Brand-specific influenza vaccine effectiveness in Europe Statistical Analysis Plan Season 2019/20

777363 - DRIVE

Development of robust and innovative vaccine effectiveness

WP7 - IVE studies

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Due date	NA
Delivery date	NA
Deliverable type	R
Dissemination level	PU

Document History

Version	Date	Contribution	Description
V0	10/01/2020	Kaat Bollaerts: SAP Anke Stuurman and Cintia Muñoz Quiles: collection of site data	For sharing with WP7 and sites
V1	31/01/2020	Anke Stuurman, Margarita Riera: incorporated feedback from sites and WP7	For sharing with ISC and EFPIA
V2	05/05/2020	Kaat Bollaerts, Jorne Biccler, Margarita Riera incorporated feedback from ISC and EFPIA	Addressing comments EFPIA - ISC

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aTIV	Adjuvanted trivalent influenza vaccine
BIVE	Italian Hospital Network
BMI	Body mass index
CI	Confidence interval
CIRI-IT	Centro Interuniversitario di Ricerca sull'Influenza e sulle altre infezioni trasmissibili
DRIVE	Development of Robust and Innovative Vaccine Effectiveness
DRIVE ESSA	DRIVE Electronic Study Support Application
DRIVE QCAC	DRIVE Quality Control and Audit Committee
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
F-CRIN	French clinical research infrastructure network
FISABIO	Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana
GPP	Good Participatory Practice
GTPUH	Germans Trias I Pujol University Hospital
HCW	Healthcare worker
HUS	Helsinki University Hospital
ILI	Influenza like illness
IMI	Innovative Medicines Initiative
INSERM	Institut National de la Santé et de la Recherche Médicale
I-REIVAC	Innovative clinical research network in vaccinology
ISS	Istituto Superiore di Sanita
IVE	Influenza vaccine effectiveness
LAIV	Live-attenuated influenza vaccine
LCI	Laboratory-confirmed influenza
LNS	Laboratoire National de Santé
LPUH	La Paz University Hospital
MUV	Medical University Vienna
NIID	National Institute for Infectius Diseases "Prof. Dr. Matei bals"
NVR	National Vaccination Register
OR	Odds ratio
QIV	Non-adjuvanted quadrivalent influenza vaccine
RCGP	Royal College of General Practitioners
RCGPRSC-OX	Royal College of General Practitioners / Research and Surveillance Centre / Oxford University
RE MA	Random-effects meta-analysis
REML	Restricted maximum likelihood
RR	Relative risk
RT-PCR	Reverse transcription polymerase chain reaction
SAP	Statistical Analysis Plan
SARI	Severe acute respiratory infection
THL	The Finnish Institute for Health and Welfare
TIV	Non-adjuvanted trivalent influenza vaccine
TIV-HD	High-dose trivalent influenza vaccine
TND	Test negative design
UNIS	University of Surrey
UoA	National and Kapodistrian University of Athens

UK	United Kingdom
VE	Vaccine effectiveness
VHUH	Vall d'Hebron University Hospital

1 Background

The Development of Robust and Innovative Vaccine Effectiveness (DRIVE) project is a public-private partnership aiming to build capacity in Europe for estimating brand-specific influenza vaccine effectiveness (IVE). The DRIVE Project, which is funded by the Innovative Medicines Initiative (IMI), was initiated as a response to the changes for licensing of influenza vaccines in Europe. The new guidance on influenza vaccines by the European Medicines Agency (EMA) came into effect in the beginning of 2017. This guidance states that the performance of influenza vaccines should no longer be assessed based on serological assays, but should be based on post-authorization effectiveness studies [1].

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.
The main objective of DRIVE is to establish a sustainable network to estimate brand-specific seasonal IVE in Europe. The DRIVE network is expanding over the course of the project, and not all vaccine brands used in Europe are likely to be covered during the expansion phase of DRIVE.

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 [2]. In the pilot study, there were four test-negative design studies (TND) and one register-based cohort study. The DRIVE network is continuously expanding. For the 2019/20 season, the DRIVE network includes 13 TND studies and one register-based cohort study.

This Statistical Analysis Plan (SAP) describes the characteristics of the participating study sites, the site-specific statistical analysis as well as the statistical analysis to pool data across study sites for the 2019/20 influenza season.

2 Reference documents

The SAP has been developed in companion to the following document:

- DRIVE Mock Report Season 2019/20.

The SAP has been developed using the following documents:

- DRIVE Generic protocols (D7.1 and D7.2).
- DRIVE 2019/20 local study protocols.
- DRIVE Generic SAP: combining information on Influenza Vaccine Effectiveness across study sites (D4.4).
- DRIVE data management plan (D4.2).

The following supplementary files are provided:

- Study team members (ANNEX 1).
- DRIVE minimal data requirements (ANNEX 2).

3 Amendment related to COVID-19

Due to the COVID-19 outbreak a number of sites had to end the data collection earlier than planned. The study period has therefore been adjusted, see Section 7.

4 Objectives

The objectives listed below are a revision of the objectives listed in the generic protocol. More specifically, the changes in the objectives represent the current state of discussions regarding the confounders that should be adjusted for. The details of the confounder adjustment have therefore been moved to the analysis section (Section 16).

4.1 Primary objective

To estimate confounder-adjusted seasonal **overall** and **brand-specific** IVE against laboratory-confirmed influenza stratified by setting (primary care, hospital-based or mixed setting in case the source of the cases cannot be obtained) and age group (6m-17yr, 18-64 yr, ≥ 65yr), by type of outcome:

- any laboratory-confirmed influenza;
- laboratory-confirmed influenza A, overall and by subtype (A(H1N1), A(H3N2));
- laboratory-confirmed influenza B, overall and by lineage (B Victoria, B Yamagata).

4.2 Secondary objective

To estimate confounder-adjusted seasonal **vaccine-type** IVE against laboratory-confirmed influenza stratified by setting (primary care, hospital-based or mixed) and age group (6m-17yr, 18-64 yr, ≥65yr), by type of outcome:

- any laboratory-confirmed influenza;
- laboratory-confirmed influenza A, overall and by subtype (A(H1N1), A(H3N2));
- laboratory-confirmed influenza B, overall and by lineage (B Victoria, B Yamagata).

The following vaccine types will be considered:

- Trivalent non-adjuvanted influenza vaccine (TIV).
- Trivalent adjuvanted influenza vaccine (aTIV).
- Trivalent high-dose influenza vaccine (TIV-HD).
- Quadrivalent live attenuated influenza vaccine (LAIV).
- Quadrivalent inactivated egg-based influenza vaccine (QIVe).
- Quadrivalent inactivated cell-based influenza vaccine (QIVc).

5 Study design

A multi-centre study with data available from five primary care based TND studies, eight hospital based TND studies and one register-based cohort.

5.1 Participating study sites

A list of the participating study sites according to study design and setting and their respective national or regional influenza surveillance systems are given in Table 1. All the TND studies and the register-based cohort follow closely the DRIVE generic protocols (D7.1 and D7.2) for their respective study designs. Key characteristics of the TND studies and the register-based cohort study are summarized in Figure 1, and presented in more detail in Table 2-Table 3 for the TND studies and Table for the register-based cohort study. More details on the individual studies are provided in the subsequent sections. When feasible, additional site-specific studies might be included in the analysis if test data will be made available prior to 15th April 2020.

Table 1. Overview of the participating study-sites, 2019/20

Type of study, setting:	Influenza surveillance systems
Test-negative design studies, primary care:	
1. Medical University Vienna (MUV), Austria	Diagnostic Influenza Network Austria, DINÖ
2. Centro Interuniversitario di Ricerca sull'Influenza e sulle altre infezioni trasmissibili (CIRI-IT), Italy	CIRI-IT Physicians network
3. Royal College of General Practitioners Research and Surveillance Centre (RCGPRSC) & University of Oxford (OX), United Kingdom	English sentinel surveillance network, Point of Care Testing subset (12 general practices)
4. Istituto Superiore di Sanita (ISS), Italy	National sentinel influenza surveillance system, INFLUNET
5. Laboratoire National de Santé (LNS), Luxembourg	National influenza sentinel surveillance
Test-negative design studies, hospital based:	
1. Helsinki University Hospital (HUS), Jorvi Hospital, Finland	Part of the Finnish sentinel surveillance, THL
2. Italian Hospital Network (BIVE), Italy	
3. National Institute for Infectious Disease "Prof. Dr. Matei Balș", Bucharest, Romania	
4. Vall d'Hebron University Hospital (HUVH), Barcelona, Spain	Information Plan for Acute Respiratory Infections in Catalonia, PIRIDAC
5. Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO), Spain	Valencia Hospital Network for the Study of Influenza, VAHNSI
6. Hospital Universitario La Paz (LPUH), Madrid, Spain	
7. Hospital Universitario Germans Trias i Pujol (GTPUH), Badalona, Spain	Information Plan for Acute Respiratory Infections in Catalonia, PIRIDAC
8. Institut National de la Santé et de la Recherche Médicale (INSERM), France	National surveillance of influenza vaccine effectiveness
Register-based cohort study	
1. The Finnish Institute for Health and Welfare (THL), Finland	Online surveillance of influenza vaccine effectiveness

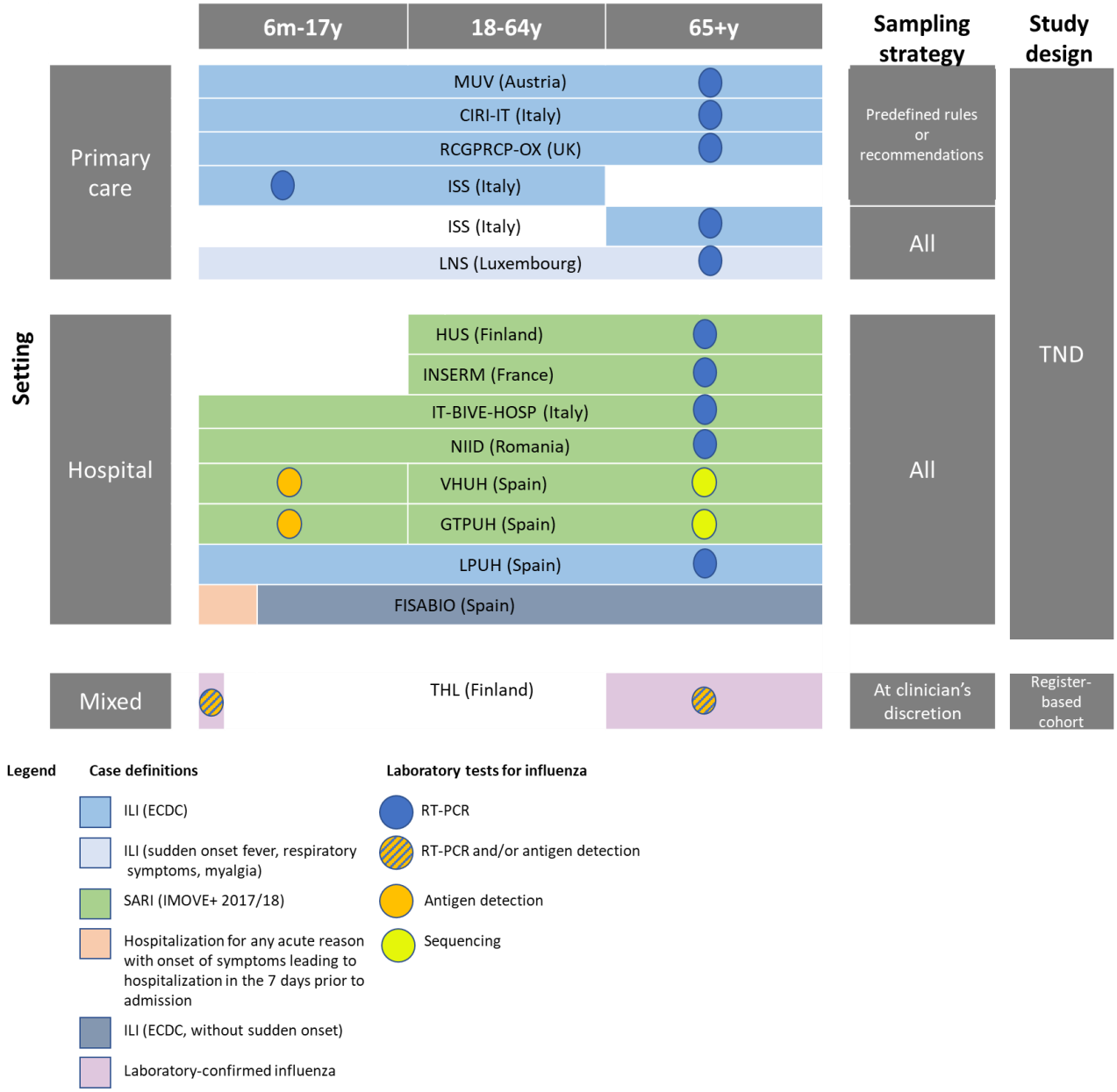


Figure 1. Overview of study characteristics, TND case control and register-based cohort, 2019/20.

Table 2. Overview of test-negative design study sites characteristics, primary care – 2019/20

Site **Country**	**MUV** **Austria**	**CIRI-IT** **Italy**	**ISS** **Italy**	**LNS** **Luxembourg**	**RCGPRSC-OX** **UK**
Setting	Primary care	Primary care	Primary care	Primary care	Primary care
Source of cases	96 primary care physicians	38 primary care physicians	Ca. 245 primary care physicians	21 primary care physicians	12 primary care practices
Population	General population ≥6 months	General population ≥6 months	General population ≥6 months	General population ≥6 months	General population ≥6 months
Cases					
Case definition	ILI[(1)]	ILI[(1)]	ILI[(1)]	ILI[(2)]	ILI[(1)]
Influenza cases	ILI + LCI	ILI + LCI	ILI + LCI	ILI + LCI	ILI + LCI
Case identification	During consultation	During consultation	During consultation	During consultation	During consultation
Matched controls	No	No	No	No	No
Sampling strategy[(3)]	All / Predefined rules	All / Recommendations	<65y: Recommendations formulated 65y+: All	At clinician's discretion	Recommendations formulated
Swab					
Type of swab	Nasopharyngeal	Oropharyngeal	Throat swab	Nasal	Nasal
Laboratory testing					
Laboratory test influenza	For all samples: RT-PCR Antigen testing Viral growth in cell culture Antigenic characterization For 20% of samples: Sequencing of H and N, For 30-100 samples (mostly ICU): whole genome sequencing	RT-PCR	RT-PCR	RT-PCR	Rapid molecular point of care testing
A/subtype available	Yes	Yes	Yes	Yes	No
B/lineage available	Yes	Yes	Yes	Yes	No
Laboratory test subtyping	RT-PCR	RT-PCR	RT-PCR	RT-PCR	n/a
Data sources					
Case definition	Primary data collection	Primary data collection	Primary data collection	Primary data collection	Primary data collection
Vaccination status	-GP medical records -Patient/ relatives' interview (if ILI patient is	GP medical records	GP medical records	-GP Medical records -Patient/relative interview	GP medical records

Site Country	MUV Austria	CIRI-IT Italy	ISS Italy	LNS Luxembourg	RCGPRSC-OX UK
	not consulting their regular GP)				
Vaccine brand and date	GP medical records	GP medical records	GP medical records	GP medical records	GP medical record
Baseline clinical data	Primary data collection	-Primary data collection -GP medical records	GP medical records	GP medical records	GP medical records
Recommended* covariates available for adjustment	1+ chronic condition, pregnancy	1+ chronic condition, pregnancy, nr of primary care visits in last 12 months	1+ chronic condition, nr of primary care visits in last 12 months		1+ chronic condition, pregnancy, nr of primary care visits in last 12 months
Individual or aggregated data shared	Individual	Individual	Individual	Individual	Individual

ILI: influenza-like illness; LCI: laboratory-confirmed influenza; HCW: healthcare worker; RT-PCR: Reverse transcription polymerase chain reaction.

*Recommended covariates are at least 1 chronic condition, pregnancy, nr of primary care visits in last 12 months (for primary care studies) and nr of hospitalisations in the last 12 months (for hospital studies). The mandatory covariates are age, sex and calendar time at symptom onset.

(1) ECDC case definition, (2) WHO case definition: Sudden onset of fever, respiratory symptoms and myalgia, (3) Sampling strategies: a) All: all patients with ILI or SARI are sampled; b) Predefined rules: systematic sampling according to predefined rules; c) At clinician's discretion: non-systematic sampling at practitioner's discretion; 4) Sampling recommendations (RCGPRSC-OX: encouraged sampling of ILI and SARI patients, especially those with chronic conditions).

Table 3. Overview of test-negative design study sites characteristics, hospital – 2019/20 (part 1)

Site **Country**	**HUS** **Finland**	**INSERM** **France**	**BIVE** **Italy**	**NIID** **Romania**
Setting	Hospital	Hospital	Hospital	Hospital
Source of cases	1 hospital	5 hospitals	5 hospitals	1 hospital
Population	General population ≥18 years	General population ≥18 years	General population ≥6 months	General population ≥6 months
Cases				
Case definition	SARI[(1)]	SARI[(1)]	SARI[(1)]	SARI[(1)]
Influenza cases	SARI + LCI	SARI + LCI	SARI + LCI	SARI + LCI
Case identification	From hospitalized patients	From hospital databases From hospitalized patients	From hospital databases [(4)]	From hospitalized patients
Matched controls	No	No	No	No
Sampling strategy[(5)]	All	All	All	All
Swab				
Type of swab	Nasal and throat or nasopharyngeal	Nasopharyngeal or bronchoalveolar lavage or tracheal aspiration	Nasal and throat or nasopharyngeal	<14y: nasopharyngeal and nasal ≥14y: nasopharyngeal and pharyngeal
Laboratory testing				
Laboratory test influenza	RT-PCR	RT-PCR	RT-PCR	RT-PCR
A/subtype available	Yes	Yes	Yes	Yes
B/lineage available	Yes	Yes	Yes	Yes
Laboratory test subtyping	Real-time RT-PCR	RT-PCR	RT-PCR or multiplex RT-PCR	RT-PCR
Data sources				
Case definition	-Primary data collection -HUS medical records	-Primary data collection -Secondary data collection	Primary data collection Secondary data collection	-Primary data collection -Hospital medical records
Vaccination status	-Patient interview -Vaccine register (incomplete for private sector)	-Patient or relatives' interview -GP or pharmacists' interview -Vaccine card	Patient interview	
Vaccine brand and date	-National Vaccination register -Electronic Vaccine card -Hospital medical records -National Kanta archive of patient records from public/private healthcare providers (for all patients that are vaccinated)	-GP or pharmacists' interview (medical records) for those that reported being vaccinated -Vaccine card	-GP interview (medical records) for those that reported being vaccinated	-Vaccine card -Primary care physician interview -Hospital records -Patient /relatives interview

Site Country	HUS Finland	INSERM France	BIVE Italy	NIID Romania
	-HUS medical records -Provider of occupational work health care			
Baseline clinical data	Primary data collection, secondary data collection	Primary data collection Secondary data collection	Primary data collection Secondary data collection	-Medical records -Patient /relatives interview -Interview with attending physician
Recommended* covariates available for adjustment	1+ chronic condition, pregnancy, nr of hospitalisations in last 12 months	1+ chronic condition, pregnancy, nr of hospitalisations in last 12 months	1+ chronic condition, pregnancy, nr of hospitalisations in last 12 months	1 + chronic condition, pregnancy, nr of hospitalisations in last 12 months
Individual-level or aggregate data shared	Individual	Individual	Individual	Individual

H: hemagglutinin; ICU: intensive care unit; ILI: influenza-like illness; LCI: laboratory-confirmed influenza; HCW: healthcare worker; RT-PCR: Reverse transcription polymerase chain reaction. SARI: severe acute respiratory infection.

*Recommended covariates are at least 1 chronic condition, pregnancy, nr of primary care visits in last 12 months (for primary care studies) and nr of hospitalisations in the last 12 months (for hospital studies). The obligatory covariates are age, sex and calendar time at symptom onset.

(1) IMOVE+ 2017/2018 case definition. (2) With symptom onset in the 7 days prior to admission (3) ECDC case definition, without “sudden onset” (4) At four of the five hospitals in the network, patients are identified using the hospital databases, in one hospital patients are additional identified during consultations. (5) Sampling strategies 1) all: all patients with ILI or SARI are sampled; 2) ‘predefined rules/recommendations’: systematic sampling according to predefined rules or recommendations; 3) ‘undefined’: non-systematic sampling; 4) sampling recommendations

Table 3. Overview of test-negative design study sites characteristics, hospital – 2019/20 (part 2)

Site **Country**	**LPUH** **Spain**	**GTPUH** **Spain**	**VHUH** **Spain**	**FISABIO** **Spain**
Setting	Hospital	Hospital	Hospital	Hospital
Source of cases	1 hospital	1 hospital	1 hospital	4 hospitals
Population	General population ≥14years	General population ≥6 months	General population ≥6 months	General population ≥6 months
Cases				
Case definition	ILI(3)	SARI(1)	SARI(1)	<5y:Hospitalized for any acute reason(2) ≥5y: ILI(3)
Influenza cases	ILI/SARI + LCI	SARI + LCI	SARI + LCI	As above + LCI
Case identification	During consultation at ED	From laboratory (all those tested for influenza) and then hospital databases (to check if they fulfil SARI criteria)	From hospital database	From hospitalized patients
Matched controls	No	Yes 1:1, matched by epidemiological week, age (6m-17y, 18-64y, 65-74y, 75+y) and sex	Yes 1:1, matched by epidemiological week (same or adjacent week), and age (6m-17y, 18-64y, 65-74y, 75+y)	No
Sampling strategy(4)	All	All	All	All
Swab				
Type of swab	Nasopharyngeal	Nasopharyngeal	< 18y: usually nasopharyngeal >18 y: nasopharyngeal and/or pharyngeal and/or bronchoalveolar	<14y: nasopharyngeal and nasal ≥14y: nasopharyngeal and pharyngeal
Laboratory testing				
Laboratory test influenza	RT-PCR	< 18y: Antigen detection > 18y:PCR	< 18y: Antigen detection > 18y: PCR	RT-PCR
A/subtype available	Yes (sent to FISABIO)	Yes	Yes	Yes
B/lineage available	Yes (sent to FISABIO)	Yes (sent to VHUH)	Yes	Yes
Laboratory test subtyping	RT-PCR	sequencing	sequencing	RT-PCR
Data sources				
Case definition	Primary data collection Secondary data collection	Hospital medical records	Hospital medical records	Primary data collection

Site Country	LPUH Spain	GTPUH Spain	VHUH Spain	FISABIO Spain
Vaccination status	Patient interview (incl vaccination through campaign or self-bought)	-Records of Catalan Institute of Health	Records of Catalan Institute of Health	Vaccine register
Vaccine brand and date	-Patient interview (incl vaccination through campaign or self-bought) -Primary care electronic health records -GP interview (medical records) -Pharmacy interview	-Records of Catalan Institute of Health	Records of Catalan Institute of Health	Vaccine register
Baseline clinical data	-Medical records -Patient /relatives interview	-Medical records	-Medical records	-Medical records -Patient interview
Recommended* covariates available for adjustment	1 chronic condition or more pregnancy, nr of hospitalisations in last 12 months	1+ chronic condition, pregnancy, nr of hospitalisations in last 12 months	1+ chronic condition, pregnancy, nr of hospitalisations in last 12 months	1+ chronic condition, pregnancy, nr of hospitalisations in last 12 months
Individual-level or aggregate data shared	Individual	Individual	Individual	Individual

H: hemagglutinin; ICU: intensive care unit; ILI: influenza-like illness; LCI: laboratory-confirmed influenza; HCW: healthcare worker; RT-PCR: Reverse transcription polymerase chain reaction. SARI: severe acute respiratory infection

*Recommended covariates are at least 1 chronic condition, pregnancy, nr of primary care visits in last 12 months (for primary care studies) and nr of hospitalisations in the last 12 months (for hospital studies). The obligatory covariates are age, sex and calendar time at symptom onset.

(1) IMOVE+ 2017/2018 case definition. (2) With symptom onset in the 7 days prior to admission (3) ECDC case definition, without “sudden onset” (4) At four of the five hospitals in the network, patients are identified during consultation, in one hospital patients are additional identified using ICD codes. (5) Sampling strategies 1) all: all patients with ILI or SARI are sampled; 2) ‘predefined rules/recommendations’: systematic sampling according to predefined rules or recommendations; 3) ‘undefined’: non-systematic sampling; 4) sampling recommendations

Table 4. Overview of register-based cohort study, 2019/20

Site	THL
Country	Finland
Setting	Primary care and hospital
Source of cases	All healthcare facilities in Finland
Population	General population 6-months-6 years and ≥65 years
Population size	~1593300 (31.12.2018)
Start data collection	Ongoing
Case	LCI positive
Sampling strategy(1)	undefined
Type of swab	Nasopharyngeal swabs or nasal and/or throat swabs or nasopharyngeal aspirates (sometimes other clinical samples) analysed by real time RT-PCR, multiplex RT-PCR, culture and/or antigen detection
Who takes swab	HCW
Laboratory test influenza diagnosis	RT-PCR, Antigen detection
A/subtype available	No
B/lineage available	No
Laboratory test subtyping	n/a
Source of vaccination status	National Vaccination Register
Recommended* covariates available for adjustment	Calendar week, 1 chronic condition or more, number of hospitalizations in 2018, number of primary care consultations in the last 12 months

LCI: laboratory-confirmed influenza; n/a: not applicable; RT-PCR: Reverse transcription polymerase chain reaction, HCW: healthcare worker

*Recommended covariates are at least 1 chronic condition, pregnancy, nr of primary care visits in last 12 months (for primary care studies) and nr of hospitalisations in the last 12 months (for hospital studies). The obligatory covariates are age, sex and calendar time at symptom onset.

(1) Sampling strategies 1) all: all patients with ILI or SARI are sampled; 2) 'predefined rules/recommendations': systematic sampling according to predefined rules or recommendations; 3) 'undefined': non-systematic sampling; 4) sampling recommendations

6 Study population

In all TND studies and the register-based study, the population under study is the general population.

Table 5. Catchment population for studies in the general population, 2019/20

	Catchment population
TND primary care	
Austria MUV	Ca. 1-1.2% of population Austria
Italy CIRI-IT	Ca. 2% of population Liguria and Veneto
Italy ISS	Ca. 0.5% of population Italy
Luxembourg LNS	Ca. 3% of population Luxembourg
UK RCGPRSC-OX	Ca. 0.1% of population England
TND hospital	
Italy BIVE	Tertiary care hospitals serving Siena province (population 250,000), Liguria region (845,000), Lazio region (700,000 0-12y old*), Rome (3,000,000) and Bari province (1,100,000)
Finland HUS	Tertiary care hospital serving cities of Espoo, Kauniainen and Kirkkonummi (population 332,500)

France INSERM	Tertiary care hospitals located in Paris (2 hospitals, population served: 1 620 000), Lyon (1 hospital, population 520 000), Rennes (1 hospital, population 220 000) and Montpellier (1 hospital, population 300 000)
Romania NIID	Hospital serves Bucharest, Ilfov, Dambovita, Giurgiu, Prahova, Arges, Teleorman, Ialomita, Dolj, Valcea, Olt (population 5,937,382)
Spain FISABIO	Hospitals serving part of Valencia region (1,119,000, 22% of Valencia region)
Spain GTPUH	Tertiary care hospital serving a population of more than 250,000 inhabitants of Badalona, Sant Adrià de Besòs, and various municipalities of Maresme. In addition, it is a referral hospital for more than 800,000 citizens of Barcelona province.
Spain LPUH	Tertiary care hospital local in Madrid (serving a population of 600,000)
Spain VHUH	Tertiary care hospital located in the north of the city of Barcelona (serving a population >400,000)
Register-based cohort	
Finland THL	90% of all children 6m-6y and 96% of all elderly 65-100y in Finland

*Real access to this hospital probably largely underestimated as this is the only paediatric hospital in central-southern Italy.

7 Study period

For the TND studies, the study period for the 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, based on the data as provided to DRIVE) in the country/region. The study period will finish after the influenza season (defined as the end of the week prior to the first of two consecutive weeks when no influenza viruses are detected at the study site level, based on the data as provided to DRIVE) or April 30th 2020, whichever occurred first. The study period of analysis might be different for different study sites.

In the particular case of THL (Finland), data is continuously collected throughout the year since they use the national registers. The study period for analysis goes from week 40 till April 30th 2020.

Amendment due to COVID-19 pandemic

Due to the ongoing COVID-19 pandemic from March onwards the data collection efforts and procedures were adjusted in some sites and five sites had to stop data collection before April 30th. Therefore, the end of the study period has been changed to the 29th of February. The effect of using the available data recorded during the original study period will be explored in a sensitivity analysis, see Sections 16.1.4, 16.2.4, and 16.3.5.

8 Case definitions

8.1 Influenza-like illness (ILI)

A case of influenza like illness (ILI) will be defined by the ECDC case definition [3] as an individual who presents with a:

- sudden onset of symptoms;

AND, 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;
- shortness of breath.

8.2 Severe acute respiratory infection (SARI)

A case of severe acute respiratory infection (SARI) will be defined by the IMOVE+ 2017/2018 case definition as a hospitalised person, 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. Only patients with a suspicion of infection are screened for SARI.

8.3 Adherence to the case definitions

All study sites follow the ILI or SARI clinical case definitions with the exception of Luxembourg LNS and Spain FISABIO.

LNS Luxembourg (TND primary care) uses the WHO case definition instead of the ECDC case definition.

FISABIO Spain (TND hospital-based):
For children <5 years, a clinical case is defined as a person with a hospitalization for any acute reason whose symptom onset (of any symptom possibly related to influenza: acute upper and lower respiratory disease; dyspnea breath anomaly shortness of breath, tachypnea; asthma; pneumonia and influenza; heart failure; myalgia; altered consciousness, convulsions, febrile convulsions; fever or fever unknown origin or non-specified; cough; apnea; gastrointestinal manifestations; sepsis, systemic inflammatory response syndrome) was in the 7 days prior to admission.
For subjects 5 years and above, a modified ECDC ILI case definition is used, being hospitalized with at least one systematic symptom (fever or feverishness, malaise, headache or myalgia) and at least one respiratory symptom (cough, sore throat or shortness of breath) whose onset was in the 7 days prior to admission.

Spain LPUH (TND hospital-based) uses the ECDC ILI case definition.

9 In- and exclusion criteria

9.1 Test-negative design studies

9.1.1 Recommended 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. is institutionalised at the time of symptoms onset;
5. will 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/hospitalisation.
7. is potentially vaccinated (positive vaccination status is based on recall alone and cannot be confirmed by registers or is otherwise ambiguous).

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. is institutionalised at the time of symptoms onset;
5. will have the respiratory specimen taken ≥ 8 days after SARI onset;
6. tested positive for any influenza virus in the current season before the onset of symptoms leading to the current primary care visit/hospitalisation;
7. was previously hospitalised < 48 hours prior to SARI onset;
8. had his/her ILI/SARI onset ≥ 48 hours after hospital admission.
9. is potentially vaccinated (positive vaccination status is based on recall alone and cannot be confirmed by registers or is otherwise ambiguous).

Note: a patient can be enrolled several times as long as he/she does not have a previous laboratory confirmed influenza in the current season.

9.1.2 Adherence to the recommended ILI/SARI exclusion criteria

All variables related to the exclusion criteria are listed as obligatory variables in the Minimal Data Requirements (ANNEX 1). An overview of the adherence to the ILI and SARI exclusion criteria given in Table 5. Records that violate the exclusion criteria will be discarded either at data transfer stage or at central analysis stage, whenever possible.

Table 5. Test-negative design studies: overview of exclusion criteria applied at study recruitment, 2019/20

Site	MUV	CIRI-IT	ISS	LNS	RCGPR SC-OX	HUS	BIVE	INSERM	NIID	FISABIO	VHUH	LPUH	GTPUH
Country	Austria	Italy	Italy	Luxembourg	UK	Finland	Italy	France	Romania	Spain	Spain	Spain	Spain
Setting	PC	PC	PC	PC	PC	HO	HO	HO	HO	HO	HO	HO	HO
Clinical case definition	ILI	ILI	ILI	ILI	ILI	SARI	SARI	SARI	SARI	ILI	SARI	ILI	SARI
1. Unwilling or unable to give consent	Yes (R)	Yes (R)	Yes (R)	N.a.[1]	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	N.a[1]	Yes (R)	N.a[1]
1. Age <6 months at symptom onset	Yes (R)	Yes (R)	Yes (R)	Yes (A)	Yes (R)	n/a	Yes (R)	n/a	Yes (R)	Yes (A)	Yes (R)	Yes (R)	Yes (R)
2. Contraindication	No	Yes (R)	Yes (R)	No	Yes (A)	Yes (T)	Yes (R)	Yes (R)	Yes (R)	Yes (A)	Yes (R)	Yes (R)	Yes (R)
3. Institutionalized	Yes (R)	Yes (R)	Yes (R)	No	Yes (A)	Yes (R)	Yes (R)	Yes (R)[7]	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)
4. Respiratory specimen taken ≥ 8 days after ILI onset	Yes (R)	Yes (R)	Yes (R)	Yes (A)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)
5. Prior influenza infection in current season	Yes (R)	Yes (R)	Yes (R)	No	Yes (A)	Yes (T)	Yes (R)	Yes (R)	Yes (R)	Yes (A)	Yes (R)	Yes (R)	Yes (R)
6. Previously hospitalised < 48 hours prior to ILI onset	n/a	n/a	n/a	n/a	n/a	Yes (R)	Yes (R)	Yes (T)	Yes (R)	Yes (R)[2]	Yes (R)	Yes (R)	YES (R)
7. ILI onset ≥ 48 hours after hospital admission	n/a	n/a	n/a	n/a	n/a	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)
Other local exclusion criteria	No	No	No	No	No	Yes (R)[3]	Yes (R)[4]	No	No	Yes (R)[5]	Yes (R)[6]	No	Yes (R)[6]
8. Potentially vaccinated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

ILI: influenza like illness; HO: hospital; n/a: not applicable, PC: primary care; SARI: severe acute respiratory infection

(R) Exclusion criterion applied at the time of recruitment (T) Exclusion criterion applied at time of data transfer. (A) Exclusion criterion applied at the time of analysis

(1) No informed consent was required as no intervention required for the study fall outside the usual practice of the Hospital Universitari Vall d'Hebron during the influenza season. (2) Patients hospitalized < 30 days from the current hospitalisation are excluded. (3) Not a resident of Espoo, Kauniainen or Kirkkonummi. (4) Remain in hospital for less than 24 hours.(5) Not residing in hospitals catchment area for at least previous 6 months; Remains in hospital for less than 24 hours. (6) A patient not belonging to the Institut Català de la Salut network. (7) Institutionalized patient without regular community interaction.

9.2 Cohort studies

9.2.1 THL Finland: register-based cohort study

In the Finnish register-based cohort study, all subjects belonging to the study population and contributing data to the study period (starting 2019, week 40) are included, with the following exclusion criterion applied: subjects with presumably incomplete vaccination records in 2019/20 or 2018/19.

10 Outcome

10.1 Outcome definition

The outcome of interest is laboratory-confirmed influenza, using the following definitions:

Estimating seasonal overall, brand-specific and type-specific IVE against **any** medically attended laboratory-confirmed **influenza** (stratified by healthcare setting and age group):

- Positive: any laboratory-confirmed influenza.
- Negative: no laboratory-confirmed influenza.

Estimating seasonal overall, brand-specific and type-specific IVE against any medically attended laboratory-confirmed **influenza type, subtype or lineage** (stratified by healthcare setting and age group):

- Positive: laboratory-confirmed influenza of the specific type, subtype or lineage of interest.
- Negative: no laboratory-confirmed influenza.

10.2 Case identification

For the TND studies, ILI and SARI cases are identified among all patients presenting to primary care or hospital.

At THL (Finland, register-based cohort study), only positive results of the influenza tests are available.

10.3 Swab sampling strategy

Different sampling strategies were used for collecting respiratory samples from patients meeting the ILI/SARI clinical case definitions:

- ‘all’: all patients with ILI or SARI are sampled;

- ‘predefined rules/ sampling recommendations’’: systematic sampling according to predefined rules or recommendations for preferential sampling certain patients;
- ‘undefined’: non-systematic sampling at practitioner’s discretion.

All patients that met the case definition at TND hospital sites were swabbed. For the TND primary care studies, the sampling strategies are different for the different sites and might also differ between subpopulations from the same study site. Details on the sampling strategies are given in Table 6.

Swabs are performed by healthcare workers (HCW) in all studies. The types of swabs are either nasal, nasopharyngeal, oropharyngeal, pharyngeal or throat swabs (Table 2-Table 3). Samples taken >=8 days after ILI onset will be excluded from all TND analyses.

Table 6. Test-negative design studies: overview of swab sampling strategies used, 2019/20.

Sampling strategy*	**Sites**
All	Italy BIVE, Finland HUS, France INSERM, Romania NIID, Spain FISABIO, Spain VHUH, Spain LPUH, Spain GTPUH
Predefined rules/ recommendations	Italy CIRI-IT: Sampling all ILI patients is encouraged, however if not feasible, encouraged to sample the first 3 ILI that present each week UK RCGPRSC-OX: All cases of ILI (ARI in those <5y) are encouraged to be swabbed in this study, especially those with chronic conditions Austria MUV: All (up to 30 swabs/weeks), if more than 30 ILI patients per week then systematic sampling (depending on the number of ILI patients, every 2nd, 3rd, 4th, etc) Italy ISS: Systematic sampling of the first 2 ILI patients that present each week, and if possible all ≥65years ILI cases
Undefined rules	Luxembourg LNS (when the GP thinks the patient has an influenza infection)

10.1 Laboratory testing

The influenza laboratory confirmation was done using antigen detection, culture, PCR, rapid diagnostic tests, or real-time RT-PCR, and subtyping/lineage testing was done using PCR, real-time-PCR or sequencing. Except THL (Finland, register-based cohort) and RCGPRSC-OX (UK), all sites are collecting information on influenza subtypes (A/H1N1, A/H3N2) and /lineages (B/Victoria, and B/Yamagata). An overview of the type of swabs and laboratory tests is given in (Table 2-Table 4).

11 Exposure

11.1 Exposure definition

The exposure of interest is influenza vaccination administered before and during the influenza season 2019-20. For all objectives, the following exposure definitions will be used.

Scenario A:

An individual aged >9 years, or a child aged <9 who has been fully vaccinated (at least two injectable doses or one LAIV dose) during the previous influenza season will be considered as:

- **vaccinated** with the influenza vaccine of interest if he/she has a record of influenza vaccine administration >14 days before ILI/SARI symptom onset;
- **partially vaccinated** if he/she has a record of influenza vaccine administration ≤14 days before ILI/SARI symptom onset;
- **unvaccinated** if he/she has no influenza vaccine record for the current season;

Scenario B:

A child aged < 9 years who has not been fully vaccinated (see above) during the previous influenza season will be considered as:

- **vaccinated** with the influenza vaccine of interest if >14 days have elapsed since the second record of injectable vaccination or since the first record of LAIV vaccination during the current season:
- **partially vaccinated:**
    - after the first record of injectable vaccination until the second record of vaccination during the current season;
    - during the first 14 days after the second record of injectable vaccination or the first record of LAIV vaccination during the current season;
- **unvaccinated** until the first vaccination record during the season;

Note 1: The *partially* and *potentially* vaccinated groups will be excluded from primary analysis. The significance of the partially vaccinated subjects will be assessed in sensitivity analyses.

Note 2: If no information on exposure in the previous season is available in the dataset, the exposure definition 'scenario A' will be used for all subjects.

Note 3: For cohort studies, vaccination status will be treated as time-varying variable whereas for the case-control studies, vaccination status is a fixed variable.

11.2 Source of exposure information

The sources to obtain information on the exposure status were either vaccine registers, medical records or, vaccination cards. (see Table 2-Table 4). Patients for whom the vaccination status is based on recall only, not verified based on vaccination register, medical record or vaccination card are considered 'potentially vaccinated' (see Section 11.1),and will be discarded from analysis (see sections 16.1.1 and 16.2.1).

For all the TND studies in primary care, vaccination status, vaccine brand and vaccination date are retrieved from the GP records.

- In Austria MUV, if the patient is not consulting his/her own GP, the information will be obtained by patient interview. In UK RCGPRSC-OX, the GP is informed if vaccination takes place elsewhere (e.g. pharmacy, school).
- In the UK most flu vaccines are given in primary care, with brand and batch number recorded in the computerised medical records. Notification of LAIV given at school, by employers and community pharmacy may be less reliable and the notification often does not contain brand or batch information [4].

The way vaccination status, vaccine brand and vaccination date are ascertained in the TND hospital studies varies.

- In Spain FISABIO, vaccination status, vaccine brand and vaccination date are retrieved from the vaccine registry. Completing the vaccination registry is part of routine care in Valencia. The information is retrieved by FISABIO using unique identifiers.
- In Spain VHUH and Spain GTPUH, the information is retrieved from the electronic records of the Catalan Institute of Health (whose primary care centres serve 75,2% of the population of Catalonia).
- In Finland HUS, vaccination status is retrieved through patient interview. If the patient reports being vaccinated, vaccine brand and vaccination date are retrieved from electronic medical records, electronic vaccination card, and/or the National Vaccination Register (NVR). If the patient reports not having been vaccinated, the NVR is checked to confirm lack of vaccination and only possible discrepancies with the NVR will be verified from electronic medical records and/or vaccination card.
- In Italy BIVE, vaccination status is retrieved through patient interview. Subsequently, for patients that reported having received influenza vaccination, the patient's GP is contacted to retrieve the vaccine brand and the vaccination date from their records.
- In France (INSERM), vaccination status is retrieved through patient or relatives' interview, GP or pharmacists' interview (medical record) or vaccine card. For the vaccine brand and vaccination date, patient's GP or pharmacist are contacted to retrieve information from their records.
- In Spain LPUH, vaccination status is retrieved through patient interview. The vaccine brand is assessed by asking the patient if they were vaccinated through the campaign or bought the vaccine themselves. If they were vaccinated through the campaign, it is assumed the brand recommended for the age group was used (i.e. Chiroflu for those <65yr and Chiromas for those 65+yr). If the patient doesn't remember

the vaccination date, the date will be ascertained by contacting the GP or from the hospital's medical records. If the vaccine is self-bought, the health centre or pharmacy will be contacted for confirmation of the vaccine brand and vaccination date.

- In Romania NIID, the information is retrieved from one of multiple sources: the vaccination card, by contacting the patient's GP (in case they are part of a risk group), from hospital records (for patients with chronic conditions only, as they are sometimes vaccinated in the hospital). If the above are not available, the information will be retrieved through patient interview.
- In Finland THL, all information is retrieved from the National Vaccination Register.

11.3 Expected influenza vaccine brands

The vaccine types and vaccine brands that are expected to be used in the study areas are summarized in Table 7.

Table 7. Expected vaccine brands and type – all studies, 2019/20.

	Approved age indication	MUV Austria	HUS Finland	THL Finland	INSERM France	BIVE Italy	CIRI-IT Italy	ISS Italy	LNS Luxembourg	NIID Romania	FISABIO Spain	VHUH Spain	LPUH Spain	GTPUH Spain	RCGP RSC-OX UK
TIV brands															
Sandovac/ Chiroflu / Agrippal	≥ 6m	x					x					x	x	x	
Influvac/ FluVaccinol/Batrevac/Vacciflu /Serinflu	≥ 6m	x			x										
aTIV brands															
Fluad/ Chiromas	≥ 65y	x				x	x	x			x	x	x	x	x
QIVe brands															
Fluarix Tetra/ Alpharix Tetra	≥ 6m	x				x	x	x	x						
Vaxigrip Tetra	≥ 6m	x	x	x	x	x	x	x	x	x	x	x		x	x
Influvac Tetra/ Influvac S Tetra/FluVaccinol Tetra/Xanaflu Tetra/Batrevac Tetra/Influenza vaccine Tetra MYL	≥ 3y	x			x	x	x	x		x					x
High dose QIV (Phase III Sanofi)	≥ 65y (not yet approved in EU)			x											
QIVc brands															
Flucelvax Tetra	≥ 9y	x				x	x	x	x		x	x		x	x
LAIV brands															
Fluenz Tetra	≥ 2y			x				x		x					x

aTIV: Trivalent adjuvanted; LAIV: Quadrivalent live attenuated; TIV: Trivalent non-adjuvanted; QIVc: cell-based quadrivalent inactivated; QIVe: egg-based quadrivalent inactivated.

12 Matching of cases and controls

For Spain VHUH and Spain GTPUH, the data collection followed a matched 1:1 case-control design, where information on exposure and covariates was obtained only for controls that could be matched to a case by epidemiological week (same or adjacent week) and age group (6m–17y, 18-64y, and 65-74 and 75+y). Additionally, Spain GTPUH matched for sex. All other studies used an unmatched design.

13 Covariates

An overview of the covariates available from the different study sites is given in Table 10. The covariates age, sex and calendar time are obligatory. The covariates presence of at least one chronic condition, pregnancy and number of GP consultations or hospitalizations are optional.

Table 8. Data collected on obligatory and recommended covariates – all studies, 2019/20.

Site	MUV	CIRI-IT	ISS	LNS	RCGPRSC-OX	HUS	BIVE	NIID	FISABIO	VHUH	INSERM	LPUH	GPTUH	THL
Country	Austria	Italy	Italy	Luxembourg	UK	Finland	Italy	Romania	Spain	Spain	France	Spain	Spain	Finland
Setting	PC	PC	PC	PC	PC	HO	HO	HO	HO	HO	HO	HO	HO	PC+HO
Mandatory														
Age at symptom onset [(1)]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes[(2)]
Sex	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Date of symptom onset	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Recommended														
Presence of at least one chronic condition	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pregnancy	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	n/a
Number of hospitalizations in the last 12 months	No	Yes [(3)]	Yes [(3)]	No	Yes	Yes	Yes [(3)]	Yes	Yes	Yes	Yes	Yes	Yes	Yes [(4)]
Number of primary care consultations in the last 12 months	No	Yes	Yes	No	Yes	nm	nm	nm	nm (Yes)	nm	nm (Yes)	nm	nm (Yes)	Yes[(5)]

HO: hospital; Nm: not recommended for the setting; PC: primary care

(1) Age in months for children < 1 year, otherwise age in years
(2) Age at season onset or cohort inclusion instead of at symptom onset
(3) Number of hospitalizations for any of the chronic conditions of interest in the last 12 months
(4) Number of hospitalizations in 2018
(5) Likely to be an underestimate as private care visits are not counted; follow-up visits are not distinguished from new visits

13.1 Age

Age in years (months for children <1year) at symptom onset. For the Finland THL cohort study, the age is defined at the start of the influenza season (e.g. at day 1 of week 40).

13.2 Sex

Male or female.

13.3 Date at symptom onset/calendar time

To adjust for time, date at ILI/SARI symptom onset will be used for TND studies whereas calendar time (in weeks) will be used for cohort studies.

13.4 Chronic conditions

Chronic conditions will be defined as the presence of at least one chronic condition as not all study sites provide information on chronic conditions separately. The chronic conditions include obesity (BMI ≥30) but exclude smoking and pregnancy. The definitions of the chronic conditions are given in Table 9.

Table 9. Definitions of chronic conditions.

Condition	Definition
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
Diabetes	Any of the following dg codes (ICD-10)*: E10-E14, O24 INCLUDING: Any form of diabetes, including sequelae & DM in pregnancy
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.
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 follow-up, 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 ≥5 years.
Immuno-deficiency 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: ≥2week 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).

Table 12. Definitions of chronic conditions, continued

Condition	Definition
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, J95-99 INCLUDING: 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.
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)
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, Z90.5 EXCLUDING: Clinically nonsignificant kidney cysts
Dementia	Any of the following dg codes (ICD-10)*: F00-03, F05.1, G30-31 EXCLUDING delirium w/o underlying dementia, hydrocephalus.
History of stroke	Any of the following dg codes (ICD-10)*: I61-64, I67.8, I69, G93.1 INCLUDING: 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).
Rheumato-logic diseases	Any of the following dg codes (ICD-10)*: M05–09, M13, M30–36, M45 INCLUDING rheumatoid diseases with presumed autoimmune origin and primarily musculoskeletal presentation. EXCLUDING: arthrosis, gout, scoliosis, infectious conditions etc.
Obesity	BMI ≥30 or the dg codes (ICD-10)*: E66, E68 EXCLUDING: local adiposity and "other hyperalimentation" (=vitamin overdoses etc.)

BMI: body mass index; ICD: International classification of diseases.

*or corresponding codes in other diagnostic coding systems.

Deviations from DRIVE Data Requirements

For UK RCGPRSC-OX, a set of codes that matched with the UK's Chief Medical Officers' definition is used [5], which are similar to but not exactly the same as those in the DRIVE codebook.

13.5 Pregnancy

Pregnancy (any trimester) at symptom onset: yes versus no. This covariate will be considered for adjustment only in the 18-64y age group.

13.6 Number of hospitalizations

The number of hospitalizations in the previous 12 months will be categorized as “0”, “1 to 2” and “more than 2”. The number of hospitalization is used as a proxy for the severity of chronic conditions.

Deviations from DRIVE Data Requirements

For Italy BIVE and Italy CIRI-IT this is restricted to hospitalizations for any of the chronic conditions of interest in the last 12 months.

For Finland THL, the number of hospitalizations refers to the number of hospitalizations in 2018.

13.7 Number of primary care consultations

The number of primary care consultations in the previous 12 months (not counting follow-up visits for the same cause) will be categorized as “0”, “1 to 5” and “more than 5”.

Deviations from DRIVE Data Requirements

For Spain FISABIO and France INSERM, only the number of primary care visits in the previous 3 months is available. For these two sites, this variable will be categorized as “0”, “1 to 2” and “more than 2”. This variable is used as a proxy for health care utilization.

For Finland THL, follow-up visits cannot be distinguished from new visits.

14 Data management

14.1 Data pre-processing at site level

The database custodians at the local sites are responsible to transform their data in the requested format and to subset to the requested population. Details will be available in the local study reports.

14.2 Data transfer

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), a password protected web application. The data flow to the DRIVE Research server is described in Figure 2. The study data will be to the ESSA environment first. 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.

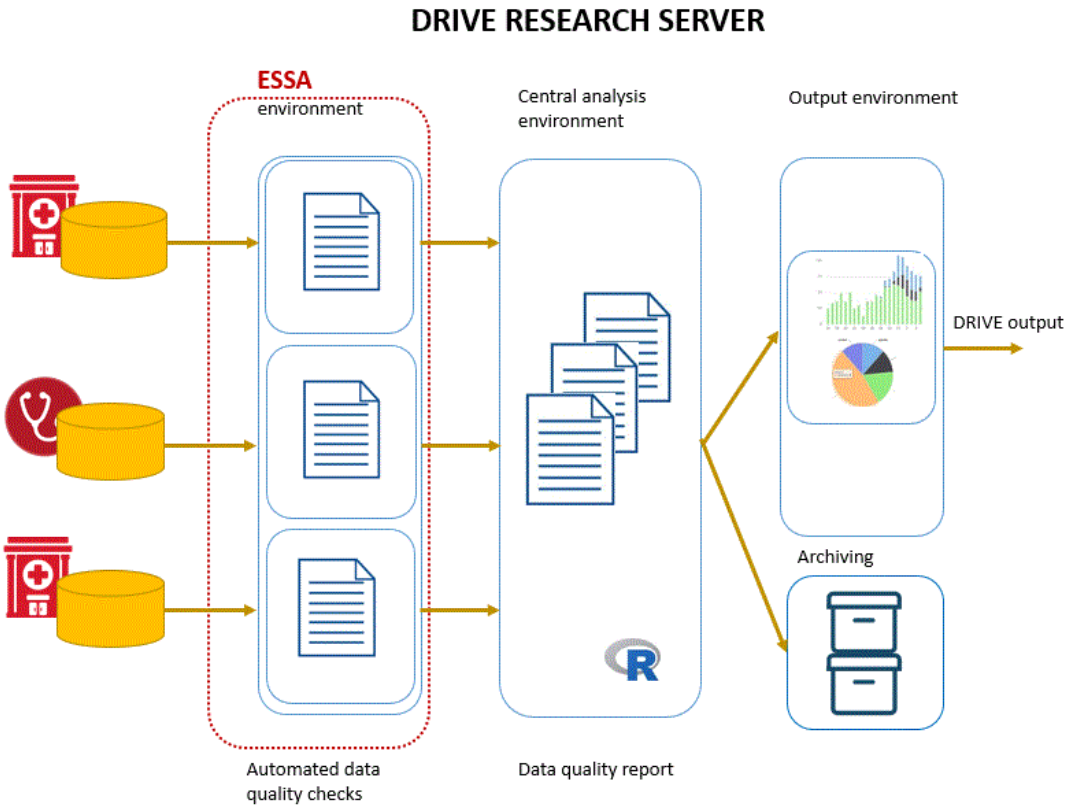


Figure 2. DRIVE Electronic Study Support Application: data flow.

14.3 Central data storage

All data will be stored at the DRIVE Research server, which is a highly secured IT environment and network with strict rules for data access provided by P95. The general architecture of the DRIVE research server has three environments: the data import or ESSA Environment, the Central Analysis Environment and the Output Environment. The DRIVE research server is only accessible through the secure file transfer protocol (with upload capability to the ESSA Environment and download capability out of the Output Environment) and the remote desktop protocol allowing data analysts/statisticians to log into the Central Analysis Environment. The transfer of any data between the different environments is done solely by the server administrator (or his back-up when needed) where data privacy assessments are carried out if deemed necessary. Every interaction on the DRIVE research server is logged, and these logs are accessible upon request.

14.4 Data quality

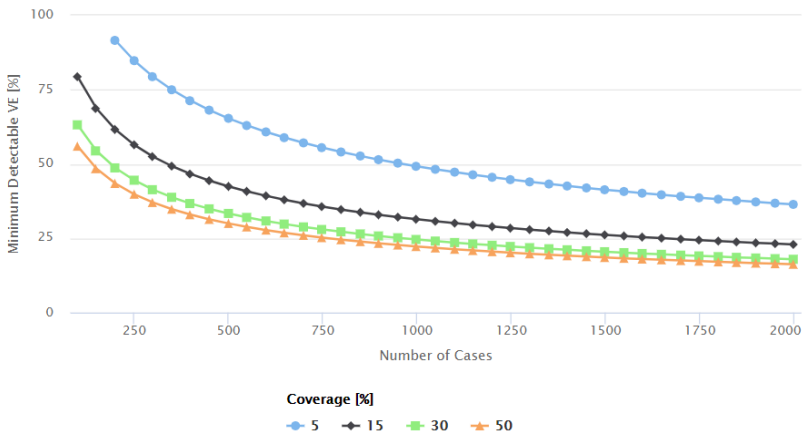
All data uploaded to the Central Analysis Environment will be checked for quality by the P95 team. The same types of quality checks will be performed as the ones automatically generated upon uploading TND data to the ESSA environment. When data quality issues will be found, the data site responsible person will be contacted, and the data will either be corrected or discarded from further analysis. After performing the data quality checks and implementing the corrective measures, the study in/exclusion criteria will be applied and records with missing data in the outcome, exposure and the obligatory covariate information will be discarded.

For every site separately, a data quality report will be produced. These reports will contain a description of the results of the quality checks performed, the amount of data that was retained for analysis after applying the in- and exclusion criteria and graphical summaries of the retained data. The data quality report will be send to the study site for approval.

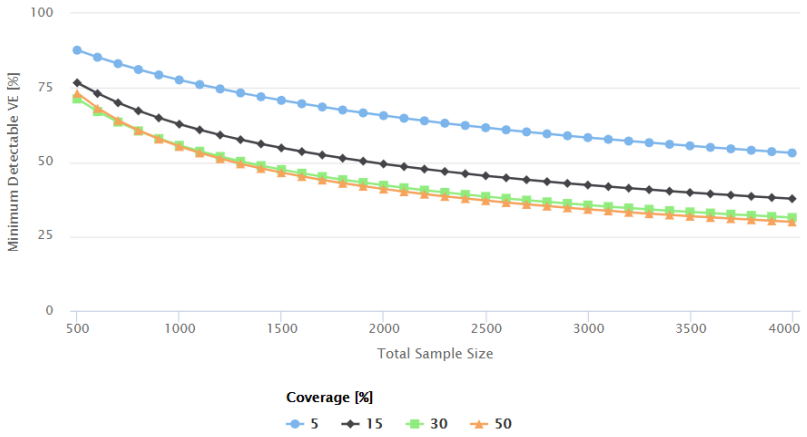
15 Sample size considerations

The minimal detectable overall VE, or the smallest VE that can be detected as significantly greater than zero, for a range of samples sizes for TND and cohort designs is given in Figure 2 and Tables Table 10-Table 11. The calculations are performed assuming 80% power, two-sided 95% confidence levels and overall vaccination coverages of 5%, 15%, 30% and 50%. For TND, it is additionally assumed to have a 1:1 control per case allocation ratio. For the cohort studies, it is additionally assumed to have attack rates among the unvaccinated of 7% (reflective of the attack rate in adults) and 25% (reflective of the attack rate in children).

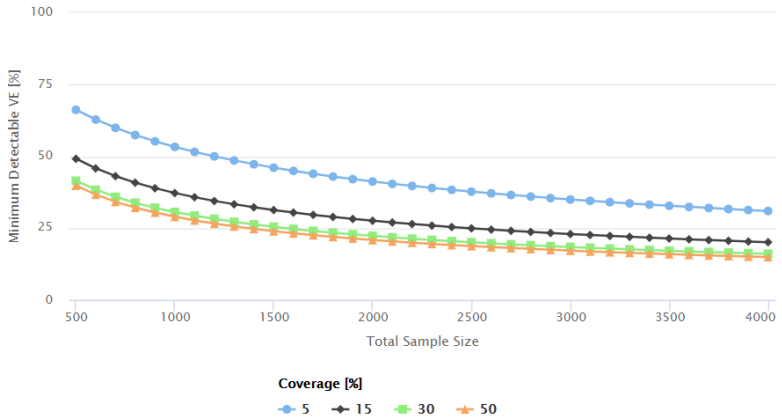
We generally recommend a minimum of 100 influenza positive cases for TND studies and a minimum of 1000 subjects for cohort studies. As the optimal sample size strongly depends on the local vaccination coverage and brand distribution, site-specific sample size recommendations will be formulated as part of the network expansion and site selection. Sample sizes smaller than recommended are allowed as capacity building is an ongoing activity within the DRIVE project. A user-friendly web-application to perform sample size calculations for IVE studies has been developed and is available from http://apps.p-95.com/drivesamplesize/.



Test-negative design



Cohort design (attack rate = 7%)



Cohort design (attack rate = 25%)

Figure 2. Minimal detectable overall Vaccine effectiveness (VE) for test-negative and cohort design studies, assuming 80% power, two-sided 95% confidence intervals and overall vaccination coverage of 5%, 15%, 30% and 50%. For the test-negative design, a 1:1 control per case allocation ratio is assumed. For the cohort design, attack rates of 7% and 25% are assumed.

Table 10. Minimum detectable overall Vaccine effectiveness (VE) for the test-negative design studies, assuming 80% power, two-sided 95% confidence intervals, a 1:1 control per case allocation ratio and overall vaccination coverage of 5%, 15%, 30% and 50%.

	Minimum detectable VE			
Number of cases	**5% Coverage**	**15% Coverage**	**30% Coverage**	**50% Coverage**
100	NA	79.35	63.16	55.98
200	91.57	61.58	48.67	43.44
500	65.35	42.45	33.35	30
750	55.49	35.64	27.95	25.22
1000	49.21	31.39	24.59	22.23

Table 11. Minimum detectable overall Vaccine effectiveness (VE) for cohort design studies, assuming 80% power, two-sided 95% confidence intervals, 7% and 25% attack rate in the unvaccinated and overall vaccination coverage of 5%, 15%, 30% and 50%.

		Minimum detectable VE			
Sample size	**Attack rate %**	**5% Coverage**	**15% Coverage**	**30% Coverage**	**50% Coverage**
500	7	87.66	76.69	71.29	73.16
1000	7	77.65	62.76	55.64	55.29
2000	7	65.64	49.38	42.2	40.96
3000	7	58.26	42.29	35.54	34.13
4000	7	53.09	37.69	31.35	29.92
500	25	66.2	49.12	41.46	39.8
1000	25	53.28	37.21	30.6	28.95
2000	25	41.21	27.56	22.27	20.85
3000	25	34.96	22.94	18.4	17.16
4000	25	30.96	20.1	16.05	14.93

16 Statistical analysis

16.1 Site-specific analysis: test-negative design studies

16.1.1 Attrition diagram

Records will be discarded from the primary and secondary objectives when:

- Date of ILI/SARI onset is outside the study period (see Section 7).
- Subjects do not adhere to the study in- and exclusion criteria (see Section 9).
- The ILI/SARI episode is not the first episode from recurrent episodes within the study period.
- Subjects have missing information on the symptom onset date, swab date, outcome of interest, exposure of interest, age and sex (see Section 13).
- Subjects that are potentially vaccinated (see Section 11.1).
- Subjects that are partially vaccinated (see Section 11.1).

The number and percentage of partially vaccinated subjects will be calculated. When that percentage is >= 5% the impact of partial vaccination will be assessed in sensitivity analysis.

For every TND study site, an attrition diagram will be created. The attrition diagram describes the amount of records excluded from the statistical analysis at the central analysis level, by reason of exclusion. Note that for some sites the exclusion criteria are applied at recruitment level or at data transfer level (Table 5), which will not be captured in the attrition diagrams generated at the central analysis level. See Mock report for an example of an attrition diagram.

16.1.2 Descriptive analysis

For every TND study site, visualizations based on the final data for analysis will be created including:

- Number of controls and laboratory-confirmed influenza infections (by type and by subtype/lineage) over time.
- Pie chart of the distribution of vaccine brands.
- Distribution of covariates among cases and controls.

Example visualizations are given in Mock Report xx. For every TND study site, a table based on the final data will be created with characteristics of cases and controls as described in the Mock Report xx.

For the combined TND data, visualizations based on the final data for analysis will be created by age group and setting, including:

- Vaccination coverage among study participants and distribution of vaccine brands.
- Number of controls and laboratory-confirmed influenza infections (by type and by subtype/lineage) over time.

For the combined TND data, tables based on the final data will be created with characteristics of cases and control by age group and setting (see Mock Report).

16.1.3 Influenza vaccine effectiveness estimation

For every TND study site, crude and confounder-adjusted IVE (any influenza vaccine, by brand and by vaccine type) against laboratory-confirmed influenza (any, by influenza type and subtype/lineage) will be estimated stratified by age (6m-17yr, 18-64 yr, >=65yr), as:

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

where *OR* denotes the confounder-adjusted odds ratio, comparing the odds of vaccination among influenza-positive study participants to the odds of vaccination among influenza-negative study participants.

Confounder-adjusted IVE estimates will be derived from multivariable logistic regression models. For the primary and secondary objectives, a parsimonious set of confounders will be used. The parsimonious set of confounders will include sex, a smooth function of age and a smooth function of calendar time (~symptom onset date) as, based on a post-hoc analysis of the 2018/19 TND data, it has been shown that this parsimonious confounder-adjustment performs equally well.

The analysis to estimate brand-specific IVE will account for the differences in approved indications (see Table 6), discarding from the analysis subjects for which the vaccine brand of interest is not indicated.

All analyses will be a complete case analysis, dropping records with missing information for the outcome, exposure of interest or the covariates. The smooth functions of age and symptom onset date will be modelled by penalized cubic regression splines and estimated using restricted maximum likelihood for smoothness selection [6].

16.1.4 Sensitivity analysis

The following sensitivity analysis will be conducted for the primary and secondary objectives:

Extended confounder-adjustment:

A sensitivity analysis will be performed, using an extended set of confounders including sex, a smooth function of age, a smooth function of calendar time, pregnancy, presence of at least one chronic condition and number of GP visits/hospitalizations (when available) to allow further exploration of the impact of covariate adjustment on the IVE estimates.

Extended study period

A sensitivity analysis will be performed using the available data collect up to the 30th of April 2020.

When the percentage of partially vaccinated subjects >= 5%:

- partially vaccinated subjects (see Section 11.1) will be considered unvaccinated.
- partially vaccinated subjects (see Section 11.1) will be considered vaccinated.

Time between ILI/SARI onset and swab:

- subjects will be excluded when the respiratory specimen was taken ≥ 4 days after ILI/SARI onset.

16.2 Site-specific analysis: cohort study

16.2.1 Attrition diagram

Only aggregated data will be shared on the DRIVE Central Analysis Environment. No attrition diagram at the central analysis level will be created.

16.2.2 Descriptive analysis

Visualizations based on the final data for analysis will be created, including:

- Number of controls and laboratory-confirmed influenza infections (by type) over time.
- Pie chart of the distribution of vaccine brands.
- Distribution of covariates among vaccinated and unvaccinated subjects for the cohort study.

A table based on the final data will be created with characteristics of the exposed and unexposed subjects. See Mock Report.

16.2.3 Influenza vaccine effectiveness estimation

Semi-crude (adjusted only for calendar time) and confounder-adjusted IVE (any influenza vaccine, by brand and by vaccine type) against any laboratory-confirmed influenza will be estimated stratified by age (6m-17yr, 18-64 yr, >=65yr), as:

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

where *RR* denotes the confounder-adjusted relative risk, comparing the influenza incidence among the vaccinated subjects to the influenza incidence among the unvaccinated subjects.

Confounder-adjusted IVE estimates will be derived from multivariable Poisson regression models. For the primary and secondary objectives, a parsimonious set of confounders will be used similarly as in Lane *et al* [7]. The parsimonious set of confounders will include sex, a smooth function of age and a smooth function of calendar time (~symptom onset date).

The analysis will be a complete case analysis, dropping records with missing information for the outcome, exposure of interest or any of the covariates. The smooth functions of age and calendar time will be modelled by penalized cubic regression splines [8] estimated using restricted maximum likelihood for smoothness selection [6]

16.2.4 Sensitivity analysis

The following sensitivity analysis will be conducted:

Extended confounder-adjustment:
A sensitivity analysis will be performed , using an extended set of confounders including sex, a smooth function of age, a smooth function of calendar time, presence of at least one chronic condition and number of GP visits/hospitalizations to allow further exploration of the impact of covariate adjustment on the IVE estimates.

Extended study period
A sensitivity analysis will be performed using the available data collect up to the 30th of April 2020.

When the percentage of partially vaccinated subjects >= 5%:

- partially vaccinated subjects (see Section 11.1) will be considered unvaccinated;
- partially vaccinated subjects (see Section 11.1) will be considered vaccinated.

16.3 Pooled analysis

16.3.1 Inclusion of influenza vaccine effectiveness estimates

Only estimates provided by the TND studies will be considered for obtaining pooled estimates stratified by age group (6m-17yr, 18-64 yr, >=65yr) and setting (primary care, hospital).

The population-based cohort study (THL, Finland) will not be considered for inclusion in the pooled analysis when primary care based or hospitalized laboratory-confirmed influenza cases cannot be disentangled.

16.3.2 Meta-analysis

Random effects meta-analysis (RE MA) [9] will be used to pool the site-specific confounder-adjusted IVE estimates. This meta-analytical approach is preferred by DRIVE over a 1-stage pooling approach as both approaches have been shown to be equivalent [10-12]. The meta-analytical approach additionally allows to easily combine estimates obtained using different study designs or to combine the DRIVE IVE estimates with estimates obtained by other networks when appropriate.

Pooled estimates will be stratified by age group (6m-17yr, 18-64 yr, >=65yr) and setting (primary care, hospital). Random effects meta-analysis will be performed on the log-transformed odds ratio (OR) estimates. Restricted maximum likelihood (REML) will be used to obtain the pooled (meta-analysed) estimate (and 95% confidence intervals – CIs), as the REML estimator outperforms other RE MA estimators in terms of bias and statistical efficiency [13]. The modified Hartung-Knapp correction will be used to estimate the variance of the mean effect as it has been shown to outperform other methods in terms of the coverage of the 95% CIs in case of large between-study heterogeneity and varying study sizes [14]. The estimates (and 95% CIs) will then be back-transformed to obtain the pooled IVE estimate (and 95% CIs), expressed in %.

16.3.3 Quantifying between-study heterogeneity

An indication for the heterogeneity among estimates from different study sites will be obtained by calculating I^2 according to Higgins et al [15]. The I^2 statistic is to be interpreted as the proportion of total variation in the estimates of treatment effect that is due to heterogeneity between studies. This measure will be used as a summary measure of the between-study heterogeneity and not to decide on the appropriateness of pooling as the RE MA model accounts for different levels of between-study heterogeneity.

16.3.4 Outlier and influence analysis, and exploring reasons for potential outlying studies

For every meta-analysis performed, the potential impact of outliers and influential estimates on the pooled estimate will be evaluated. Studentized deleted residuals *r* will be used to identify outliers in the meta-analysis. Site-specific IVE estimates will be considered outlying from meta-analysis when $|r| > 2.5$, where $|r|$ indicates the absolute value of the residual.

The standardized DFBETAs statistic will be used to identify influential estimates, examining the change in the averaged IVE from the random-effects model when excluding one site-specific estimate in turn. Site-specific estimates will be considered influential from meta-analysis when |DFBETAs| > $2/\sqrt{n}$, where |DFBETAs| indicates the absolute value of the DFBETAs statistics and *n* is the number of effect estimates [16].

Site-specific estimates that are both outlying and influential will be excluded from meta-analysis and the reason for being outlying will be investigated.

16.3.5 Sensitivity analysis

The following sensitivity analysis will be conducted:

Extended confounder-adjustment:

A sensitivity analysis will be performed , using an extended set of confounders including sex, a smooth function of age, a smooth function of calendar time, pregnancy, presence of at least one chronic condition and number of GP visits/hospitalizations (when available) to allow further exploration of the impact of covariate adjustment on the IVE estimates.

Extended study period:

A sensitivity analysis will be performed using the available data collect up to the 30th of April 2020.

When the percentage of partially vaccinated subjects is >= 5%:

- partially vaccinated subjects (see Section 11.1) will be considered unvaccinated;
- partially vaccinated subjects (see Section 11.1) will be considered vaccinated.

Time between ILI/SARI onset and swab:

- subjects will be excluded when the respiratory specimen was taken ≥ 4 days after ILI/SARI onset.

Outlying/influential studies:

- Outlying/influential studies will be included in the meta-analysis, if any.

17 Presentation of results

The presentation of the results is described in detail in the Mock Report.

18 Software

All data management and statistical analyses will be conducted in R 3.6.2. GitHub will be used for version control.

19 Limitations

It is difficult to know the sample size required for brand-specific IVE as it depends on many unknown factors, including the influenza attack rates, vaccination coverage, distribution of brands and (for the pooled estimates) the between-study heterogeneity. For the 2019/20 season, we will likely have sufficient sample size to obtain sufficiently precise (with CI width < 40%) IVE estimates for some brands, but not for all brands used in Europe in the 2019/20 season. Obtaining sufficient sample for brand-specific IVE estimates will remain a priority for DRIVE. Focussing on specific age groups or settings when expanding the DRIVE network might be an appropriate future strategy. The current definition of a sufficiently precise estimate (CI width < 40%) might have to be revisited or gradually tightened alongside the expansion of the DRIVE network.

For some study sites, no information is available on influenza subtypes/lineages, the information on covariates is limited or primary care or hospital based cases cannot be distinguished. It remains to be decided what information is minimally required for obtaining robust IVE estimates, and hence which are the minimum study requirements for the DRIVE studies and how these study requirements can be different for primary data collections versus database studies. The sustainability of the DRIVE network should be taken into account as in general, simple data collection systems are easier to maintain. Bias by indication is a challenge in IVE studies and will also likely affect the IVE estimates of this season. It will be particularly important to understand the target groups for influenza vaccination as well as the target groups for vaccination with specific influenza vaccine brands.

Having the data and evidence timely available is crucial for public health decision making in general, and for influenza in particular. Speeding up the analysis and reporting of results remains a priority for DRIVE.

20 Quality control procedures

20.1 Documentation

The following study documents will be generated and are available upon request: Generic site-specific protocols, description of minimum data requirements, season-specific protocol per study site, season-specific SAP, study summary sheets and codebook of variables within the analytical datasets, data quality report for each participating site.

20.2 Record retention

Documents that permit evaluation of the conduct of a study and the quality of the data will be retained for a period of 5 years in accordance with Good Participatory Practice (GPP) guidelines. These documents will be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement between study partners.

The analytical datasets and data analysis scripts used to produce the site-specific IVE estimates will be retained at the participating study sites and made available for quality control upon request. The syntaxes used for the pooled analysis will be documented and made available for quality control upon request.

20.3 Data analysis and results

Quality control of R programs will include a review of the whole process of the results generation:

- Review of all analysis R programs;
- Review of R logs for errors, uninitialized variables and warnings;
- Review of all tables, listings and figures for completeness and correctness.

19.4 Monitoring of quality

The Quality Control and Audit Committee (QCAC) of DRIVE is composed of external quality control advisors (who may or may not represent consortium members). The QCAC will perform a 3-step assessment of the quality of the studies:

- Study conduct: whether study was conducted in compliance with regulatory standards, the site protocol and the local SOPs.
- Quality of the data: whether data collected from the field were processed in compliance with the DRIVE Data Management Plan (DMP).

- Quality of the analysis: whether the site-specific and pooled statistical analysis report matches with the Statistical Analysis Plan (SAP).

To evaluate these points, the QCAC will develop three checklists in agreement with DRIVE WP3 and P95. Based on the evaluation, the QCAC will provide recommendations to DRIVE Steering Committee. The conclusion of QCAC will be described in a quality report and attached to the final study report.

21 Ethics considerations

21.1 Ethics approval

Ethics committee clearance was required for yearly IVE assessment, with the exception of Finland THL, Italy ISS, Luxembourg LNS and Spain FISABIO. Finland THL and Italy ISS sought the ethics committee clearance nonetheless, and Spain FISABIO obtained approval for the first year in 2009 (Table19). The submissions to ethics committee were mostly performed during summer, often in July, before the beginning of the influenza season. The average time from submission to endorsement from the ethics committee was 5 weeks, ranging from 1 to 12 weeks.

Table 12. DRIVE 2019/20 study sites: ethics committees and date of approval.

Site	Country	Ethics committee	Date of approval
MUV	Austria	Ethics committee of the MUV	May 6, 2019
HUS	Finland	Regional Ethics Committee of the Expert Responsibility Area of Helsinki University Hospital	Oct 3, 2019
THL	Finland	Institutional review board of the National Institute for Health and Welfare, Finland	June 2, 2016
INSERM	France	Comité de Protection des Personnes, Ile-de-France IV (Institutional Review Board Agreement of US Department of Health and Human Services) Ref: 2013/44	Oct 31, 2019
BIVE	Italy	Comitato Etico Regionale	Sept/Oct , 2019
CIRI-IT	Italy	Comitato Etico Regionale	Sept 16, 2019
ISS	Italy	Not required, but submitted to ISS Ethics committee for information	Nov 23, 2018
NIIS	Romania	Bioethics committee of the NIIS	Oct 6, 2019
FISABIO	Spain	National Ethics Committee	Dec 21, 2009
VHUH	Spain	Comité Ético de Investigación Clínica del Hospital Universitari Vall d'Hebron	Nov 15, 2019

21.2 Informed consent

At all sites except VHUH, GTPUH and THL informed consent was required. For the THL register-based cohort study, informed consent was not required as the study makes use of secondary data from routine databases. For the VHUH and GTPUH study, informed consent was not required as no interventions that fall outside the usual practice at both hospitals during the influenza season were needed.

22 References

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Irma Casas García. MD, PhD. Physician at the Preventive Medicine and Epidemiology Department. Task: vaccination and coordination of the Control Infection Group.

Mario Auñón Recacha. Nurse at the Preventive Medicine and Epidemiology Department. Task: Data collection.

María Esteve Pardo. MD, PhD. Head of the Preventive Medicine and Epidemiology Department. Task: vaccination and coordination of the Infectious Diseases Committee.

Lurdes Matas Andreu. MD, PhD. Head of Microbiology Department. Task: coordination of the laboratory tasks performed for the project.

Cristina Casañ. Physician at the Microbiology Department -Task: validation of the results from the detection of influenza viruses. Report of virological information for a database that will be shared with the collaborators working in the Preventive Medicine and Epidemiology Department.

Maria Carrasco Díaz. Laboratory Technician, Molecular biology Unit, Microbiology Department. Task: determination of influenza by real time PCR assay (including the nucleic acid extraction procedure), conservation and sending positive samples to HVH Microbiology department.