus disease-2019 (COVID-19) are both respiratory infections which might share similar clinical presentation (e.g. acute respiratory syndrome and influenza-like illness). During the season 2020/21, circulation of SARS-CoV-2 in the EU impacted on influenza VE studies in terms of case detection, health care usage, and testing practices though the period of co-circulation of influenza and SARS-CoV-2 was limited, given the seasonality of influenza versus SARS-CoV-2. A similar impact may also occur in the 2021/22 season.

It is important to note that since the 2020/2021 season, DRIVE Associate Partners can contribute with data from any age group and either from the hospital or primary care setting. However, single hospitals or hospital networks catering to the adult and older adult population can join the DRIVE network as Research Collaborators through the annual Call for Tenders.

Background

Influenza is a major public health burden. It is responsible for an estimated 50 million disease episodes and 15,000 to 70,000 deaths in the European Union (EU) and European Economic Area (EEA) Member States each year, although with considerable variation from season to season [2] and by methodology used [3]. Complications including deaths are more common in the elderly and in children younger than one year of age [4]. Vaccination is considered as the most effective means for preventing influenza and its complications [5] and the World Health Organization (WHO) has set a vaccination coverage (VC) target of at least 75% in the elderly population and among risk groups [6].

Due to frequent genetic and antigenic changes in influenza viruses, the seasonal vaccine is regularly reformulated (almost annually) to match with the characteristics of the viruses circulating and annual vaccination is recommended.

Observed IVE varies year-to-year due to a variety of reasons including mismatch between the vaccine virus strains and the circulating strains, waning immunity and possible interference from previous vaccinations [6, 7]. In the last two decades, controversies have sprung around the effectiveness of influenza vaccines [8]. While past IVE estimation efforts have led to significant achievements using generic protocols, standard methodologies and laboratory confirmation, several questions about IVE remain open.

In its guideline on influenza vaccines, the European Medicines Agency (EMA) [9] requires that observational IVE studies be conducted in the EU/EEA as part of the post-licensure requirements of the vaccine manufacturers. Specifically, manufacturers are requested to replace the annual clinical immunogenicity trials (with no clear correlates of protection) with vaccine effectiveness (VE) to provide product (brand) specific data. To reach this goal, manufacturers are encouraged to liaise with organisations/institutions/public health authorities. The studies are expected to be conducted in line with Good Epidemiological Practice (GEP) guidelines and with European Network of Centres for Pharmacoepidemiology & Pharmacovigilance (ENCePP) guidelines.

This document presents the generic DRIVE protocol for the field-based test-negative design (TND) study with patients seeking care for influenza-like illness (ILI) or severe acute respiratory infections (SARI). This TND protocol is intended to be adapted to each individual study site for the season 2021/22. While each of the study sites can be analyzed separately, pooling them into one analysis is expected to provide a sample size large enough to answer more specific study questions (such as type and age specific VE estimates) with a reasonable/greater precision.

The protocol builds upon the European Centre for Disease Prevention and Control (ECDC) Protocol for case-control studies to measure pandemic and seasonal influenza vaccine effectiveness in the European Union and European Economic Area Member States [10] and the WHO guide to the design and interpretation of observational studies [11]. It is updated periodically, starting from the 2018/2019 season.

For the coming season 2021/22, the generic TND protocol has been updated to account for probable co-circulation of SARS-CoV-2 and influenza viruses during the next season, and to take into account the possible effect of COVID-19 on influenza occurrence. Therefore, the collected data will include COVID-19 positivity and date of positive test, COVID-19 vaccination status per brand, date of COVID-19 vaccination and if the subject is fully vaccinated. The study sites already investigating influenza VE will also be able to collect epidemiological data on the COVID-19 impact in participating countries.

The details of each site-specific study will be provided in the study annexes (e.g. ethical committee clearance, data collection strategy, reporting form for protocol deviations, etc.).

Objectives

Primary objective

To estimate seasonal overall, age-specific (6m-17 yr, 18-64 yr, ≥65 yr) and brand-specific IVE against medically attended (primary care/hospital) laboratory-confirmed influenza, by virus type (A or B), subtype (A/H1N1 or A/H3N2) and lineage (B/Victoria or B/Yamagata).

Secondary objectives

To estimate seasonal vaccine-type IVE against medically attended laboratory-confirmed influenza by virus type/subtype [A, (A/H1N1, AH3/N2), B (B/Victoria, B/Yamagata)]. The following vaccine types will be considered:

- trivalent inactivated recombinant vaccine (TIV)
- high-dose TIV
- high-dose QIV
- adjuvanted TIV (aTIV)
- live attenuated quadrivalent egg-based vaccine (LAIV)
- quadrivalent inactivated egg-based vaccine (QIVe)
- quadrivalent inactivated cell-based vaccine (QIVc)

Exploratory objectives

To explore if SARS-CoV-2 co-infection or COVID-19 vaccination are effect modifiers of influenza infection and influenza vaccination, and if COVID-19 vaccination is a confounder of influenza vaccine effectiveness.

Methods

Study design

➢ In each participating study site, an observational case-control study using the test-negative design will be conducted

Study setting

The studies will take place in primary care or hospital setting. The study setting is defined by each study site depending on the available data. Each patient with ILI or hospitalized with Severe Acute Respiratory Infection (SARI) will be tested for the detection of both influenza and SARS-CoV-2 viruses.

➢ Each study site to specify if the study is nested into the national influenza surveillance scheme (the ILI/SARI surveillance system) or is organized differently

➢ Each study site to specify national policy for influenza surveillance and vaccination and available vaccine brands on the market

➢ Each study site to specify the target groups for which influenza vaccination is recommended and provide information on vaccination uptake for previous season by age groups

➢ Each site to specify how they manage influenza and COVID-19 in terms of screening/triage strategy and testing (i.e. with the same swab or not, simultaneous tests, first SARS-CoV-2 test and then influenza or the opposite)

Study period

Surveillance period

The start of the surveillance period at individual study sites will be defined as the first of:

- Starting date as determined by local/regional/national guidelines, or
- The first of two consecutive weeks when influenza viruses are detected at the study site level, or
- December 1st, 2021.

Study period for analysis

The site-specific study period for analysis will start when the influenza virus circulation begins (first week of two consecutive weeks when influenza viruses are detected at the study site level) and will finish at the end of the influenza season (the end of the week prior to the first of two consecutive weeks when no influenza viruses are detected at the study site level, or 30th of April, whichever is first).

Study population

The study population consists of patients seeking care (i.e. subjects consulting a GP or an emergency department/hospital) for symptoms compatible with ILI/SARI aged 6 months and above, with no contraindication for influenza vaccination.

For the inclusion in the study, the subject will be tested for influenza, and also for SARS-CoV-2. In the case only an influenza test will be done, the record of SARS-CoV-2 testing will be recorded as unknown. People who are or perceive themselves at greater risk, could be included multiple times as test-negative controls.

Influenza-like illness

A case of influenza like illness (ILI) will be defined by the EU case definition (European Commission Decision of 30 April 2009 amending Decision 2002/253/EC laying down case definitions for reporting communicable diseases to the Community network under Decision N. 2119/98/EC of the European Parliament and of the Council. Luxembourg: Publications Office of the European Union. 1.5.2009. L 110/58) as an individual who presents with a sudden onset of symptoms including at least one of the following four systemic symptoms:

- fever or feverishness;
- malaise;
- headache;
- myalgia;

AND at least one of the following three respiratory symptoms:

- cough;
- sore throat; and
- shortness of breath.

Severe acute respiratory infection

A case of severe acute respiratory infection (SARI) will be defined by the IMOVE+ 2017/2018 case definition as a hospitalised person with a suspicion of a respiratory infection, with at least one of the following systemic symptoms or signs;

- fever or feverishness;
- malaise;
- headache;
- myalgia;

- deterioration of general condition (asthenia or loss of weight or anorexia or confusion or dizziness)

AND at least one respiratory symptom or sign e.g.

- cough;
- sore throat;
- shortness of breath;

at admission or within 48 hours after admission.

The symptoms should not have started (or, if chronic, clearly worsened) more than 7 days before swabbing.

➢ Study sites that do not follow the above ILI or SARI clinical case definitions should specify the modified definitions (i.e. WHO, modified EU, etc.)

Outcomes

The outcome of interest is type-specific virologically-confirmed influenza in the study population. More specifically:

- subtype-specific virologically-confirmed influenza A (A/H1N1, A/H3N2);
- lineage-specific virologically-confirmed influenza B (B Victoria/B Yamagata).

Case definition

Primary care studies

Case: ILI laboratory-confirmed influenza. An ILI patient will be defined as a person in the study population, meeting the ILI - EU case definition with a respiratory sample positive for influenza (see Laboratory testing section).

Control: ILI negative for Influenza. A control will be defined as an ILI patient in the study population, meeting the ILI - EU case definition for clinical criteria, with a respiratory sample negative for influenza.

The case/control definition will be based only on the influenza test, irrespective from the SARS-CoV-2 result. Patients who will be tested only for COVID-19 and do not have a test result for influenza (within a certain timeframe) will be excluded.

Hospital studies

Case: SARI confirmed as Influenza. A SARI patient will be defined as a person in the study population, meeting the clinical case definition with a respiratory sample positive for influenza.

Control: SARI negative for Influenza. A control will be defined as a SARI patient in the study population, meeting the clinical case definition with a respiratory sample negative for influenza.

Cases and controls will include positive or negative influenza tests respectively, regardless of their SARS-CoV-2 testing results.

Case finding

ILI and SARI patient identification

Patients will be identified among people who present at a healthcare provider (general practitioners (GPs) or hospitals) with ILI or SARI.

➢ Each study site to provide exclusion criteria applied, if different from the list described below

➢ Each study site to describe procedures to identify study participants

➢ Any aspect of physician's discretion to decide on inclusion should be described

➢ Each site should describe how the concepts of random swabbing or systematic swabbing are defined

➢ Each site should describe the study procedure (i.e. the procedure to screen and test patients)

Inclusion criteria

ILI/SARI patients are eligible if they accept to participate and do not fulfill any of the exclusion criteria.

Exclusion criteria

The following exclusion criteria will be applied to subjects presenting with ILI:

1. is unwilling to participate or unable to communicate and give consent (the consent may also be given by her/his legal representative, or by specific consent procedures, acceptable according to the local ethical review process)
2. is less than 6 months of age at the time of the onset of the symptoms
3. has a contraindication for influenza vaccine
4. lives in a communal establishment (e.g. in a long-term care facility) at the time of symptoms onset

5. does not have the respiratory specimen taken <8 days after ILI onset
6. tested positive for any influenza virus in the current season before the onset of symptoms leading to the current primary care visit/hospitalization
7. influenza vaccine administration <14 days before ILI symptoms onset

The following exclusion criteria will be applied to subjects presenting with SARI:

1. is unwilling to participate or unable to communicate and give consent (the consent may also be given by her/his legal representative, or by specific consent procedures, acceptable according to the local ethical review process)
2. is less than 6 months of age at the time of the onset of the symptoms
3. has a contraindication for influenza vaccine
4. lives in a communal establishment (e.g. in a long-term care facility) at the time of symptoms onset
5. does not have the a respiratory specimen sample taken <8 days after SARI onsettested positive for any influenza virus in the current season before the onset of symptoms leading to the current primary care visit/hospitalisation
6. was previously hospitalised < 48 hours prior to SARI onset
7. had his/her ILI/SARI onset ≥ 48 hours after hospital admission
8. influenza vaccine administration <14 days before SARI symptoms onset

Exposure

Exposure of interest

The exposure of interest is vaccination with any influenza vaccine in the season under investigation. It is crucial to know precisely the date of vaccine administration, the type/brand of the vaccine, and the date of symptoms' onset as well as the date of specimen collection. The lack of these details will result in subject exclusion at the time of analysis.

Vaccination status ascertainment

The sources of information for the vaccination status may include:

- vaccination registry
- medical records
- vaccination card

When vaccination status is positive according to any of the above sources they will be coded as vaccinated.

➢ Each study site to describe the precise way of vaccination status ascertainment (i.e. vaccinated yes/no) and vaccine brand and vaccination date ascertainment.

Definition of vaccination status

An individual aged ≥9 years will be considered as:

- **Vaccinated** with the influenza vaccine of interest if influenza vaccine was administered in the current season and >14 days before ILI/SARI symptom onset
- **Unvaccinated** if no influenza vaccine was administered in the current season

A child aged <9 years (for whom two doses are recommended if they have not previously received influenza vaccine) will be considered as:

- **Vaccinated** with the influenza vaccine of interest if the last dose of influenza vaccine in the current season was administered >14 days before ILI/SARI symptom onset
- **Unvaccinated** if no influenza vaccine was administered in the current season

Children <9 years for who the record shows that they received two doses will only be considered vaccinated 14 days after. In case the records shows that a child <9 years only received one dose it is assumed that the child is vaccinated

Baseline descriptive, potential confounders and effect modifiers

The following list, based on available literature, presents known and potential confounders and effect modifiers in population-based influenza vaccine effectiveness studies (please also refer to DRIVE D4.1: Framework for analysis of influenza vaccine effectiveness studies).

In the context of the planned inclusion of COVID-19-related objectives for the season 2021/22, the following variables will be collected:

- SARS-CoV-2 testing result
- COVID-19 vaccination status

The mandatory set of covariates to be collected for the pooled analysis is marked with an asterisk (*); however, data collection of additional covariates other than the mandatory variables is preferred. If available and relevant, the other variables may be used in individual study site analyses, and if possible, they will be harmonised between the study sites for pooled analysis according to the Statistical Analysis Plan (SAP):

- Age*

- Sex*
- Date of influenza symptoms onset*
- Date of positive SARS-CoV-2 test (most recent)
- COVID-19 vaccination status (not vaccinated, partially vaccinated, fully vaccinated); patient recalled COVID-19 vaccination status is permitted
- Date(s) of COVID-19 vaccination
- COVID-19 vaccine brand(s)
- Any underlying chronic conditions*
- If possible, to define the type of chronic condition (like chronic pulmonary disease, cardiovascular disease, diabetes, liver disease, renal disease, neurologic/neuromuscular conditions, treatment-induced immunosuppression and disease-induced immunosuppression (see Annex 1)
- Number of primary care visits 12 months prior to the study period describing a study subject's healthcare-seeking behavior
- Number of hospitalizations 12 months prior to the study period to be used as a proxy for the severity of the chronic conditions
- Influenza vaccination in previous influenza season
- Contraindication to influenza vaccination
- Pregnancy
- Use of influenza antivirals
- Use of statins and other selected co-medications
- Pneumococcal vaccination
- Socio-economic status or applicable proxy
- Smoking behavior or parental smoking behavior (for subjects ≤18 years)
- Death

➢ Each study site to describe the covariates included in the study & how these are identified.

Data collection

Data collection and entry will be conducted at the site level. Data will be collected using a standardised questionnaire/data collection form, administered by clinicians at the moment of swabbing. The

questionnaire will be developed before the beginning of the study period according to the list of variables adopted at the study site level.

➢ Each study site to describe the data collection tools used

➢ Each study site to describe if and how informed consent is obtained

➢ Each study site to document any protocol violations

➢ Each site to aim a detailed data collection on the aspects that help to understand and account for the COVID-19 pandemic condition.

➢ Each site to detail screening strategy, case definition, samples and testing strategies for the season 2020-21 as COVID-19 pandemic may impact routine practices

Virological testing

Respiratory specimens will be collected from all eligible patients (ILI and/or SARI). We strongly encourage the use of systematic sampling for primary care studies recruiting ILI (e.g. swabbing the first 3 ILI cases presenting to a GP on the second day of the week of practice) and all hospitalized SARI cases (e.g. all SARI cases presenting at the Emergency Department of a Hospital and being admitted to the hospital).

Laboratory confirmation should be done through one of the following laboratory tests: reverse transcription-polymerase chain reaction (RT-PCR, preferred option), viral culture, and immunofluorescence or rapid influenza diagnostic tests. In case point of care tests (PoCT) are used, the method should be clearly described. Each positive test result is to be classified by influenza type (A and B) and preferably also subtype/lineage (A/H1N1, A/H3N2, B/Victoria, and B/Yamagata).

The primary analysis will be performed using RT-PCR only; sensitivity analyses may be considered for other influenza tests.

➢ Each study site to describe the specimen collection (i.e. to include a description of the criteria and procedure for swabbing at the site level).

➢ Each study site to describe the specimen storage & transport procedures

➢ Each study site to describe the laboratory tests used & the selection of specimens and the procedures for genetic and antigenic characterisation (including whether COVID-19 and influenza testing was sequential or multiplex)

➢ Each study site to describe if the laboratory participates in QA/QC (Quality Assurance/Quality Control) schemes

Sample size considerations

To prevent the use of resources on performing the analysis and writing the final report when it is unlikely that statistically significant IVE estimate can be obtained, these activities will only be undertaken when a minimal number of influenza cases are observed in the dataset.

The number of influenza cases needed in a single TND study to reach a power of at least 50% or 80% to detect a crude IVE different from 0 was calculated for a range of study parameters. The calculations were performed for each combination of the following study parameters and the required number of influenza cases can be found in Table 1.

1. Power of 50% or 80%
2. True IVE of 30% or 60%
3. Control:case ratio of 1, 2, or 4
4. Overall vaccination coverage among control subjects of 10%, 25%, or 60%

In DRIVE data from multiple TND studies is analysed, however as this introduces extra heterogeneity the required number of cases to reach the pre-specified power will be higher than the numbers specified in Table 1.

Table 1. Expected number of influenza cases required to reach a power of 50% for several combinations of the IVE, control:case ratio and overall vaccination coverage.

IVE	Control:case ratio	Vaccination coverage among control subjects	Expected number of influenza cases required (Power = 50%)	Expected number of influenza cases required (Power = 80%)
30%	1	10%	781	1593
60%	1	10%	155	314
30%	2	10%	557	1171
60%	2	10%	102	223
30%	4	10%	445	959
60%	4	10%	75	176
30%	1	25%	357	727
60%	1	25%	66	134
30%	2	25%	259	538
60%	2	25%	45	96
30%	4	25%	209	443
60%	4	25%	34	77
30%	1	60%	246	502
60%	1	60%	38	77
30%	2	60%	186	377
60%	2	60%	29	57
30%	4	60%	156	315
60%	4	60%	24	47

For each combination of setting and age group, the control:case ratio and the vaccination coverage among the control subjects observed in the 2019/20 season was used to select the number of required influenza cases (Table 2). The required number of influenza cases was selected assuming an IVE of 60% as the required number of cases tended to be lower when an IVE of 30% was assumed and hence leads to a less stringent cut-off value. Additionally, the required number of influenza cases was based on the calculations assuming a power of 50%. In the design phase of studies (e.g. clinical trials), often a power of 80% (or even 90%) is required, however, within DRIVE the occurrence of non-significant estimates is not necessarily problematic and requiring a power of 80% would lead to more stringent cut-off values as compared to a power of 50%. Since the distribution of brands and therefore also the brand-specific coverage tends to vary more across seasons than the overall vaccine coverage, it was decided to not calculate separate cut-off values for the brand-specific analyses but instead rely on the values obtained for the analysis of any influenza vaccine.

The cut-offs will only be applied to the analysis of the IVE for any vaccine against any influenza strain. In case this analysis is performed for a certain setting and age group all the other analyses applying to this population will also be performed.

Table 2. Vaccination coverage among control subjects and control:case ratio observed in the DRIVE data from the 2019/2020 season and the number of influenza cases required to perform the analyses in the 2021/22 season.

	Primary care			Hospital setting		
	6m-17yr	18-64yr	≥65yr	6m-17yr	18-64yr	≥65yr
Observed coverage among the controls	13%	10%	61%	5%	23%	56%
Control:case ratio	0.8	1.7	4.3	1.1	2.2	4.5
Number of influenza cases required for performing the analysis	155	102	24	155	45	18

Data management

Each study site is responsible for the data collection, data validation, and data management of their individual study. DRIVE has developed a generic data management plan (D4.8) and set up the necessary infrastructure for data collection and analysis of the pooled data. To consult such documents go to http://www.drive-eu.org/index.php/results/deliverables/.

➢ Each study site to specify how data are collected (e.g. web-based, paper forms) and validated

➢ Each study site to specify procedures of data management.

➢ Each study site to provide a codebook that includes the variable names, variable descriptions, and the coding of variable values, if not following the DRIVE procedures/codebooks/tools.

➢ Each study site to provide any checks in place in the data entry system to avoid mistakes in data entry, and whether source data verification was conducted and how.

➢ Each study site to specify the data checking and cleaning process

Summary and frequency tables, as well as visual representations of appropriate variables, will be used to find implausible or missing values within the dataset. Checks for inconsistencies will be carried out (e.g. date of respiratory specimen collection before the date of onset of symptoms). Any changes to the data will be documented and stored separately from the crude database. Any additional recording of data during the data cleaning phase will be documented. A guide and/or an example file for data cleaning will be provided if needed.

Quality control

The study data will be uploaded by the DRIVE research study sites to the DRIVE Research server using the DRIVE Electronic Study Support Application (DRIVE ESSA). Upon uploading TND data to the ESSA Environment, data quality checks and visualisations are automatically generated and a list with data quality issues can be downloaded by the study site. As such, potential data quality issues can still be solved by the study site before transferring the data to the DRIVE Central Analysis Environment.

The DRIVE ESSA performs 7 different types of quality checks, related to compliance with minimal data requirements, the presence of duplicated records, variable formats and implausible values, inconsistencies between variables and missing values. In addition to the quality checks, the DRIVE ESSA provides seven different data visualizations, summarizing the number of vaccinated subjects over time, the distribution of vaccine brands, the number of cases and controls over time, the age-gender pyramid and the distribution of covariates (sex, age, number of hospitalizations during the last 12 months, and presence of at least 1 chronic condition) among cases and controls.

Representativeness of subjects included in the study

➢ Study teams to describe the potential limitations in terms of representativeness of the subjects included

The study includes ILI and SARI cases. Health-seeking behaviour (referring to how individuals use health services: e.g. the decision to access healthcare, time from onset of illness to consultation, the type of healthcare provider consulted and the adherence to recommended treatment) may differ by country depending on the case management strategy (e.g. recommendation of seeing a GP first). In some cases, the management strategy will have an impact on the delay between onset of symptoms and hospitalisation. This, in turn, may have an impact on the time lag between onset and respiratory specimen collection and may affect positivity rates between study sites.

Statistical analysis

This section describes the main principles for the study site-level analysis. The details of adjustment for confounders will be detailed in the annual Statistical Analysis Plan.

Demographics and baseline characteristics

The baseline characteristics of the study participants will be presented by study setting and will be described and tabulated for cases and controls separately and for vaccinated and unvaccinated subjects within each group (by brand and overall).

Measure of effect

The crude (or unadjusted) IVE will be estimated as

$$VE = (1 - OR) \times 100\%,$$

where OR denotes the odds ratio, comparing the odds of vaccination among the cases to the odds of vaccination among controls. The 95% confidence intervals will be obtained as well.

Confounder-adjusted IVE estimates will be obtained from multivariable logistic regression models, regressing the outcomes on the confounders of interest. The confounders that will be adjusted for will be specified in the SAP.

Missing data

The analysis will be a complete case analysis, dropping records with missing information for the outcome, exposure of interest or any of the covariates.

For covariates for which the amount of missing data is substantial (≥10%), multiple imputation methods could be applied assuming that the missingness does not depend on unobserved variables.

COVID-19 impact on IVE

Potential effect modification and/or confounding by COVID-19 status / COVID-19 vaccination will be explored by adding appropriate terms and interaction terms to the logistic regression model

Sensitivity analyses

When appropriate, sensitivity analyses may be conducted for the primary and secondary objectives to test the impact of different choices made (e.g. outcome definitions, symptoms, exposure definitions, subset of the data, influenza testing methods (i.e. tests other than RT-PCR)), time between symptom onset and swab, COVID-19 positivity (e.g. excluding subjects that test positive for SARS-CoV-2), inclusion/exclusion of the sites that have the influenza onset date not available).

Additional analyses (e.g. based on testing policies, vaccine recommendations, age subgroups, or other) may be considered if considered relevant by WP7.

DRIVE Secondary use of Data policy

Data can be re-used for additional analysis to advance the knowledge on infectious diseases and their prevention or treatment following approval of their data request application via completion of the additional analysis request form and under the following conditions:

- The data can only be used for relevant scientific research and as pre-defined in the data access application/protocol when approved by the DRIVE Steering Committee and Independent Scientific Committee
- The data requestor will only be provided access to the data as needed for the purposes set out in the data access application/protocol approved by DRIVE.
- The data will remain at all times at the P95 server.

The local TND study protocols adapted from DRIVE's generic TND protocol should account for the secondary use of the data generated in DRIVE. The specifics of this policy, as stated above, should be explicitly mentioned in the sites local protocols.

Adverse events reporting

This is a non-interventional epidemiological study for assessing the effectiveness of routine influenza vaccination. The organization conducting the study will follow local requirements as regards the submission of cases of suspected adverse reactions to the competent authority in the Member State where the reaction occurred.

Ethical evaluation and other relevant approvals

Each study site will comply with the relevant international, national and regional legal and ethics requirements and the declaration of Helsinki and ensures that the ethics committee of the institution has approved the study. Copies of the appropriate approvals from each site will be collected at the study site level and archived according to the local law, but at least for 5 years.

Informed consent will be required from all participants or legal tutors; the national ethics committees will specify whether oral or written consent will be required. The following information should be specified: who is responsible for the study, aim of the study, nature of processed data, purposes of processing, purpose of the use of the data, recipients of possible data transfers, rights of data subject & consequences of not accepting the informed consent.

For more guidance on the Informed Consent to be used in DRIVE, please see Annex 4, which includes the DRIVE Informed Consent form template. This Informed Consent Form (ICF) template is conceived to be adapted and implemented by DRIVE study sites. Site specific adaptations and translation to the local language might be required. If a local ICF is used, we recommend to adapt it and at least include the points listed below in the DRIVE ICF minimum criteria.

The only exception is where the study is part of an ongoing routine program evaluation required by the ministry of health or a requisite part of the public health institution's work, and would therefore fall

outside the mandate for ethics committees. In these cases, a statement that no formal approval from the ethics committee is required is sufficient.

➢ Each study site to describe the procedures to comply to the national ethics committee requirements and the type of informed consent needed as well as whether consent can be obtained for a legal tutor.

➢ Each study site to provide a copy of the ethical approval, Independent Review Board or equivalent, or a statement on why this is not needed.

Dissemination of results

The study site will remain the owner of the data and may disseminate the study results according to their local practices. The data will be submitted to WP7 for pooled analyses across DRIVE sites. EFPIA members do not have access to this data. DRIVE will disseminate the results of its analyses according to its Communications plan (DRIVE D5.4).

Study reports

Each study site will write a report at the end of the season and submit it to DRIVE WP7. DRIVE WP7 will write a final report presenting the results of the pooled estimates.

Publications

Study sites may publish their own data independently from DRIVE. If DRIVE funds were used to collect the data, this should be acknowledged in the publications. Data should be published before the next influenza season.

Authorship of joint DRIVE publications follows the rules of the International Committee of Medical Journal Editors (ICMJE).

Logistical aspects

Study sites

A study site is any entity that administers and conducts the individual studies according to the regulations and ethical codes of the EU and the country and institutions involved. The study site collects data and provides it to DRIVE. EFPIA members do not have access to this data. Each study site must have a principal investigator responsible for all aspects of the individual study and data transfer to DRIVE WP7. Study sites may be local, regional or national; examples include GP and hospital networks, influenza surveillance schemes and public health institutes utilizing routine health care, social service and demographic databases.

Study leader

In each study site, a study leader (principal investigator) will coordinate the study at the study site level and act as a focal point towards DRIVE. The WP7 of DRIVE is in charge of the pooled analyses across DRIVE study sites.

➢ Each study site to introduce the study leader and the study team with brief CVs and Declarations of Interest.

Standard operating procedures

Standard operating procedures (SOPs) developed and harmonised in DRIVE should be adapted to the individual studies and used by investigators during all the steps of the study for identification of study subjects, data collection, laboratory methods, data entry, monitoring, etc. as provided in DRIVE.

Potential systematic or major deviations from the SOP and study level SAP should be described for further development of the methodology and for interpretation of the results (see D2.1 Standard Operating Procedures and Templates: Guidance and Recommendations). DRIVE Quality Control & Audit Committee (QCAC) will further evaluate the quality of the studies and develop guidelines and methods for improving the quality.

➢ Each study site to adapt DRIVE study SOP to be used by the study team, and provide a summary of systematic or other major deviations from them to WP7, to be stored in order to identify bias and potential confounders for pooling.

Training

➢ Each study site to describe the trainings to be organized.

Archiving

Each study site will archive the data used for the analyses, the description of the data (metadata), the study-specific protocol including the analysis plan(s), a description of major deviations from the generic or study-specific protocols, SAP and SOPs, the ethical and other relevant approvals according to the EU level and local regulations, however at least for 5 years.

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Annex 1: Update DRIVE Minimum Dataset requirements

Variable	Obligatory	Description	Additional info	Format	Values/coding	Example
idcountry	Obligatory	Country code defined in ISO3166-1 alpha-2		2 letters text		UK
idstudy	Obligatory	Name of the study		Text		JorviTND
region	Optional	Region name		Text		Wales
idunit	Obligatory (for studies which include >1 GP offices /hospitals)	Identifier of the GP practice or hospital where the patient was seen		Text		JS123
setting	Optional	Type of unit (outpatient, e.g. GP practice, or inpatient, e.g. hospital)		Numeric (Categorical)	1=Outpatient 2=Inpatient 9999 = No information	2
id	Obligatory	Patient identification number		Unique integer		101
sex	Obligatory	Sex		Numeric (Binary)	0=Female 1=Male	0
age	Obligatory	Age in years (at the onset of the symptoms)		Numeric		1984

agemonths	Obligatory for childre n<1 year of age	Age in months (only for children<1 year old)		Numeric		6
onsetdate	Obligatory	Date of symptoms onset		dd/mm/yyyy	Date within the study period	29/12/2017
swabdate	Obligatory	Date of swabbing		dd/mm/yyyy	Date within the study period	30/12/2017
visitdate	Obligatory	Date of visit to the GP or admission to the hospital	In hospital, the first point of contact (often, arrival at the emergency room)	dd/mm/yyyy	Date within the study period	30/12/2017
death	Optional	Has the patient died?	During hospitalization or within 30 days after discharge	Numeric (Binary)	0=Alive 1=Dead	0
deathdate	Optional	Date of death		dd/mm/yyyy	Date within the study period	99/99/9999
fever	Preferred	Fever or feverishness	A measured fever of ≥38°C or temperature 37-38°C with patient-reported feverishness	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	1
headache	Preferred	Headache		Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	1

myalgia	Preferred	Myalgia		Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	0
malaise	Preferred	Fatigue/Malaise		Numeric (Categorical	0 = No 1 = Yes 9999 = No information	1
suddenonset	Preferred	Sudden onset of symptoms	Within 7 days before admission	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	1
cough	Preferred	Cough		Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	1
diffbreath	Preferred	Difficulty breathing	Subjective evaluation of breathing difficulty by patient or caregiver, or any of the following: respiratory rate≥25/min (adults) or SpO2 <90% (unless chronic) or PaO2 <8 kPa or respiratoryacidosis	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	0
sorethroat	Preferred	Sore throat		Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	1

deterioration	Preferred	Deterioration of general condition (asthenia, loss of weight, anorexia, confusion or dizziness)		Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	1
covid	Preferred	Date of SARS-CoV-2 positive test	Most recent positive COVID-19 test in past 12 months	dd/mm/yyyy	Date	29/10/2021
ili	Obligatory (for outpatient)	Influenza like illness	Fulfilling the EU ILI case definition (or local adaptation)	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	1
sari	Obligatory (for inpatient)	Severe acute respiratory infection	Fulfilling the I-MOVE+ SARI case definition (or local adaptation)	Numeric (Categorical	0 = No 1 = Yes 9999 = No information	1
hosp48h	Obligatory	Was the subject previously hospitalised <48 hours prior to ILI onset		Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	1
contra	Obligatory	Any contraindication for influenza vaccination	Based on locally used criteria.	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	1

consent	Obligatory	Consent given		Numeric (Categorical)	0 = No 1 = Yes 9999 = Not applicable	1
consentkin	Obligatory	Consent given by family member (or alternatively tutor, where applicable)		Numeric (Categorical)	0 = No 1 = Yes 9999 = Not applicable	1
comm	Optional	Whether communication with the patient OR consent from next of kin was possible.		Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	1
inst	Obligatory	Institutionalized	Living in a residence or nursing home (any such institution where nurse present 24/7)	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	0
prevflu	Obligatory	Did the patient have a previous lab-confirmed influenza in this season?		Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	0

labfluvirus1	Obligatory	Laboratory result: influenza virus type		Numeric (Categorical)	0=No influenza 1=A 2=B 3=Other influenza not specified 9999 = No information	2
labflusubtype1	Obligatory	Laboratory results: influenza virus subtype/lineage		Numeric (Categorical)	0=No influenza 1=A(H1N1)pdm092=A(H3N2)3=B Yamagata 4=B Victoria 5=Other influenza 9999 = Subtype/lineage unknown	3

labfluvirus2	Optional	Laboratory results: influenza virus type (co-infection)		Numeric (Categorical)	0=No influenza 1=A 2=B 3=Other influenza not specified 9999 = No information	2
labflusubtype2	Optional	Laboratory results: virus subtype (co-infection)		Numeric (Categorical)	0=No influenza 1=A(H1N1)pdm092=A(H3N2) 3=B Yamagata 4=B Victoria 5=Other influenza 9999 = Subtype/lineage unknown	3
labsarscov2virus	Preferred	Was SARS-CoV-2 present in the same sample?		Numeric (Categorical)	0 = Presence of SARS-CoV-2 was assessed but not identified, 1 = yes, 9999 = Presence of SARS-CoV-2 not assessed/unknown	0

labothervirus	Optional	Was a virus other than influenza present in the sample?		Numeric (Categorical)	0=Presence of other viruses was assessed but none were identified, 1 = yes RSV 2 = yes parainfluenzavirus 3 = yes other virus 9999=Presence of other viruses was not assessed	1
seasvaccany	Obligatory	Received influenza vaccination in current season		Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	1
seasvaccbrand	Obligatory	Vaccine brand		Text		Vaxigriptetra
seasvaccbrand2	Obligatory	Vaccine brand dose 2		Text		Vaxigriptetra
Seasvaccdate	Obligatory	Date of influenza vaccination in current season		dd/mm/yyyy		11/1/2022
seasvaccindate2	Obligatory	Date of influenza vaccination dose 2 in current season		dd/mm/yyyy		

seasvaccn1	Preferred	Received influenza vaccination in previous season(season n – 1)		Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	
pneumovac	Optional	Received any pneumococcal vaccination	Any time.	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	1
pneumovaccdat	Optional	Date of pneumococcal vaccination	Latest dose.	dd/mm/yyyy		11/1/2018
covidvac	Preferred	COVID-19 vaccination status		Numeric (Categorical)	0 = Not vaccinated 1 = Partially vaccinated 2 = Fully vaccinated 3 = Primary course + booster dose 9999 = No information	1
covidvaccbrand	Optional	COVID-19 vaccine brand		Text		Comirnaty
covidvaccbrand2	Optional	COVID-19 vaccine brand dose 2		Text		Comirnaty
covidvaccbrand3	Optional	COVID-19 vaccine brand dose 3		Text		Comirnaty

covidvaccdate	Preferred	Date of COVID-19 vaccination		dd/mm/yyyy		22/03/2021
covidvaccdate2	Preferred	Date of COVID-19 vaccination dose 2		dd/mm/yyyy		24/04/2021
covidvaccdate3	Preferred	Date of COVID-19 vaccination dose 3		dd/mm/yyyy		
chronic	Obligatory	Does the patient have at least one chronic disease?	Including obesity (BMI ≥30). Not including smoking or pregnancy.	Numeric (Binary)	0 = No 1 = Yes 9999 = No information	1
liverdis	Optional	Chronic liver disease	Any of the following dg codes (ICD-10): B18, K70-74, K75.0-75.1, K75.3-75.9, K76-77 INCLUDING: Alcoholic liver disease, Toxic liver disease, Hepatic failure, Chronic hepatitis (viral & other), Fibrosis and cirrhosis of liver, Other inflammatory liver diseases, Other diseases of liver EXCLUDING: Clinically insignificant liver cysts	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	0

diabetes	Optional	Diabetes	Any of the following dg codes (ICD-10): E10-E14, O24INCLUDING: Any form of diabetes, including sequelae & DM in pregnancy	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	0

cardiovasc	Optional	Cardiovascular diseases	Any of the following dg codes (ICD-10): A52.0, B37.6, I01-02, I05-09, I11.0, I13.0, I13.2, I20-25, I26-28, I30-43, I44- 46, I48, I49.0, I49.5, I50-52, I70-71,Q20-Q28 INCLUDING: all conditions of heart & large vessels that are chronic or likely to have chronic sequelae. Cardiovascular syphilis, endo-, myo- and pericarditis, rheumatic fever, chronic rheumatic heart diseases, congenital malformations, hypertensive (renal) diseases with heart failure, ischaemic heart diseases, diseases of pulmonary circulation, atherosclerosis, cardiomyopathies, most conduction disorders, heart failure, aortic aneurysms & dissecation, other heart diseases and their complications. EXCLUDING: uncomplicated hypertension, previous uncomplicated pulmonary embolism (with no lasting cardiac insufficiency), paroxysmal tachycardias, most cases of premature depolarization.	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	1

cancer	Optional	Cancer	Any of the following dg codes (ICD-10): C00-97, D37-48, Z85, Z92.3, Z92.6.INCLUDING: All malignant neoplasms (both solid and haematologic) with potential to metastasize, either in treatment, active followup, or <5 years post curative treatment. EXCLUDING: Benign & in situ neoplasms. Basal cell carcinomas. Any cancer previously treated with curative intent & in complete remission for ≥5years.	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	0

immuno	Optional	Immunodeficiency or organ transplant	Any of the following dg codes (ICD-10): B20-B24, D80–84, D89, Z94 INCLUDING:HIV infections, immunodeficiencies & organ transplants. or iatrogenic: ≥2 week systemic treatment, in the 3 months preceding symptom onset, with any of the following: corticosteroid (≥20 mg prednisolone daily or equivalent), ciclosporin, tacrolimus, mycophenolate, methotrexate, azathioprine, TNF-α blockers and other biological or cytostatic drugs with immunosuppressive effect EXCLUDING: Disorders of the immune system which do not lead to immunosuppression (e.g. some autoimmune conditions).	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	0

lungdis	Optional	Lung disease	Any of the following dg codes (ICD-10): A15-16, A19, A31.0, B33.4, E84.0, J40- 47, J60-70, J80-84, J85-86, J90-91, J92.9, J93-94, J95-99INCLUDING: TB (pulmonary, miliary but not that of other systems), atypical mycobacteria, cystic fibrosis, asthma, COPD, bronchiectasis and other chronic sequelae of infections, chronic lung diseases due to external agents, interstitial lung diseases, pleural diseases, respiratory failure. EXCLUDING: acute respiratory infections, lung cancer, diseases of pulmonary circulation, pleural plaques without asbestos, previous uncomplicated pneumothorax.	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	1
anemia	Optional	Anemia	Any of the following dg codes (ICD-10): D50-D64 diagnosed before the onset of symptoms. EXCLUDING: coagulopathies, uncomplicated hypersplenism, hepato/splenomegaly (D65-69, D70-77,D80-84, D86, D89)	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	0

rendisease	Optional	Renal disease	Any of the following dg codes: (ICD-10): I12-13, M10.30, N00-19, N20.0,N25-27, N28.0, N28.9, Q63.9, Z90.5EXCLUDING: Clinically nonsignificant kidney cysts	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	0
dement	Optional	Dementia	Any of the following dg codes (ICD- 10): F00-03, F05.1, G30-31EXCLUDING delirium w/o underlying dementia, hydrocephalus.	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	0
stroke	Optional	History of stroke	Any of the following dg codes (ICD-10): I61-64, I67.8, I69, G93.1INCLUDING: both ischaemic and haemorrhaegic strokes and anoxic brain damage. Also counting previous episodes and clear ischaemic findings seen in cranial imaging (even if fully recovered / no symptoms).	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	0

rheumat	Optional	Rheumatologic diseases	Any of the following dg codes:ICD-10: M05–09, M13, M30–36, M45INCLUDING rheumatoid diseases with presumed autoimmune origin and primarily musculoskeletal presentation. EXCLUDING: arthrosis, gout, scoliosis, infectious conditions etc.	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	0
obesity	Optional	Obesity	BMI ≥30 or the dg codes (ICD-10): E66, E68EXCLUDING: local adiposity and "other hyperalimentation" (=vitamin overdoses etc.)	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	0
childrisk	Optional	In children: Any perinatal or congenital risk factor?		Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	2
nhosp	Preferred	Number of hospitalizations in the last year	Any overnight stay in hospital. (One disease episode counts as one hospitalization even if a patient is moved from one unit to another)	Numeric	≥0 or 9999 = No information	2
gpvisit	Preferred (for GP studies)	Number of GP consultations in the last year	Any consultation to nurse/GP/specialist in a primary care setting. Not counting follow-up visits for the same cause.	Numeric	≥0 or 9999 = No information	5

antiviral_flu	Optional	Has the patient received an antiviral treatment for influenza within the 2 weeks before swabbing?		Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	1
antiviral_covid	Optional	Has the patient received an antiviral treatment for COVID-19 within the 2 weeks before swabbing?		Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	1
statin	Optional	Statin use	At the time of vaccination.	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	1
pregnancy	Optional	Pregnancy	Any trimester at symptom onset.	Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	0
hcw	Optional	Is the patient a healthcare worker?		Numeric (Categorical)	0 = No 1 = Yes 9999 = No information	0
siblings	Optional	(In children) Number of siblings		Numeric	≥0 or 9999 = No information	2

bmi	Optional	Body Mass Index		Numeric	10 to 55 or 9999 = No information	22,4
smoking	Optional	Smoking status (cigarettes, cigars, pipe, hookah). Not counting exclusively chew tobacco or snus.	Never-smoker: <100 cigarettes during their lifetime. Ex-smoker: has smoked ≥100 cigarettes over lifetime but has stopped ≥3 months ago. Occasional smoker: has smoked ≥100 cigarettes over lifetime and has still smoked in the 3 months preceding symptom onset, but not daily. Daily smoker: has smoked ≥100 cigarettes over lifetime and smokes daily.	Numeric (Categorical)	0=Never-smoker 1=Ex-smoker 2=Occasional smoker 3=Daily smoker 9999=No information	0
functstatus	Optional	Dependency / Patient has difficulty in at least 1 of these categories: bathing dressing eating going to the toilet stairs walk wheelchair user	Difficulty = needs help from others	Numeric (Categorical)	0 = No 1 = Yes 9999 = Not applicable	0

Annex 2: Sample size considerations for case-control studies

The document "Sample size considerations for case-control studies", available on the DRIVE website, provides sample size estimations for estimating overall and brand-specific influenza vaccine effectiveness (VE) using the case-control design. The minimal detectable VE as well as precision estimates are provided for various parameter settings and recommendations are formulated.

Annex 3: Generic Statistical Analysis Plan for pooled analysis

The generic statistical analysis plan can be found in the DRIVE: DRIVE D4.4 Generic Statistical Analysis Plan: combining information on Influenza Vaccine Effectiveness across study sites. A SAP specific to the 2021/22 season will be prepared.

Annex 4: DRIVE Informed Consent Form template

*Instructions for DRIVE study sites: This **Informed Consent Form** (ICF) template is conceived to be adapted and implemented by DRIVE study sites. Site specific adaptations and translation to the local language might be required. If a local ICF is used, we strongly recommend to adapt it and at least include the points listed below in the DRIVE ICF minimum criteria.*

I. List of minimum criteria for DRIVE study sites to include in local ICFs

If not implementing the DRIVE template ICF, study sites should include the following mandatory information in their local ICFs:

- **General information about processing:**
  The ICF should inform the patient that DRIVE will collect and process personal information, including:
  - the age and gender of the study participant,
  - the medical history of the study participant (including any chronic conditions body mass index (BMI), pregnancy status with due date when applicable…)
  - relevant results of the laboratory tests and examinations a study participant will undertake for a current/on-going condition,
  - The vaccination history of the study participant.

- **To be added in the section related to the data privacy:**

  "The collection, transfer and processing of personal data from patients participating in this study will be done in accordance the European General Data Protection Regulation (GDPR), effective from May 25, 2018 and with [the country law of dd-Mmm-YYYY] for the protection of natural

persons with regard to the processing of personal data. Your coded (pseudonymized[1]) data will be stored on a dedicated and secured central server. This server is hosted by P95 (a company specialized in data managing and processing, and also a DRIVE consortium partner) and is located in two different locations in Europe (main location and back-up location). Following the applicable regulations and guidance's, DRIVE will keep your data for 10 years after study end.

We will do everything we can to ensure that no one except the study doctor and study staff know who you are. We do this by coding your personal information and using a code instead of your name; only your study doctor and study staff will have the key to the code".

- **To be added in the section Secondary use of data statement.**
  "In order to get the answers for the study described in this document, we need to collect personal information about you and your health.

  Your patient data after coding can be reused for additional analysis and for purposes related to investigate respiratory infectious diseases and the prevention of these diseases. Your patient data (after coding) are moreover to be made available to universities, research institutions, and companies in the framework of the DRIVE consortium for additional analysis aiming at investigating respiratory infectious diseases in general and the prevention of these diseases.

  The sole aim of these additional analysis is to improve the diagnosis and prevention of respiratory infectious disease, as well as to improve the methods used in this type of studies. Your patient data (after coding) will be used for a variety of medical research purposes to the benefit of society as a whole".

- **To be added in the section "Ability to exercise rights" or equivalent:** for the content see section 6 "Your Rights if you decide to participate"

II. Study participant information for participation in a research study on influenza vaccines.

Study title à DRIVE: A multi-centre case-control study to measure the brand-specific influenza vaccine effectiveness in Europe.

You are invited to take part in this research study, and as part of the screening process aiming to verify your eligibility for participation, first we would like to provide you with information about the study itself.

You are receiving this letter because you have been hospitalized with severe respiratory symptoms, or you are seeking care at your General Practitioner, in your primary care center, with influenza-like

[1] How your personal data is coded? Personal data is pseudonymized (coded) and processed in such a manner that the personal data can no longer be attributed to you without the use of additional information. For this study an internal identifier is set and your associated patient data can no longer be directly traced back to you.

respiratory symptoms.

This study is conducted in order to provide valuable data to DRIVE, a research collaboration funded by the European Commission for the understanding of the influenza vaccine effectiveness. DRIVE stands for Development of Robust and Innovative Vaccine Effectiveness and aims to assess influenza vaccine effectiveness (more details are provided under section 1 "General information" and section 2 "Purpose of the research").

Your decision to take part in this study is voluntary and in order to **participate your written consent is required**. **You can change your decision and leave the study at any time without giving any reason**.

Before you decide whether you want to take part in this study, the study staff will explain the study and the information in this consent form to you. **Please ask about anything you do not understand**. You are welcome to bring a family member, friend or someone you trust to the conversation.

The study has been reviewed and approved by an Independent Ethics Committee (IEC) or an equivalent board. IECs protect the rights, safety and well-being of people who take part in research studies.

1. General information

Influenza vaccination at is part of the national recommendation of [your country] to protect at-risk groups against influenza and the associated risks of infection. Influenza vaccines are re-formulated every year, so it is very important to check their effectiveness from year to year.

This study was designed by DRIVE (www.drive-eu.org) a public-private partnership to estimate brand-specific seasonal influenza vaccine effectiveness in Europe) and is being conducted in various hospitals and primary care centers in Europe. DRIVE is an EU collaborative effort funded by the European Commission's Innovative medicines initiative (IMI, https://www.imi.europa.eu/) for a better understanding of the effectiveness of influenza vaccines.

2. Purpose of the research

The purpose of this study is to evaluate how well the influenza vaccines prevent the influenza disease under real-world conditions, in different age groups (from 6 months onwards) and in every influenza season (usually ranging from October to April in the northern hemisphere countries). This knowledge is very valuable to contribute to the public health decision-making on vaccination strategies, and for pharmaceutical companies to fulfill their regulatory commitments with the European Medicines Agency.

3. Type of Research study

This study will estimate the effectiveness of influenza vaccines against lab-confirmed influenza through the DRIVE partnership. You will not be vaccinated as part of this study. However, you may have received your annual influenza vaccination as part of routine vaccination.

If you meet the eligibility criteria you will be asked to take part in this multi-centre, hospital or -primary care-based, case-control study. Data will be collected through a wide network of hospitals and primary care networks located in different European countries.

4. What will be expected from you – The course of the study

The study does not require additional visits or assessments other than those required in routine clinical practice for a patient with your condition. The study doctor or nurse may ask you some questions or will provide you with a short questionnaire to obtain some important information on your health conditions and behavior.
Your responsibilities as a study participant include the following:

- Report as accurately and comprehensively as possible your medical history, vaccination history and current conditions,
- Complete the questionnaires upon request of the study doctor or nurse,
- Agree to be contacted by the study team as necessary, by telephone or through writing.
- Allow your GP or pharmacy to be contacted by the study team to obtain additional information required for this study.
- If you have to withdraw from the study, inform the study doctor or nurse
- If you agree to take part in the study or you agree to allow your child to participate, you will be asked to sign an Informed Consent Form (ICF) or Inform Assent Form (IAF), respectively. You will be given a copy of this informed consent/assent form to keep.

If you do not want to participate, or would like to stop participating in the study: Participation in this study is voluntary and you have the right to leave the study at any time. You do not have to give any reason if you choose not to participate or if you choose to leave the study. Please contact your study doctor, if you wish to withdraw your consent. The decision whether or not to participate in this study will not have any negative impact on the quality of care or the relationship with the treating study doctor(s). If you withdraw your consent, the data collected up to the time of your cancellation will be retained. This is to guarantee the validity of the study. No new information will be collected.

5. Confidentiality: Use and storage of your data and respiratory samples

<u>Use and storage of your data</u>

In order to get the answers for the study described in this document, we need to collect personal information about you and your health.

Your patient data after coding (including biological samples can be reused for additional analysis and for purposes related to investigate respiratory infectious diseases and the prevention of these diseases. Your patient data (after coding) are moreover to be made available to universities, research

institutions, and companies in the framework of the DRIVE consortium for additional analysis aiming at investigating respiratory infectious diseases in general and the prevention of these diseases.

How your personal data is coded? Personal data is pseudonymized (coded) and processed in such a manner that the personal data can no longer be attributed to you without the use of additional information. For this study an internal identifier is set and your associated patient data can no longer be directly traced back to you.

The sole aim of these additional analysis is to improve the diagnosis and prevention of respiratory infectious disease. Your patient data (after coding) will be used for a variety of medical research purposes to the benefit of society as a whole, in the framework of the DRIVE consortium and respiratory infectious diseases research.

The patient data used by DRIVE includes, for example:

- your age and gender,
- your medical history (including any chronic conditions, body mass index (BMI), if you are pregnant your due date…)
- results of the laboratory tests and examinations you will have for your current condition,
- your vaccination history.
- Other medical variables of interest for the DRIVE study.

The collection, transfer and processing of personal data from patients participating in this study will be done in accordance with [the country law of dd-Mmm-YYYY] the protection of natural persons with regard to the processing of personal data and the European General Data Protection Regulation (GDPR[2]), effective from May 25, 2018. Your coded data will be firstly stored on a dedicated and secured central server. This server is hosted by P95, a DRIVE partner responsible of the maintenance of the IT platform of the study (https://www.p-95.com/) and is located in 2 different locations in Belgium, Europe (main location and back-up location).

We will ensure that no one except the study doctor and study staff know who you are. We do this by coding your personal information and using a code instead of your name; only your study doctor and study staff will have the key to the code.

In order to check the quality of the study, your non-coded personal data or information from your medical file relevant to this study may be inspected by people other than the study staff. This access takes place under the supervision of the researcher and these persons are bound by professional secrecy or by means of a confidentiality agreement. This may include:

- personnel designated by DRIVE (Monitors and Auditors) and people or organizations who provide services to or collaborate with the client. However, they will never pass on your name and contact details to the client.

[2] https://www.privacy-regulation.eu/en/index.htm

- inspectors from the competent Health Authorities from the European Union and the United Kingdom
- persons appointed by the Ethics Committee.

For how long will your data be used?

Your coded data will be used only for as long as it is needed for the study and further research, with your consent. It may be kept for longer, where required by law. Following the applicable regulations and the Good Epidemiological Practices (GEP) guidance's, DRIVE will keep your data for a minimum of 10 years after study end.

Use and storage of biological samples

A respiratory sample (swab) will be taken, processed and stored as part of the standard care, to determine the whether you have been infected with influenza or another respiratory pathogen. This means that no extra samples will be collected from you (or your child) for the purpose of the study.

- This sample will be analyzed as part of the study (primary use of biological samples).
- The sample will not be destroyed immediately after use.
- The sample might be stored in order to perform new assessments related to the research questions (secondary use of biological samples, e.g. sequencing).

6. Your Rights if you decide to participate

In accordance with the European General Data Protection Regulation and the Data Protection Act, you have the right to ask the researcher which data is collected about you and what it is used for in this study. You have the right to;

- Access and check this data.
- To receive the collected personal data.
- Ask for correction if they are incorrect.
- Restrict the processing of your data.
- Oppose the processing of your personal data.
- Withdraw your consent to the processing of personal data. Your personal data already collected. prior to your withdrawal will be retained to avoid misinterpretation of study results.

You may also withdraw at any time without giving any reason, even if you have previously agreed to participate. Your decision will not affect your relationship with the investigator or your treating physician, or the quality of your future medical care.

7. Benefits and risks for participation in this study

Since all the medical procedures required for this study are part of the standard and routine medical care for your condition, **your participation in this study is not expected to pose any health risk.**

Participation in this study will not bring you any direct personal benefits. Nevertheless, If you participate you will contribute to a better understanding about influenza and the vaccine effectiveness of the seasonal influenza vaccines (which will help us to understand how well these vaccines work every year).

DRIVE consortium and [insert name of the study site here] are responsible for your personal information. All results resulting from the research described in this document are property of the FISABIO as project coordinator, on behalf of DRIVE consortium. More information about the confidentiality of your data can be found in section 5.

8. Sharing the results

After study closure a description and the results of this study will be published in DRIVE website (www.drive-eu.org) and international peer-reviewed journals. This report will also be submitted to Innovative Medicines Initiative (IMI) and to the European Medicines Agencies (EMA). A copy of the scientific publication can be obtained from the study doctor or the study staff. The information that will be made publicly available will not include information that can identify you.

Moreover, a description of the study will also be available on the European Union electronic Register of Post-Authorisation Studies (EU PAS Register) of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

9. Do you have any questions

If you have any questions please contact the study doctor or study nurse. If you have any complaints about the study, you can discuss this with your study doctor, if you would rather not do that, you can contact the complaints committee at your hospital.

[contact details study doctor]

[Contact details Study nurse]

[Contact details complaints committee of the hospital]

III. Adult Informed Consent

Study title: **A multi-centre case-control study for the estimation of brand-specific influenza vaccine effectiveness in Europe (DRIVE):**

I declare that,

- I have been informed of the nature, purpose, duration, possible benefits and risks of the study and that I know what is expected of me. I have read the information document and its annexes.
- I have had enough time to think about this and to talk to a person of my choice, such as my doctor or a family member.

- I have been able to ask any questions that came to mind and I have received clear answers to my questions.
- I understand that my participation in this study is voluntary and that I am free to discontinue my participation in this study without affecting my relationship with the therapeutic team in charge of my health.
- I understand that the abovementioned personal data will be collected about me during my participation in this study and that the study doctor and the sponsor ensure the confidentiality of this data in accordance with [country] law or any applicable local law (depending on the country).
- I agree to the processing of my personal data in accordance with the modalities described in the section on ensuring confidentiality also consent to the transfer to and processing of my encrypted data in other European countries.
- I agree that my coded and personal data may be used and shared by DRIVE consortium and other researchers for future research, as described in this document, provided that such processing is limited to the context of the study mentioned here for a better understanding of the respiratory infectious diseases and its prevention.
- I agree that my doctor or other health care professionals will be contacted if necessary to obtain additional information about my health.
- I have received a copy of the Participant Information and Informed Consent.

By signing this form, I agree:

- **To take part in the study**
- **That my personal and coded data can be used as described in this form.**

I, the undersigned, agree to participate voluntarily in the study

First Name (Study Participant)	Family Name (study Participant)
Your Signature	Date of signature

If a witness / interpreter is present. Witness / Interpreter

I have been present throughout the process of providing information to the participant and I confirm that information about the objectives and procedures of the study has been adequately provided, that the participant is likely to have understood the study and that participation in the study is voluntary.

First Name (witness / interpreter)	Family Name (witness / interpreter)

Capacity of the Witness

Your Signature	Date of signature

If a Legal Authorized Representative of the study participant is present

I have been present throughout the process of providing information to the participant and I confirm that information about the objectives and procedures of the study has been adequately provided, that the participant is likely to have understood the study and that participation in the study is voluntary.

First Name (Legal Authorized Representative)	Family Name (Legal Authorized Representative)

Your Signature	Date of signature

Attending study doctor

I, the undersigned treating study doctor / authorized representative, declare that I have provided the necessary information regarding this study orally as well as a copy of the information document to the participant.

I confirm that no pressure has been placed on the participant to get him / her to agree to participate in the study and I am willing to answer any additional questions.

First Name (study doctor /authorized representative)	Family Name (study doctor /authorized representative)
Your Signature	Date of signature

Annex 5: Identification, classification and reporting of protocol deviations

This Annex is intended to be used for reporting of protocol deviations.

Introduction

During the 2018/2019 DRIVE influenza season, a Quality Control and Audit Committee (QCAC) has been set up with quality control and assurance experts from manufacturing industry partners. Their mission is to evaluate the quality of the study conduct, data reporting and the pooled analysis, in order to further ensure that reliable data are delivered or if necessary identify areas for improvement.
Among the recommendations made, it has been acknowledged the importance to better define and harmonise the potential protocol deviations that occur during the study conduct. The sites conducting Influenza Vaccine Effectiveness (IVE) studies in the context of DRIVE should be provided with a harmonised guidance to the participating sites for them to identify, classify and report protocol deviations to the DRIVE consortium to evaluate the impact before pooled analyses are performed.
To reach this objective, Work Package 2 has developed a guidance to guide the participating sites on the approach and actions to undertake in case of protocol deviations/violations.
Deviations from the approved protocol are common and have been reported both in routine management [1] and in research [2] at various frequencies.

1. DEFINITIONS

a. What is a protocol deviation?

As stated in the ICH E3 Q&A R1, a protocol deviation is defined as *"any change, divergence, or departure from the study design or procedures defined in the protocol."*

Nevertheless, the current definition could lead to over interpretation leading to inclusion of a wide scope of events being reported. Pragmatically, it is important to clarify that:

1) Any deviation should be related to a final research protocol **approved by** an Ethics committee (EC), Institutional Review Board (IBR) or equivalent, unless a waiver is granted.
2) The event **should have occurred** and would not refer to a theoretical or potential situation;
3) The event is related to the protocol, documents or procedures referenced in the protocol [(e.g., laboratory manual, Case Report Form (CRF), Statistical Analysis Plan (SAP), as applicable]

b. How should I classify/define Important and Non-Important Protocol Deviations?

It is acknowledged that deviations might vary in their incidence and impact and have also been classified accordingly. Minor deviation of a study from the approved protocol is classified as a deviation while one that affects the quality of the data or impact subjects' safety is classified as a protocol violation[3]. Deviations are further classified as noncompliance, misconduct, or fraud. A single instance of a deviation could be classified as a noncompliance while repeated and systematic noncompliance (usually despite warnings) are considered as misconduct. Whenever there is a financial motive behind the noncompliance, it may be classified as a fraud.

Misconduct is defined as "fabrication", falsification, or plagiarism in proposing, performing or reviewing research, or in reporting research results. Polan- in-Huk define fraud as "an intentional deception made for personal gain or to manage another individual, for instance, intentionally falsifying and/or fabricating research data, and misleading reporting of the results[4]. It is necessary for study managers need to correct and prevent further non-compliance depending according to the classification, as appropriate.

Protocol deviation: Any change, divergence, or departure from the approved study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB, and *does not affect* the participant's safety, rights, or welfare and/or the completeness, accuracy and integrity of the study data. This term, though sometimes used interchangeably with the term "violation," is (i) most often used when the variance is intended for the safety of one or more research participants or is an unintended change that is not considered as serious as a violation, (ii) is considered *minor* or administrative, and (iii) may involve no more than minimal risk to participants or others.

Protocol Violation: Any deviation that *may affect* the subject's rights, safety, or welfare, and/or the completeness, accuracy and integrity of the study data. This term though sometimes used interchangeably with "deviation" is often considered a *major*, more serious, variance from an approved protocol than a deviation.

In case of major deviation or suspected protocol deviation an investigation for serious breach should be implemented. Further guidance is reported in the EMA guidance on the "Guidance for the notification of serious breach" [5]

c. What action should I undertake (as participating site) if a protocol deviation/violation occurs as part of the conduct of IVE studies in DRIVE

To record all protocol deviations/violations that occur at a study site, DRIVE developed a tracking tool aiming to provide a comprehensive list of the relevant events. Once completed this tracker will need to be sent to the WP7 prior to the start of the pooled analysis optimally at the time the data are transferred to the ESSA (DRIVE secured server).
Importantly, this tool is complementary to, and does not replace, the requirement to report potential serious breaches of the Protocol to the Sponsor and/or competent authorities if appropriate (see EMA guidance for further insights)[5]

Guidance for completion of the Protocol Deviation tracker:
- Ensure Study Title/ Sponsor/Principal investigator (PI) and site details are completed on all forms.
- Record protocol deviations/violations in the tracker as they occur, to ensure completeness and accuracy of data.
- The site PI should sign each form after it has been completed.
- The deviations should be reviewed and corrective preventive action completed and recorded. (e.g., amendment to the protocol).
- Events should be numbered sequentially, commencing with no. 1.
- The tracker should be filed in the Essential Documents Folder (i.e. Trial Master File/Investigator Site File) in either a specific labelled section (Protocol Deviations) or with the study protocol.
- Pages should be filed in reverse chronological order, with the newest pages of the log placed at the front of the section.
- At the conclusion of the study, ensure all forms are complete and signed by the Principal Investigator.

Examples of protocol deviation may include:
- A rescheduled study visit
- Missing a visit window because the subject is traveling for Instance
- Failure to collect a secondary self-report questionnaire
- Subject's refusal to complete scheduled research activities

Examples of protocol violation may include:

- Failure to obtain valid informed consent prior to enrollment (e.g., obtained informed consent on a

non-date stamped form)
- Loss of laptop computer that contained identifiable, private information about subjects
- Not following inclusion/exclusion criteria
- Multiple visits missed or outside permissible windows
- Mishandled samples
- Subject repeated non-compliance with study requirements
- Intentional deviation from protocol, or regulations by study personnel

Protocol Deviation/violation tracker

Study title:	Sponsor: FISABIO, on behalf of DRIVE consortium
Principal investigator:	Site:

A protocol deviation is defined as *"any change, divergence, or departure from the study design or procedures defined in the protocol."* If the deviation has an impact on patient safety or data integrity this may constitute a serious breach and should be reported to DRIVE consortium and competent authorities as appropriate.

Event N°	**Event date**	**Description of the deviation**	**Document/procedure impacted by the deviation (e.g., consent procedure, inclusion/exclusion criteria, study procedures, laboratory assessment)**	**Classification of the deviation (e.g., protocol deviation, protocol violation)**	**Corrective/preventive action taken to avoid recurrence e.g., protocol amendment, SAP amendment**

Investigator signature date

[1] Salerno SM, Wrenn KD, Slovis CM. Monitoring EMS protocol deviations: A useful quality assurance tool. Ann Emerg Med. 1991;20:1319–24
[2] Théroux P, Ouimet H, McCans J, Latour JG, Joly P, Lévy G, et al. Aspirin, heparin, or both to treat acute unstable angina. N Engl J Med. 1988;319:1105–11.
[3] Bhatt A. Protocol deviation and violation. Perspect Oin Res 2012;3:117.
[4] Polan.in-Huk J, Huk J, Filip R. Fraud and misconduct in clinical research. J Pre Oin Clin Res 2010;4:158-60.
[5] Guideline for the notification of serious breaches of 3 Regulation (EU) No 536/2014 or the clinical trial protocol - 31 January 2017 EMA/430909/2016