Brand-specific influenza vaccine effectiveness in Europe Statistical Analysis Plan Season 2020/21

777363 - DRIVE

Development of robust and innovative vaccine effectiveness

WP7 - IVE studies

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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
COVID-19	Coronavirus disease 2019
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
EL	Embætti landlæknis
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
GP	General Practitioner
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
LPUH	La Paz University Hospital
MUV	Medical University Vienna
NIID	National Institute for Infectious Diseases "Prof. Dr. Matei bals"
NVR	National Vaccination Register
OR	Odds ratio
PCR	Polymerase chain reaction
PC	Primary care
QIV	Non-adjuvanted quadrivalent influenza vaccine
QIVe	Quadrivalent inactivated egg-based influenza vaccine
QIVc	Quadrivalent inactivated cell-based influenza vaccine
QIVa	Quadrivalent adjuvanted influenza vaccine
RCGPRSC-OX	Royal College of General Practitioners / Research and Surveillance Centre / Oxford University
RE MA	Random-effects meta-analysis
REML	Restricted maximum likelihood
RJCUH	Hospital Universitario Rey Juan Carlos
RR	Relative risk
RT-PCR	Reverse transcription polymerase chain reaction
SAP	Statistical Analysis Plan
SARI	Severe acute respiratory infection
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2
SUH	Hospital Universitario de Salamanca
HUJT	Hospital Universitari de Girona Doctor Josep Trueta
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
UK	United Kingdom
URTI	Upper respiratory tract infections
VE	Vaccine effectiveness
HUVH	Vall d'Hebron University Hospital
WHO	World Health Organization

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 analyzed 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. The 2018/19 season was based on a multi-center 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). For the 2019/20 season, the DRIVE network included 13 TND studiesand one register-based cohort study and for the current 2020/21 season, 13 TND studies, of which 3 were not included in the 2019/20 season, and one register-based cohort study are included.

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 2020/21 influenza season.

As of the start of February 2021, the circulation of influenza in Europe has remained at interseasonal levels (3). The most likely explanation for this is that non-pharmaceutical interventions used to limit COVID-19 spread also reduces the spread of influenza within Europe. As it is expected that some of these measures will remain in place for the rest of the 2020/21 season it seems plausible that the influenza circulation will remain very low during the remainder of the 2020/21 season. This poses a major challenge to DRIVE as it implies that the data necessary for performing some of the planned analyses will not be available.

2 Reference documents

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

- DRIVE Mock Report Season 2020/21.

The SAP has been developed using the following documents:

- DRIVE Generic protocols (D7.1.2 and D7.2).
- DRIVE 2020/21 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 Objectives

3.1 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, 18-64yr, ≥ 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).

3.2 Secondary objectives

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, 18-64yr, ≥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).
- Quadrivalent live attenuated influenza vaccine (LAIV).
- Quadrivalent inactivated egg-based influenza vaccine (QIVe).
- Quadrivalent inactivated cell-based influenza vaccine (QIVc).
- Quadrivalent adjuvanted influenza vaccine (QIVa)
- Quadrivalent high-dose influenza vaccine (QIV-HD)

The 2020/21 DRIVE TND core protocol also included the following secondary objective: *To estimate the COVID-19 impact on IVE (COVID-19 positive versus COVID-19 negative) within the adults/older adults in the hospital setting, given the COVID-19 epidemiology*. Given that the sample size requirements to investigate this objective are larger than those for IVE estimation and given that the flu activity was still at interseasonal levels at the end of January 2021 (3), performing these analyses was deemed infeasible this season and will not be done.

3.3 Exploratory objectives

To describe clinical signs and symptoms as well as laboratory features and demographic characteristics, around the point of admission, among hospitalized COVID-19 cases as compared to influenza cases.

4 Study design

A multi-center study with data available from three primary care-based TND studies, ten hospital-based TND studies, and one register-based cohort.

4.1 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 4 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 are made available prior to 15th April 2021.

Table 1. Overview of the participating study-sites, 2020/21

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.	Istituto Superiore di Sanità (ISS), Italy	National sentinel influenza surveillance system, INFLUNET
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)
Test-negative design studies, hospital based:		
1.	Centro Interuniversitario di Ricerca sull'Influenza e sulle altre infezioni trasmissibili Italian Hospital Network (CIRI-IT BIVE), Italy	
2.	National Institute for Infectious Disease "Prof. Dr. Matei Balş", Bucharest, Romania	
3.	Vall d'Hebron University Hospital (HUVH), Barcelona, Spain & Hospital Universitari Doctor Josep Trueta (HUJT), Gerona, Spain	Information Plan for Acute Respiratory Infections in Catalonia, PIRIDAC
4.	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
5.	Hospital Universitario La Paz (LPUH), Madrid, Spain	
6.	Germans Trias i Pujol University Hospital (GTPUH), Badalona, Spain	Information Plan for Acute Respiratory Infections in Catalonia, PIRIDAC
7.	Institut National de la Santé et de la Recherche Médicale (INSERM), France	National surveillance of influenza vaccine effectiveness
8.	Hospital Universitario de Salamanca (SUH)	
9.	Hospital Universitario Rey Juan Carlos (RJCUH)	Castilla y León IRD surveillance system (Red Centinela Sanitaria de Castilla y León (VIGIRA Network) / National Influenza Centre Valladolid).
10.	Directorate of Health - Embætti landlæknis (EL), Iceland	National Icelandic influenza surveillance system

Register-based cohort study		
1.	The Finnish Institute for Health and Welfare (THL), Finland	Online surveillance of influenza vaccine effectiveness

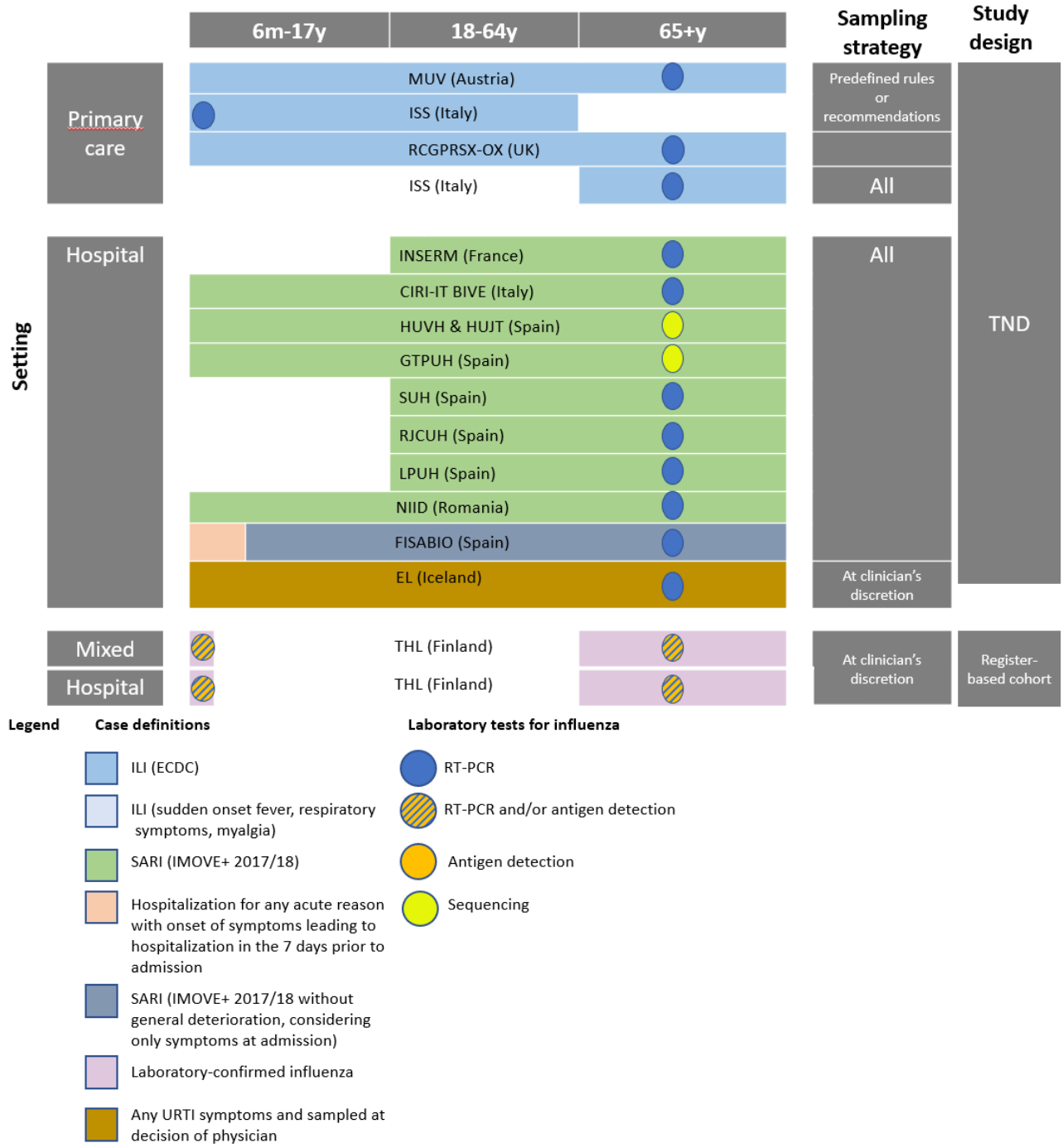


Figure 1. Overview of study characteristics, TND and register-based cohort, 2020/21.

Table 2. Overview of test-negative design study sites characteristics, primary care – 2020/21

Site Country	MUV Austria	ISS Italy	RCGPRCS-OX
Setting	Primary care	Primary care	Primary care
Source of cases	250 primary care physicians	Ca. 245 primary care physicians	12 primary care practices
Population	General population ≥6 months	General population ≥6 months	General population ≥6 months
Cases			
Case definition	ILI(1)	ILI(1)	ILI(1)
Influenza cases	ILI + LCI	ILI + LCI	ILI + LCI
Case identification	During consultation	During consultation	During consultation
Matched controls	No	No	No
Sampling strategy(3)	All / Predefined rules At physician's discretion	<65y: Recommendations formulated 65y+: All	Recommendations formulated
Swab			
Type of swab	Nasopharyngeal	Throat or nasopharyngeal swab	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 whole genome sequencing	RT-PCR	Rapid molecular point of care testing
A/subtype available	Yes	Yes	No
B/lineage available	Yes	Yes	No
Laboratory test subtyping	RT-PCR	RT-PCR	n/a
Data sources			
Case definition	Primary data collection	Primary data collection	Primary data collection
Vaccination status	-GP medical records -Patient/ relatives' interview (if ILI patient is not consulting their regular GP)	GP medical records	GP medical records
Vaccine brand and date	GP medical records Vaccination card	GP medical records	GP medical record
Baseline clinical data	Primary data collection	GP medical records	GP medical records
Recommended* covariates available for adjustment	1+ chronic condition, pregnancy	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

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

*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 hospitalizations 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

Table 3. Overview of test-negative design study sites characteristics, hospital – 2020/21 (part 1)

Site **Country**	**INSERM** **France**	**SUH** **Spain**	**CIRI-IT BIVE** **Italy**
Setting	Hospital	Hospital	Hospital
Source of cases	8 hospitals	1 hospital	5 hospitals
Population	General population ≥18 years	Adults 18-65y Elderly (65+)	General population ≥ 18 years
Cases			
Case definition	SARI[(1)]	SARI[(1)]	SARI[(1)]
Influenza cases	SARI + LCI	SARI + LCI	SARI + LCI
Case identification	From hospital databases From hospitalized patients	From hospital or primary care database or register and from emergency room	From hospital databases
Matched controls	No	Yes, attempt to match 1:2 or 1:3 depending on the workload	No
Sampling strategy[(4)]	All	All ILI/SARI patients	All
Swab			
Type of swab	Nasopharyngeal or bronchoalveolar lavage or tracheal aspiration	Nasopharyngeal	Nasal and throat or nasopharyngeal
Laboratory testing			
Laboratory test influenza	RT-PCR	RT-PCR	RT-PCR
A/subtype available	Yes	Yes	Yes
B/lineage available	Yes	No	Yes
Laboratory test subtyping	RT-PCR	PCR-based assays are usually used for the rapid (GeneXpert Flu/RSV) laboratory-confirmation of influenza in respiratory specimens from adults. In addition, a routine real-time multiplex PCR (Qiastat Respiratory Panel Assay (Quiagen)) is used for the laboratory-confirmation of influenza and other respiratory viruses in respiratory specimens. A specific real-time PCR assay is used for influenza A (H1pdm09/H3) subtyping of all detected viruses.	RT-PCR or multiplex RT-PCR
Data sources			

Site **Country**	**INSERM** **France**	**SUH** **Spain**	**CIRI-IT BIVE** **Italy**
Case definition	-Primary data collection -Secondary data collection	Primary data collection (patient/next of kin interview)	Primary data collection Secondary data collection
Vaccination status	-Patient or relatives' interview -GP or pharmacists' interview -Vaccine card	Vaccination registry (local/regional/national)	-Medical records -Vaccination registry
Vaccine brand and date	-GP or pharmacists' interview (medical records) for those that reported being vaccinated -Vaccine card	-Vaccination registry (local/regional/national) -Vaccination card -Patient / next of kin	-Medical records -Vaccination registry
Baseline clinical data	Primary data collection Secondary data collection	Secondary data (registers/medical records)	Primary data collection Secondary data collection
Recommended* covariates available for adjustment	1+ chronic condition, pregnancy, nr of hospitalizations in last 12 months, influenza vaccination in previous season (two)	-Chronic conditions -Pregnancy -Number of hospitalizations in last 12 months -Influenza vaccination in previous season (two)	1+ chronic condition, pregnancy, nr of hospitalizations in last 12 months
Individual-level or aggregate data shared	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 hospitalizations 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) modified SARI case definition, in which only symptoms at admission are considered, “deterioration of general condition” is not considered. (4) 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, (5) in the LPUH study both ILI and SARI cases are sampled, in the DRIVE analysis only the SARI will be included. (6) in the 2020/21 season, the NIID hospital is dedicated to COVID-19 infections and all LCI cases will be co-infections.

Table 3. Overview of test-negative design study sites characteristics, hospital – 2020/21 (part 2)

Site **Country**	**LPUH** **Spain**	**GTPUH** **Spain**	**HUVH & HUJT** **Spain**	**FISABIO** **Spain**
Setting	Hospital	Hospital	Hospital	Hospital
Source of cases	1 hospital	1 hospital	2 hospitals	4 hospitals
Population	General population ≥14years	General population ≥6 months	General population ≥6 months	General population ≥6 months
Cases				
Case definition	ILI[3]/SARI	SARI[1]	SARI[1]	<5y: Hospitalized for any acute reason[2] ≥5y: SARI[3]
Influenza cases	ILI/SARI [5] + LCI	SARI + LCI	SARI + LCI	SARI[3] + LCI
Case identification	From Microbiology department (all those tested for Influenza.	From laboratory (all those tested for influenza) and then hospital databases (to check if they fulfill SARI criteria)	From hospital database	From hospitalized patients
Matched controls	No	No	No	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	Yes	Yes	Yes
B/lineage available	Yes	Yes (sent to HUVH)	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
Vaccination status	Electronic medical record and patient interview (incl vaccination through campaign or self-bought)	Records of Catalan Institute of Health	Records of Catalan Institute of Health	Vaccine register

Site Country	LPUH Spain	GTPUH Spain	HUVH & HUJT Spain	FISABIO Spain
Vaccine brand and date	-Electronic medical record and 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, pregnancy, nr of hospitalizations in last 12 months	1+ chronic condition, pregnancy, nr of hospitalizations in last 12 months	1+ chronic condition, pregnancy, nr of hospitalizations in last 12 months	1+ chronic condition, pregnancy, nr of hospitalizations 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, PCR: 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 hospitalizations 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) modified SARI case definition, in which only symptoms at admission are considered, "deterioration of general condition" is not considered. (4) 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, (5) in the LPUH study both ILI and SARI cases are sampled, in the DRIVE analysis only the SARI will be included. (6) in the 2020/21 season, the NIID hospital is dedicated to COVID-19 infections and all LCI cases will be co-infections.

Table 3. Overview of test-negative design study sites characteristics, hospital – 2020/21 (part 3)

Site Country	RJCUH Spain	EL Iceland	NIID Romania
Setting	Hospital	Hospital	Hospital [6]
Source of cases	1 hospital	1 hospital	1 hospital
Population	Adults 18-65y Elderly (65+)	All ages	General population ≥6 months
Cases			
Case definition	SARI[1]	Other: Any URTI symptoms and sampled at clinician decision of physician	SARI[1]

Influenza cases	SARI + LCI	Any URTI symptoms and sampled at clinician decision of the physician	SARI + LCI
Case identification	From hospital or Primary care database or register (microbiology Lab)	Other: if a respiratory sample is sent to virology lab	From hospitalized patients
Matched controls	No	No	No
Sampling strategy[4]	All SARI patients	At physician's discretion (4 swabs per patient)	All
Swab			
Type of swab	Nasopharyngeal	Nasopharyngeal	<14y: nasopharyngeal and nasal ≥14y: nasopharyngeal and pharyngeal
Laboratory testing			
Laboratory test influenza	RT-PCR and Antigen testing	RT-PCR	RT-PCR
A/subtype available	Yes	Yes	Yes
B/lineage available	Yes	Yes	Yes
Laboratory test subtyping	RT-PCR	RT-PCR	RT-PCR
Data sources			
Case definition	Secondary data (registers/medical records)	Secondary data (registers/medical records)	-Primary data collection -Hospital medical records
Vaccination status	- Electronic health record system of madrid - Public health registry of Madrid	Vaccination registry (local/regional/national)	-Vaccine card -Primary care physician interview -Hospital records -Patient /relatives interview
Vaccine brand and date	Secondary data (registers/medical records)	Vaccination registry (local/regional/national)	-Vaccine card -Primary care physician interview -Hospital records -Patient /relatives interview
Baseline clinical data	Secondary data (registers/medical records)	Secondary data (registers/medical records)	-Medical records -Patient /relatives interview -Interview with attending physician
Recommended* covariates available for adjustment			1 + chronic condition, pregnancy, nr of hospitalizations in last 12 months
Individual-level or aggregate data shared	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, URTI: upper respiratory tract 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 hospitalizations 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) modified SARI case definition, in which only symptoms at admission are considered, “deterioration of general condition” is not considered. (4) 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, (5) in the LPUH study both ILI and SARI cases are sampled, in the DRIVE analysis only the SARI will be included. (6) in the 2020/21 season, the NIID hospital is dedicated to COVID-19 infections and all LCI cases will be co-infections.

Table 4. Overview of register-based cohort study, 2020/21

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	~1,593,300 (31.12.2018)
Start data collection	Ongoing
Case	LCI positive, LCI positive + inpatient episode
Sampling strategy(1)	undefined
Type of swab	Nasopharyngeal swabs or nasal and/or throat swabs or nasopharyngeal aspirates (sometimes other clinical samples) analyzed 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 2019, number of primary care consultations in the last 12 months before 29.09.2020

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 hospitalizations in the last 12 months (for hospital studies). The obligatory covariates are age, sex, and calendar week at diagnosis.

(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

5 Study population

In all TND studies and the register-based study, the population under study is the general population. In the 2020/21 season, the NIID hospital is dedicated to the treatment of COVID-19, hence, for NIID the study population is the general population with a hospitalized COVID-19 infection.

Table 5. Catchment population for studies in the general population, 2020/21.

	Catchment population
TND primary care	
Austria MUV	Ca. 1-1.5% of the population of Austria (8,859,000)
Italy ISS	Ca. 0.5% of the population of Italy (60,360,000)
UK RCGPRSC-OX	Ca. 0.1% of population England (55,980,000)
TND hospital	
Italy CIRI-IT BIVE	Tertiary care hospitals serving Siena province (population 250,000), Genoa metropolitan area (650,000), Rome (3,000,000) and Bari province (1,200,000), Milan city (1,350,000).
France INSERM	Tertiary care university 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), Nantes (1 hospital, population 300 000), Dijon (1 hospital, population 160 000) and Saint-Etienne (1 hospital, population 170 000)
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 university hospital serving a population of more than 250,000 inhabitants of Badalona, Sant Adrià de Besòs, and various municipalities of

	Maresme area. In addition, it is a referral hospital for more than 800,000 citizens of Barcelona province.
Spain LPUH	Tertiary care university hospital local in Madrid (serving a population of 800,000)
Spain HUVH & HUJT	HUVH has a primary catchment area of 430.000 inhabitants (secondary over 2 million) in the province of Barcelona and HUJT 156.000 in the province of Girona
Iceland EL	100% of the population of Iceland (340 000 inhabitants)
Spain SUH	332,234 inhabitants
Spain RJCUH	200,000 inhabitants
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 pediatric hospital in central-southern Italy.

6 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 2021, whichever will occur first. The study period of analysis might be different for different study sites.

In the particular case of THL (Finland), data are continuously collected throughout the year since the national registers are used. The study period for analysis goes from week 40 till April 30th, 2021.

For each study site, the actual start of the influenza surveillance in 2020/21 and the number of lab-confirmed influenza cases detected by 26th of January 2021 are described in Table 6.

Table 6. Description of the date on which the sites started their surveillance and the number of lab-confirmed influenza cases observed by the end of January 2021.

Study site	Number of lab-confirmed influenza cases by January 2021	Actual start 2020/21 season
NIID	1 lab-confirmed SARS-CoV-2 and influenza B co-infection in a child	Early December 2020
RJCUH	0 lab-confirmed cases	End of December 2020
HUVH & HUJT	0 lab-confirmed cases	October 2020
FISABIO	Available soon	9th December 2020
THL	30 lab-confirmed cases	October 2020
ISS	0 lab-confirmed cases	October 2020
CIRI-IT BIVE	0 lab-confirmed cases	Early November 2020
LPUH	0 lab-confirmed cases	December 2020
GTPUH	1 lab-confirmed case	October 2020
SUH	0 lab-confirmed cases	January 2021
MUV	1 lab-confirmed influenza B case	2nd November 2020
INSERM IREIVAC	15 lab-confirmed cases within the whole network (not restricted to participating hospitals)	12th January 2021
EL	0 lab-confirmed cases	October 2020

7 Case definitions

7.1 Influenza-like illness (ILI)

A case of influenza like illness (ILI) will be defined by the ECDC case definition (4) 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.

7.2 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 hospitalized 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.

7.3 COVID-19

A case of COVID-19 will be defined as a laboratory detection of SARS-CoV-2 nucleic acid in a clinical specimen.

7.4 Adherence to the case definitions

All study sites follow the ILI or SARI clinical case definitions except for Spain FISABIO, Spain LPUH, Iceland, and THL.

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 SARI case definition is used. More particularly, only symptoms at admission are considered, "deterioration of general condition" is not considered, and the symptoms could not start more than 7 days before the date of admission instead of the date of sampling.

LPUH Spain (TND hospital-based) recruits both cases meeting either the ILI (ECDC definition) or SARI case definitions. As the cases can also be recruited in the emergency care setting, hospitalization of the ILI cases cannot be guaranteed. In DRIVE only the subjects meeting the SARI case definition will be included in the analyses.

EL Iceland (TND hospital-based) samples subjects with any URTI symptoms at the physician's discretion. URTI is defined as any symptom of a respirotary infection, including cough, ILI symptoms, etc.

8 In- and exclusion criteria

8.1 Test-negative design studies

8.1.1 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 institutionalized 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/hospitalization.
7. is potentially vaccinated (positive vaccination status is based on recall alone and cannot be confirmed by registers or is otherwise ambiguous).
8. age not part of the brand-specific licensed age-indication (only applicable for vaccinated subjects)*

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 institutionalized at the time of symptoms onset;
5. had 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/hospitalization;

7. was previously hospitalized < 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).
10. age not part of the brand-specific licensed age-indication (only applicable for vaccinated subjects)

*Note: as age at vaccination is not collected within DRIVE, the brand-specific age-indication criterium will be based on the age at onset.

8.1.2 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 2). An overview of the adherence to the ILI and SARI exclusion criteria given in Table 7. Records that violate the exclusion criteria will be discarded either at the data transfer stage or at the central analysis stage, whenever possible.

Table 7. Test-negative design studies: overview of exclusion criteria applied at study recruitment, 2020/21

Site	MUV	ISS	RCGPRS-OX	CIRI-ITBIVE	INSERM	NIID	FISABIO	HUVH & HUJT	LPUH	GTPUH	SUH	RJCUH	EL
Country	Austria	Italy	UK	Italy	France	Romania	Spain	Spain	Spain	Spain	Spain	Spain	Iceland
Setting	PC	PC	PC	HO	HO	HO	HO	HO	HO	HO	HO	HO	HO
Clinical case definition	ILI	ILI	ILI	SARI	SARI	SARI	SARI [(1)]	SARI	SARI	SARI	SARI	SARI	URTI
1. Unwilling or unable to give consent	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	N.a[(2)]	Yes (R)	N.a[(2)]	N.a.	N.a.	N.a.
2. Age <6 months at symptom onset	Yes (R)	Yes (R)	Yes (R)	Yes (R)	n/a	Yes (R)	Yes (A)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)
3. Contraindication	No	Yes (R)	Yes (A)	Yes (R)	Yes (R)	Yes (R)	Yes (A)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)
4. Institutionalized	Yes (R)	Yes (R)	Yes (A)	Yes (R)	Yes (R)[(3)]	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)
5. Respiratory specimen taken ≥ 8 days after ILI/SARI onset	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)
6. Prior influenza infection in current season	Yes (R)	Yes (R)	Yes (A)	Yes (R)	Yes (R)	Yes (R)	Yes (A)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)
7. Previously hospitalized < 48 hours prior to SARI onset	n/a	n/a	n/a	Yes (R)	Yes (T)	Yes (R)	Yes (R)[(4)]	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)
8. SARI onset ≥ 48 hours after hospital admission	n/a	n/a	n/a	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)	Yes (R)
9. Potentially vaccinated	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)
10. Age not within age-indication	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)	Yes (A)

(vaccinated subjects only)													
Other local exclusion criteria	No	No	No	Yes (R)[5]	No	No	Yes (R)[6]	Yes (R)[7]	No	Yes (R)[7]	No	No	No

ILI: influenza like illness; HO: hospital; n/a: not applicable, PC: primary care; SARI: severe acute respiratory infection, URTI: upper respiratory tract infection
(R) Exclusion criterion applied at the time of recruitment (T) Exclusion criterion applied at the time of data transfer. (A) Exclusion criterion applied at the time of analysis

(1) Modified SARI case definition, in which only symptoms at admission are considered, “deterioration of general condition” is not considered. (2) No informed consent was required as no intervention required for the study fall outside the usual practice of the HUVH & HUJTGH and GTPUH during the influenza season. (3) Institutionalized patient without regular community interaction. (4) Patients hospitalized < 30 days from the current hospitalization are excluded. (5) Remains in hospital for less than 24 hours. (6) Not residing in the hospital's catchment area for at least the previous 6 months; Remains in hospital for less than 24 hours. (7) A patient not belonging to the Institut Català de la Salut network.

8.2 Cohort studies

8.2.1 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 2020, week 40) are included, with the following exclusion criterion applied:

- exclusion of subjects with presumably incomplete vaccination records in 2020/21 or 2019/20
- exclusion of FinFluHD trial participants
- exclusion of subjects with presumably incomplete hospital records in 2020/21 (for "hospital setting"-like analysis only)

9 Outcome

9.1 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.

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

- Laboratory confirmed influenza irrespective of whether the sample was taken in primary care or the hospital setting
- Inpatient laboratory confirmed influenza cases defined as cases hospitalized (>= 24h stay in hospital and/or emergency room care) for any reason starting (or ongoing) on the day of laboratory confirmation.

9.2 Case identification

For the TND studies, ILI and SARI cases are identified among all patients presenting to primary care or hospital. In Iceland EL, all patients for who a sample was sent to the laboratory of the participating hospital are considered.

9.3 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 the 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. In all sites, the subjects were tested for both influenza and COVID-19, and for most sites, this happened using the same swab. Details on the sampling strategies are given in Table 8.

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 8. Test-negative design studies: overview of influenza and COVID-19 swab sampling strategies used, 2020/21.

Site	MUV	ISS	RCGPRSC-OX	CIRI-IT BIVE	INSERM	NIID	FISABIO	HUVH & HUJT	LPUH	GTPUH	SUH	RJCUH	EL
Country	Austria	Italy	UK	Italy	France	Romania	Spain	Spain	Spain	Spain	Spain	Spain	Iceland
Setting	PC	PC		HO	HO	HO	HO	HO	HO	HO	HO	HO	HO
Clinical case definition	ILI	ILI		SARI	SARI	SARI	SARI (1)	SARI	ILI	SARI	SARI	SARI	URTI
Sampling strategy	Predefined rule (2)	Predefined rule(3)		All	All	All	All	All	All	All	All	all	At the physician's discretion
Same swab used for COVID-19 and influenza test	Yes	Yes		Yes	Yes (4)	No (5)	Yes	Yes (HUVH), No (HUJT)	Yes	No	Yes	Yes	Yes
Influenza and COVID-19 screening testing and triage	All subjects tested for both at same time	All subjects tested for both at same time		All subjects tested for both at same time	All subjects tested for both at same time	All subjects tested for both at same time	All subjects tested for both at same time	All subjects tested for both at same time	All subjects tested for both at same time	All subjects tested for both at same time	All subjects tested for both at same time	All subjects tested for both at same time	All subjects tested for both at same time

ILI: influenza-like illness; HO: hospital; n/a: not applicable, PC: primary care; SARI: severe acute respiratory infection, URTI: upper respiratory tract infection. (1) modified SARI case definition, in which only symptoms at admission are considered, "deterioration of general condition" is not considered, and for which the symptoms did not start more than 7 days before admission (2) 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). (3) Systematic sampling of the first 2 ILI patients that present each week, and if possible all ≥65years ILI cases. (4) For some patients, nasopharyngeal swabs or aspirates are first tested for COVID-19 and subsequently for influenza (if sufficient material remaining). (5) In case the patient is already confirmed with COVID-19 a separate swab for influenza will be taken. In the emergency department, the same swab can be used.

9.4 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 for THL (Finland, register-based cohort), and SUH (Spain), 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).

10 Exposure

10.1 Exposure definition

The exposure definition has changed as compared what is stated in the core TND protocol. The previous definition was depended on vaccination information from the previous which is not consistently available among the different sites. The current definition should reflect the available data more closely.

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

Note 1: For cohort studies, vaccination status will be treated as a time-varying variable whereas, for the case-control studies, vaccination status is a fixed variable.
Note 2: Children <9 years for who received two doses will hence only be considered vaccinated 14 days after the second dose. In case the records shows that a child <9 years only received one dose it is assumed that the child is vaccinated

10.2 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 10.1), and will be discarded from analysis (see sections 15.2.1.1 and 15.2.5).

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 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 (5).

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 HUVH & HUJT and GTPUH, the information is retrieved from the electronic records of the Catalan Institute of Health (whose primary care centers serve 75,2% of the population of Catalonia).
- In Italy CIRI-IT BIVE, vaccination status is collected by study staff using medical records or vaccination registry or GPs registry.
- 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 and vaccine brand are retrieved through electronic medical records. If the information is not available in the electronic medical records it is obtained by phone interview with the patient. 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 ≥65yr). If the patient doesn't remember the vaccination date, the date will be ascertained by contacting the GP. If the vaccine is self-bought, the health center 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 is not available, the information will be retrieved through patient interview.
- In Finland THL, all information is retrieved from the National Vaccination Register.
- In Iceland EL, the information is retrieved from the vaccination registry
- In Spain SUH, the information is retrieved from one of multiple sources: the vaccination card, the vaccination registry, or through patient interview
- In Spain RJCUH, the information on vaccination status is retrieved from the electronic clinical history from the hospital and primary care healthcare system of Madrid. In case no vaccination record is retrieved the subject is considered unvaccinated. The information on the vaccine brand is obtained from the vaccine providers to the different centers of the Public Health Agency of Madrid.

10.3 Expected influenza vaccine brands

The vaccine types and vaccine brands that are expected to be used in the study areas are summarized in Table 9.

Table 9. Expected vaccine brands and type – all studies, 2020/21.

	Approved age indication	MUV Austria	ISS Italy	RCGPRSC-OX UK	INSERM France	CIRI-ITBIVE Italy	NIID Romania	FISABIO Spain	HUVH Spain	LPUH Spain	GTPUH Spain	EL Iceland	SUH Spain	RJCUH Spain	THL Finland
TIV brands															
Sandovac/ Chiroflu / Agrippal	≥ 6m		x					x		x			x	x	
aTIV brands															
Fluad/ Chiromas	≥ 65y	x	x			x		x	x	x	x			x	
QIVe brands															
Fluarix Tetra/ Alpharix Tetra	≥ 6m	x	x		x	x			x		x				
Vaxigrip Tetra	≥ 6m	x	x		x	x	x	x	x		x	x	x		x
Influvac Tetra/ Influvac S Tetra/FluVaccinol Tetra/ Influenza vaccine Tetra MYL	≥ 3y	x	x		x	x	x	x							
aQIV															
Fluad Tetra	≥ 65y		x			x									
High dose QIV															
Efluelda / Fluzone HD	≥ 65y	x	x		x	x		x							
QIVc brands															
Flucelvax Tetra	≥ 9y	x	x			x		x							
QIV LAIV brands															
Fluenz Tetra	≥ 2y	x					x								x

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

11 Matching of cases and controls

For Spain SUH, the data collection will follow a matched 1:2 or 1:3 case-control design, where information on exposure and covariates will be obtained only for controls that could be matched to a case by epidemiological week (same or adjacent week) and age group (6m–17yr, 18-64yr, and 65-74yr and 75+yr).

12 Covariates

An overview of the covariates available from the different study sites is given in Table 10. The covariates age, sex, and disease onset time are obligatory. The covariates presence of at least one chronic condition, pregnancy, the number of GP consultations or hospitalizations, COVID-19 positivity in the current season, covid-19 positivity in the previous season, time of positive COVID-19 test, fever, headache, myalgia, fatigue/malaise, sudden onset of symptoms, cough, difficulty breathing, sore throat, deterioration of general condition, pneumonia, anosmia, and ageusia are optional.

Table 10. Data collected on obligatory and recommended covariates – all studies, 2020/21.

Site	MUV	ISS	RCGPRSC -OX	CIRI-IT BIVE	NIID	FISABIO	HUVH & HUJT	INSERM	LPUH	GPTUH	EL	JRCUH	THL
Country	Austria	Italy	UK	Italy	Romania	Spain	Spain	France	Spain	Spain	Iceland	Spain	Finland
Setting	PC	PC	PC	HO	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(2)
Sex	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	No
Recommended													
Presence of at least one chronic condition	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Pregnancy	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	n/a
Number of hospitalizations in the last 12 months	No	Yes (3)	Yes	Yes (3)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes (4)
Number of primary care consultations in the last 12 months	No	Yes	Yes	nm	nm	nm (Yes)	nm	nm (Yes)	nm	nm (Yes)	No	No	Yes(5)
COVID-19 covariates													
Time of positive COVID-19 test	No			Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NO	No
Fever	Yes			Yes	Yes	Yes	No	Yes	Yes	Yes	NO	Yes	No
Headache	Yes			Yes	Yes	Yes	No	Yes	Yes	Yes	NO	Yes	No
Myalgia	Yes			Yes	Yes	Yes	No	Yes	Yes	Yes	NO	Yes	No
Fatigue/malaise	Yes			Yes	Yes	Yes	No	Yes	Yes	Yes	NO	Yes	No
Sudden onset of symptoms					Yes	Yes	No	Yes	Yes	Yes	NO	Yes	No
Cough	Yes			Yes	Yes	Yes	No	Yes	Yes	Yes	NO	Yes	No
Difficulty breathing	Yes			Yes	Yes	Yes	No	Yes	Yes	Yes	NO	Yes	No
Sore throat	Yes			Yes	Yes	Yes	No	Yes	Yes	Yes	NO	Yes	No
Deterioration of general condition	Yes			Yes	Yes	Yes	No	Yes	Yes	Yes	NO	Yes	No
Pneumonia					Yes	Yes	No	Yes	Yes	Yes	NO	Yes	No
Anosmia	Yes			Yes	Yes	Yes	No	Yes	Yes	Yes	NO	Yes	No
Ageusia	Yes			Yes	Yes	Yes	No	Yes	Yes	Yes	NO	Yes	No

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 2019
(5) Number of primary care visits in the last 12 months before 28.09.2020. Likely to be an underestimate as private care visits are not counted; follow-up visits are not distinguished from new visits

12.1 Age

Age in years (months for children <1yr) 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).

12.2 Sex

Male or female.

12.3 Date at symptom onset/calendar time

To adjust for the effect of time, the date at ILI/SARI symptom onset will be used for TND studies whereas calendar week will be used for cohort studies.

12.4 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 11.

Table 11. Definitions of chronic conditions.

Condition	Definition
Chronic liver disease	Any of the following diagnostic 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 diagnostic codes (ICD-10)*: E10-E14, O24 INCLUDING: Any form of diabetes, including sequelae & diabetes metilious in pregnancy
Cardiovascular diseases	Any of the following diagnostic 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 & dissection, 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 diagnostic 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 diagnostic 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 diagnostic 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 diagnostic 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 diagnostic 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 diagnostic codes (ICD-10)*: F00-03, F05.1, G30-31 EXCLUDING delirium w/o underlying dementia, hydrocephalus.
History of stroke	Any of the following diagnostic codes (ICD-10)*: I61-64, I67.8, I69, G93.1 INCLUDING: both ischaemic and haemorrhagic 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 diagnostic 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 diagnostic 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 (6), which are similar to but not exactly the same as those in the DRIVE codebook.

12.5 Pregnancy

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

12.6 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 Finland THL, the number of hospitalizations refers to the number of hospitalizations in 2019.

12.7 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, the number of primary care consultations is based on the number of consultations occurring before Sept 28th,2020 additionally follow-up visits cannot be distinguished from new visits.

12.8 Time of positive COVID-19 test

In case the subject has had a positive COVID-19 test the date of the positive test is reported.

12.9 Symptoms to differentiate between influenza and COVID-19

The symptoms listed in Table 10 will be recorded as either present or absent at the time of admission.

13 Data management

13.1 Data pre-processing at the 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.

13.2 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 uploaded 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.

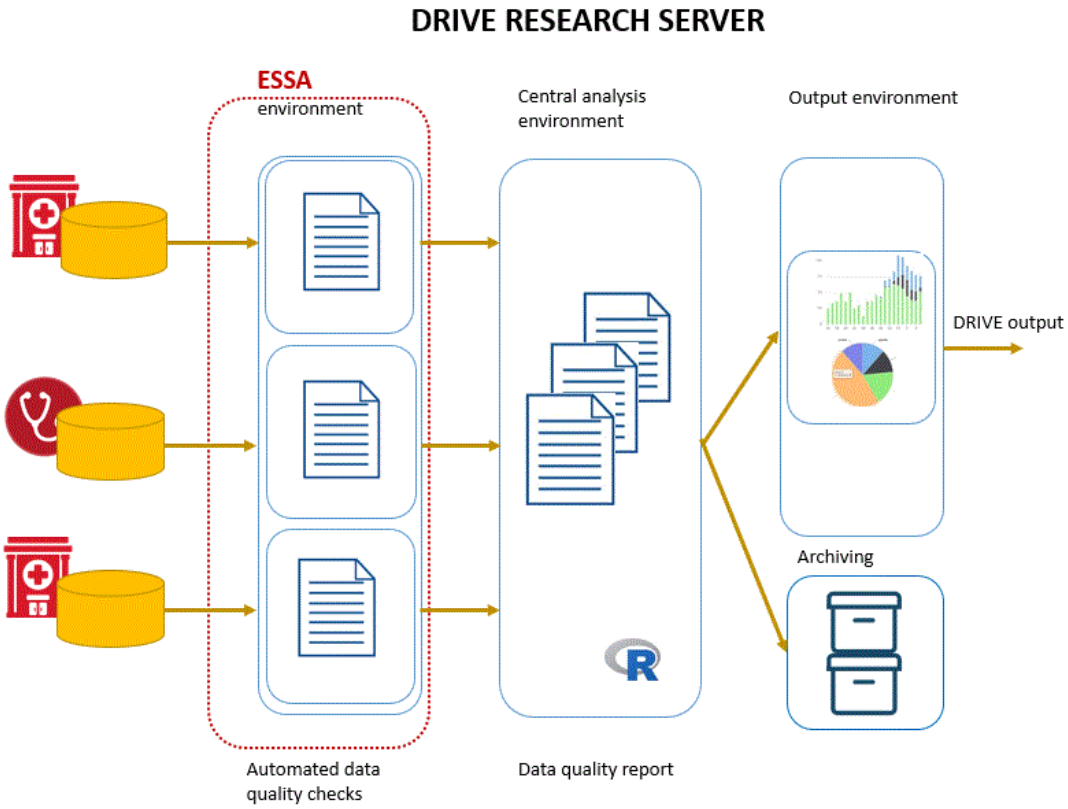


Figure 2. DRIVE Electronic Study Support Application: data flow.

13.3 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.

13.4 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 are 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.

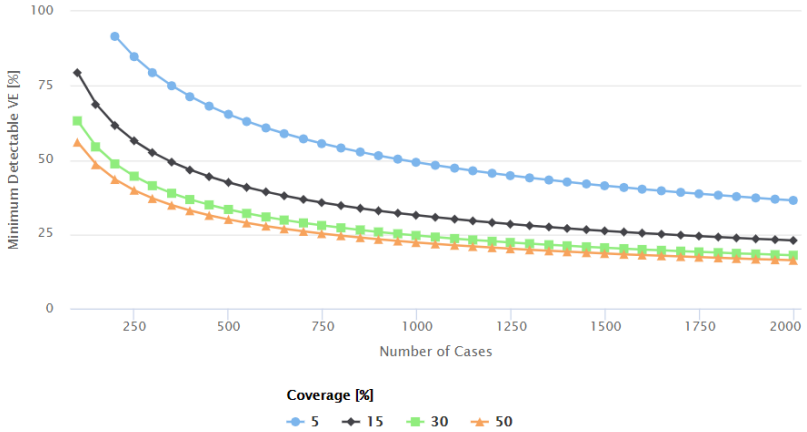
For every site separately, a data quality report will be produced. These reports will contain a description of the results of the quality checks performed, the amount of data that was retained for analysis after applying the in-and exclusion criteria, and graphical summaries of the retained data. The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

14 Sample size considerations

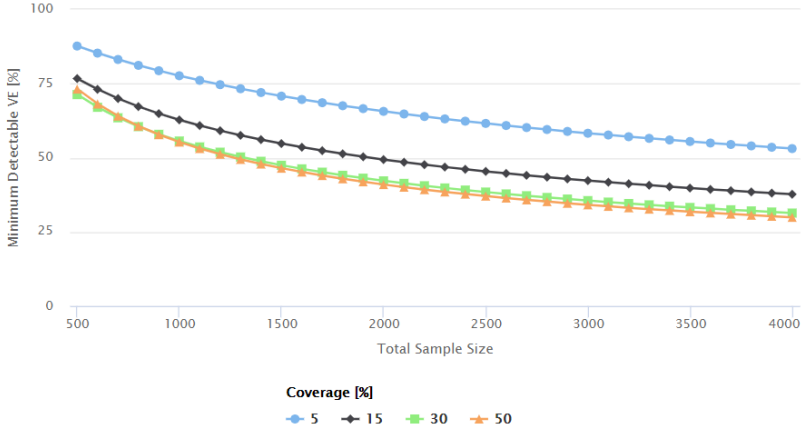
14.1 General sample size considerations

The minimal detectable overall VE, i.e., the smallest VE that can be detected as significantly greater than zero, for a range of sample sizes for TND and cohort designs is given in Figure 2 and Table 12-Table 13. The calculations are performed assuming 80% power, two-sided 95% confidence levels, and overall vaccination coverages of 5%, 15%, 30%, and 50%. For TND studies, 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).

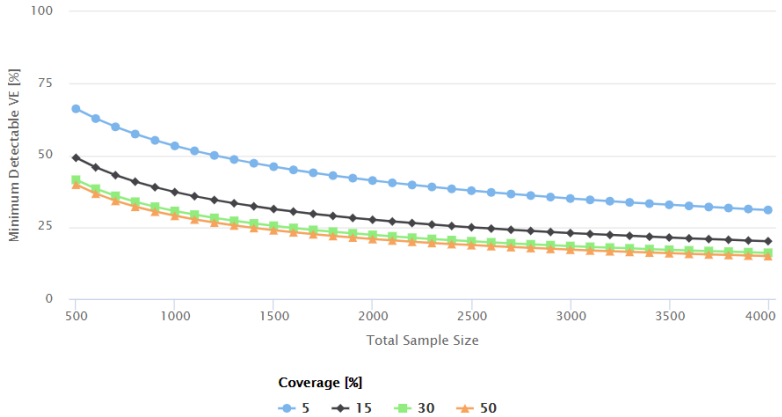
To estimate the overall IVE we generally recommend a minimum of 100 influenza-positive cases for TND studies and a minimum of 1000 subjects for cohort studies. As the optimal sample size strongly depends on the local vaccination coverage and brand distribution, site-specific sample size recommendations 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 12. 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 13. 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	66.20	49.12	41.46	39.80
1000	25	53.28	37.21	30.60	28.95
2000	25	41.21	27.56	22.27	20.85
3000	25	34.96	22.94	18.40	17.16
4000	25	30.96	20.10	16.05	14.93

14.2 Sample size considerations in the 2020/21 season

As the flu activity in the 2020/21 season is influenced by measures taken to curb the spread of COVID-19 the number of influenza cases observed within the DRIVE network will likely be too small to conduct a meaningful vaccine effectiveness analysis. To prevent the use of resources on performing the analysis and writing the final report when it is likely that no statistically significant IVE estimate can be obtained, these activities will only be undertaken when a minimal number of vaccinated influenza cases are observed in the dataset.

The number of vaccinated 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 vaccinated influenza cases can be found in Table 14

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 analyzed, however as this introduces extra heterogeneity the required number of exposed cases to reach the pre-specified power will be higher than the numbers specified in Table 14.

Table 14. Expected number of vaccinated 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 vaccinated influenza cases required (Power = 50%)	Expected number of vaccinated influenza cases required (Power = 80%)
30%	1	10%	57	115
60%	1	10%	7	14
30%	2	10%	41	85
60%	2	10%	5	10
30%	4	10%	33	70
60%	4	10%	4	8
30%	1	25%	68	138
60%	1	25%	8	16
30%	2	25%	49	102
60%	2	25%	6	12
30%	4	25%	40	84
60%	4	25%	5	10
30%	1	60%	126	258
60%	1	60%	15	29
30%	2	60%	96	194
60%	2	60%	11	22
30%	4	60%	80	162
60%	4	60%	9	18

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 vaccinated influenza cases (Table 15). The required number of vaccinated influenza cases was selected assuming an IVE of 60% as the required number of vaccinated 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 vaccinated 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. Additionally, for some age groups, the influenza vaccination coverage has been reported to be higher in the 2020/21 season as compared to the 2019/20 season. For the combinations of input parameters considered, the required number of exposed cases increased with increasing vaccination coverage, and the required number of vaccinated cases reported in Table 15 is expected to be lower than if it was based on the vaccination coverage of 2020/21, this is in line with preventing the cut-off from being too stringent.

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 15. Vaccination coverage among control subjects and control:case ratio observed in the DRIVE data from the 2019/2020 season and the number of vaccinated influenza cases required to perform the analyses in the 2020/21 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 exposed influenza cases required for performing the analysis	7	5	9	7	6	9

15 Statistical analysis

15.1 Descriptive analyses not directly related to the IVE analyses

Several tables describing the data retrieved, epidemiological aspects, and characteristics of the vaccine distribution will be constructed using the data on all subjects which adhered to the in- and exclusion criteria (see Section 8). More particularly the following data will be reported:

- A table describing the site-specific dates of the first and last recorded swabs and the study period (Mock Report Table 2).
- A table describing which brands were observed to have been used in the different countries by age group (Mock Report Table 3).
- A table describing the influenza characteristics, including the distribution of the subtypes and lineages observed in the DRIVE dataset (Mock Report Table 4).
- A table comparing the clinical signs and symptoms around the point of admission among hospitalized influenza and hospitalized COVID-19 cases (Mock Report Table 14). A similar site-specific table will be included in the Web Appendix.
- A table comparing the site-specific vaccine coverage among controls in the seasons 2018/19 to 2020/21 will be created, for any vaccine (see Mock Report Table 9) and by brand.

15.2 Site-specific analysis: test-negative design studies

15.2.1.1 **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 6). In case no study period could be defined for a specific site, no analyses will be performed for that site.
- Subjects do not adhere to the study in- and exclusion criteria (see Section 8).
- 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 12).
- Subjects that are potentially vaccinated (see Section 10.1).
- Subjects that are vaccinated <14 days prior to symptom onset (see Section 10.1).

For every TND study site, an attrition diagram will be created. The attrition diagram describes the number 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 the recruitment level or at the data transfer level (Table 7),

which will not be captured in the attrition diagrams generated at the central analysis level. See the Mock report for an example of an attrition diagram. In the case no subjects are included for a specific site after the attrition diagram criteria have been applied, the data will not be considered in the IVE analyses.

15.2.2 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.
- Influenza positivity rate over time.
- Distribution of vaccine brands.
- Distribution of covariates among cases and controls.

Example visualizations are given in Mock Report Figures 3, 4, and 5. For every TND study site, the Web Annex will include a table based on the final data will be created with characteristics of cases and controls (overall and by vaccination status and brand) In case a descriptive table contains cells with a single subject, which might allow the identification of individuals, all table cells with a frequency equal to either the smallest or second smallest frequencies reported in the table will be left blank.

15.2.3 Influenza vaccine effectiveness estimation

In case the number of influenza cases included in the pooled data set meets the criteria outlined in Section 14.2 the IVE estimated will be calculated for each TND study.

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 by subtype/lineage) will be estimated stratified by age (6m-17yr, 18-64yr, ≥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 similar to the set of confounders used in Lane *et al* (7) will be used similarly. The parsimonious set of confounders will include sex, a smooth function of age, and a smooth function of the onset date. The selection of this set of confounders was based on a post-hoc analysis of the 2018/19 TND data in which no major differences in the results were observed when using either the parsimonious set of confounders or all available confounders. The smooth functions of age and onset date will be modeled using 10-dimensional cubic regression splines. The spline effects and coefficients included in the logistic regression model will be estimated using restricted maximum likelihood estimation (REML) which is also used to select an optimal smoothing parameter (8). In case fewer than 10 unique age or onset date values are observed, the effect of age or onset date will be modeled using a linear function instead.

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.

15.2.4 Sensitivity analysis

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

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

Extended confounder-adjustment, number of GP visits/hospitalizations:
A sensitivity analysis will be performed, using an extended set of confounders including sex, a smooth function of age, a smooth function of the date of symptom onset, and the number of GP visits/hospitalizations (when available) to allow further exploration of the impact of covariate adjustment on the IVE estimates.

Extended confounder-adjustment, pregnancy:
A sensitivity analysis will be performed, using an extended set of confounders including sex, a smooth function of age, a smooth function of the date of symptom onset, and pregnancy to allow further exploration of the impact of covariate adjustment on the IVE estimates.

Time between ILI/SARI onset and swab:
Subjects will be excluded when the respiratory specimen was taken ≥ 4 days after ILI/SARI onset.

Estimation using Firth corrected estimation procedure
A sensitivity analysis in which the logistic regression model parameters are estimated using the Firth corrected maximum likelihood estimator (9). This method allows the estimation of finite coefficients when the standard maximum likelihood estimator leads to infinite estimates, e.g. when a cell of the corresponding exposure—disease 2x2 table is zero.

Site-specific analysis: cohort study

15.2.5 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.

15.2.6 Descriptive analysis

The number of vaccinated and unvaccinated person-years and influenza cases by age group will be reported (Mock Report Table 6).

Visualizations based (Mock Report Figure 6) on the final data for analysis will be created, including:

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

The Web Annex will include a table based on the final data and describe the characteristics of the exposed and unexposed subjects. The table will be constructed with both laboratory-confirmed influenza and inpatient laboratory-confirmed influenza as the outcome of interest

15.2.7 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 (any and by influenza type) and against any inpatient laboratory-confirmed influenza (any and by influenza type) will be estimated stratified by age (6m-17yr, 18-64yr, ≥65yr), as:

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

where *IRR* denotes the confounder-adjusted incidence rate ratio, 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 similar to the set of confounders used in Lane *et al* (7) will be used similarly. The parsimonious set of confounders will include sex, a smooth function of age, and a smooth function of the calendar week.

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 week will be modeled by penalized cubic regression splines (8) estimated using restricted maximum likelihood for smoothness selection (10).

15.2.8 Sensitivity analysis

The following sensitivity analysis will be conducted:

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

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

15.3 Pooled analysis

As this season NIID is a dedicated COVID-19 hospital all subjects will be infected with COVID-19. As all influenza infections are therefore co-infections, NIID will be excluded from the main analysis. An analysis with the NIID data included will be considered in a sensitivity analysis.

15.3.1 Descriptive analysis

The number of cases and controls and the proportion vaccinated will be shown by age group for the primary care and the hospital setting (Mock Report Table 5).

For the combined TND data, visualizations (Mock Report Figures 3, 4, and 5) 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.
- Influenza positivity rate over time

For the combined TND data, a table showing for each combination of setting, age group and exposure the total number of subjects, number of cases and controls overall and by vaccination status will be created (see Mock Report Tables 7 and 8); and tables based on the final data will be created with characteristics of cases and control by age group and setting).

15.3.2 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, 18-64yr, ≥65yr) and setting (primary care, hospital).

The population-based cohort study (THL, Finland) will not be considered for inclusion in the pooled analysis as potential issues due to differences between the study types, e.g., differences in case definitions, likely outweigh the limited added value.

15.3.3 Meta-analysis

Random-effects meta-analysis (RE MA) (11) 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 (12-14). The meta-analytical approach additionally allows to easily combine DRIVE IVE estimates with estimates obtained by other networks when appropriate.

Pooled estimates will be stratified by age group (6m-17yr, 18-64yr, ≥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-analyzed) estimate (and 95% confidence intervals – CIs), as the REML estimator outperforms other RE MA estimators in terms of bias and statistical efficiency (15). 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 (16). The estimates (and 95% CIs) will then be back-transformed to obtain the pooled IVE estimate (and 95% CIs), expressed in %. In case site-specific estimates could not be obtained due to convergence issues they will be excluded from the meta-analysis and the corresponding descriptive tables.

15.3.4 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 (17). 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 for deciding on the appropriateness of pooling as the RE MA model accounts for different levels of between-study heterogeneity.

15.3.5 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 in the meta-analysis stage 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 (18).

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

15.3.6 Sensitivity analysis

The following sensitivity analysis will be conducted:

Extended confounder-adjustment, presence of at least one chronic condition:
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, and the presence of at least one chronic to allow further exploration of the impact of covariate adjustment on the IVE estimates.

Extended confounder-adjustment, number of GP visits / hospitalizations:
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, and the number of GP visits/hospitalizations (when available) to allow further exploration of the impact of covariate adjustment on the IVE estimates.

Extended confounder-adjustment, pregnancy:
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, and pregnancy to allow further exploration of the impact of covariate adjustment on the IVE estimates.

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.

Inclusion of NIID
The data from NIID will be included in the meta-analysis.

Site-specific estimates obtained using estimation method with Firth correction
As a sensitivity analysis, the IVE estimates obtained using the Firth corrected estimation procedure will be pooled using the two-stage estimation procedure.

One-stage pooling
A sensitivity analysis in which the IVE is estimated using a generalized linear mixed model will be explored. The model will be based on the site-specific model and include the parsimonious set of confounders. To account for site-specific differences, a random site effect will be added to the intercept and all other regression coefficients. In case inclusion of all random effects leads to convergence issues, a model in which only the intercept and vaccination variable have a random effect will be used instead. All random effects will be assumed to have a normal distribution.

16 Presentation of results

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

17 Software

All data management and statistical analyses will be conducted in R 4.0.3. Git will be used for version control.

18 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. This is especially relevant in the 2020/21 season in which non-pharmaceutical interventions are widely used to limit the spread of COVID-19 which will likely impact the number of influenza cases included in the individual studies. Additionally, due to the ongoing COVID-19 pandemic the influenza vaccination patterns are likely to be significantly different in the 2020/21 season as compared to previous seasons. Similarly, also heathcare seeking behaviour and healthcare access is likely to have changed as compared to previous seasons.

For three 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.

19 Quality control procedures

19.1 Documentation

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

19.2 Record retention

Documents that permit evaluation of the conduct of a study and the quality of the data will be retained for 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.

19.3 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 the 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 reported site-specific and pooled statistical analyses match with the 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 the DRIVE Steering Committee. The conclusion of QCAC will be described in a quality report and attached to the final study report.

20 Ethics considerations

20.1 Ethics approval

Ethics committee clearance was required for yearly IVE assessment, with the exception of Finland THL, Italy ISS, 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 (Table 16). The submissions to the ethics committee were mostly performed during summer, often in July, before the beginning of the influenza season. The average time from submission to the endorsement from the ethics committee was 5 weeks, ranging from 1 to 12 weeks.

Table 16. DRIVE 2020/21 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
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 20, 2020
CIRI-IT BIVE	Italy	Comitato Etico Regionale	Sept 15, 2020
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	CEIC de la Dirección General de Salud Pública y del Centro Superior de Investigación en Salud Pública	Dec 21, 2009
HUVH	Spain	Comité Ético de Investigación Clínica del Hospital Universitari Vall d'Hebron	Oct 13, 2020
LPUH	Spain	Comité de Ética de la Investigación con medicamentos del Hospital Universitario La Paz	Dec 3, 2020
SUH	Spain	Comité de Ética de la Investigación con medicamentos del Área de Salud de Salamanca	Oct 28, 2020
HURJC	Spain	CEIM Instituto de Investigación Sanitaria – Fundación Jiménez Díaz (FIIS-FJD)	Oct 23, 2020

20.2 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.

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