Brand-specific influenza vaccine effectiveness in Europe Statistical Analysis Plan Season 2018/19

777363 - DRIVE

Development of robust and innovative vaccine effectiveness

WP7 - IVE studies

Lead contributor	Kaatje Bollaerts (P95)
Other contributors	Anke Stuurman (P95) Maria Alexandridou (P95) Marga Riera (P95)

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aTIV	Adjuvanted trivalent influenza vaccine
BIVE-HOSP	Italian Hospital Network
BMI	Body mass index
CI	Confidence interval
CIRI-IT	Centro Interuniversitario di Ricerca sull'Influenza e sulle altre infezioni trasmissibili
DRIVE	Development of Robust and Innovative Vaccine Effectiveness
DRIVE ESSA	DRIVE Electronic Study Support Application
DRIVE QCAC	DRIVE Quality Control and Audit Committee
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
FISABIO	Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana
GPP	Good Participatory Practice
HCW	Healthcare worker
HUCH	Helsinki University Central Hospital
ILI	Influenza like illness
IMI	Innovative Medicines Initiative
ISS	Istituto Superiore di Sanita
IVE	Influenza vaccine effectiveness
LAIV	Live-attenuated influenza vaccine
LCI	Laboratory-confirmed influenza
MUV	Medical University Vienna
NIID	National Institute for Infectius Diseases "Prof. Dr. Matei bals"
OR	Odds ratio
QIV	Non-adjuvanted quadrivalent influenza vaccine
RCGP	Royal College of General Practitioners
RE MA	Random-effects meta-analysis
REML	Restricted maximum likelihood
RR	Relative risk
RT-PCR	Reverse transcription polymerase chain reaction
SAP	Statistical Analysis Plan
SARI	Severe acute respiratory infection
THL	National Institute for Health and Welfare
TIV	Non-adjuvanted trivalent influenza vaccine
TND	Test negative design
UNIS	University of Surrey
UoA	National and Kapodistrian University of Athens
UK	United Kingdom
VE	Vaccine effectiveness
VHUH	Vall d'Hebron University Hospital

1 Background

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

In DRIVE, data from several independently operating national or regional study sites will be analysed jointly to obtain sufficient geographical coverage and sample size for brand-specific IVE estimates.

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 tools and processes developed during the pilot season 2017/18, will be used and further improved in the 2018/19 season.

The main objective of the 2018/19 season is to estimate brand-specific seasonal IVE in Europe by health care setting and age group. The DRIVE platform is still expanding, and not all vaccine brands used in Europe will be covered during the 2018/19 season.

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 2018/19 influenza season.

2 Reference documents

For this pilot season, the SAP has been developed using the following documents:

- DRIVE Generic protocols (D7.1 and D7.2)
- DRIVE 2018/19 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:

- DRIVE minimal data requirements (ANNEX 1)
- DRIVE Electronic Study Support Application (ESSA) user manual (ANNEX 2)
- List of chronic conditions by study site

3 Study team

3.1 DRIVE WP7

Margarita Riera. MD. Epidemiologist. P95, Leuven, Belgium.
Kaatje Bollaerts PhD. Statistician. P95, Leuven, Belgium.
Anke Stuurman. MSc. Epidemiologist. P95, Leuven, Belgium.
Maria Alexandridou MSc. Data analyst. P95, Leuven, Belgium.
Jorne Biccler PhD. Statistician. P95, Leuven, Belgium.
Tom De Smedt Ir. DRIVE Research server system administrator. P95, Leuven, Belgium.
Topi Turunen. MD, Scientific Project Manager, FISABIO-Public Health.
Ritva Syrjänen. MD, PhD. Expert Scientist. Department of Public Health Solutions. THL, Tampere, Finland
Hanna Nohynek. MD PhD Chief Physician. Deputy Head of Unit of Infectious Diseases Control and Vaccinations. Co-lead of Expert group on Influenza and Viral Acute Respiratory Infections. THL, Helsinki Finland.
Miriam Levi. MD, PhD. Epidemiology Unit, Department of Prevention, Local Health Unit Tuscany Center, Florence, Italy.
Caterina Rizzo. MD. Epidemiologist. Ospedale Pediatrico Bambino Gesu (Rome, Italy). National Focal Point for the Influenza and other respiratory viruses ECDC Program.
Uy Hoang. Dr. MBBS, MPH, Research Fellow, University of Surrey, Guildford, UK.
Stefania Bellino. PhD. Statistician, Senior Researcher, Istituto Superiore di Sanità, Rome, Italy
Ornella Punzo. MD, MScPH, Internal Medicine Specialist, Researcher, Istituto Superiore di Sanità, Rome, Italy

3.2 Independent Scientific Committee (ISC)

Hector Izurieta, MD, Food & Drug Administration, United States

Liz Miller, Prof, Public Health England, United Kingdom

Mark Miller, MD, National Institutes of Health, United States

Marianne van der Sande, MD, Prof, Institute of tropical medicine Antwerp, Belgium

Stefania Salmaso, MD, independent consultant; formerly National Institute of Health, Italy

3.3 Study sites

Medical University Vienna (MUV), Austria

Monika Redlberger-Fritz. PhD, MD, Center of Virology, Medical University Vienna (MUW), Kinderspitalgasse 15, 1090 Vienna, Austria. Principal investigator, coordinating investigator and protocol author.

Therese Popow-Kraupp. Prof. MD, Center of Virology, MUW, Kinderspitalgasse 15, 1090 Vienna, Austria. Investigator and protocol author.

Helsinki University Central Hospital (HUCH), Finland

Kirsi Skogberg. MD PhD Specialist in infectious diseases and internal medicine. Division of Infectious Diseases, HUCH Inflammation Center, Helsinki University Central Hospital, Jorvi Hospital, Espoo, Finland. Primary investigator.

Raija Auvinen. MD, clinical coordinator, Division of Internal Medicine and Rehabilitation, Helsinki University Hospital, Finland. Co-investigator.

Outi Debnam. Division of Infectious Diseases, HUCH Inflammation Center, Helsinki University Hospital, Finland. Study nurse.

Marja-Leena Michelsson. Division of Infectious Diseases, HUCH Inflammation Center, Helsinki University Hospital, Finland. Study nurse (part time).

Raisa Loginov. PhD, specialist in virology, Helsinki University Hospital, Helsinki. Co-investigator.

Niina Ikonen. MSc, Senior specialist (virology), Department of Health Security, Unit of Expert Microbiology, Helsinki. Co-investigator.

Ritva Syrjänen. MD, PhD, Senior researcher, Department of Public Health Solutions, Public Health Evaluation and Projection Unit, Tampere. Co-investigator.

The National Institute for Health and Welfare (THL), Finland

Hanna Nohynek. MD PhD Chief Physician. Deputy Head of Unit of Infectious Diseases Control and Vaccinations. Co-lead of Expert group on Influenza and Viral Acute Respiratory Infections. National Institute for Health and Welfare (THL), Helsinki Finland. Principal Investigator of the study.

Ulrike Baum. MSc. Statistical researcher. Department of Public Health Solutions. THL, Helsinki, Finland. Principal statistician of the study.

Ritva Syrjänen. MD PhD Senior Researcher. Department of Public Health Solutions. THL, Tampere, Finland. Clinical trials and register study specialist of the study.

Pregnancy: 1st Department of Obstetrics and Gynecology, "Alexandra" General Hospital of Athens, National and Kapodistrian University of Athens (UoA), Medical School, Athens, Greece

Helena Maltezou. Dr. Head, Department for Interventions in Healthcare Facilities, Hellenic Center for Disease Control and Prevention, Athens, Greece, Principal investigator.

Alexandros Rodolakis. Prof. 1st Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens, «Alexandra» General Hospital of Athens, Athens, Greece. Co-principal investigator.

Dimitrios Loutradis. Prof. , Chairman 1st Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens, «Alexandra» General Hospital of Athens, Athens, Greece. Scientific advisor.

Centro Interuniversitario di Ricerca sull'Influenza e sulle altre infezioni trasmissibili (CIRI-IT), Italy

Giancarlo Icardi. MD Director of CIRI-IT. Full Professor of Hygiene and Preventive Medicine Department of Health Sciences, University of Genoa, Italy. Hospital Policlinico San Martino Genoa. Principal investigator. Laboratory Coordinator.

Donatella Panatto. PhD. Member of the CIRI-IT scientific committee. Associate Professor of Hygiene and Preventive Medicine Department of Health Sciences, University of Genoa, Italy. Co-investigator.

Paolo Durando. MD. PhD. Member of the CIRI-IT scientific committee. Associate Professor of Occupational Medicine Department of Health Sciences, University of Genoa, Italy. Hospital Policlinico San Martino Genoa. Co-investigator.

Andrea Orsi. MD. PhD. Member of the CIRI-IT scientific committee. Researcher of Hygiene and Preventive Medicine Department of Health Sciences, University of Genoa, Italy. Hospital Policlinico San Martino Genoa. Co-investigator. Laboratory Coordinator of Genoa Unit

Piero Luigi Lai. PhD. Department of Health Sciences, University of Genoa, Italy. Technical project and data manager.

Elena Pariani. PhD. Member of the CIRI-IT scientific committee. Department of Biomedical Sciences for Health, University of Milan, Italy. Co-investigator. Laboratory Coordinator of Milan Unit

Silvana Castaldi. Department of Biomedical Science for Health, University of Milan, Italy - Fondazione IRCCS Ca' Granda Ospedale Maggiore di Milano, Italy. Co-investigator.

Istituto Superiore di Sanita (ISS), Italy

Maria Rita Castrucci. PhD. Biologist. Head of the National Influenza Center at the Department of Infectious Diseases, ISS, Rome, Italy. Influenza virus expert.

Simona Puzelli. PhD. Biologist at the Department of Infectious Diseases, ISS, Rome, Italy. Influenza virus expert.

Antonino Bella. Statistician in the Department of Infectious Diseases of the National Institute of Health, ISS, Rome, Italy. Head of the Influenza Surveillance System (InfluNet). Statistician and data manager.

Italian Hospital Network (IT-BIVE-HOSP), Italy

Caterina Rizzo. MD. Innovation Unit and Clinical Paths, Directorate of Clinical Departments. Bambino Gesù Children's Hospital, Rome, Italy. Principal investigator.

Elisabetta Pandolfi. MD Innovation Unit and Clinical Paths, Directorate of Clinical Departments. Bambino Gesù Children's Hospital, Rome, Italy. Technical project manager.

Francesco Gesualdo. MD Innovation Unit and Clinical Paths, Directorate of Clinical Departments. Bambino Gesù Children's Hospital, Rome, Italy. Technical project manager.

Christian Napoli. MD Department of medical-surgical sciences and translational medicine, University of Rome "Sapienza", Lazio Region. Principal Investigator in one of the participating hospitals.

Maria Chironna. Biologist. Department of Biomedical science and medical Oncology of the University of Bari, Puglia Region. Principal Investigator in one of the participating hospitals.

Andrea Orsi. MD IRCCS University Hospital San Martino, Genoa, Liguria Region. Principal Investigator in one of the participating hospitals.

Ilaria Manini. Biologist. Department of Physiopathology, Experimental Medicine and Public Health, University of Siena, Tuscany Region Principal Investigator in one of the participating hospitals.

National Institute for Infectious Diseases "Prof. Dr. Matei Balș", Romania

Anca Drăgănescu, MD, PhD. Senior specialist paediatrics. Specialist infectious diseases. National Institute for Infectious Diseases "Prof. Dr. Matei Balș", Bucharest, Romania. Project manager and principal investigator – children.

Daniela Pițigoi, MD, PhD. Senior specialist epidemiology. Assoc. Prof. Epidemiology. National Institute for Infectious Diseases "Prof. Dr. Matei Balș", Bucharest, Romania. Technical project manager.

Oana Săndulescu, MD, PhD. Specialist infectious diseases. Assoc. Prof. infectious diseases National Institute for Infectious Diseases "Prof. Dr. Matei Balș", Bucharest, Romania. Principal investigator – adults.

Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO), Spain

Javier Díez-Domingo. PhD. MD. Paediatrician. Head of the Vaccine Research Department of FISABIO-Public Health. (Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana). Avenida de Cataluña, 21, 46020, Valencia. Principal investigator.

Ainara Mira-Iglesias. Mathematician. Master's degree in Biostatistics. Statistician in the Vaccine Research Department of FISABIO-Public Health. Avenida de Cataluña, 21, 46020, Valencia. Data analyst of the study.

F. Xavier López-Labrador. PhD. Virologist. Senior Laboratory Coordinator in the Genomics Department of FISABIO-Public Health. Avenida de Cataluña, 21, 46020, Valencia. Consorcio de Investigación Biomédica de Epidemiología y Salud Pública (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain. Laboratory Coordinator and Virologist of the study.

Javier García-Rubio. Pharmacist. Master's degree in Clinical Trials. Research assistant in the Vaccine Research Department of FISABIO-Public Health. Avenida de Cataluña, 21, 46020, Valencia. Data Manager of the study.

Mario Carballido-Fernández. PhD. MD. Hospital General Universitario de Castellón, Castellón, Spain. Universidad CEU Cardenal Herrera, Castellón, Spain. Principal investigator in one of the participating hospitals.

Miguel Tortajada-Girbés. PhD. MD. Hospital Universitario Doctor Peset, Valencia, Spain. Principal investigator in one of the participating hospitals.

Juan Mollar-Maseres. PhD. MD. Hospital Universitario y Politécnico La Fe, Valencia, Spain. Principal investigator in one of the participating hospitals.

German Schwarz-Chavarri. PhD. MD. Hospital General Universitario de Alicante, Alicante, Spain. Principal investigator in one of the participating hospitals**.**

Vall d'Hebron University Hospital (VHUH), Barcelona, Spain

Magda Campins Martí. (MD,PhD) Head of the Department, Preventive Medicine and Epidemiology Department, HUVH, Barcelona, Spain. Principal investigator.

José Ángel Rodrigo Pendás (MD) Clinical researcher, Preventive Medicine and Epidemiology Department, HUVH, Barcelona, Spain. Investigator.

Sonia Uriona (MD) Clinical researcher, Preventive Medicine and Epidemiology Department, HUVH, Barcelona, Spain. Investigator.

Eva del Amo (PhD) Researcher, Preventive Medicine and Epidemiology Department, HUVH, Barcelona, Spain. Research technician.

Andrés Antón Pagarolas (PhD) Head of Respiratory Viruses Unit, Microbiology Department, HUVH, Barcelona, Spain. Investigator.

Royal College of General Practitioners (RCGP) & University of Surrey (UNIS), United Kingdom

Prof Simon de Lusignan. Prof. Professor of Primary Care and Clinical Informatics. Chair in Health Care Management, University of Surrey, UK. Principal Investigator.

Uy Hoang. Research Fellow. Department of Clinical and Experimental Medicine, University of Surrey, UK.

Ivelina Yonova. Department of Clinical and Experimental Medicine, University of Surrey, UK. Practice Liaison Officer.

Rachel Byford Senior Database Developer. Department of Clinical and Experimental Medicine, University of Surrey, UK.

Dr Mark Joy. Senior Lecturer in Data Modelling and Population Health. Department of Clinical and Experimental Medicine, University of Surrey.

Filipa Ferreira. PhD Department of Clinical and Experimental Medicine, University of Surrey, UK. Project Manager

Tristan Clark. Associate Professor and Honorary Consultant in Infectious Diseases. NIHR Post-Doctoral Fellow. Academic Unit of Clinical and Experimental Sciences, University of Southampton.

4 Objectives

4.1 Primary objective

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

- any laboratory-confirmed influenza
- laboratory-confirmed influenza A, overall and by subtype (A(H1N1), A(H3N2))
- laboratory-confirmed influenza B, overall and by lineage (B Victoria, B Yamagata)
- brand-specific IVE only: any laboratory-confirmed influenza subtype/lineage included in the vaccine brand

4.2 Secondary objective

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

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

any laboratory-confirmed influenza subtype/lineage included in the vaccine type
The following vaccine types will be considered:

- Trivalent non-adjuvanted
- Trivalent adjuvanted
- Quadrivalent live attenuated
- Quadrivalent inactivated

4.3 Exploratory objective

To estimate seasonal **overall** IVE against laboratory-confirmed influenza stratified by setting (primary care, hospital-based or mixed) and age group (6m-17yr, 18-64 yr, ≥65yr whenever relevant),within **risk groups**, 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 risk groups will be considered:

- Pregnant women
- Healthcare workers
- Presence of chronic conditions by the following sub-categories;
    - Cardiovascular disease
    - Lung disease
    - Diabetes

Pregnant women and healthcare workers were selected as risk groups of interest as two studies were specifically designed to investigate these risk groups (pregnancy study by University of Athens, healthcare workers study by CIRI-IT, Italy). The three chronic conditions (cardiovascular disease, lung disease and diabetes) were chosen to explore the feasibility of estimating IVE by risk group as they are believed to be chronic conditions with the highest prevalence (see Section 12.4).

5 Study design

A multi-centre study with data available from four 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). A list of the participating study sites according to study design and setting is 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. The characteristics of the site-specific studies are summarized in Table 2 for the TND studies and Table 3-Table 5 for the cohort studies. 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 their data becomes available prior to 15th May 2019.

National Institute for Infectious Diseases "Prof. Dr. Matei Balș", Romania

Table 1. Overview of the participating study-sites, 2018/19

Test-negative design studies, primary care: 1. Medical University Vienna (MUV), Austria 2. Centro Interuniversitario di Ricerca sull'Influenza e sulle altre infezioni trasmissibili (CIRI-IT), Italy 3. Royal College of General Practitioners (RCGP) & University of Surrey (UNIS), United Kingdom 4. Istituto Superiore di Sanita (ISS), Italy
Test-negative design studies, hospital based: 1. Medical University Vienna (MUV), Austria 2. Helsinki University Central Hospital (HUCH), Finland 3. Italian Hospital Network (IT-BIVE-HOSP), Italy 4. Centro Interuniversitario di Ricerca sull'Influenza e sulle altre infezioni trasmissibili (CIRI-IT), Italy 5. Vall d'Hebron University Hospital (VHUH), Barcelona, Spain 6. Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO), Spain 7. National Institute for Infectious Diseases 'Prof. Dr. Matei Bals' (NIID), Romania
Register-based cohort study: 1. The National Institute for Health and Welfare (THL), Finland
Clinical cohort studies: 1. Pregnancy: 1st Department of Obstetrics and Gynecology, "Alexandra" General Hospital of Athens, National and Kapodistrian University of Athens (UoA), Medical School, Athens, Greece 2. Healthcare workers: Centro Interuniversitario di Ricerca sull'Influenza e sulle altre infezioni trasmissibili (CIRI-IT), Italy

Table 2. Overview of test-negative design study sites characteristics - 2018/19

Site	MUV	CIRI-IT	ISS	RCGP/ UNIS	MUV	HUCH	BIVE-HOSP	NIID	VHUH	FISABIO
Country	Austria	Italy	Italy	UK	Austria	Finland	Italy	Romania	Spain	Spain
Setting	Primary care	Primary care	Primary care	Primary care	Hospital	Hospital	Hospital	Hospital	Hospital	Hospital
Source of cases	80 primary care physicians	21 primary care physicians	Ca. 1000 primary care physicians	6 primary care practices	1 hospital	1 hospital	5 hospitals	1 hospital	1 hospital	4 hospitals
Population	General population ≥6 months	General population ≥6 months	General population ≥6 months	General population ≥6 months	General population ≥6 months	General population ≥18 years	General population ≥6 months	General population ≥6 months	General population ≥6 months	General population ≥6 months
Expected sample size (number lab confirmed)	900* (n.a.) *together with hospital	1,500 (500)	2,380 (n.a.)	1,200 (400)	900* (n.a.) *together with hospital	600 (125)	2,488 (n.a.)	400 (150)	1,600 (800)	2,000 (n.a.)
Start data collection	01.10.2018	05.11.2018	15.10.2018	11.02.2019	01.10.2018	26.11.2018	26.11.2018	12.11.2018	13.12.2018	10.09.2018
Case definition	ILI[(1)]	ILI[(1)]	ILI[(1)]	ILI[(1)]	SARI[(2)]	SARI[(2)]	SARI[(2)]	SARI[(2)]	SARI[(2)]	<5y:Hospitalized for any acute reason ≥5y: ILI[(3)]
Case										
Sampling strategy[(4)]	Undefined	Predefined rules	All	Predefined rules	Undefined	All	All	All	All	All
Type of swab	Naso-pharyngeal	Nasal or oropharyngeal	Throat swab	Nasal	Nasopharyngeal	Nasal and throat or nasopharyngeal	Pharyngeal or nasopharyngeal	<14y: nasopharyngeal and nasal ≥14y: nasopharyngeal and pharyngeal	< 18y: usually nasopharyngeal >18 y: nasopharyngeal and/or pharyngeal and/or bronchoalveolar l	<14y: nasopharyngeal and nasal ≥14y: nasopharyngeal and pharyngeal
Who swabs	HCW	HCW	HCW	HCW	HCW	HCW	HCW	HCW	HCW	HCW

Table 2. Overview of test-negative design study sites characteristics - 2018/19, continued

Site	MUV	CIRI-IT	ISS	RCGP/ UNIS	MUV	HUCH	BIVE-HOSP	NIID	VHUH	FISABIO
Country	Austria	Italy	Italy	UK	Austria	Finland	Italy	Romania	Spain	Spain
Laboratory test influenza	RT-PCR	RT-PCR or rapid diagnostic test	RT-PCR	RT-PCR desktop analyser	RT-PCR	RT-PCR	RT-PCR	RT-PCR	< 18y: Antigen detection > 18y: PCR	RT-PCR
A/subtype	Yes	Yes	Yes	No	Yes	Yes	Yes	Partial (H only)	Yes	Yes
B/lineage	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Laboratory test subtyping	RT-PCR	RT-PCR	RT-PCR	n/a	RT-PCR	Real-time RT-PCR	RT-PCR	RT-PCR		RT-PCR
Source of vaccination status	-Medical records -Otherwise, patient/ relatives interview	-Vaccine register -Medical records	-Medical records	- Medical records	-Medical records	-Vaccine register -Vaccine card	-Primary care physician interview (for patients indicating being vaccinated or not knowing vaccination status)	-Vaccine card -HCW interview -Patient/ relatives interview	-Vaccine register -Medical records -Vaccine card -Otherwise, patient/ relatives interview	-Vaccine register

Table 2. Overview of test-negative design study sites characteristics - 2018/19, continued

Site	MUV	CIRI-IT	ISS	RCGP/ UNIS	MUV	HUCH	BIVE-HOSP	NIID	VHUH	FISABIO
Country	Austria	Italy	Italy	UK	Austria	Finland	Italy	Romania	Spain	Spain
Covariates available for adjustment	Age, sex, date of swab, 1+ chronic condition, pregnancy	Age, sex, date of swab, 1+ chronic condition, pregnancy, nr of primary care visits in last 12 months, influenza vaccination in previous season	Age, sex, date of swab, 1+ chronic condition, nr of primary care visits in last 12 months, influenza vaccination in previous season	Age, sex, date of swab, 1+ chronic condition, pregnancy, nr of primary care visits in last 12 months, influenza vaccination in previous season	Age, sex, date of swab, 1+ chronic condition, pregnancy,	Age, sex, date of swab, 1+ chronic condition, pregnancy, nr of hospitalisations in last 12 months, influenza vaccination in previous season	Age, sex, date of swab, 1+ chronic condition, influenza vaccination in previous season, nr of hospitalisations in last 12 months, for 65+: frailty	Age, sex, date of swab, 1 chronic condition or more pregnancy, nr of hospitalisations in last 12 months, influenza vaccination in previous season	Age, sex, date of swab, 1+ chronic condition, pregnancy, nr of hospitalisations in last 12 months, influenza vaccination in previous season	Age, sex, date of swab 1+ chronic condition, pregnancy, nr of hospitalisations in last 12 months, influenza vaccination in previous season

H: hemagglutinin; ILI: influenza-like illness; LCI: laboratory-confirmed influenza; n/a: not applicable; HCW: healthcare worker; RT-PCR: Reverse transcription polymerase chain reaction. (1) ECDC case definition (2) IMOVE+ 2017/2018 case definition
(3) ECDC case definition, without "sudden onset" (4) Sampling strategies 1) all: all patients with ILI or SARI are sampled; 2) 'predefined rules': systematic sampling according to predefined rules; 3) 'undefined': non-systematic sampling at practioner's discretion. More details on the sampling strategies are given in Table 8.

Table 3. Overview of register-based cohort study, 2018/19

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	~1555300 (31.12.2017)
Start data collection	Ongoing
Case	LCI positive
Sampling strategy(1)	undefined
Type of swab	Nasopharyngeal swabs or nasal and/or throat swabs or nasopharyngeal aspirates (sometimes other clinical samples) analysed by real time RT-PCR, multiplex RT-PCR, culture and/or antigen detection
Who takes swab	HCW
Laboratory test influenza diagnosis	RT-PCR, Antigen detection
A/subtype available	No
B/lineage available	No
Laboratory test subtyping	n/a
Source of vaccination status	Vaccine register
Covariates available for adjustment	Age, sex, calendar week at influenza test, 1 chronic condition or more, number of hospitalizations in the last 12 months, number of primary care consultations in the last 12 months, influenza vaccination in previous season

LCI: laboratory-confirmed influenza; n/a: not applicable; RT-PCR: Reverse transcription polymerase chain reaction, HCW: healthcare worker
(1) Sampling strategies 1) all: all patients with ILI or SARI are sampled; 2) 'predefined rules': systematic sampling according to predefined rules; 3) 'undefined': non-systematic sampling

Table 4. Overview of clinical cohort study in pregnant women and their young adults, 2018/19

Site	**UoA**
Country	Greece
Source of cases	Department of obstetrics and gynaecology from 1 hospital
Population	Pregnant women (18y-≤45y), and their infants (≤6 months)
Targeted study size	700 pregnant women in the cohort, 25 laboratory confirmed influenza cases in pregnant women and 140 in infants
Start data collection	17.10.2018
Case definition	ILI (ECDC case definition)
Case	Above clinical case definition + LCI positive
Sampling strategy(1)	All
Type of Swab	Nasal-pharyngeal
Who takes swab	HCW
Laboratory test influenza diagnosis	PCR
A/subtype available	Yes
B/lineage available	Yes
Laboratory test subtyping	PCR
Source of vaccination status	Medical records
Covariates available for adjustment	Age, sex, date of swab, 1 chronic condition or more, gestational age at vaccination (for pregnant women), influenza vaccination in previous season, education, ethnicity, nr of household members, number of children < 5 years, number of labors in the past

ILI: influenza-like illness; LCI: laboratory-confirmed influenza; HCW: health care worker, RT-PCR: Reverse transcription polymerase chain reaction
(1) Sampling strategies 1) all: all patients with ILI or SARI are sampled; 2) 'predefined rules': systematic sampling according to predefined rules; 3) 'undefined': non-systematic sampling at practioner's discretion

Table 5. Overview of clinical cohort study in healthcare workers, 2018/19

Site	**CIRI-IT**
Country	Italy
Source of cases	2 hospitals
Population	Healthcare workers, all ages (≥ 18 years)
Targeted study size	6,000 health care workers in the cohort, 500-700 ILI cases and 200-400 laboratory confirmed influenza cases
Start data collection	08.10.2018
Case definition	ILI (ECDC case definition)
Case	Above clinical case definition + LCI positive
Sampling strategy	All
Swab	Nasal or oropharyngeal
Who takes swab	Self-collected or collected by CIRI-IT medical staff
Laboratory test influenza diagnosis	RT-PCR or rapid diagnostic test
A/subtype available	Yes
B/lineage available	Yes
Laboratory test subtyping	RT-PCR
Source of vaccination status	Vaccine register
Covariates for adjustment	age, sex, date at swab, 1 chronic condition or more, pregnancy, number of hospitalizations in the last 12 months, influenza vaccination in previous season

ECDC: European Center for Disease Prevention and Control; H: hemagglutinin; ILI: influenza-like illness; LCI: laboratory-confirmed influenza; RT-PCR: Reverse transcription polymerase chain reaction; y: years
*Sampling strategies 1) all: all patients with ILI or SARI are sampled; 2) 'predefined rules': systematic sampling according to predefined rules; 3) 'undefined': non-systematic sampling at practioner's discretion
systematic sampling according to predefined rules; 3) 'undefined': non-systematic sampling at practioner's discretion

6 Study population

In all TND studies and the register-based study, the population under study is the general population. In the two clinical cohort studies, the populations under study were pregnant women and their young infants and healthcare workers.

7 Study period

The start of the data collection for the 2018/19 influenza season differs between the sites (Table 2-Table 5).

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 and 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). The study period of analysis might be different for different study sites.

In the particular case of THL (Finland), data is continuously collected throughout the year since they use the national registers. The study period for analysis goes from week 40 till week 20.

8 Case definitions

8.1 Influenza-like illness (ILI)

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

- sudden onset of symptoms

AND, at least one of the following four systemic symptoms:

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

AND, at least one of the following three respiratory symptoms:

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

8.2 Severe acute respiratory infection (SARI)

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

- fever or feverishness;
- malaise;
- headache;
- myalgia;
- deterioration of general condition (asthenia or loss of weight or anorexia or confusion or dizziness)

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

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

at admission or within 48 hours after admission.

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

8.3 Adherence to the case definitions

All study sites follow the ILI or SARI clinical case definitions with the exception of FISABIO (Spain)

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 – Table 6) was in the 7 days prior to admission. For subjects 5 years and above, a modified ECDC ILI case definition is used, being hospitalized with at least one systematic symptom (fever or feverishness, malaise, headache or myalgia) and at least one respiratory symptom (cough, sore throat or shortness of breath) whose onset was in the 7 days prior to admission.

Table 6. FISABIO: symptoms possibly related to influenza

Eligibility diagnosis, symptoms and signs
Acute upper and lower respiratory disease
Dyspnea breathing 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

9 In- and exclusion criteria

9.1 Test-negative design studies

9.1.1 Recommended exclusion criteria

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

1. is unwilling to participate or unable to communicate and give consent (the consent may also be given by her/his legal representative, or by specific consent procedures, acceptable according to the local ethical review process)
2. is less than 6 months of age at the time of the onset of the symptoms
3. has a contraindication for influenza vaccine
4. is institutionalised at the time of symptoms onset
5. will have the respiratory specimen taken ≥ 8 days after ILI onset

6. tested positive for any influenza virus in the current season before the onset of symptoms leading to the current primary care visit/hospitalisation

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

1. is unwilling to participate or unable to communicate and give consent (the consent may also be given by her/his legal representative, or by specific consent procedures, acceptable according to the local ethical review process)
2. is less than 6 months of age at the time of the onset of the symptoms
3. has a contraindication for influenza vaccine
4. is institutionalised at the time of symptoms onset
5. will have the respiratory specimen taken ≥ 8 days after SARI onset
6. tested positive for any influenza virus in the current season before the onset of symptoms leading to the current primary care visit/hospitalisation
7. was previously hospitalised < 48 hours prior to SARI onset
8. had his/her ILI/SARI onset ≥ 48 hours after hospital admission

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

9.1.2 Adherence to the recommended ILI/SARI exclusion criteria

An overview of the adherence to the ILI and SARI exclusion criteria at study recruitment is given in Table 7. All variables related to the exclusion criteria are listed as obligatory variables in the Minimal Data Requirements (ANNEX 1). Records that violate the exclusion criteria will be discarded at analysis stage, whenever possible.

Table 7. Test-negative design studies: overview of exclusion criteria applied at study recruitment, 2018/19

Site	MUV	MUV	HUCH	BIVE-HOSP	CIRI-IT	ISS	NIID	FISABIO	VHUH	RCGP/ UNIS
Country	Austria	Austria	Finland	Italy	Italy	Italy	Romania	Spain	Spain	UK
Setting	PC	HOSP	HOSP	HOSP	PC	PC	HOSP	HOSP	HOSP	PC
Clinical case definition	ILI	SARI	SARI	SARI	ILI	ILI	SARI	ILI	SARI	ILI
1. Unwilling or unable to give consent	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No(1)	Yes
2. Age <6 months at symptom onset	Yes	Yes	n/a	Yes	Yes	Yes	Yes	No*	Yes	Yes
3. Contraindication	No	Yes	Yes	Yes	Yes	Yes	Yes	No*	Yes	Yes*
4. Institutionalized	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes*
5. Respiratory specimen taken ≥ 8 days after ILI onset	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Prior influenza infection in current season	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes*
7. Previously hospitalised < 48 hours prior to ILI onset	n/a	Yes	Yes	Yes	n/a	n/a	Yes	Yes(2)	Yes	n/a
8. ILI onset ≥ 48 hours after hospital admission	n/a	Yes	Yes	Yes	n/a	n/a	Yes	Yes	Yes	n/a
Other local exclusion criteria	No	No	Yes(3)	Yes(4)	No	No	No	Ye(5)	Yes(6)	No

n/a: not applicable, ILI: influenza like illness

* Can be excluded at analysis stage

(1) No informed consent was required as no intervention required for the study fall outside the usual practice of the Hospital Universitari Vall d'Hebron during the influenza season. (2) Patients hospitalized < 30 days from the current hospitalisation are excluded. (3) Not a resident of Espoo, Kauniainen or Kirkkonummi. (4) Antiviral therapy; Remain

in hospital for less than 24 hours.(5) Not residing in hospitals catchment area for at least previous 6 months; Remains in hospital for less than 24 hours. (6) A patient not belonging to the Institut Català de la Salut network

9.2 Cohort studies

9.2.1 THL Finland: register-based cohort study

In the Finnish register-based cohort study, all subjects belonging to the study population and contributing data to the study period (starting 2018, week 40) are included, with the following exclusion criterion applied;

Exclusion criteria:

- subjects with presumably incomplete vaccination records in 2018/19 or 2017/18

9.2.2 Pregnancy cohort

The following in- and exclusion criteria will be applied to all study subjects;

Inclusion criteria:

- age 18 to ≤45 years
- stable health
- presented to the outpatient clinic of the department of obstetrics and gynaecology between October 1 and December 31, 2018

Exclusion criteria:

- is unwilling to participate or unable to communicate (in Greek or English) and give consent
- received influenza vaccine < 6 months prior to study entry
- received any investigational drug or product < 30 days prior to study entry
- history of Guillain-Barré syndrome
- history of hypersensitivity to influenza vaccines or its components
- immunosuppression
- received immunoglobulins or blood products < 3 months

9.2.3 Healthcare workers

The following in- and exclusion criteria will be applied to all study subjects;

Inclusion criteria:

- in service prior to start of follow-up in Week 42 2018

Exclusion criteria:

- is unwilling to participate or unable to communicate and give consent

10 Outcome

10.1 Outcome definition

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

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

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

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

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

For trivalent vaccines, estimating seasonal brand-specific and type-specific IVE against any medically attended laboratory-confirmed influenza included in the vaccine

- Positive: laboratory-confirmed influenza of any of the subtypes and lineage included in the vaccine
- Negative: no laboratory-confirmed influenza

10.2 Case identification

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

At UoA (Greece, pregnancy cohort), all enrolled women are actively followed-up through weekly telephone calls asking about the onset of a febrile episode, acute respiratory infection, ILI, acute otitis media and/or pneumonia, SARI, healthcare seeking, hospitalization and use of antibiotics in women and their infants.

At CIRI-IT (Italy, HCW cohort), all participants were regularly sent reminders through e-mail to call the study team in case of ILI.

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

10.3 Swab sampling strategy

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

- 'all': all patients with ILI or SARI are sampled
- 'predefined rules': systematic sampling according to predefined rules
- 'undefined': non-systematic sampling at practitioner's discretion

The sampling strategies are different for the different sites and might also differ between subpopulations from the same study site. Details on the sampling strategies are given in Table 8.
Swabs are performed by HCW in all studies with the exception of the CIRI-IT HCW cohort, where swabs are self-collected or collected by CIRI-IT medical staff. Self-collected swabs have similar sensitivity to those taken by health-care workers [4, 5] and the extent of postal delay is not associated with the likelihood of PCR positivity for influenza [5].
The type of swabs are either nasal, nasopharyngeal, oropharyngeal, pharyngeal or throat swabs (Table 2-Table 5).
Samples taken >=8 days after ILI onset will be excluded from analysis.

Table 8. Test-negative design studies: overview of swab sampling strategies used, 2018/19

Sampling strategy	Site (Country)
All	BIVE-HOSP (Italy), HUCH (Finland), NIID (Romania) VHUH (Spain), FISABIO (Spain), UoA (Greece, pregnancy cohort), CIRI-IT (Italy, HCW cohort)
Predefined rules	CIRI-IT (Italy): Systematic sampling is encouraged, for example, the first 3 ILI that present each week ISS (Italy): Systematic sampling of the first 2 ILI patients that present each week, and if possible all ≥65years ILI cases RCGP/UNIS (UK): All cases of ILI are encouraged to be swabbed in this study, up to a maximum of 10 per practice, per day
Undefined rules	MUV (Austria), THL (Finland)

10.4 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 or real-time-PCR. Except THL (Finland, register-based cohort) and RCGP/UNIS (UK), all sites are collecting information on influenza subtypes/lineages (A/H1N1, A/H3N2, B/Victoria, and B/Yamagata). An overview of the type of swabs and laboratory tests is given in (Table 2-Table 5).

11 Exposure

11.1 Exposure definition

The exposure of interest is influenza vaccination administered during the season 2018-19.For all objectives, the following exposure definitions will be used.

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

- **vaccinated** with the influenza vaccine of interest if he/she has a record of influenza vaccine administration >14 days before ILI/SARI symptom onset
- **partially vaccinated** if he/she has a record of influenza vaccine administration ≤14 days before ILI/SARI symptom onset
- **unvaccinated** if he/she has no influenza vaccine record for the current season
- **potentially vaccinated** if the positive vaccination status is based on recall alone and cannot be confirmed by registers, or is otherwise ambiguous.

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

- **vaccinated** with the influenza vaccine of interest if >14 days have elapsed since the second record of injectable vaccination or since the first record of LAIV vaccination during the current season
- **partially vaccinated**
    - after the first record of injectable vaccination until the second record of vaccination during the current season
    - during the first 14 days after the second record of injectable vaccination or the first record of LAIV vaccination during the current season
- **unvaccinated** until the first vaccination record during the season
- **potentially vaccinated** if the positive vaccination status is based on recall alone and cannot be confirmed by registers, or is otherwise ambiguous.

Note 1: The *partially* and *potentially* vaccinated groups will be excluded from primary analysis. The significance of the partially vaccinated subjects will be assessed in sensitivity analyses.
Note 2: If no information on exposure in previous season is available in the dataset, the exposure definition 'scenario A' will be used for all subjects.
Note 3: For cohort studies, vaccination status will be treated as time-varying variable whereas for the case-control studies, vaccination status is a fixed variable.

11.2 Source of exposure information

The sources to obtain information on the exposure status were either vaccine registers, medical records or, vaccination cards. (see Table 2-Table 5). Patients for whom the vaccination status is based on recall only, not verified based on vaccination register, medical record or vaccination card are considered ‘potentially vaccinated’ (see Section 11.1), and will be discarded from analysis (see sections 14.1.1 and 14.2.1).

11.3 Expected influenza vaccine brands

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

Table 9. Expected vaccine brands and type – all studies, 2018/19

	Site	MUV	CIRI-IT	ISS	RCGP/ UNIS	MUV	HUCH	BIVE-HOSP	NIID	VHUH	FISABIO	THL	UoA	CIRI-IT
	Country	Austria	Italy	Italy	UK	Austria	Finland	Italy	Romania	Spain	Spain	Finland	Greece	Italy
	Study design	TND	TND	TND	TND	TND	TND	TND	TND	TND	TND	Cohort	Cohort	Cohort
	Setting	PC	PC	PC	PC	HOSP	HOSP	HOSP	HOSP	HOSP	HOSP			
	Approved indication													
TIV Brands														
Afluria	5 years and older		X	X				X						X
Agrippal	6 months and older	X	X	X				X		X				X
Influvac	6 months and older	X	X	X	X	X		X	X		X			X
Vaxigrip	6 months and older		X	X				X						X
Intanza	60 years and older													
QIV brands														
Fluarix tetra	6 months and older	X	X	X	X	X		X		X				X
Influvac tetra	3 years and older	X			X	X			X					
Vaxigrip tetra	6 months and older	X	X	X	X	X	X	X	X			X	X	X
aTIV Brands														
Fluad	65 years and older	X	X	X	X	X		X		X	X			X
LAIV brands														
Fluenz tetra	24 months to 17 years	X			X	X						X		

TIV: Trivalent non-adjuvanted; QIV: Quadrivalent inactivated; aTIV: Trivalent adjuvanted; LAIV: Quadrivalent live attenuated

12 Covariates

The additional covariates collected for adjustment are age, sex, presence of at least one chronic condition, pregnancy, number of GP consultations or hospitalizations, and vaccination status in the previous season. An overview of the covariates are given in Table 10 for the TND studies and in Table 11 for the cohort studies.

Table 10. Data collected on covariates – test-negative design studies, 2018/19

Site	MUV	CIRI-IT	ISS	RCGP/ UNIS	MUV	HUCH	BIVE-HOSP	NIID	FISABIO	VHUH
Country	Austria	Italy	Italy	UK	Austria	Finland	Italy	Romania	Spain	Spain
Setting	PC	PC	PC	PC	HO	HO	HO	HO	HO	HO
Age at symptom onset (1)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes(2)	Yes
Sex	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Presence of at least one chronic condition	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pregnancy	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Number of hospitalizations in the last 12 months	No	Yes (3)	Yes(3)	Yes	No	Yes	Yes (3)	Yes	Yes	Yes
Number of primary care consultations in the last 12 months	No	No	Yes	Yes	No	Yes	Yes(3)	Yes	Yes (4)	Yes
Receipt of influenza vaccination in 2017-18	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

(1) Age in months for children < 1 year, otherwise age in years
(2) Age at hospital admission
(3) Number of hospitalized for any of the chronic conditions of interest (see Annex 3) in the last 12 months
(4) Number of primary care visits during the last 3 months

Table 11. Data collected on covariates – cohort studies, 2018/19

Site	**THL**	**UoA**		**CIRI-IT**
Country	Finland	Greece		Italy
		Pregnant women	Young children	
Age at season onset/cohort inclusion [1]	Yes	Yes	Yes	Yes
Sex	Yes	Yes	Yes	Yes
Presence of at least one chronic condition	Yes	Yes	?	Yes
Pregnancy	n/a	Yes	n/a	Yes
Number of hospitalisations in last 12 months	Yes	No	No	Yes
Number of primary care consultations in the last 12 months	Yes[2]	No	No	No
Receipt of influenza vaccination in 2017-18	Yes	No[3]	n/a	Yes

(1) Age in months for children < 1 year, otherwise age in years

(2) Likely to be an underestimate as private care visits are not counted and follow-up visits are not distinguished from new visits

(3) Any history of influenza vaccination

12.1 Age

Age in years (months for children <1year) at symptom onset.

12.2 Sex

Male or female.

12.3 Date at symptom onset/calendar time

To adjust for time, date at ILI/SARI symptom onset will be used for cohort studies whereas calendar time (in weeks) 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 12. Listings of chronic conditions included per study site can be found in ANNEX 3.

Table 12. Definitions of chronic conditions

Condition	Definition
Chronic liver disease	Any of the following dg codes (ICD-10)*: B18, K70-74, K75.0-75.1, K75.3-75.9, K76-77 INCLUDING: Alcoholic liver disease, Toxic liver disease, Hepatic failure, Chronic hepatitis (viral & other), Fibrosis and cirrhosis of liver, Other inflammatory liver diseases, Other diseases of liver EXCLUDING: Clinically insignificant liver cysts
Diabetes	Any of the following dg codes (ICD-10)*: E10-E14, O24 INCLUDING: Any form of diabetes, including sequelae & DM in pregnancy
Cardiovascular diseases	Any of the following dg codes (ICD-10)*: A52.0, B37.6, I01-02, I05-09, I11.0, I13.0, I13.2, I20-25, I26-28, I30-43, I44-46, I48, I49.0, I49.5, I50-52, I70-71, Q20-Q28 INCLUDING: all conditions of heart & large vessels that are chronic or likely to have chronic sequelae. Cardiovascular syphilis, endo-, myo- and pericarditis, rheumatic fever, chronic rheumatic heart diseases, congenital malformations, hypertensive (renal) diseases with heart failure, ischaemic heart diseases, diseases of pulmonary circulation, atherosclerosis, cardiomyopathies, most conduction disorders, heart failure, aortic aneurysms & dissecation, other heart diseases and their complications. EXCLUDING: uncomplicated hypertension, previous uncomplicated pulmonary embolism (with no lasting cardiac insufficiency), paroxysmal tachycardias, most cases of premature depolarization.
Cancer	Any of the following dg codes (ICD-10)*: C00-97, D37-48, Z85, Z92.3, Z92.6. INCLUDING: All malignant neoplasms (both solid and haematologic) with potential to metastasize, either in treatment, active followup, or <5 years post curative treatment. EXCLUDING: Benign & in situ neoplasms. Basal cell carcinomas. Any cancer previously treated with curative intent & in complete remission for ≥5 years.
Immuno-deficiency or organ transplant	Any of the following dg codes (ICD-10)*: B20-B24, D80–84, D89, Z94 INCLUDING: HIV infections, immunodeficiencies & organ transplants. or iatrogenic: ≥2 week systemic treatment, in the 3 months preceding symptom onset, with any of the following: corticosteroid (≥20 mg prednisolone daily or equivalent), ciclosporin, tacrolimus, mycophenolate, methotrexate, azathioprine, TNF-α blockers and other biological or cytostatic drugs with immunosuppressive effect EXCLUDING: Disorders of the immune system which do not lead to immunosuppression (e.g. some autoimmune conditions).

Table 12. Definitions of chronic conditions, continued

Condition	Definition
Lung disease	Any of the following dg codes (ICD-10)*: A15-16, A19, A31.0, B33.4, E84.0, J40-47, J60-70, J80-84, J85-86, J90-91, J92.9, J93-94, J95-99 INCLUDING: TB (pulmonary, miliary but not that of other systems), atypical mycobacteria, cystic fibrosis, asthma, COPD, bronchiectasis and other chronic sequelae of infections, chronic lung diseases due to external agents, interstitial lung diseases, pleural diseases, respiratory failure. EXCLUDING: acute respiratory infections, lung cancer, diseases of pulmonary circulation, pleural plaques without asbestos, previous uncomplicated pneumothorax.
Anemia	Any of the following dg codes (ICD-10)*: D50-D64 diagnosed before the onset of symptoms. EXCLUDING: coagulopathies, uncomplicated hypersplenism, hepato/splenomegaly (D65-69, D70-77, D80-84, D86, D89)
Renal disease	Any of the following dg codes: (ICD-10)*: I12-13, M10.30, N00-19, N20.0, N25-27, N28.0, N28.9, Q63.9, Z90.5 EXCLUDING: Clinically nonsignificant kidney cysts
Dementia	Any of the following dg codes (ICD-10)*: F00-03, F05.1, G30-31 EXCLUDING delirium w/o underlying dementia, hydrocephalus.
History of stroke	Any of the following dg codes (ICD-10)*: I61-64, I67.8, I69, G93.1 INCLUDING: both ischaemic and haemorrhaegic strokes and anoxic brain damage. Also counting previous episodes and clear ischaemic findings seen in cranial imaging (even if fully recovered / no symptoms).
Rheumato-logic diseases	Any of the following dg codes (ICD-10)*: M05–09, M13, M30–36, M45 INCLUDING rheumatoid diseases with presumed autoimmune origin and primarily musculoskeletal presentation. EXCLUDING: arthrosis, gout, scoliosis, infectious conditions etc.
Obesity	BMI ≥30 or the dg codes (ICD-10)*: E66, E68 EXCLUDING: local adiposity and "other hyperalimentation" (=vitamin overdoses etc.)

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

*or corresponding codes in other diagnostic coding systems.

12.5 Pregnancy

Pregnancy (any trimester) at symptom onset: yes versus no.

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.

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”. For FISABIO, only the number of primary care visits in the previous 3 months is available. For FISABIO, 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.

12.8 Vaccination status in previous season

Influenza vaccination status in the previous season will be defined as having received influenza vaccination (any influenza vaccine) during season 2017/2018 as reported in the dataset.

13 Data management

13.1 DRIVE Electronic Study Support Application (ESSA)

The final 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 serving the following purposes:

- Aiding research sites to do the quality assurance of their data by automatically performing data quality checks
- Providing visual summaries of the data
- Allowing research sites to share the visual summaries and tables for monitoring purposes
- Allowing research sites to safely upload their data to the central DRIVE Research Server for statistical analysis

The data flow to the DRIVE Research server is described in Figure 1. The interim and final study data is uploaded by the DRIVE research study sites to the ESSA Server. The DRIVE research study site can decide to share data for monitoring or to transfer the final data to the DRIVE Research Server for statistical analysis. The DRIVE ESSA also aids the research sites providing TND data to do the quality assurance of their data by automatically performing data quality checks and providing visual summaries of their data. 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, influenza vaccination previous season, number of hospitalizations during the last 12 months, and presence of at least 1 chronic condition) among cases and controls. More information on the DRIVE ESSA can be found in the DRIVE ESSA user manual (ANNEX 2). Similar data quality checks will be performed for the cohort studies. Performing quality checks for the cohort studies is currently not yet implemented in the DRIVE ESSA and will be done by writing separate data management scripts.

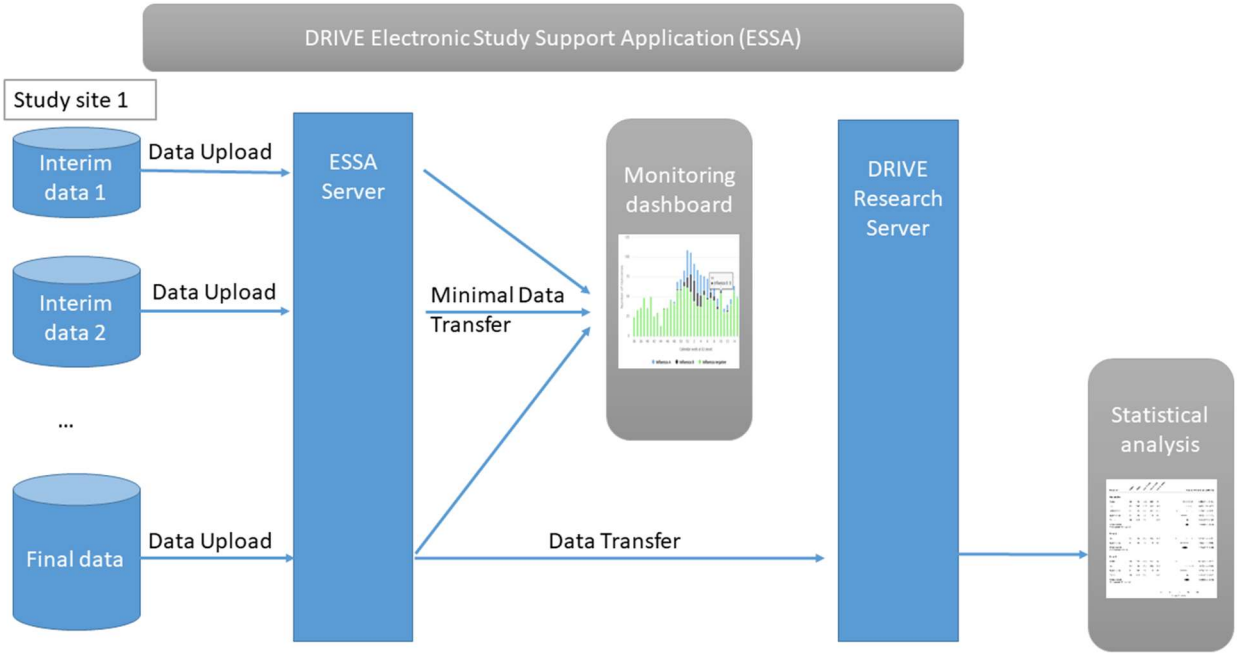


Figure 1. DRIVE Electronic Study Support Application: data flow

13.2 DRIVE Research server

The DRIVE Research server, provided by P95, is a highly secured IT environment and network with strict rules for data access. The architecture of the DRIVE research server is given in Figure 2. The general architecture of the DRIVE research server has three compartments: the data import compartment, the data analysis compartment and the evidence export compartment. The DRIVE research server is only accessible through the secure file transfer protocol (with upload capability to the data import compartment and download capability out of the data export compartment) and the remote desktop protocol allowing data analysts/statisticians to log into the data analysis compartment. The transfer of any data between the different compartments is done solely by the server administrator where data privacy assessments should be carried out if deemed necessary. Every interaction on the DRIVE research server will be logged, and these logs will be accessible upon request.

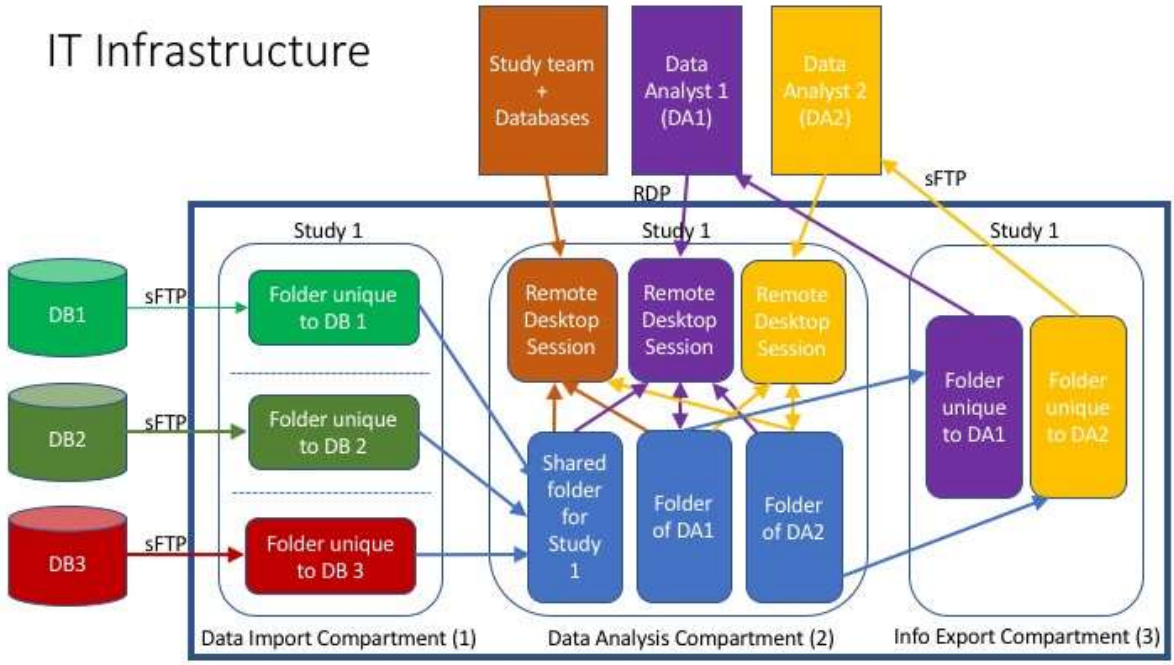
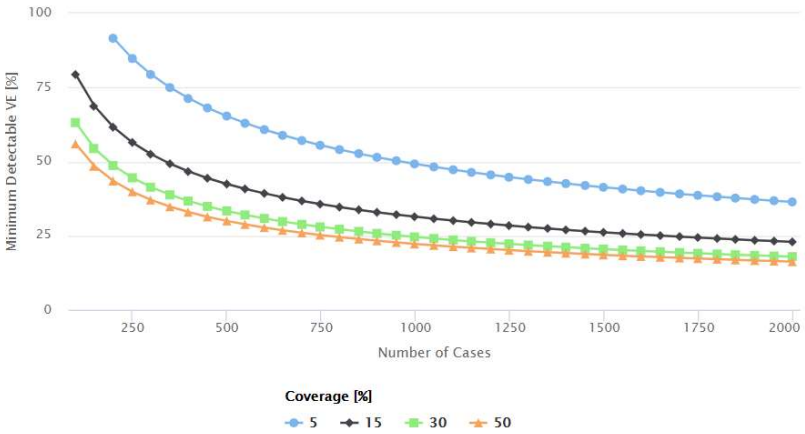


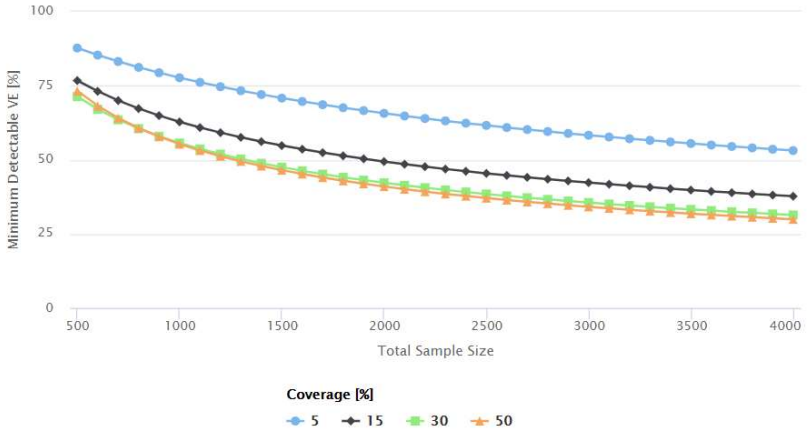
Figure 2. DRIVE Research server: architecture

14 Sample size considerations

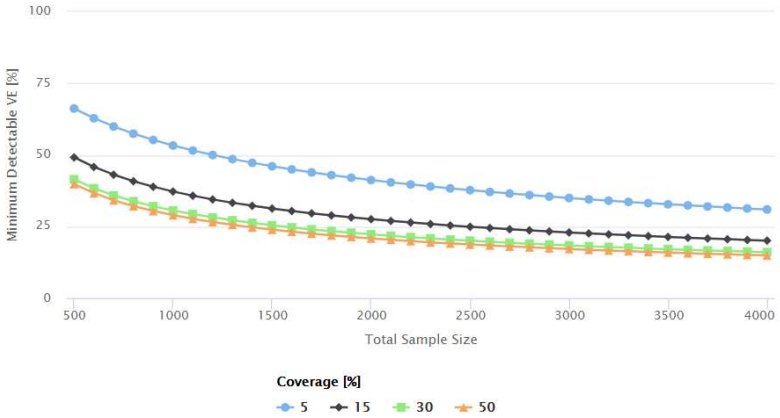
The minimal detectable overall VE, or the smallest VE that can be detected as significantly greater than zero, for a range of samples sizes for TND and cohort designs is given in Figure 3 and Tables Table 13-Table 14. The calculations are performed assuming 80% power, two-sided 95% confidence levels and overall vaccination coverages of 5%, 15%, 30% and 50%. For TND, it is additionally assumed to have a 1:1 control per case allocation ratio. For the cohort studies, it is additionally assumed to have attack rates among the unvaccinated of 7% (reflective of the attack rate in adults) and 25% (reflective of the attack rate in children).



Test-negative design



Cohort design (attack rate = 7%)



Cohort design (attack rate = 25%)

Figure 3. 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 13. 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
1250	44.72	28.4	22.24	20.13
1500	41.32	26.15	20.47	18.54
2000	36.4	22.92	17.93	16.26

Table 14. 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
1500	7	70.78	54.77	47.47	46.48
2000	7	65.64	49.38	42.2	40.96
2500	7	61.58	45.4	38.43	37.07
3000	7	58.26	42.29	35.54	34.13
3500	7	55.48	39.78	33.24	31.81
4000	7	53.09	37.69	31.35	29.92
500	25	66.2	49.12	41.46	39.8
1000	25	53.28	37.21	30.6	28.95
1500	25	46.04	31.29	25.45	23.91
2000	25	41.21	27.56	22.27	20.85
2500	25	37.69	24.93	20.06	18.74
3000	25	34.96	22.94	18.4	17.16
3500	25	32.77	21.38	17.11	15.93
4000	25	30.96	20.1	16.05	14.93

We recommend a minimum of 200 influenza positive cases for TND studies and a minimum of 1000 subjects for cohort studies. As data from different sites will be pooled and as capacity building is an ongoing activity within DRIVE, smaller sample sizes per site are allowed. To not spread resources too thinly, it is recommended to select study sites that are expected to provide at least 100 cases in the case of TND studies and 500 subjects in the case of cohort studies. A user-friendly web-application to perform sample size calculations for IVE studies has been developed and is freely available from http://apps.p-95.com/drivesamplesize/.

15 Statistical analysis

15.1 Site-specific analysis: test-negative design studies

15.1.1 Attrition diagram

Records will be discarded from analysis when:

- Date of ILI/SARI onset is outside the study period (see Section 7)
- Subjects do not adhere to the study in- and exclusion criteria (see Section 8).
- The ILI/SARI episode is not the first episode from recurrent episodes within the study period
- Subjects have missing information on the outcome of interest or exposure or any of the covariates for adjustment (see Section 11)
- Subjects that are potentially vaccinated (see Section 11.1)

Subjects that are partially vaccinated (see Section 11.1) will be excluded from the primary analysis. The impact of partially vaccinated subjects will be assessed in sensitivity analysis.

When a covariate contains a large percentage of missing data (>= 10%), no adjustment will be made for that covariate to avoid losing too many records, unless the covariate adjustment is considered more important than the information loss. In that case or when the covariate is not available, missing information on that specific covariate will not be a reason for exclusion.

For every TND study site (n = 11), an attrition diagram as outlined in Figure 4 will be created. The attrition diagram describes the amount of records excluded from the statistical analysis by reason of exclusion.

It is expected that some study sites will provide data to DRIVE with the exclusion criteria applied at study recruitment or during data cleaning before sharing data while for other sites the exclusion criteria will be applied by the DRIVE study team.

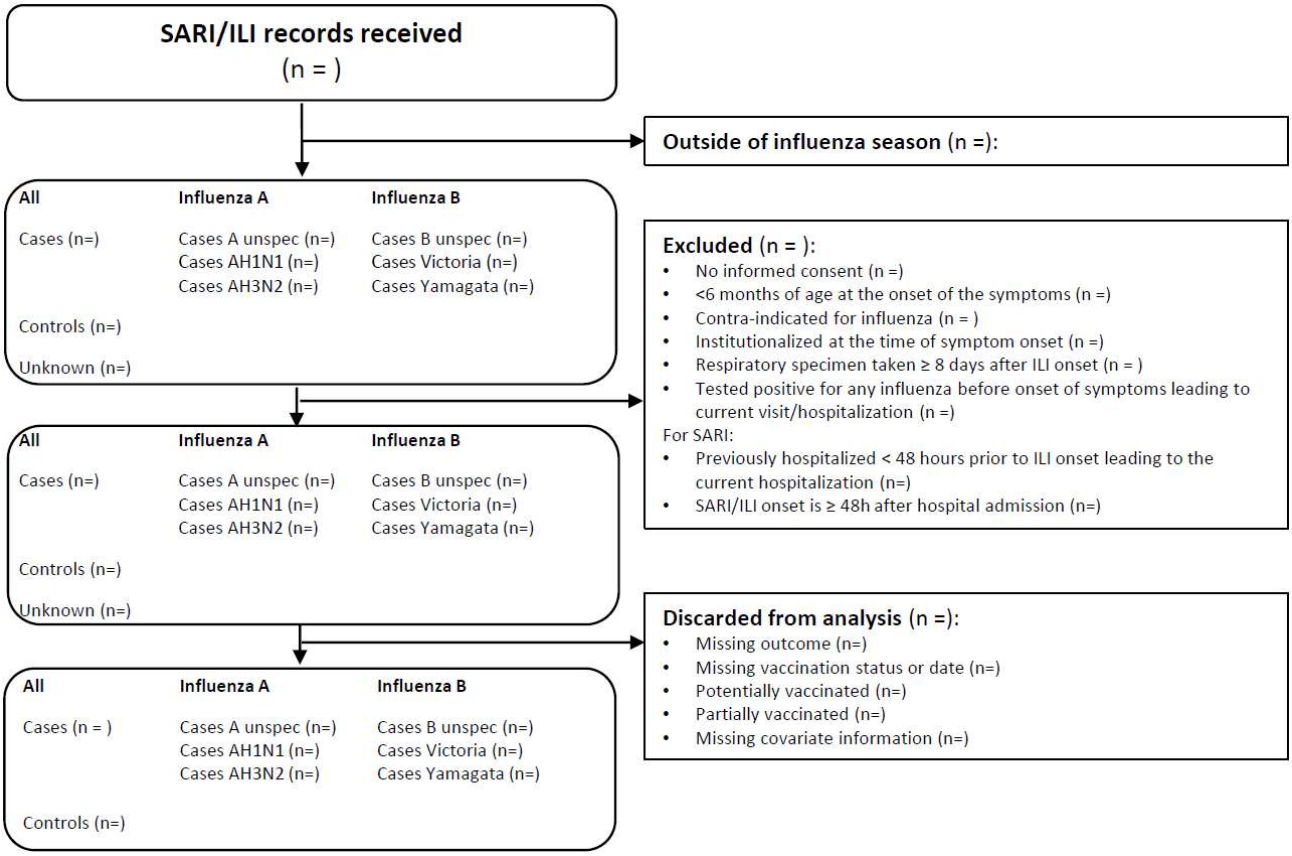


Figure 4. Attrition diagram, study site A

15.1.2 Descriptive analysis

For every TND study site, visualizations based on the final data (e.g. data for analysis) will be created similar as the ones generated by the DRIVE ESSA (ANNEX 2), including:

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

For every TND study site (n = 11), a table based on the final data will be created with characteristics of cases and controls as outlined in Table 15.

Table 15. Table shell: characteristics of laboratory confirmed cases, overall and by influenza type, and controls, study site A (setting), 2018/19

Characteristic	Cases N (%) all	A (H1N1/H3N2)	B (Vict/Yama)	Controls N (%)
Age group				
6m-17 yr				
18-64 yr				
≥65 yr				
Sex				
female				
male				
At least 1 chronic condition				
Yes				
Cardiovascular disease				
Lung disease				
Diabetes				
Immunodeficiency or organ transplant				
Chronic liver disease				
Cancer				
Anemia				
Renal disease				
Dementia				
Stroke				
Rheumatologic diseases				
Obesity				
No				
Unknown				
Pregnancy				
Yes				
No				
Unknown				
Number of primary care visits in the previous 12 months				
0				
1-5				
>5				
Unknown				
Number of hospitalizations in the previous 12 months				
0				
1-5				
>5				
Unknown				
Influenza vaccination status in previous season				
Vaccinated				
Unvaccinated				
Unknown				
Influenza vaccination status in current season				
Vaccinated				
Afluria				
Agrippal				
…				
undefined				
Unvaccinated				
Total				

15.1.3 Influenza vaccine effectiveness estimation

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

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

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

Confounder-adjusted IVE estimates will be derived from multivariable logistic regression models. A fixed set of confounders will be considered for each individual site, including sex, a smooth function of age, a smooth function of symptom onset date, presence of at least one chronic condition, pregnancy, number of primary care visits (FISABIO: “0”, “1 to 2” and “2 or more”; all other sites: “0”, “1 to 5” and “5 or more”) in the previous 12 months (for primary care studies) or number of hospitalizations (“0”, “1 to 2” and “2 or more”) in the previous 12 months (for hospital based studies) and influenza vaccination in the previous season. This set of confounders is available for the majority of study sites. (See also Table 10 for the confounders available per site).

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.

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 symptom onset date will be modelled by penalized cubic regression splines and estimated using restricted maximum likelihood for smoothness selection [6].

For sites for which some confounders are entirely missing, the IVE estimates will be confounder-adjusted to the extent possible.

For the trivalent vaccines and trivalent vaccine types (i.e. trivalent non-adjuvanted, trivalent adjuvanted, trivalent high-dose), an additional IVE estimate against any vaccine subtype/lineage included in the vaccine will be obtained.

For each study site, the estimates will be presented as in Table 16. A similar table as Table 16 will be made for the crude IVE estimates. This will yield a total of 22 tables for the TND studies.

Table 16. Table shell: confounder-adjusted influenza vaccine effectiveness [95% confidence intervals], study site A (setting), 2018/19

Study site (setting)	Influenza Vaccine Effectiveness [95% CI]*						
	Any	**Any vaccine strain**	**AH1N1**	**AH3N2**	**B**	**B Victoria**	**B Yamagata**
Age group							
6m-17 yr							
Any vaccine							
Vaccine brand							
Afluria(1)							
Agrippal							
…							
Vaccine type							
Trivalent adj							
Trivalent non-adj							
…							
18-64 yr							
Same as above							
…							
>=65 yr							
Same as above							
…							

CI: confidence interval
(1) all brands available at the study site

15.1.4 Sensitivity analysis

The following sensitivity analysis will be conducted:

Partially vaccinated subjects:

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

Time between ILI/SARI onset and swab:

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

15.2 Site-specific analysis: cohort studies

15.2.1 Attrition diagram

Records will be discarded from the analysis when:

- Date of ILI/SARI onset is outside the study period (see Section 6)*
- Subjects do not adhere to the study in- and exclusion criteria (see Section 9).
- Subjects have missing information on the outcome of interest, exposure or any of the covariates for adjustment (see Section 11)
- Subjects that are potentially vaccinated (see Section 11.1)

Note 1: Date of ILI/SARI onset cannot be verified in the THL register-based cohort study. Only the date of influenza test is available.

Note2: The in- and exclusion criteria are different for the different cohort studies.

When a covariate contains a large percentage of missing data (>= 10%), no adjustment will be made for that covariate to avoid losing too many records, unless the covariate adjustment is considered more important than the information loss.

For every cohort study, an attrition diagram similar to the one given in Figure 4 will be created. The attrition diagram describes the amount of records excluded from the statistical analysis by reason of exclusion.

It is expected that some study sites will provide data to DRIVE with the exclusion criteria applied before sharing data while for other sites the exclusion criteria will be applied by the DRIVE study team.

15.2.2 Descriptive analysis

For every cohort study, visualizations based on the final data (e.g. data for analysis) will be created similar as the ones created for the TND studies (see Section 14.1.2), including:

- Pie chart of the distribution of vaccine brands
- Cumulative number of vaccinated subjects over time
- Number of laboratory-confirmed influenza infections (by type and subtype/lineage) over time
- Distribution of covariates among exposed and unexposed subjects

For every cohort study, a table based on the final data will be created with characteristics of the exposed and unexposed subjects as outlined in Table 17. Table 17 uses the UoA pregnancy cohort (Greece) as an example. Similar tables will be made for the other cohort studies.

Table 17. Table shell: characteristics of the exposed and unexposed subjects, 2018/19 . UoA (Greece, pregnancy cohort) as example.

Characteristic	vaccinated		Unvaccinated	
	N	Person time	N	Person time
Age group				
18-29 yr				
30-45 yr				
≥65yr				
Ethnicity				
Greek				
Roma				
Immigrant				
At least 1 chronic condition				
Yes				
No				
Unknown				
Influenza vaccination in previous season				
Vaccinated				
Unvaccinated				
Unknown				
Number of children < 5 yr				
0				
1-2				
>2				
Unknown				
Influenza vaccination status in current season				
Vaccinated				
Afluria				
Agrippal				
…				
undefined				
Partially vaccinated				
Unvaccinated				
Total				

15.2.3 Influenza vaccine effectiveness estimation

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

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

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

Confounders include sex, a smooth function of age, a smooth function of calendar week, presence of at least one chronic condition, pregnancy, number of primary care visits (“0”, “1 to 5” and “5 or more”) in the previous 12 months (for primary care studies) or number of hospitalizations (“0”, “1 to 2” and “2 or more”) in the previous 12 months (for hospital based studies) and influenza vaccination in the previous season, whenever available (See Table 11).

The analysis will be a complete case analysis, dropping records with missing information for the outcome, exposure of interest or any of the covariates. The smooth functions of age and calendar time will be modelled by penalized cubic regression splines [7] estimated using restricted maximum likelihood for smoothness selection [6]

The crude and confounder-adjusted estimates will be presented as in Table 16. For the cohort studies, a total of 6 tables will be generated.

15.2.4 Sensitivity analysis

The following sensitivity analysis will be conducted:

a) Partially vaccinated subjects:

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

b) Time between ILI/SARI onset and swab:

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

For the register-based cohort study (THL, Finland), sensitivity analysis b) will not be considered as the information on ILI/SARI onset is missing.

15.3 Pooled analysis

15.3.1 Inclusion of influenza vaccine effectiveness estimates

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

The clinical cohort studies will not be considered for inclusion in the pooled analyses as they concern different populations compared to the general population covered by the TND studies (UoA Greece; pregnant women and their infants; CIRI-IT Italy; healthcare workers).

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

15.3.2 Pooled data: descriptive analysis

For the TND data, tables based on the pooled data will be created with characteristics of cases and controls similar to Table 15, stratified by healthcare setting (primary care, hospital). These two tables on the pooled data will additionally contain information on the distribution of cases and controls across the different study sites.

Additional tables will be created describing the characteristics of the subjects by exposure as outlined in Table 18 to obtain insight into potential bias by indication. As different brands have different approved indications (see Table 9), the unexposed group that will serve as a basis for comparison might be slightly different. A separate table will be created by healthcare setting and age group.

Table 18. Table shell: characteristics of the exposed and unexposed subjects by brand, setting x age group, 2018/19

	Brand 1		Brand 2 ….	
	exposed	**unexposed**	**exposed**	**unexposed**
Age at symptom onset				
Average (SD)				
Median				
Sex				
female				
male				
At least 1 chronic condition				
Yes				
Cardiovascular disease				
Lung disease				
Diabetes				
Immunodeficiency or organ transplant				
Chronic liver disease				
Cancer				
Anemia				
Renal disease				

Dementia
Stroke
Rheumatologic diseases
Obesity
No
Unknown

Pregnancy
Yes
No
Unknown

Number of primary care visits in the previous 12 months
0
1-5
>5
Unknown

Number of hospitalizations in the previous 12 months
0
1-5
>5
Unknown

Influenza vaccination status in previous season
Vaccinated
Unvaccinated
Unknown

Study site
Site 1
Site 2
…

Total

15.3.3 Meta-analysis

Random effects meta-analysis (RE MA) [8] will be used to pool the site-specific confounder-adjusted IVE estimates as given in Table 16. Pooled estimates will be stratified by age group (6m-17yr, 18-64 yr, >=65yr) and setting (primary care, hospital). Random effects meta-analysis will be performed on the log-transformed odds ratio (OR) estimates. Restricted maximum likelihood (REML) will be used to obtain the pooled (meta-analyzed) estimate (and 95% confidence intervals), as the REML estimator outperforms other RE MA estimators in terms of bias and statistical efficiency [9]. The estimates (and 95% confidence intervals) will then be back-transformed to obtain the pooled IVE estimate (and 95% confidence intervals), expressed in %.

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 [10]. The I^2 statistic is to be interpreted as the proportion of total variation in the estimates of treatment effect that is due to heterogeneity between studies. This measure will be used as a summary measure of the between-study heterogeneity and not to decide on the appropriateness of pooling as the RE MA model accounts for different levels of between-study heterogeneity.

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 from meta-analysis when $|r| > 2.5$, where $|r|$ indicates the absolute value of the residual.

The standardized DFBETAs statistic will be used to identify influential estimates, examining the change in the averaged IVE from the random-effects model when excluding one site-specific estimate in turn. Site-specific estimates will be considered influential from meta-analysis when |DFBETAs| > $2/\sqrt{n}$, where |DFBETAs| indicates the absolute value of the DFBETAs statistics and *n* is the number of effect estimates [11].

Site-specific estimates that are outlying and influential, will be excluded from meta-analysis and the reason for being outlying will be investigated and documented. The information that will be collected by the DRIVE Quality Control and Audit Committee (QCAC) will be used to evaluate potential reasons for outlying results.

15.3.6 Sensitivity analysis

The following sensitivity analysis will be conducted:

a) Partially vaccinated subjects:

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

b) Time between ILI/SARI onset and swab:

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

c) Outlying/influential studies:

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

16 Presentation of results

For every exposure of interest (any vaccine, by brand, by vaccine type), a separate multi-panel plot will be created, displaying the IVE estimates (any influenza, by type and by subtype/lineage) stratified by age group and setting/design (primary care TND, hospital-based TND, cohort studies). The pooled estimates (from the TND studies) will be represented by diamonds whereas sites-specificl estimates (from the cohort studies) will be represented using error bars. For the pooled estimates, the I^2 statistic will be given as well. Wide confidence intervals (i.e. a width > 40%) will be coloured differently compared to narrow confidence intervals (i.e. width <= 40%) to emphasize that estimates with wide confidence intervals are not considered robust. An example of such a multi-panel plot is given in Figure 5. The plots also make explicit which estimates are still missing for the current season. We anticipate to produce 16 multi-panel plots (any vaccine + 10 brands + 4 vaccine types).

For every pooled estimate, an additional forest plot with the site-specific estimates will be created to support the interpretation of the pooled estimates. An example of such a forest plot displaying different IVE estimates (by type and by subtype/lineage) is given in Figure 6.

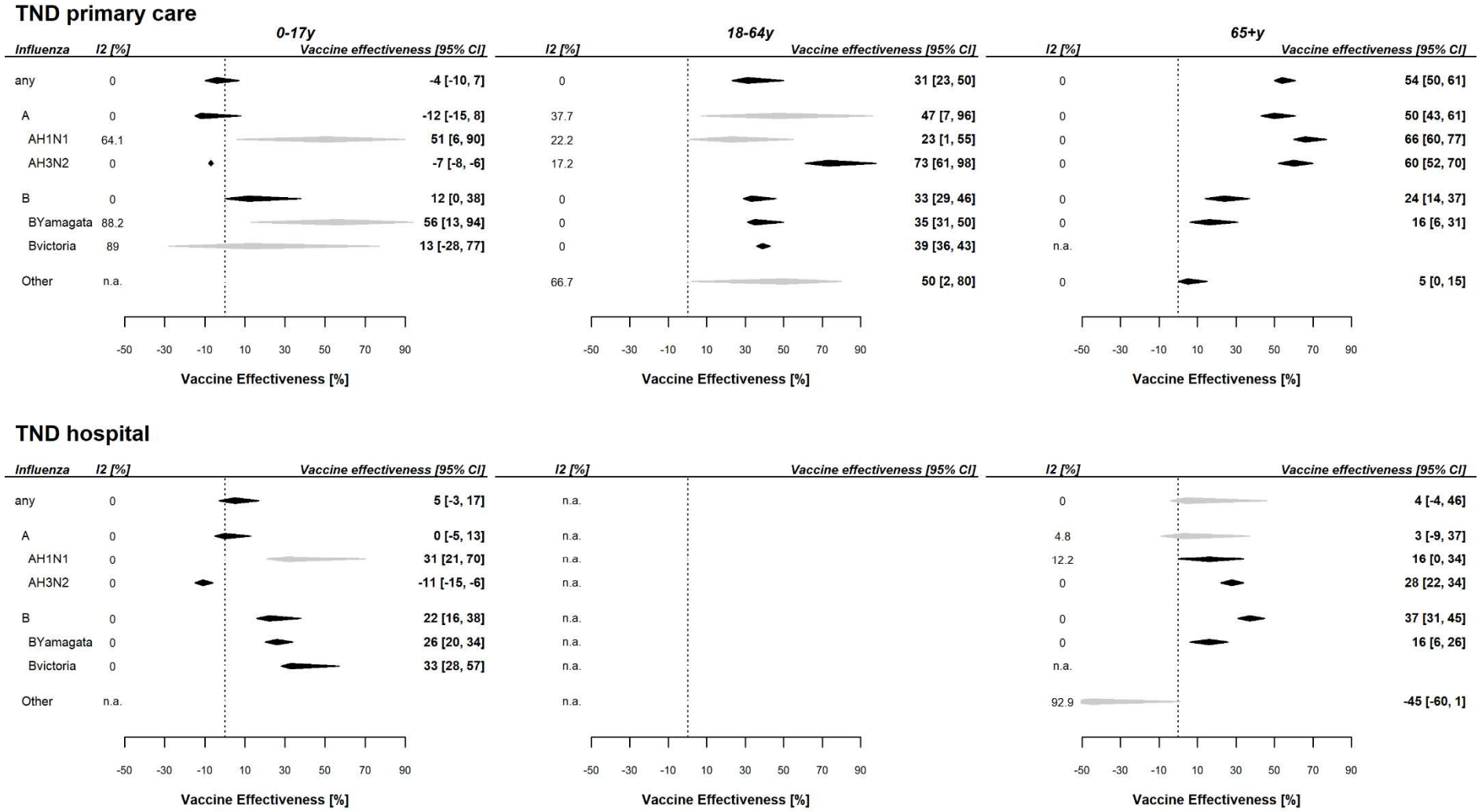


Figure 5. Example of a multi-panel plot, by exposure (artificial example)

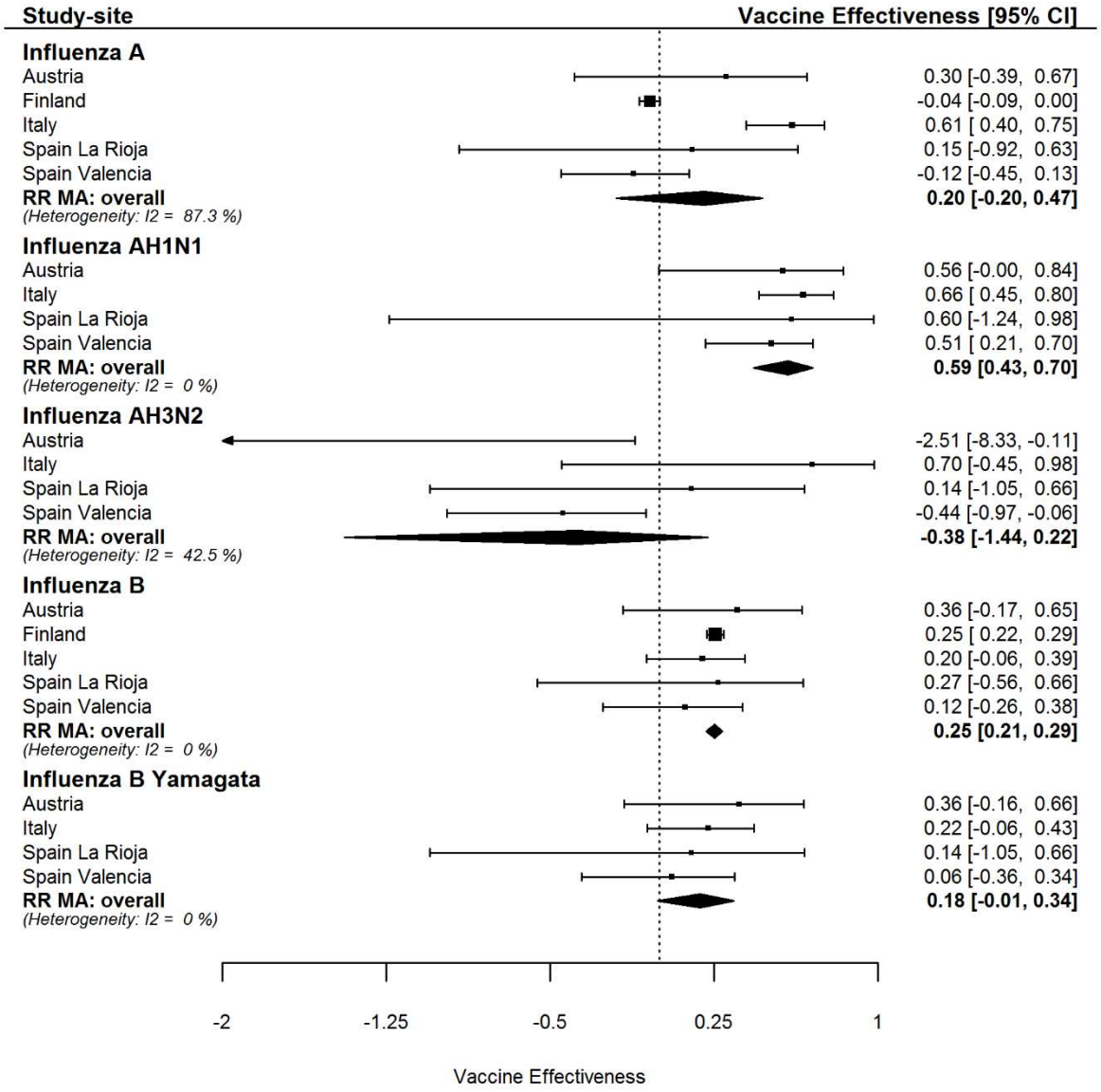


Figure 6. Example of a forest plot associated with pooled Influenza vaccine effectiveness estimates (setting A , age group B , exposure CSee) by influenza type and subtype/lineage (based on data from pilot study)

17 Software

All data management and statistical analyses will be conducted in R 3.5.2.

18 Limitations

The populations of the clinical cohort studies are different from the general population as studies by the TND and Finnish population-based cohort study. As such, the results from the clinical cohort studies cannot be pooled with the results from the other studies. At this moment, it is still unclear how much such clinical cohort studies can contribute to DRIVE's primary objective of estimating brand-specific IVE in Europe.

For some study sites, no information is available on influenza subtypes/lineages, the information on covariates is limited or primary care or hospital based cases cannot be distinguished. It remains to be decided what information is minimally required for obtaining robust IVE estimates, and hence which are the minimum study requirements for the DRIVE studies.

All TND studies closely follow the generic TND study protocol. However, the study sites are still different in many important aspects, including the sampling strategy and covariates available for adjustment. Several potential confounders are currently not available such as socio-economic status and smoking. The covariates 'at least 1 chronic condition' or 'influenza vaccination in the last season' might not be sufficiently granular to allow for proper confounder adjustment.

It is difficult to know the sample size required for brand-specific IVE as it depends on many unknown factors, including the influenza attack rates, vaccination coverage, distribution of brands and (for the pooled estimates) the between-study heterogeneity. For the 2018/19 season, we will likely have sufficient sample size to obtain robust and precise (with CI width < 40%) IVE estimates for some brands, but not for all brands used in Europe in the 2018/19 season. Obtaining sufficient sample for brand-specific IVE estimates will remain a challenge and a careful selection of DRIVE study sites will be required.

Bias by indication is a challenge in IVE studies and will also likely affect the IVE estimates of this season, despite attempts to correct for bias by indication through covariate adjustment. 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.

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 minimum data requirements, season-specific protocol per study site, season-specific SAP, study summary sheets and codebook of variables within the analytical datasets.

19.2 Record retention

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

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

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 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 pooled statistical analysis report matches with the Statistical Analysis Plan (SAP).

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

20 Ethics considerations

20.1 Ethics approval

Participating sites obtained ethics committee approval as required. The ethics committee that approved the study at each site and the date of approval are listed in Table 19. For ISS (Italy), separate ethics committee approval was not required as these studies are part of their respective National Influenza Surveillance activities.

Table 199. DRIVE 2018/19 study sites: ethics committees and date of approval

Site	Country	Ethics committee	Date of approval
MUV	Austria	Ethics committee of the MUV	May 4, 2018
HUCH	Finland	Regional Ethics Committee of the Expert Responsibility Area of Helsinki University Hospital	Nov 14, 2018
THL	Finland	Institutional review board of the National Institute for Health and Welfare, Finland	June 2, 2016
UoA	Greece	Ethics Committee of the "Alexandra" General Hospital of Athens	Oct 16, 2018
BIVE-HOSP	Italy	Ethics committee of the Bambino Gesù Children's Hospital, Rome Ethics committee of the Sant'Andrea Hospital, Rome Ethics committee of the University Hospital, Bari Ethics committee of the San Martino Hospital, Genova Ethics committee of the Le Scotte Hospital, Siena	Sept 2018 (all committees)
CIRI-IT (TND)	Italy	Ethics committee of the Liguria Region	Oct 1, 2018
CIRI-IT (HCW)	Italy	Ethics committee of the Liguria Region	Oct 1, 2018
ISS	Italy	Not required, but submitted to ISS Ethics committee for information	Nov 23, 2018
NIIS	Romania	Bioethics committee of the NIIS	Nov 12, 2018
FISABIO	Spain	National Ethics Committee	Dec 21, 2009
VHUH	Spain	Comité Ético de Investigación Clínica del Hospital Universitari Vall d'Hebron	Dec 13, 2018
RCGP/UNIS	UK	NRES Committee West Midlands, Solihull. IRAS project ID: 252081, REC reference: 19/WM/0015	Feb 4, 2019

20.2 Informed consent

At all sites except VHUH 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 study, informed consent was not required as no interventions that fall outside the usual practice at VHUH during the influenza season were needed.

21 References

(1) Committee for Medicinal Products for Human Use. Guideline on Influenza Vaccines - Non-clinical and Clinical Module. EMA/CHMP/BWP/310834/2012. In. London: Eur Med Agency, 2016.
(2) **DRIVE consortium**. D7.4 Setting up brand-specific influenza vaccine effectiveness studies in Europe – results of the pilot season 2017/18. Accessible from: https://www.drive-eu.org/wp-content/uploads/2018/12/D7_4_Report-pilot-season-201718_v1.0.pdf; October 2018 October 2018.
(3) ECDC. EU case definitions / Influenza including Influenza A(H1N1). In. Stockholm 2018. Accessible: https://ecdc.europa.eu/en/surveillance-and-disease-data/eu-case-definitions.
(4) **Dhiman N, et al.** Effectiveness of patient-collected swabs for influenza testing. *Mayo Clin Proc* 2012; **87**(6): 548-554.
(5) **Hayward AC, et al.** Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study. *Lancet Respir Med* 2014; **2**(6): 445-454.
(6) **Marra G, Wood SN.** Practical variable selection for generalized additive models. *Computational Statistics and Data Analysis* 2011: 15.
(7) **Wood S**. *Generalized additive models: an introduction with R*. London: CRC Press, 2017.
(8) **DerSimonian R, Laird N.** Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**(3): 177-188.
(9) **Viechtbauer W.** Bias and efficiency of meta-analytic variance estimators in the random-effects model. *Journal of Educational and Behavioral Statistics* 2005; **30**.
(10) **Higgins JP, Thompson SG.** Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**(11): 1539-1558.
(11) **Viechtbauer W, Cheung MW.** Outlier and influence diagnostics for meta-analysis. *Res Synth Methods* 2010; **1**(2): 112-125.