D7.6 Brand-specific influenza vaccine effectiveness in Europe Season 2018/19

777363 - DRIVE

Development of robust and innovative vaccine effectiveness

WP7 - IVE studies

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V2.3	August 30, 2019	Marga Riera (P95)	Lay summary added

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Executive Summary

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 new guidance on influenza vaccines by the European Medicines Agency (EMA) that 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.

In DRIVE, data from several independently operating national or regional study sites is analysed jointly to increase geographical coverage and sample size for brand-specific IVE estimates. The main objective of the 2018/19 season was 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 are covered during the 2018/19 season.

Objectives

The objectives were to estimate seasonal (1) **overall**, **brand-specific** and (2) **type-specific** IVE against laboratory-confirmed influenza stratified by setting (primary care, hospital-based) and age group (6m-17y, 18-64 y, 65+y), by type of outcome: any laboratory-confirmed influenza, influenza A and A subtypes, influenza B and B lineages, and by group of subtypes/lineages included in the vaccine brand or vaccine type.

Methods

TND studies

TND studies were conducted in primary care (4 networks) and hospital settings (3 individual hospitals and 2 hospital networks) (Table 1). Swabs were collected from subjects presenting with influenza-like illness (ILI, ECDC case definition) in the primary care setting and with severe acute respiratory infection (SARI) (IMOVE+ 2017/18 case definition) in the hospital setting (except for one hospital network where an alternative case definition was used). Swabs were tested for influenza using RT-PCR (except at one hospital where pediatric swabs were tested using antigen detection). Influenza A subtypes were available from all but one primary care site. The study population consisted of non-institutionalized subjects ≥6 months of age, with no contraindication for influenza vaccination, no prior positive influenza test in the same season, and with a swab taken < 8 days after ILI/SARI onset. In hospital settings, subjects hospitalized <48h prior to symptom onset or with symptom onset ≥48h after hospital admission were excluded. Vaccine brand was collected for vaccinated subjects.

Table 1. Primary care and hospital sites where TND studies were conducted, 2018/19

Country	Site name	Source of cases and controls
Primary care		
Austria	Medical University Vienna (MUV)	Ca. 90 physicians
Italy	Centro Interuniversitario di Ricerca sull'Influenza e sulle altre infezioni trasmissibili (CIRI-IT)	21 physicians
Italy	Istituto Superiore di Sanita (ISS)	245 physicians
England	Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC)	6 practices
Primary care, included as post-hoc sensitivity analysis		
Luxembourg	Laboratoire National de Santé (LNS)	15 physicians
Hospital		
Italy	Italian Hospital Network (BIVE)	5 hospitals
Spain	Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO)	4 hospitals
Finland	Helsinki University Central Hospital (HUS)	1 hospital
Spain	Vall d'Hebron University Hospital (HUVH)	1 hospital
Romania	National Institute for Infectious Diseases "Prof. Dr. Matei Balș" (NIID)	1 hospital

Register-based cohort

One register-based cohort study was conducted at THL Finland, by linking five registers (Population Information System, National Vaccination Register, National Infectious Diseases Register, Register of Primary Health Care Visits, Care Register for Health Care) through person identifiers. The study population consisted of all registered Finnish residents aged 6m-6y and 65-100y. The case definition was laboratory-confirmed influenza, as registered in the National Infectious Diseases Register. Laboratory testing was done using RT-PCR or antigen detection. Persons with presumably incomplete vaccination register in 2018/19 or 2017/18 were excluded.

Data flow and statistical methods

Data collected at the study sites was transferred to the DRIVE Research Server where it was analysed centrally by P95.

TND studies

Individual-level data was available for analysis. Only subjects presenting during the locally-defined influenza season were retained for analysis. The start of the season was locally defined as the first week of two consecutive weeks when influenza viruses were detected at the study site level; the end, as the week prior to the first of two consecutive weeks when no influenza viruses were detected at study site level or April 30, 2019, whichever occurred first. Subjects with missing outcome, missing or unconfirmed vaccination status or date, and those recently vaccinated (≤14 days) were excluded. Site-specific age-stratified (6 months(m) – 17 years (y), 18-64y, 65+y) crude and confounder-adjusted odds ratios (OR) and 95% confidence intervals (CI)

were estimated using logistic regression and the formula VE = (1 – OR) x 100%. A fixed set of confounders was 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, influenza vaccination in the previous season and respectively number of primary care visits or hospitalization in the previous 12 months for primary care and hospital studies. For each site, a complete case analysis was performed unless covariate information was missing for >10% of the subjects, in which case it was excluded from the model. Pooled VE estimates by age and setting were obtained through random-effects meta-analysis of site-specific estimates. Robust VE estimates were defined as VE estimates with a CI width of <40%. The statistical analysis plan is registered at ENCEPP (EUPAS29817).

Register-based cohort study

Aggregated data was available for analysis. The study period for analysis was from week 40 2018 to week 17 2019. Age-stratified (6m-6y, 65+y) crude and confounder-adjusted relative risks (RR) and 95%CI were estimated using Poisson regression and the formula VE = (1 – RR) x 100%. Confounders included sex, a smooth function of age, a smooth function of calendar week, presence of at least one chronic condition, number of primary care visits (“0”, “1 to 5” and “5 or more”) in the previous 12 months, number of hospitalizations (“0”, “1 to 2” and “2 or more”) in the previous 12 months and influenza vaccination in the previous season.

Results

Influenza vaccines 2018/19

Ten vaccines were licensed in Europe in 2018/19 and seven brands were identified in the DRIVE dataset (Table 2). In the countries of participating sites, medical and occupational risk groups are recommended for vaccination, along with the population aged 65+y. Additionally, in the UK there is a universal vaccination recommendation for children aged 2-10 y and in Finland for children aged 6m-6y. In Austria, a universal influenza recommendation vaccination is in place, nonetheless vaccine coverage is low. In most countries, type-specific vaccine recommendations were in place for specific risk groups and age groups.

Table 2. Vaccines identified in the DRIVE pooled dataset, 2018/19

Vaccine brand	Manufacturer	Valency	Live-attenuated	Adjuvanted	Age indication
Agrippal	Seqirus	Trivalent	No	No	≥6m
Influvac	Abbott Biologicals	Trivalent	No	No	≥6m
Fluarix Tetra	GlaxoSmithKline	Quadrivalent	No	No	≥6m
Influvac Tetra	Abbott Biologicals	Quadrivalent	No	No	≥3y
Vaxigrip Tetra	Sanofi Pasteur	Quadrivalent	No	No	≥6m
Fluad	Seqirus	Trivalent	No	Yes	≥65y

Fluenz Tetra	AstraZeneca	Quadrivalent	Yes	No	≥2y

Influenza season 2018/19

The 2018/19 influenza season in Europe was characterized by co-circulation of influenza A/H1N1pmd09 and A/H3N2, with little to no circulation of influenza B. Generally A/H1N1 in first part of season, A/H3N2 in second part of season. Overall, A/H1N1 and A/H3N2 circulation was approximately equal at Italy ISS (A/H1N1 50.9%), Spain HUVH (56.4%), Spain FISABIO (56.5%), whereas A/H3N2 was dominant at Finland HUS (61.4%) and Italy CIRI (60.3%), and A/H1N1 was dominant at Italy BIVE (65.5%, Romania NIID (67.1%) and Austria (68.9%). There was a good match between the vaccine virus and the circulating viruses for A/H1N1 but not for A/H3N2. The season was milder thanthe 2017/18 season.

Number of subjects

The number of subjects in the TND studies and the register-based cohort is shown in Table 3.

Table 3. Number of subjects in TND studies and register-based cohort study, 2018/19

TND	**6m-17y**		**18-64y**		**65+y**	
Setting	**Cases (VC)**	**Controls (VC)**	**Cases (VC)**	**Controls (VC)**	**Cases (VC)**	**Controls (VC)**
PC	934 (6%)	1071 (9%)	814 (8%)	1222 (13%)	144 (61%)	277 (63%)
Hosp	512 (3%)	1083 (5%)	371 (14%)	722 (20%)	559 (48%)	1635 (61%)

Register-based cohort	**6m-6y**			**65+y**		
	Vac (py)	**Unvac (py)**	**Cases**	**Vac (py)**	**Unvac (py)**	**Cases**
Setting						
Mixed	37781	130240	1843	236298	354097	4545

Hosp: hospital; PC: primary care; Py: person-years; rb cohort: register-based cohort; vac: vaccinated; VC: vaccine coverage among subjects in the study; unvac: unvaccinated; y: years

IVE estimates: Pooled TND

Three robust confounder-adjusted pooled VE estimates for any vaccine exposure were obtained; other estimates were non-robust and should be interpreted with caution. In the primary care setting, for the age groups 6m-17y, pooled IVE against A/H1N1 was estimated at 70% [95%CI 44-84] (crude) and 77% [95%CI 53-89] (adjusted). In the hospital setting, for the age group 65+y, pooled IVE against any influenza and influenza A was estimated at 29% [95%CI 12-43] (crude) and 27% [95%CI 6-44] (adjusted).

Limited amount of data captured per vaccine brand, distributed over appropriate-yet multiple strata (age, setting, and type of outcome) resulted in non-robust IVE estimates with wide to very wide CIs. Brand-specific IVE estimates in children aged 6m-17y were calculated for 4 brands (4 in primary care setting, 3 in hospital setting), 5 brands in adults 18-64y (4 in primary care setting, 4 in hospital setting), and 5 brands in elderly aged 65+y (3 in primary care setting, 5 in hospital setting). Similarly, type-specific IVE estimates were calculated were non-robust.

IVE estimates: Register-based cohort

All IVE estimates obtained from the THL register-based cohort were robust. These could not be pooled with the TND results because stratification by setting (primary care vs hospital) was not available.

IVE in the age group 6m-6y was estimated at 44% [95%CI 36-51]. In this age group, two vaccine brands were used, Fluenz Tetra and Vaxigrip Tetra. IVE for Fluenz Tetra was estimated at 36% [95%CI 24-45] and for Vaxigrip Tetra at 54% [95%CI 43-62].

IVE in the age group 65+y was estimated at 30% [95%CI 25-35]. In this age group, only Vaxigrip Tetra was used.

Discussion

From the pooled TND studies, three robust estimates were obtained for any vaccine. No robust brand-specific estimates were obtained. This is in part because the influenza season was mild, however, obtaining sufficient sample for brand-specific IVE estimates is expected to be challenging also in more intense seasons than this year. Even for the primary objective estimating IVE for any vaccine, sample size was insufficient for most strata.

Limitations

The data from the register-based cohort could not be pooled with the TND studies as information on setting was not available. For the register-based cohort and the TND study at UK RCGP no subtype/lineage data was available. The completeness of the covariates varied. The list of predefined confounders for adjustment meant that records missing information for any of these confounders were excluded. A careful trade-off between inclusion of possible confounder information and the risk of losing records and having data of sufficient quality must be made.

Strengths

The DRIVE network has expanded from 5 sites in the pilot season to 13 sites in 2018/19. Studies were further harmonized, as generic protocols are in use, minimum data requirements defined, and several site visits were performed prior to the start of data collection. The DRIVE GDPR-compliant Research Server was expanded to include an Electronic Study Support Application (ESSA) where sites were able to upload their data and perform automated quality checks. The statistical analysis plan was improved and age- and setting- stratified IVE estimates were calculated. Re-usable and quality controlled R-functions were developed, that were pre-

programmed prior to the receipt of data, and this enabled completion of the data analysis of the TND studies and the register-based cohort in a two week time-frame. Data quality reports were centrally produced for each site.

Conclusion

The primary objectives were not met in the 2018/19 season due to insufficient sample size per strata, particularly at the brand level. Few robust IVE estimates were obtained. Ways to increase sample size should be further explored for next season.

Recommendations

The sample size needs to be increased to allow brand-specific IVE estimation while considering also the sustainability of the network in the future. The use of secondary data, such as register or other electronic healthcare databases, could be a potential sustainable solution to the problem of obtaining sufficient sample size and warrants further exploration. Finally, increased data sharing throughout Europe may enable the pooling of a larger number of studies.

Milestones

	Date
Start of surveillance period	September 9, 2018
End of surveillance period	May 13, 2019
Data received	May 28, 2019 (last dataset)
Database freeze	June 5, 2019 (last dataset)[1]
IVE results available	June 14, 2019 (first draft)
Report to EFPIA	June 28, 2019 (second draft)

[1] RCGP RSC submitted first on May 28th, and later resubmitted the data with additional brand data requested with final database lock on June 27, 2019

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List of abbreviations

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
HUS	Helsinki University Central Hospital
HUVH	Vall d'Hebron University 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
LNS	Laboratoire National de Santé
MUV	Medical University Vienna
NIID	National Institute for Infectious Diseases "Prof. Dr. Matei Bals"
OR	Odds ratio
QIV	Non-adjuvanted quadrivalent influenza vaccine
RCGP RSC	Royal College of General Practitioners Research and Surveillance Centre
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

UoA	National and Kapodistrian University of Athens
UK	United Kingdom
VE	Vaccine effectiveness

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].

DRIVE seeks to establish a sufficiently sized network for robust, high quality, brand-specific effectiveness estimates for all influenza vaccines used in the EU each season. In DRIVE, data from several independently operating national or regional study sites is analysed jointly to increase 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, were used and further improved in the 2018/19 season.

The main objective of the 2018/19 season was 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 are covered during the 2018/19 season, nor was sufficient sample size achieve to estimate brand-specific VE for all brands.

Age is an effect modifier in IVE studies. In addition, patients presenting to different healthcare setting (primary care vs. hospital) are expected to have different levels of disease severity. To reduce clinical heterogeneity, estimates in the 2018/19 season were stratified by age and setting wherever possible.

This Study Report describes the characteristics of the participating study sites, the methods used, and the IVE estimates obtained for the 2018/19 influenza season, as well as the challenges and proposed recommendations for next season.

2 Objectives

2.1 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-17y, 18-64 y, 65+y), 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

2.2 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-17y, 18-64 y, 65+y), 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)
- trivalent vaccines only: 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

2.3 Exploratory objective

To estimate seasonal **overall** IVE against laboratory-confirmed influenza stratified by setting (primary care, hospital-based or mixed) and age group (6m-17y, 18-64 y, 65+y 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 were 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 Italy CIRI-IT). 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 SAP ANNEX 1 for definitions of chronic conditions).

3 Methods

3.1 Study design

A multi-centre study with data available from five primary care based TND studies, five 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.

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 & University of Surrey (RCGP RSC), United Kingdom 4. Istituto Superiore di Sanita (ISS), Italy 5. Laboratoire National de Santé (LNS), Luxembourg
Test-negative design studies, hospital based: 1. Helsinki University Central Hospital (HUS), Finland 2. Italian Hospital Network (BIVE), Italy 3. National Institute for Infectious Disease "Prof. Dr. Matei Balș", Bucharest, Romania 4. Vall d'Hebron University Hospital (HUVH), Barcelona, Spain 5. Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO), Spain
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

The following studies were embedded in their respective national or regional influenza surveillance systems:

- Spain FISABIO (Valencia Hospital Network for the Study of Influenza, VAHNSI)
- Italy ISS (National sentinel influenza surveillance system, INFLUNET)
- Spain HUHV (Information Plan for Acute Respiratory Infections in Catalonia, PIRIDAC)
- Finland HUS (ICU ward only) (Finnish sentinel surveillance)
- Luxembourg LNS (national influenza sentinel surveillance)
- Austria MUV (Diagnostic Influenza Network Austria, DINÖ)
- UK RCGP RSC (English sentinel surveillance network)

- Finland THL (online surveillance of influenza vaccine effectiveness)

As Luxembourg LNS joined the DRIVE project in June 2019, the results were included in a post hoc sensitivity analysis.

3.2 Overview of study characteristics

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 4. Study characteristics for the clinical cohort studies are presented in ANNEX 3. Further details are provided in the subsequent sections.

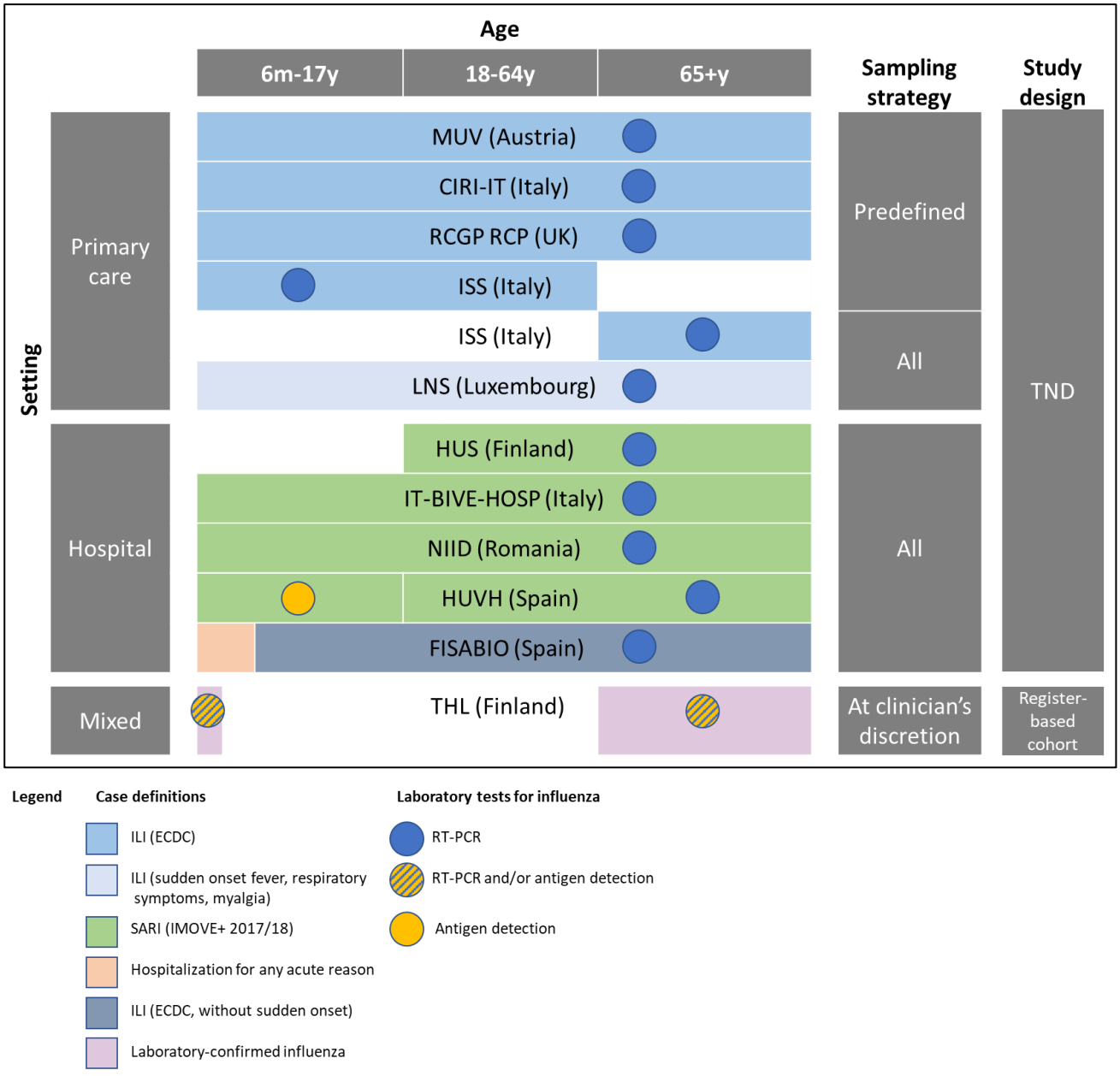


Figure 1. Overview of study characteristics, TND case control and register-based cohort, 2018/19

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

Site	**MUV**	**CIRI-IT**	**ISS**	**LNS**	**RCGP RSC**
Country	**Austria**	**Italy**	**Italy**	**Luxembourg**	**UK**
Setting	Primary care	Primary care	Primary care	Primary care	Primary care
Source of cases	Ca. 90 primary care physicians	21 primary care physicians	Ca. 245 primary care physicians	15 primary care physicians	6 primary care practices
Population	General population ≥6 months	General population ≥6 months	General population ≥6 months	General population ≥6 months	General population ≥6 months
Time					
First and last swab date	04.10.2018; 10.04.2019	10.09.2018; 13.5.2019	5.11.2018; 29.04.2019	27.9.2018; 28.3.2019	18.2.2019; 10.04.2019
Study period of analysis	Week 48 to week 14	Week 44 to week 15	Week 47 to week 15	To do	Week 48 to week 16
Cases					
Case definition	ILI[(1)]	ILI[(1)]	ILI[(1)]	ILI[(2)]	ILI[(1)]
Influenza cases	ILI + LCI	ILI + LCI	ILI + LCI	ILI + LCI	ILI + LCI
Sampling strategy[(3)]	All (or predefined rules if >10 ILI per sentinel physician per week)	Predefined rules	<65y: predefined rules 65y+: All	All	Predefined rules
Swab					
Type of swab	Nasal or nasopharyngeal	Nasal or oropharyngeal	Throat swab	Throat and nose swabs	Nasal
Who swabs	HCW	HCW	HCW	HCW	HCW
Laboratory testing					
Laboratory test influenza	RT-PCR	RT-PCR	RT-PCR	RT-PCR	RT-PCR desktop analyzer
A/subtype available	Yes	Yes	Yes	Yes	No
B/lineage available	Yes	Yes	Yes	No	No
Laboratory test subtyping	RT-PCR	RT-PCR	RT-PCR	RT-PCR	n/a
Data sources					
Case definition	Primary data collection	Primary data collection	Primary data collection	Primary data collection	Primary data collection

Site	**MUV**	**CIRI-IT**	**ISS**	**LNS**	**RCGP RSC**
Country	**Austria**	**Italy**	**Italy**	**Luxembourg**	**UK**
Vaccination status	-Medical records -Otherwise, patient/ relatives' interview (if ILI patient is not consulting his/her regular GP)	-Vaccine register -Medical records	-Medical records	Medical records	- Medical records
Baseline clinical data	Primary data collection	Medical records	Medical records	Medical records	Medical records
Covariates available for adjustment	Age, sex, date of onset, 1+ chronic condition, pregnancy	Age, sex, date of onset, 1+ chronic condition, pregnancy, nr of primary care visits in last 12 months, influenza vaccination in previous season	Age, sex, date of onset, 1+ chronic condition, nr of primary care visits in last 12 months, influenza vaccination in previous season	Age, sex	Age, sex, date of onset, 1+ chronic condition, pregnancy, nr of primary care visits in last 12 months, influenza vaccination in previous season
Individual or aggregate data shared	Individual	Individual	Individual		Individual

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

(1) ECDC case definition, (2) 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.

For Spain HUVH, the data collection followed a matched 1:1 case-control design, where information on exposure and covariates was obtained only for controls that could be matched to a case by epidemiological week and age group (6m–17y, 18-64y and 65+y).

Table 3. Overview of test-negative design study sites characteristics, hospital - 2018/19

Site	**HUS**	**BIVE-HOSP**	**NIID**	**HUVH**	**FISABIO**
Country	**Finland**	**Italy**	**Romania**	**Spain**	**Spain**
Setting	Hospital	Hospital	Hospital	Hospital	Hospital
Source of cases	1 hospital	5 hospitals	1 hospital	1 hospital	4 hospitals
Population	General population ≥18 years	General population ≥6 months	General population ≥6 months	General population ≥6 months	General population ≥6 months
Time					
First and last swab date	23.11.2018; 30.04.2019	16.11.2018; 27.04.2019	13.11.2018; 30.04.2019	13.12.2018; 14.4.2019	10.09.2018;13.05.2019
Study period of analysis	Week 48 to week 17	Week 47 to week 16	Week 47 to week 16	Week 49 to week 15	Week 51 to week 16
Cases					
Case definition	SARI[(1)]	SARI[(1)]	SARI[(1)]	SARI[(1)]	<5y:Hospitalized for any acute reason[(2)] ≥5y: ILI[(3)]
Influenza cases	SARI + LCI	SARI + LCI	SARI + LCI	SARI + LCI	As above + LCI
Sampling strategy[(4)]	All	All	All	All	All
Swab					
Type of swab	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	<14y: nasopharyngeal and nasal ≥14y: nasopharyngeal and pharyngeal
Who swabs	HCW	HCW	HCW	HCW	HCW
Laboratory testing					

Site	**HUS**	**BIVE-HOSP**	**NIID**	**HUVH**	**FISABIO**
Country	**Finland**	**Italy**	**Romania**	**Spain**	**Spain**
Laboratory test influenza	RT-PCR	RT-PCR	RT-PCR	< 18y: Antigen detection > 18y: PCR	RT-PCR
A/subtype available	Yes	Yes	Partial (H only)	Yes	Yes
B/lineage available	Yes	Yes	Yes	Yes	Yes
Laboratory test subtyping	Real-time RT-PCR	RT-PCR	RT-PCR	sequencing	RT-PCR
Data sources					
Case definition	Primary data collection	Primary data collection	Primary data collection	Medical records	Primary data collection
Vaccination status	-Vaccine register -Vaccine card -Medical records	Primary care physician interview for patients who reported being vaccinated (or unsure), the physician consulted medical records	-Vaccine card -Primary care physician interview	-Vaccine register -Medical records -Vaccine card	-Vaccine register
Baseline clinical data	-Medical records -Registers -Patient/relatives interview -Interview with hospital ward personnel	-Medical records -Patient interview	-Medical records -Patient /relatives interview -Interview with attending physician	-Medical records	-Medical records -Patient interview
Covariates available for adjustment	Age, sex, date of onset, 1+ chronic condition, pregnancy, nr of hospitalisations in last 12 months, influenza	Age, sex, date of onset, 1+ chronic condition, influenza vaccination in previous season, nr of	Age, sex, date of onset, 1 chronic condition or more pregnancy, nr of hospitalisations in last 12 months, influenza	Age, sex, date of onset, 1+ chronic condition, pregnancy, nr of hospitalisations in last 12 months, influenza	Age, sex, date of onset 1+ chronic condition, pregnancy, nr of hospitalisations in last 12 months, influenza

Site	HUS	BIVE-HOSP	NIID	HUVH	FISABIO
Country	**Finland**	**Italy**	**Romania**	**Spain**	**Spain**
	vaccination in previous season	hospitalisations in last 12 months, for 65+: frailty	vaccination in previous season	vaccination in previous season	vaccination in previous season
Individual-level or aggregate data shared	Individual	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

(1) IMOVE+ 2017/2018 case definition. (2) With symptom onset in the 7 days prior to admission (3) ECDC case definition, without “sudden onset” (4) 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.

The Finland THL register-based cohort includes all children aged 6m to 6y and adults 65+y registered in the Finnish Population Information System. This system is then linked to the National Vaccination Register to obtained vaccination status for all subjects in the cohort and the National Infectious Disease Register to identify influenza cases (Table 4).

Table 4. Overview of register-based cohort study, 2018/19

Site	**THL**
Country	**Finland**
Setting	Primary care and hospital
Population	General population 6m-6y and 65+y
Time	
Start and end of follow-up	Ongoing
Study period of analysis	Week 40 to week 17
Cases	
Case definition	LCI positive
Influenza cases	LCI positive
Sampling strategy(1)	At clinician's discretion
Swab	
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 testing	
Laboratory test influenza diagnosis	RT-PCR, Antigen detection
A/subtype available	No
B/lineage available	No
Laboratory test subtyping	n/a
Data sources	
Subjects that define the cohort	Population Information System
Case definition	National Infectious Disease Register
Vaccination status	National Vaccination Register
Baseline clinical data	Registers
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
Individual-level or aggregate data shared	Aggregate

HCW: healthcare worker; LCI: laboratory-confirmed influenza; n/a: not applicable; 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) At clinician's discretion: non-systematic sampling

3.3 Study population

In all TND studies and the register-based study, the population under study was the general population. Further details on the catchment population are presented in

Table 5. In the two clinical cohort studies, the populations under study were pregnant women and their young infants and healthcare workers respectively.

Table 5. Catchment population for studies in the general population, 2018/19

	Catchment population
TND primary care	
Austria MUV	Ca. 1-1.2% of population Austria
Italy CIRI-IT	Ca. 1.8% of population Liguria >3% of population Genoa Province
Italy ISS	Ca. 0.5% of population Italy
Luxembourg LNS	Ca. 3% of population of Luxembourg
RCGP RSC UK	Ca. 0.1% of population England
TND hospital	
Italy BIVE	Tertiary care hospitals serving Siena province (population 250,000), Liguria region (845,000), Lazio region (700,000 0-12y old*), Rome (3,000,000) and Bari province (1,100,000)
Spain FISABIO	Hospitals serving part of Valencia region (1,119,000, 22% of Valencia region)
Finland HUS	Tertiary care hospital serving cities of Espoo, Kauniainen and Kirkkonummi (population 332,500)
Spain HUVH	Tertiary care hospital located in the north of the city of Barcelona (serving a population >400,000)
Romania NIID	Hospital serves Bucharest, Ilfov, Dambovita, Giurgiu, Prahova, Arges, Teleorman, Ialomita, Dolj, Valcea, Olt (population 5,937,382)
Register-based cohort	
Finland THL	98% of all children 6m-6y and 99% 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

3.4 Study period

The start and end of the data collection for the 2018/19 influenza season differed between the sites (Table 2-Table 4). The end of the data collection for the pooled analysis was on 30 April 2019, although individual study sites may have continued data collection beyond this date according to their protocols.

For the TND studies, the study period for the analysis started when the influenza virus circulation began (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 finished 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 30 April 2019, whichever occurred first. The study period of analysis was different for different study sites.

In the particular case of Finland THL, data was continuously collected throughout the year since they use the national registers. The study period for analysis for THL was from week 40 till week 17.

3.5 Case definitions

3.5.1 Influenza-like illness (ILI)

A case of influenza like illness (ILI) was 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.

3.5.2 Severe acute respiratory infection (SARI)

A case of severe acute respiratory infection (SARI) was 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.

3.5.3 Case identification

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

At Greece UoA (pregnancy cohort), all enrolled women were 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 Italy CIRI-IT (HCW cohort), all participants were sent weekly regular reminders through e-mail and/or SMS (if the mobile was available) to call the study team in case of ILI.

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

3.5.4 Data sources case definition

For the majority of studies, the outcome was assessed through primary data collection, i.e. patient interview. For HUVH, the outcomes were assessed using medical records. In case of the register-based cohort, the National Infectious Disease Register was used (Table 2-Table 4).

3.5.5 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
- ‘at clinician’s discretion’: non-systematic sampling at practitioner’s discretion

Swab sampling strategies differed most across the TND primary care study sites, whereas ‘all’ patients meeting the case definition were swabbed in the TND hospital studies and the clinical cohort studies, and ‘no’ rules were defined for the register-based cohort study (Table 2-Table 4).

Among TND primary care study sites, ‘no’ rules were defined for Austria MUV, ‘all’ ILI patients were swabbed for LNS (Luxembourg), ‘predefined rules’ were in place for Italy CIRI-IT, UK RCGP RSC, and for Italy ISS the sampling strategy differed for age groups (‘predefined rules’ for ILI patients <65y, ‘all’ for ILI patients 65+y). The predefined rules that were in place were defined as follows:

- Austria MUV: All ILI patients were swabbed, if more than 10 patients per sentinel physician per week fulfil the case definition, then every 4th patient is swabbed
- Italy CIRI-IT: Systematic sampling was encouraged, e.g. the first 3 ILI that present each week.

- UK RCGP RSC: All cases of ILI were encouraged to be swabbed in this study, up to a maximum of 10 per practice, per day
- Italy ISS: Systematic sampling of the first 2 ILI patients that presented each week

Swabs were performed by HCW in all studies with the exception of the Italy CIRI-IT HCW cohort, where swabs were self-collected in the Milano site or collected by CIRI-IT medical staff in the Genoa site. Self-collected swabs have been shown to 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 were either nasal, nasopharyngeal, oropharyngeal, pharyngeal or throat swabs (Table 2-Table 4). Samples taken >=8 days after ILI onset were excluded from analysis.

3.5.6 Adherence to the case definitions

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

At Luxembourg LNS, a case of ILI was defined as an individual who presents with a

- Sudden onset of fever

AND

- Respiratory symptoms

AND

- Myalgia

At Spain FISABIO, the following case definitions were used:

For children <5 years, a clinical case was 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 was used, being hospitalized with at least one systemic 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

3.5.7 Case definition verification

When variables on symptoms were provided, the ILI/SARI case definition was verified. Reporting variables on the symptoms was not obligatory. An overview of the sites for which case definition verification was possible is given in Table 7.

Table 7. Verification of ILI/SARI case definition based on clinical symptoms

	All ILI/SARI case definition could be verified based on clinical symptoms	**Comment**
ILI		
Italy CIRI-IT	Yes	
Italy ISS	No	Clinical symptoms not collected
LNS, Luxembourg	No	Clinical symptoms not collected
Austria MUV	No	Missing for 99.5% of the records.
UK RCGP RSC	No	Clinical symptoms not collected
SARI		
Italy BIVE	No	Missing for 31 records, 1.9%
Spain FISABIO	No	Missing for 619 records, 17.1%
Finland HUS	Yes	
Romania NIID	Yes	
Spain HUVH	At site	The site reported that all ILI/SARI cases were confirmed based on clinical symptoms. The variables on the symptoms were not provided as they were not obligatory.

3.6 Inclusion and exclusion criteria

3.6.1 Test-negative design studies

3.6.1.1 Recommended exclusion criteria

The following exclusion criteria were applied to subjects presenting with ILI;

1. was 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. was less than 6 months of age at the time of the onset of the symptoms
3. had a contraindication for influenza vaccine
4. was institutionalised at the time of symptoms onset
5. had 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 were applied to subjects presenting with SARI;

1. was 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. was less than 6 months of age at the time of the onset of the symptoms
3. had a contraindication for influenza vaccine
4. was institutionalised 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/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 could be enrolled several times as long as he/she did not have a previous laboratory confirmed influenza for the 2018/19 season.

3.6.1.2 Adherence to the recommended ILI/SARI exclusion criteria

All variables related to the exclusion criteria were listed as obligatory variables in the Minimal Data Requirements (Annex 1 of SAP in ANNEX 1). Records that violated the exclusion criteria were discarded at the analysis stage, whenever possible.

All the recommended exclusion criteria were implemented either at study recruitment or during the analysis for the main analysis of all TND primary care and TND hospital studies, with the exception of Austria MUV and Spain HUVH where informed consent was not required (see also ANNEX 2). Four TND hospital sites applied additional exclusion criteria at recruitment:

- In the Finland HUS study, patients who were not a resident of Espoo, Kauniainen or Kirkkonummi were excluded.
- In the Spain FISABIO study, patients who were not residing in the hospitals' catchment areas for at least the previous 6 months, patients who were previously hospitalized < 30 days from the

hospitalization of interest, and patients who remained in the hospital for less than 24 hours were excluded.

- In the Romania NIID study, patients who had received antiviral therapy and patients who remained in the hospital for less than 24 hour were excluded.
- In the Spain HUVH study, patients not belonging to the Institut Català de la Salut network were excluded.

The exclusion criteria applied for Luxembourg LNS, which was included in the post-hoc sensitivity analysis, were:

1. has symptom onset outside the study period
2. is less than 6 months of age at the time of the swab date

3.6.2 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) were included, with the following exclusion criterion applied;

Exclusion criteria:

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

3.6.3 Clinical cohorts

In- and exclusion criteria for the clinical cohort studies are described in ANNEX 3.

3.7 Outcome

3.7.1 Outcome definition

The outcome of interest was 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

3.7.2 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 Finland THL (register-based cohort) and UK RCGP RSC , all sites collected 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 4).

3.8 Exposure (vaccination)

3.8.1 Exposure definition

The exposure of interest was influenza vaccination administered during the season 2018/19. For all objectives, the following exposure definitions were 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 was 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
- **recently 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 was 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

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

3.8.2 Data sources exposure status

Data sources for exposure status were either vaccine registers, medical records or vaccination cards. (see Table 2-Table 4).

Patients for whom the vaccination status was based on recall only (and could not be verified using vaccination registers, medical records or vaccination cards) were considered 'potentially vaccinated' and were discarded from analysis.

3.9 Covariates

3.9.1 Covariates

Covariates collected for adjustment were age, sex, calendar time (symptom onset time in days since start of the study), presence of at least one chronic condition, pregnancy, number of GP consultations or hospitalizations, and vaccination status in the previous season (2017/18). Availability of data on individual chronic conditions by site is presented in Table 8. See the SAP (ANNEX 1) for further details on each covariate, including definitions of chronic conditions. A site-specific overview of the covariates that were adjusted for in the analyses is given in Table 9**Errore. L'origine riferimento non è stata trovata.**.

Table 8. Availability of specific chronic conditions by site, test-negative design studies, 2018/19

Site	Cardiovascular disease	Lung disease	Diabetes	Immuno-deficiency or organ transplant	Chronic liver disease	Cancer	Anemia	Renal disease	Dementia	Stroke	Rheumatologic diseases	Obesity
TND primary care												
Austria MUV	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Italy CIRI-IT	No	No	No	No	No	No	No	No	No	No	No	No
Italy ISS	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No	Yes
Luxembourg LNS	No	No	No	No	No	No	No	No	No	No	No	No
UK RCGP RSC	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
TND hospital												
Finland HUS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Finland												
Italy BIVE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Romania NIID	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Spain HUVH	No	No	No	No	No	No	No	No	No	No	No	No
Spain FISABIO	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table 9. Covariate adjustment, test-negative design studies, 2018/19

Site	Time since season start	Sex	Age	Pregnancy	Chronic disease	Vaccinated in previous season	Number of hospitalizations / GP visits
TND studies							
Austria MUV	Yes	Yes	Yes	Yes	Yes	Yes	No
Finland HUS	Yes	Yes	Yes	No, no pregnant subjects	Yes	No, > 10% missing values	Yes
Italy BIVE	Yes	Yes	Yes	No	Yes	No, > 10% missing values	No, > 10% missing values
Italy CIRI-IT	Yes	Yes	Yes	Yes	Yes	Yes	No
Italy ISS	Yes	Yes	Yes	No	Yes	No	Yes
Luxembourg LNS	Yes	Yes	Yes	No	No	No	No
Romania NIID	Yes	Yes	Yes	No, > 10% missing values	Yes	Yes	Yes
Spain HUVH	Yes	Yes	Yes	Yes	Yes	Yes	Yes
UK RCGP RSC	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Spain FISABIO	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cohort studies							
Finland THL	Yes	Yes	Yes	No	Yes	Yes	Yes
Italy CIRI -IT	Yes	Yes	Yes	No	Yes	No	Yes
Greece UoA	Yes	No	Yes	No	Yes	No	No

3.9.2 Data sources baseline clinical data

The main sources for baseline clinical data were medical records and patient interview and, in the case of Finland THL, register (Table 2-Table 4).

3.10 Ethics considerations

Ethics considerations are described in ANNEX 2.

3.11 Data management

Please refer to the local study reports for local procedures of data cleaning and transformation (ANNEX 4). Data management at central level is described in the SAP (ANNEX 1).

3.11.1 Data pre-processing

3.11.1.1 Cleaning

Several types of quality checks were performed, including but not limited to providing all mandatory variables, adherence to the variable naming convention as specified in the minimal data requirements, presence of duplicated records, variable formats and inconsistencies between variables. When data quality issues were found, the data site responsible person was contacted, and the data were either corrected or discarded from further analysis.

After performing the data quality checks and implementing the corrective measures, the study /exclusion criteria are applied and records with missing data in the outcome, exposure and covariate information are discarded.

3.11.1.2 Data quality reports

For every site, a data quality report was produced. The report contains 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 reports for each site are presented in ANNEX 5.

3.12 Sample size considerations

Based on sample size calculations, a minimum of 200 influenza positive cases for TND studies and a minimum of 1000 subjects for cohort studies were recommended. For further details, refer to the SAP (ANNEX 1). As data from different sites was pooled and as capacity building is an ongoing activity within DRIVE, smaller sample sizes per site were allowed.

3.13 Statistical analysis

Statistical methods are described in detail in the SAP (ANNEX 1). Site-specific and pooled analyses were conducted centrally on the DRIVE Research Server. For each site, an attrition diagram was created, descriptive analyses were performed and site-specific IVE estimates were calculated. Pooled IVE estimates were obtained by meta-analysis of site-specific IVE estimates.

3.13.1 Site-specific analyses

3.13.1.1 Site-specific: Attrition diagram

For every study site, an attrition diagram was created, describing the number of records received and excluded from the statistical analysis by reason of exclusion.

3.13.1.2 Site-specific: Descriptive analyses

The following descriptive analyses were performed: a 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 (TND only), number of laboratory-confirmed influenza infections influenza infections (by type and by subtype/lineage) over time (cohorts only), distribution of covariates among cases and controls (TND only), distribution of covariates among exposed and unexposed subjects (cohort only), characteristics of cases and controls (TND), characteristics of exposed and unexposed subjects (cohort only).

3.13.1.3 Site-specific: Influenza vaccine effectiveness estimation – TND studies

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) were estimated stratified by age (6m-17y, 18-64 y, 65+y), 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 were derived from multivariable logistic regression models. A fixed set of confounders was 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 was available for the majority of study sites (Table 9).

The smooth functions of age and symptom onset date were modelled by penalized cubic regression splines and estimated using restricted maximum likelihood for smoothness selection [6]. Symptom onset time in days since start of the study was included to account for changes in the risk of infection and differences in strain circulation over the season, and it was modelled as a potentially non-linear smooth function (e.g. cubic splines with restricted maximum likelihood for smoothness selection). This means that we allowed for a flexible but smooth relationship between the calendar time and the influenza rate/risk. The smoothness selection guarantees that the function is flexible enough to capture the required time trends, but does not use more degrees of freedom than strictly required. In the absence of a time trend, the smooth function will be equal to a linear function.

The analysis to estimate brand-specific IVE accounted for the differences in approved indications (see Table 12), discarding from the analysis subjects for which the vaccine brand of interest is not indicated.

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

For sites for which some confounders were entirely missing, the IVE estimates were 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 was obtained.

3.13.1.4 Site-specific: Influenza vaccine effectiveness estimation – cohort studies

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) were estimated stratified by age (6m-17y, 18-64 y, 65+y), 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 included 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 (Table 9). Pregnancy was not available for any of the cohort studies, vaccination status in the previous season was not available for the two clinical cohort studies and number of healthcare visits was not available for the pregnancy cohort.

The analysis was 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 were modelled by penalized cubic regression splines [7] estimated using restricted maximum likelihood for smoothness selection [6].

3.13.1.5 Site-specific: Sensitivity analyses

The following sensitivity analyses were conducted:

a) Partially/recently vaccinated subjects (see Section 3.8.1):

- Partially/recently vaccinated subjects were considered unvaccinated.
- Partially/recently vaccinated subjects were considered vaccinated

b) Time between ILI/SARI onset and swab:

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

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

3.13.2 Pooled analysis

3.13.2.1 Pooled: Inclusion of influenza vaccine effectiveness estimates

Only estimates provided by the TND studies were considered for obtaining pooled estimates stratified by age group (6m-17y, 18-64 y, 65+y) and setting (primary care, hospital).

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

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

3.13.2.2 Pooled: descriptive analysis

For the TND data, tables based on the pooled data were created with characteristics of cases and controls, stratified by healthcare setting (primary care, hospital).

3.13.2.3 Meta-analysis

Random effects meta-analysis (RE MA) [8] was used to pool the site-specific confounder-adjusted IVE estimates. Pooled estimates were stratified by age group (6m-17y, 18-64 y, 65+y) and setting (primary care, hospital). Random effects meta-analysis was performed on the log-transformed odds ratio (OR) estimates. Restricted maximum likelihood (REML) was used to obtain the pooled (meta-analysed) 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) were then back-transformed to obtain the pooled IVE estimate (and 95% confidence intervals), expressed in %.

Meta-analysis is preferred over individual-level data pooling for DRIVE, as it enables the (future) incorporation of data from sites that are only willing to share aggregated data, and allows pooling of results from TND and cohort studies. Equivalence of the two approaches was demonstrated in the pilot year.

An indication for the heterogeneity among estimates from different study sites was obtained by calculating I^2 according to Higgins et al [10].

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

Site-specific estimates that were outlying and influential, were excluded from meta-analysis.

3.13.2.4 Pooled: Sensitivity analyses

The following sensitivity analysis were conducted:

a) Partially/recently vaccinated subjects (see Section 3.8.1):

- Partially/recently vaccinated subjects were considered unvaccinated.
- Partially/recently vaccinated subjects were considered vaccinated

b) Time between ILI/SARI onset and swab:

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

c) Outlying/influential studies:

- Outlying/influential studies were included in the meta-analysis

3.13.3 Deviations from the SAP

- For the exploratory objectives, the pooled estimates by chronic conditions were not calculated since all site-specific estimates had very wide confidence intervals.
- Sensitivity analysis for partially vaccinated was not conducted since only less than 0.5% of subjects were in that category, and therefore negligible.
- Restricted maximum likelihood for smoothness selection of the penalized splines for age was not used for the pregnancy cohort study. No convergence could be achieved, and a splines function with six splines was fitted as it provided a good visual fit to the data.

- Additional post-hoc sensitivity analysis with the inclusion of IVE estimates from LNS, Luxembourg in the pooled analysis.
- An exploratory nested TND case-control study was performed on the Italy CIRI-IT HCW cohort data.

3.14 Interpretation of IVE estimates

For the interpretation of robust IVE point estimates, D4.6 “Guideline for interpretation of IVE results” was used. VE point estimates of 0-30% are interpreted as ‘low’, 31-50% as ‘moderate’, 51-75% as ‘good’ and 76-100% as ‘very good’.

3.15 Quality control procedures

Quality control procedures are described in the SAP (ANNEX 1). The conclusions of the Quality Control and Audit Committee (QCAC) evaluation will be available separately.

4 Results

4.1 Influenza vaccines and influenza epidemiology in Europe, 2018/19

4.1.1 Vaccine recommendations

4.1.1.1 Target groups

National or regional vaccine recommendations at each site are summarized in Table 10. In Austria, influenza vaccination is recommended for everyone. In Finland and the UK, all children in specific age groups are recommended influenza vaccination; compared to only children with underlying medical conditions elsewhere. In all countries, adults with underlying medical conditions, healthcare workers, pregnant women and those aged 65+y are targeted for influenza vaccination.

Table 10. Target groups for vaccination in country for study sites enrolling general population, 2018/19

	Austria [1]	Finland [2]	Italy [3]	Luxembourg [4]	Romania [5]	Spain – Catalonia [6]	Spain – Valencia [7]	UK [8]
Age group								
Children								
6m-17y	Yes							
6m-6y		Yes						
Children 2-4y/ reception class/ school y 1-5								Yes
Adults								
18-64y	Yes							
Elderly								
60-64y						Yes		
65+y	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Underlying medical conditions								
6m-6y			Yes	Yes	Yes	Yes	Yes	Yes
6-18y		Yes	Yes	Yes	Yes	Yes	Yes	Yes
18-64y		Yes	Yes	Yes	Yes	Yes	Yes	Yes
Other								
Pregnancy		Yes	Yes	Yes	Yes	Yes	Yes	Yes
Healthcare workers		Yes (a,b)	Yes	Yes	Yes (b)	Yes(a)	Yes	Yes
Military		Yes						
Contacts of persons at high risk		Yes	Yes			Yes (c)	Yes (c)	
Individuals in long-term care facilities			Yes		Yes	Yes		
Essential public service workers			Yes			Yes	Yes	
Workers in direct contact with poultry and swine			Yes			Yes	Yes	

(a)Including pharmacy personnel, (b) including social workers, (c)Household members of persons at high risk. Vaccine recommendations from websites below are presented in ANNEX 6,

(1) Empfehlung Influenza-Impfung ("Grippeimpfung") Saison 2018/19 [cited June 7, 2019] Available from: https://www.sozialministerium.at/cms/site/attachments/3/3/1/CH4062/CMS1515753153756/impfplan_2018.pdf

(2) Free influenza vaccinations to begin in November [cited June 7, 2019]. Available from: https://thl.fi/en/web/thlfi-en/-/free-influenza-vaccinations-to-begin-in-november?redirect=https%3A%2F%2Fthl.fi%2Fen%2Fweb%2Fvaccination%2Fvaccination%3Fp_p_id%3D101_INSTANCE_wxSIzxpusHqd%26p_p_lifecycle%3D0%26p_p_state%3Dnormal%26p_p_mode%3Dview%26p_p_col_id%3Dcolumn-2-1%26p_p_col_count%3D1

(3) Prevenzione e controllo dell'influenza: raccomandazioni per la stagione 2018-2019 [cited June 7, 2019]. Available from: http://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2018&codLeg=64381&parte=1%20&serie=null

(4) La saison de la grippe arrive: pensez à vous fair vacciner! [cited June 27, 2019]. Available from: http://sante.public.lu/fr/actualites/2018/10/vaccination-grippe/index.html

(5) Drăgănescu A, Săndulescu O, Florea D, Vlaicu O, Streinu-Cercel A, Oţelea D, et al. The influenza season 2016/17 in Bucharest, Romania–surveillance data and clinical characteristics of patients with influenza-like illness admitted to a tertiary infectious diseases hospital. Brazilian Journal of Infectious Diseases. 2018;22:377-86.

(6) Guia técnica per a la campanya de vacunació antigripal estacional 2018 [cited June 12, 2019]. Available from: http://salutpublica.gencat.cat/web/.content/minisite/aspcat/promocio_salut/vacunacions/06vacunacio-antigripal/informacio-de-temporada/ASPCAT-GUIA-CAMPANYA-GRIP.pdf

(7) Campaña de Vacunación Gripe Estacional 2018-2019 [cited June 7, 2019]. Available from: http://www.sp.san.gva.es/sscc/opciones4.jsp?CodPunto=3507&Opcion=VACUNAS&MenuSup=SANMS&Nivel=2&Seccion=SANPS1210102

(8) The national flu immunisation programme 2018/19 [cited June 7, 2019]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/694779/Annual_national_flu_programme_2018-2019.pdf

4.1.1.2 Recommended vaccine types

Recommendations for the use of specific vaccine types are presented in Table 11. There are no type-specific recommendations in Romania. In Austria and Italy, for most target groups a preferred type is recommended, and an alternative option is given.

Table 11. Recommendations of specific vaccine types by country, 2018/19

	Preferred vaccine type (alternative vaccine type)					
	Austria [1]	**Finland [2]**	**Italy [3]**	**Spain – Catalonia [4]**	**Spain – Valencia [5]**	**UK [6]**
Age group						
Children						
6m-17y			QIV (TIV)	TIV QIV(very high risk)	TIV	
6m-2y	QIV	QIV				
2-6y		LAIV or QIV				
3-17y	LAIV or QIV (1)					
6y-17y		QIV				
School-aged children						LAIV
Adults						
18-64y	QIV (no under.cond.) aTIV or QIV (under.cond (a))	QIV	QIV (TIV)	TIV QIV(very high risk)	TIV	QIV
Elderly						
60-64y				TIV QIV(very high risk)		
65+y		QIV	aTIV (QIV, TIV)	aTIV		aTIV
60/65+y	aTIV (or QIV (1))					
65-74y					TIV (if not instit.) aTIV (if instit.)	
75+y			aTIV		aTIV	
Other						
Pregnancy			QIV or TIV			
Healthcare workers	QIV (TIV)					
Contacts of persons at high risk	QIV (TIV)					

Instit: institutionalized; under.cond.: underlying conditions. (a) For further details see reference (1). Vaccine recommendations from websites below are presented in ANNEX 6,

(1) Empfehlung Influenza-Impfung ("Grippeimpfung") Saison 2018/19 [cited June 7, 2019] Available from: https://www.sozialministerium.at/cms/site/attachments/0/0/6/CH4062/CMS1538134077648/empfehlung_zur_jaehrlichen_influenza-impfung-version_8.2.pdf

(2) Free influenza vaccinations to begin in November [cited June 7, 2019]. Available from: https://thl.fi/en/web/thlfi-en/-/free-influenza-vaccinations-to-begin-in-november?redirect=https%3A%2F%2Fthl.fi%2Fen%2Fweb%2Fvaccination%2Fvaccination%3Fp_p_id%3D101_INSTANCE_wxSIzxpusHqd%26p_p_lifecycle%3D0%26p_p_state%3Dnormal%26p_p_mode%3Dview%26p_p_col_id%3Dcolumn-2-1%26p_p_col_count%3D1

(3) Prevenzione e controllo dell'influenza: raccomandazioni per la stagione 2018-2019 [cited June 7, 2019]. Available from: http://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2018&codLeg=64381&parte=1%20&serie=null

(4) Guia técnica per a la campanya de vacunació antigripal estacional 2018 [cited June 12, 2019]. Available from: http://salutpublica.gencat.cat/web/.content/minisite/aspcat/promocio_salut/vacunacions/06vacunacio-antigripal/informacio-de-temporada/ASPCAT-GUIA-CAMPANYA-GRIP.pdf

(5) Campaña de Vacunación Gripe Estacional 2018-2019 [cited June 7, 2019]. Available from:http://www.sp.san.gva.es/sscc/opciones4.jsp?CodPunto=3507&Opcion=VACUNAS&MenuSup=SANMS&Nivel=2&Seccion=SANPS1210102

(6) The national flu immunisation programme 2018/19 [cited June 7, 2019]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/694779/Annual_national_flu_programme_2018-2019.pdf

4.1.2 Vaccine indications

Ten influenza vaccines were licensed in the EU for the season 2018/19. The ages for which vaccine brands are indicated are listed in Table 12.

Table 12. Vaccine characteristics and age indications by vaccine brand

Vaccine brand	Manufacturer	Valency	Live-attenuated	Adjuvanted	Age indication
Afluria	Seqirus	Trivalent	No	No	≥5y
Agrippal	Seqirus	Trivalent	No	No	≥6m
Influvac	Abbott Biologicals	Trivalent	No	No	≥6m
Vaxigrip	Sanofi Pasteur	Trivalent	No	No	≥6m
Fluarix Tetra	GlaxoSmithKline	Quadrivalent	No	No	≥6m
Influvac Tetra	Abbott Biologicals	Quadrivalent	No	No	≥3y
Vaxigrip Tetra	Sanofi Pasteur	Quadrivalent	No	No	≥6m
Fluad	Seqirus	Trivalent	No	Yes	≥65y
Fluenz Tetra	AstraZeneca	Quadrivalent	Yes	No	≥2y
TIV-HD	Sanofi Pasteur	Trivalent	No	No	≥65y

4.1.3 Composition of influenza vaccines

The 2018/19 Northern hemisphere trivalent vaccines contained the following strains [11]:

- A/Michigan/45/2015 (H1N1)pdm09-like virus
- A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus
- B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage)

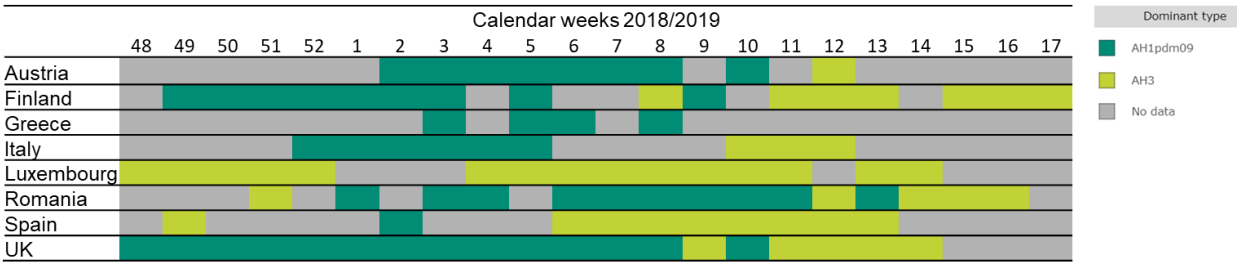
Quadrivalent vaccines contained additionally:

- B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage)

4.1.4 Influenza epidemiology in Europe

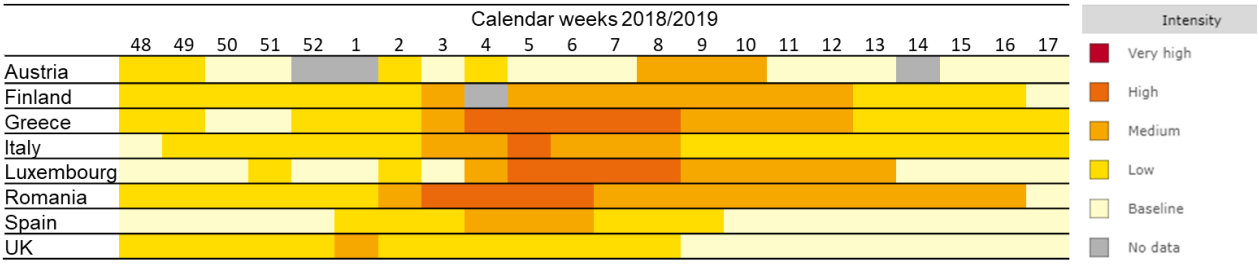
In the European Region, 10% of sentinel samples were positive from week 48/2018 and influenza activity levels returned to baseline in week 17/2019 [12]. More than 50% of sentinel samples were positive between weeks 3/2019 and 7/2019, and the peak was reached in week 5/2019. Nearly all detected influenza viruses were of type A, with little to no type B (0.7%). Both A/H1N1 and A/H3N2 circulated in the European Region, with co-circulation in some countries and predominance of either subtype in others [13]. Generally,

A/H1N1pdm09 was dominant in the first half of the season and A/H3N2 in the second half of the season (Adapted from Flu News Europe [14, 15]
Figure 2).The maximum intensity was classified as “medium” by ECDC for Austria, Finland, Spain and the UK, whereas “high” levels of intensity were reached in Greece, Italy, Luxembourg and Romania,. “Very high” levels were not reached in any EU country in the 2018/19 season (Adapted from Flu News Europe [14]
Figure 3).



Adapted from Flu News Europe [14, 15]

Figure 2. Dominant influenza virus A subtype by country, 2018/19



Adapted from Flu News Europe [14][2]

Figure 3. Intensity of influenza activity by country, 2018/19

The timing and duration of the 2018/19 season was similar to the 2017-2018, however the period of high influenza activity was shorter, and the intensity was lower. The high levels of influenza B observed in 2017/18 were not observed in 2018/19 [16].

[2] The levels of intensity were defined as follows: **Baseline or below epidemic threshold:** ILI or ARI rates that are very low and at levels usually seen throughout the inter-epidemic period. **Low:** ILI or ARI rates that are relatively low compared to rates from historical data but higher than the baseline. Influenza virus detections have been reported. **Medium:** ILI or ARI rates that are similar to rates usually observed, based on historical data. Influenza virus detections have been reported. **High:** ILI or ARI rates that are higher than rates usually observed, based on historical data. Influenza virus detections have been reported. **Very high:** ILI/ARI rates that are much higher than rates usually observed, based on historical data. Influenza virus detections have been reported.

4.1.5 Match between vaccine strain and circulating strains

For the A/H1N1 viruses, there was a good match between the circulating and the vaccine virus. A/H3N2 viruses were poorly recognized by antisera raised against the used vaccine virus. Of the 2163 A/H3 viruses that were genetically characterized, less than 3% belonged to the A/H3 clade 3c.2a1 representative A/Singapore/INFIMH-16-0019/2016 subgroup that was included in the vaccine. The majority of viruses belonged to the A/H3 clade 3C.2a1b representative A/Alsace/1746/2018 subgroup (66%) followed by the A/H3 clade 3C.3a representative A/England/538/2018 subgroup (25%) [17].

4.1.6 Influenza epidemiology in Austria (MUV)

In Austria, the epidemic period was from weeks 4/2019 to 14/2019, and peaked in week 6-7/2019. The influenza season was dominated by influenza A viruses (99.6%); A/H1N1 (66.8%) predominated over A/H3N2 (33.2%). The highest incidence rates were reported in 6m-17y age group. The majority of severe infections were due to influenza A/H1N1 (Local Report MUV, ANNEX 4).

4.1.7 Influenza epidemiology in Finland (THL and HUS)

According to preliminary information, in Finland, the influenza virus circulation started in week 44/2018 and was still ongoing in week 22/2019 (Local Report THL, ANNEX 4). The epidemic period was from weeks 2/2019 to 15/2019 and peaked in week 7-8/2019. The influenza season was dominated by influenza A viruses (99% among all typed viruses thus far). The intensity of the influenza season was about half of the intensity seen in the previous season 2017-18. The register-based cohort THL data covers the entire country, whereas HUS is a hospital located in the south.

4.1.7.1 THL

Co-circulation of A/H1N1 (57.4% of all subtyped A-viruses in the sentinel and ICU samples received by THL) and A/H3N2 (42.6% of all subtyped A-viruses in the sentinel and ICU samples received by THL as part of the routine national influenza surveillance) was observed. The beginning of the season was characterized by A/H1N1, however since weeks 8-10/2019, A/H3N2 was mostly more frequently detected.
In the entire country, about 4,000 influenza A and 20 influenza B cases were observed in the elderly. The corresponding numbers for children were 1,500 and 10. The highest incidence rates were reported in the age group 0 m-14y.

The most influenza related cases were diagnosed in the northern and eastern part of Finland.

4.1.7.2 HUS

Co-circulation of A/H1N1 (39.2%) and A/H3N2 (60.8%) was observed (Local Report HUS, ANNEX 4).

4.1.8 Influenza epidemiology in Greece (UoA)

In Greece, the epidemic period was from week 52/2018 to week 16/2019, and peaked in week 5/2019 (Local Report UoA, ANNEX 4). The influenza season was dominated by influenza A viruses (98.7%). Co-circulation of A/H1N1 (73.5% H1N1 among all subtyped type A viruses) and A/H3N2 (26.5% H3N2 among all subtyped type A viruses) was observed.

The highest incidence rates were reported in the age group 6m-17y. The majority of severe infections were due to influenza A/H1N1.

4.1.9 Influenza epidemiology in Italy

In Italy, the epidemic period was from weeks 49/2018 to 12/2019, and peaked in week 5/2019 (Local Report ISS, ANNEX 4). The influenza season was dominated by A viruses (99.7%), with the co-circulation of A/H1N1 (50.3%) and A/H3N2 (49.7%) subtypes. The start of the season was characterized by A/H1N1, however since week 7/2019, A/H3N2 was more frequently detected.
The intensity of the influenza season was high (estimated about 8 million ILI cases), with a peak of incidence rate of ILI cases equal to 14 per 1,000 inhabitants. This is in-line with the previous influenza season.

4.1.9.1 ISS

The influenza season was dominated by A viruses (99.7%), with the co-circulation of A/H1N1 (50.3%) and A/H3N2 (49.7%) subtypes (Local Report ISS, ANNEX 4). The majority of severe infections (67%) were due to influenza virus A/H1N1.

4.1.9.2 BIVE

The influenza season was dominated by A viruses (99.7%), with the co-circulation of A/H1N1 (50.3%) and A/H3N2 (49.7%) subtypes (Local Report BIVE, ANNEX 4). Most of severe infections were due to influenza A/H1N1 subtype (67%).

4.1.9.3 CIRI-IT (TND)

In Liguria, the epidemic period was from weeks 47/2018 to 11/2019 and peaked in week 6/2019 (Local Report CIRI-IT, ANNEX 4). The influenza season was dominated by influenza A viruses (96.9% of A type viruses). Co-circulation of A/H1N1 (39.8%) and A/H3N2 (60.2%) was observed. The start of the season was characterized by A/H1N1, however since week 5/2019, A/H3N2 was more frequently detected. The highest incidence rate was reported in 6m-14y age-group.

4.1.9.4 CIRI-IT (Cohort)

The influenza season in Liguria and Lombardy was dominated by influenza A viruses (100%) and characterized by co-circulation of A/H1N1 (54.2%) and A/H3N2 (45.8%) (Local Report CIRI-IT, ANNEX 4).

4.1.10 Influenza epidemiology in Luxembourg

In Luxembourg, the epidemic period was from week 51/2018 to week 13/2019 and peaked in week 7/2019. The influenza season was dominated by influenza A viruses (99.7 % of all typed viruses). Only 1 influenza B case was detected all season.

Unlike in many other European countries, circulation of A/H3N2 (80% among all subtyped type A viruses) predominated over A/H1N1 (20% among all subtyped type A viruses).

Mortality during the flu season was lower than in two previous seasons in Luxembourg.

4.1.11 Influenza epidemiology in Spain

4.1.11.1 FISABIO

The influenza season was dominated by influenza A viruses (100%), A/H3N2 (63.7%) predominated over A/H1N1 (36.3%) (Local Report FISABIO, ANNEX 4).

4.1.11.2 HUVH

In Catalonia, the epidemic period was from weeks 40/2018 to 20/2019, and peaked in week 4/2019 (Local Report HUVH, ANNEX 4). The influenza season was dominated by influenza A viruses (99.7% being 48% A/H1N1, 46% AH3N2, and 6% non-subtyped). Co-circulation of A/H1N1 (48%H1N1 among all subtyped type A viruses) and A/H3N2 (46%H3N2 among all subtyped type A viruses) was observed. Specifically, the start of the season was characterized by A/H1N1pmd09, however since week 6/2019, A/H3N2 was more frequently detected. The majority of severe infections were due to influenza A/H1N1. The highest incidence rates were reported in the 6 months-17 years age group.

Flu activity in Spain was similar to Catalonia, from the flu samples notified by the sentinel network since the beginning of the 2018/19 season 99.7% were type A (43% H1N1 and 57% H3N2).

4.1.12 Influenza epidemiology in Romania (NIID)

The epidemic period was from week 48/2018 to week 17/2019, and peaked in week 4/2019 (Local Report Romania, ANNEX 4). The influenza season was dominated by influenza A viruses (444/445, 99.8%); A/H1N1 (68.0%) predominated over A/H3N2 (32.0%). The start of the season was characterized by A/H3N2, however since week 01/2019 was also detected and since week 14/2019 A/H1N1 was most frequently detected. The majority of severe infections (SARI) were due to influenza A/H1N1.

4.1.13 Influenza epidemiology in United Kingdom (RCGP RSC)

In England, the epidemic period was from week 51/2018 to week 11/2019, and peaked in week 6/2019[15]. The influenza season was dominated by influenza A viruses.

A/H1N1 predominated over A/H3N2. The start of the season was characterized by A/H1N1, however, since week 9/2019 A/H3N2 was more frequently detected than A/H1N1[15].

4.2 Data pre-processing

Results of the data pre-processing are described in ANNEX 7. Attrition diagrams are presented in ANNEX 8.

4.3 Descriptive analysis

4.3.1 Test-negative design studies: primary care setting

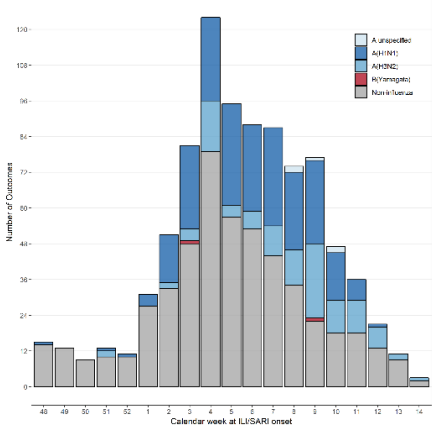
For the combined data of the primary care TND studies (included in the primary analysis), the majority of patients were children and adults 18-64y (45% and 46%) and male (51.8%). Of all patients, 20.8% suffered from at least 1 chronic condition and 14.5% were vaccinated with influenza in the current season, mostly with Fluarix Tetra, Vaxigrip Tetra and Fluad (Table 13Table 13. Study population characteristics, primary care TND studies, 2018/19). The population characteristics for the individual studies are provided in ANNEX 9. Population characteristics for each vaccine brand are provided in ANNEX 10. Graphical summaries of the site specific data are provided in Figure 4-Figure 7. The distribution of the controls and laboratory-confirmed influenza infections (by type and subtype/lineage) over time is given in Figure 4, showing there was almost no circulation of influenza type B this influenza season. The cumulative number of vaccinated subjects over time and the distribution of vaccine brands are given in Figure 5 and Figure 6, showing that some countries use multiple brands (e.g. Austria) whereas others use a few brands only (e.g. UK). The distribution of covariates among cases and controls is given in Figure 7, the percentages are given over the total number of subjects. These plots give, for every covariate maintained in the analytical dataset (Table 9), the percentage of cases with the covariate of interest, cases without the covariate of interest, controls with the covariate of interest and controls without the covariate of interest. As such, these plots show both the distribution of the covariates as well as the case-control ratios stratified by the covariates. Both Italy ISS and Austria MUV have a case-control ratio close to 1:1 whereas for UK RCGP RSC and Italy CIRI-IT the case-control ratio was much higher. These differences are likely explained by differences in the data period that could be used for analysis, especially UK RCGP RSC started late with its data collection. For all sites, the case-control ratios were similar across the covariates of interest.

Table 13. Study population characteristics, primary care TND studies, 2018/19

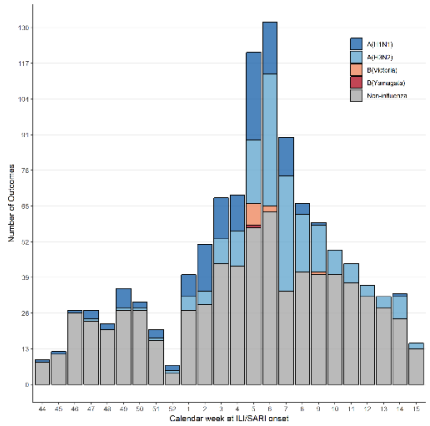
Characteristic	All N(%)	Cases N (%)								Controls N (%)
	all	A	A/H1N1	A/H3N2	A Unspecified	B	B Vict	B Yam	B unspecified	
Age group										
6m-17 y	2010 (45.0)	925 (49.2)	440 (46.2)	460 (52.8)	25 (45.5)	14 (77.8)	10 (90.9)	2 (66.7)	2 (50.0)	1071 (41.7)
18-64 y	2036 (45.6)	810 (43.1)	463 (48.6)	322 (37.0)	25 (45.5)	4 (22.2)	1 (9.1)	1 (33.3)	2 (50.0)	1222 (47.5)
65+ y	421 (9.4)	144 (7.7)	50 (5.2)	89 (10.2)	5 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	277 (10.8)
Sex										
female	2152 (48.2)	927 (49.3)	479 (50.3)	419 (48.1)	29 (52.7)	9 (50.0)	5 (45.5)	2 (66.7)	2 (50.0)	1216 (47.3)
male	2315 (51.8)	952 (50.7)	474 (49.7)	452 (51.9)	26 (47.3)	9 (50.0)	6 (54.5)	1 (33.3)	2 (50.0)	1354 (52.7)
At least 1 chronic condition*										
Yes	928 (20.8)	346 (18.4)	145 (15.2)	188 (21.6)	13 (23.6)	2 (11.1)	0 (0.0)	1 (33.3)	1 (25.0)	580 (22.6)
No	3539 (79.2)	1533 (81.6)	808 (84.8)	683 (78.4)	42 (76.4)	16 (88.9)	11 (100.0)	2 (66.7)	3 (75.0)	1990 (77.4)
Pregnancy										
Yes	15 (0.7)	2 (0.2)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	13 (1.1)
No	1041 (48.4)	415 (44.8)	216 (45.1)	178 (42.5)	21 (72.4)	8 (88.9)	5 (100.0)	2 (100.0)	1 (50.0)	618 (50.8)
Unknown	1096 (50.9)	510 (55.0)	261 (54.5)	241 (57.5)	8 (27.6)	1 (11.1)	0 (0.0)	0 (0.0)	1 (50.0)	585 (48.1)
Number of GP visits in the previous 12 months										
0	418 (9.4)	198 (10.5)	108 (11.3)	85 (9.8)	5 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	220 (8.6)
1-5	1756 (39.3)	823 (43.8)	392 (41.1)	391 (44.9)	40 (72.7)	4 (22.2)	0 (0.0)	0 (0.0)	4 (100.0)	929 (36.1)
>5	312 (7.0)	118 (6.3)	54 (5.7)	59 (6.8)	5 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	194 (7.5)
Unknown	1981 (44.3)	740 (39.4)	399 (41.9)	336 (38.6)	5 (9.1)	14 (77.8)	11 (100.0)	3 (100.0)	0 (0.0)	1227 (47.7)
Influenza vaccination status in previous season										
Vaccinated	285 (6.4)	79 (4.2)	17 (1.8)	51 (5.9)	11 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	206 (8.0)
Unvaccinated	1833 (41.0)	696 (37.0)	382 (40.1)	285 (32.7)	29 (52.7)	16 (88.9)	11 (100.0)	3 (100.0)	2 (50.0)	1121 (43.6)
Unknown	2349 (52.6)	1104 (58.8)	554 (58.1)	535 (61.4)	15 (27.3)	2 (11.1)	0 (0.0)	0 (0.0)	2 (50.0)	1243 (48.4)
Influenza vaccination status										
Vaccinated	649 (14.5)	214 (11.4)	62 (6.5)	140 (16.1)	12 (21.8)	2 (11.1)	1 (9.1)	0 (0.0)	1 (25.0)	433 (16.8)
Agrippal	16 (0.4)	7 (0.4)	2 (0.2)	5 (0.6)	0 (0.0)	1 (5.6)	1 (9.1)	0 (0.0)	0 (0.0)	8 (0.3)
Fluad	92 (2.1)	29 (1.5)	13 (1.4)	12 (1.4)	4 (7.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	63 (2.5)
Fluarix Tetra	314 (7.0)	98 (5.2)	25 (2.6)	73 (8.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	216 (8.4)
Influvac Tetra	7 (0.2)	2 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.2)
Fluenz Tetra	14 (0.3)	3 (0.2)	0 (0.0)	0 (0.0)	3 (5.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (0.4)

Characteristic	All N(%)	Cases N (%)								Controls N (%)
	all	A	A/H1N1	A/H3N2	A Unspecified	B	B Vict	B Yam	B unspecified	
Vaxigrip Tetra	178 (4.0)	67 (3.6)	19 (2.0)	46 (5.3)	2 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	110 (4.3)
Influvac	2 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)
Unvaccinated	3818 (85.5)	1665 (88.6)	891 (93.5)	731 (83.9)	43 (78.2)	16 (88.9)	10 (90.9)	3 (100.0)	3 (75.0)	2137 (83.2)
Study site										
MUV Austria	887 (19.9)	372 (19.8)	253 (26.5)	114 (13.1)	5 (9.1)	2 (11.1)	0 (0.0)	2 (66.7)	0 (0.0)	513 (20.0)
CIRI-IT Italy	1094 (24.5)	368 (19.6)	146 (15.3)	222 (25.5)	0 (0.0)	12 (66.7)	11 (100.0)	1 (33.3)	0 (0.0)	714 (27.8)
Italy ISS	2349 (52.6)	1104 (58.8)	554 (58.1)	535 (61.4)	15 (27.3)	2 (11.1)	0 (0.0)	0 (0.0)	2 (50.0)	1243 (48.4)
UK RCGP RSC	137 (3.1)	35 (1.9)	0 (0.0)	0 (0.0)	35 (63.6)	2 (11.1)	0 (0.0)	0 (0.0)	2 (50.0)	100 (3.9)
Total	4467	1879	953	871	55	18	11	3	4	2570

*Not all sites provide information on all the individual chronic conditions. See Table 8.



MUV, Austria



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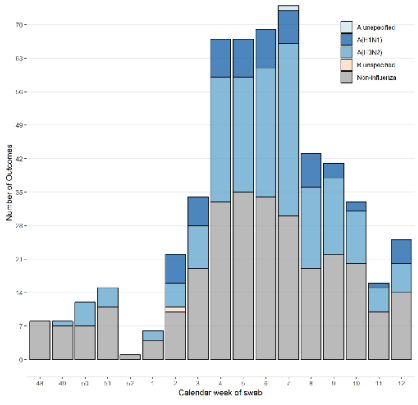
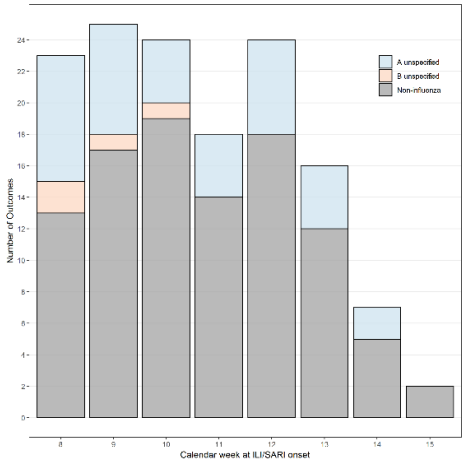


Luxembourg LNS



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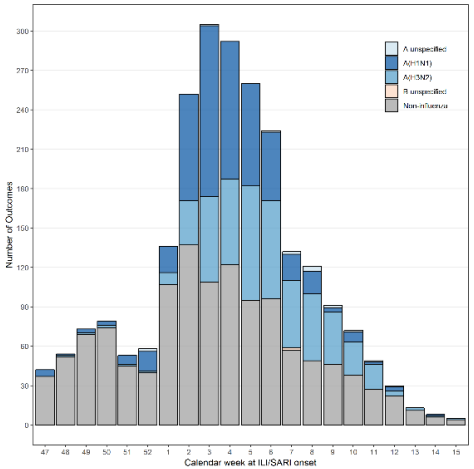
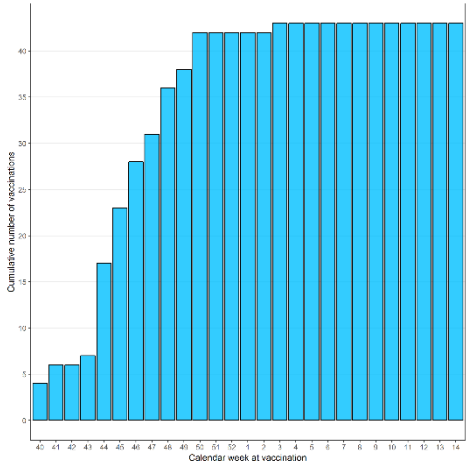


Italy ISS

Figure 4. Distribution of Influenza-like-illness cases over time; primary care TND studies, 2018/19



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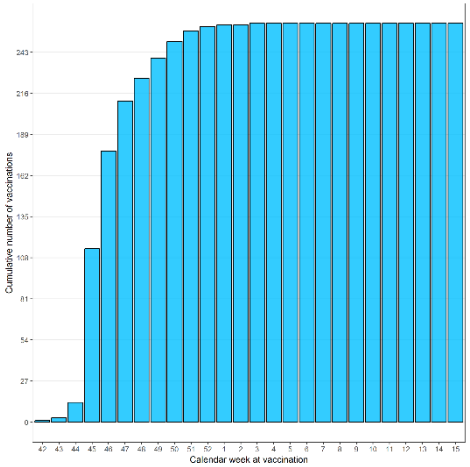
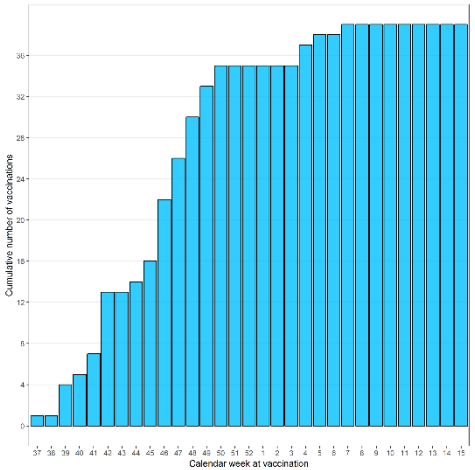


Italy CIRI-IT

Not available

LNS, Luxembourg



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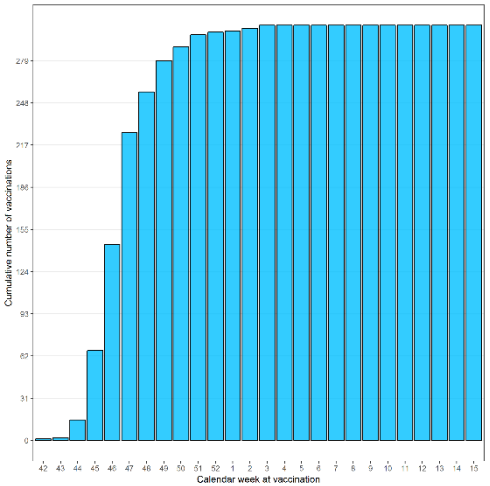
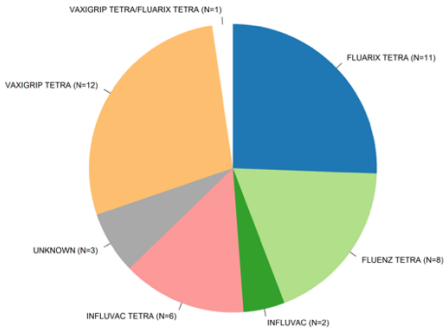


Italy ISS

Figure 5. Cumulative number of vaccinations over time; primary care TND studies, 2018/19



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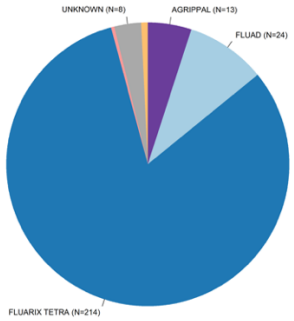
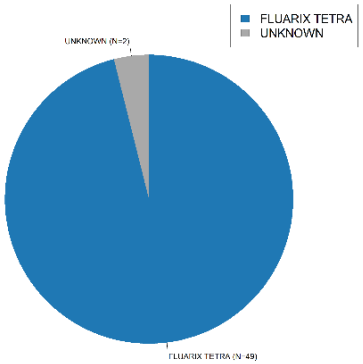
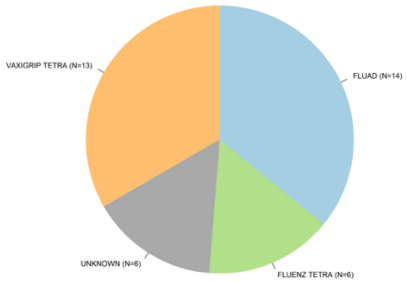


Italy CIRI-IT



Luxembourg LNS



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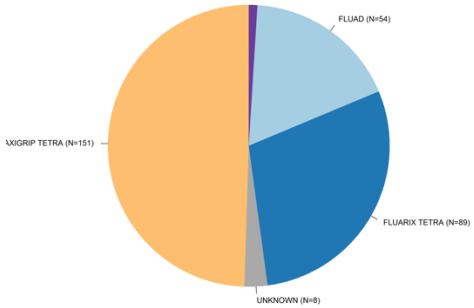
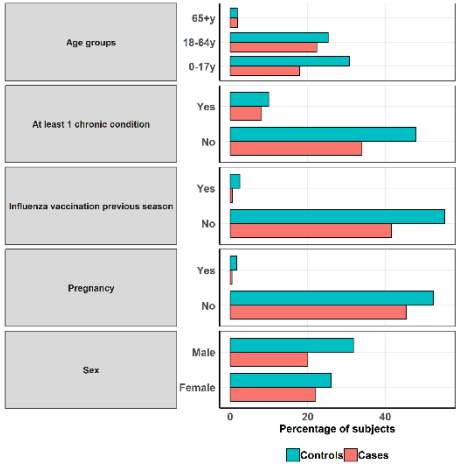
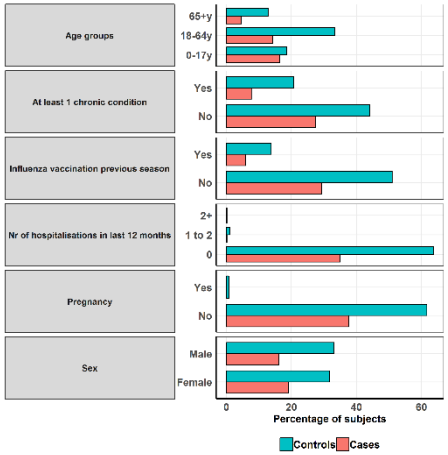


Italy ISS

Figure 6. Distribution of vaccine brands; primary care TND studies, 2018/19



Austria MUV



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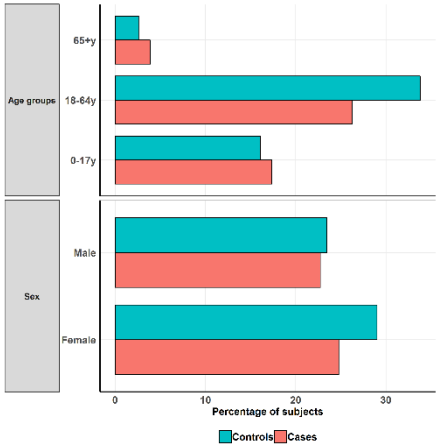

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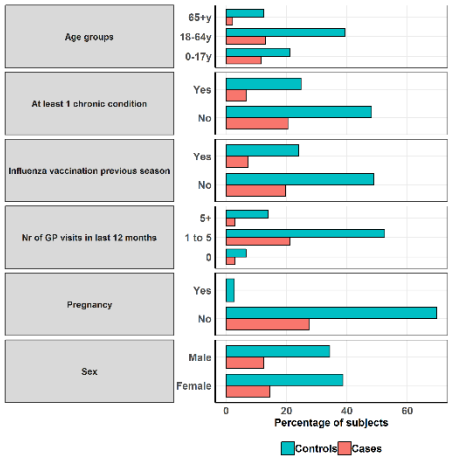

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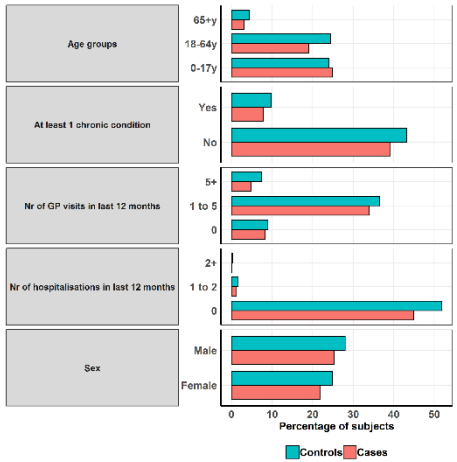


Italy ISS

Figure 7. Distribution of covariates; primary care TND studies, 2018/19.

4.3.2 Test-negative design studies: hospital setting

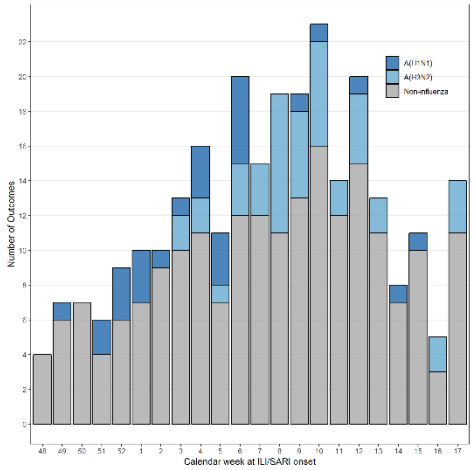
For the combined data of the hospital based TND studies (included in the primary analysis), the largest age group was elderly (44.9%) and the majority of patients were male (52.8%). Of all patients, 64.7% suffered from at least 1 chronic condition and 31.3% were vaccinated with influenza in the current season, mostly with Fluad, Influvac and Vaxigrip Tetra (Table 14). The population characteristics for the individual studies are provided in ANNEX 9. Population characteristics for each vaccine brand are provided in ANNEX 10. Graphical summaries of the site specific data are provided in Figure 8-Figure 11. The distribution of the controls and laboratory-confirmed influenza infections (by type and subtype/lineage) over time is given in Figure 8, showing there was almost no circulation of influenza type B this influenza season. The cumulative number of vaccinated subjects over time and the distribution of vaccine brands are given in Figure 9 and Figure 10. Comparing the brand distribution of the hospital based TND studies (Figure 10) with those of the primary care based TND studies (Figure 6), shows that from some brands information was predominantly collected within one type of health care setting (e.g. information on Influvac was mainly collected in hospital based studies and was restricted geographically). The distribution of covariates among cases and controls is given in Figure 11, the percentage is given over the total number of subjects. Both Finland HUS and Italy BIVE have a case-control ratio close to 1:2 while the case-control ratio is somewhat smaller for Romania NIID . The case-control ratio for Spain FISABIO is around 1:5, explained by their different and broader case definition (see Section 3.5.6). For Spain HUVH, the data collection followed a 1:1 case-control design, where only information on exposure and covariates was obtained for controls that could be matched to a case by epidemiological week and age group (6m – 17y, 18-64y and 65+y). For all sites, the case-control ratios were similar across the covariates of interest.

Table 14. Study population characteristics, hospital TND studies, 2018/19

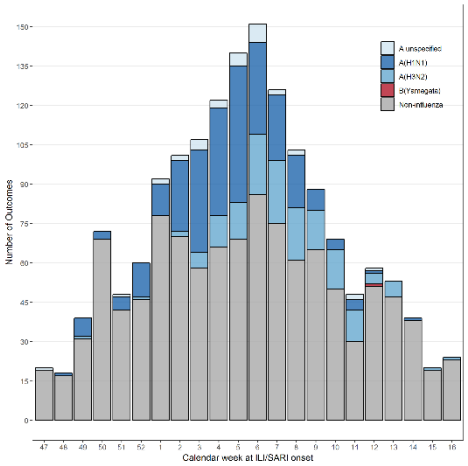
Characteristic	All N(%)	Cases N (%)							Controls N (%)
	all	A	A/H1N1	A/H3N2	A Unspecified	B	B Vict	B Yam	
Age group									
6m-17 y	1595 (32.7)	510 (35.4)	338 (44.0)	139 (26.5)	33 (22.4)	2 (100.0)	1 (100.0)	1 (100.0)	1083 (31.5)
18-64 y	1095 (22.4)	371 (25.8)	215 (28.0)	111 (21.2)	45 (30.6)	0 (0.0)	0 (0.0)	0 (0.0)	722 (21.0)
65+ y	2194 (44.9)	559 (38.8)	216 (28.1)	274 (52.3)	69 (46.9)	0 (0.0)	0 (0.0)	0 (0.0)	1635 (47.5)
Sex									
Female	2305 (47.2)	699 (48.5)	366 (47.6)	266 (50.8)	67 (45.6)	1 (50.0)	1 (100.0)	0 (0.0)	1604 (46.6)
Male	2579 (52.8)	741 (51.5)	403 (52.4)	258 (49.2)	80 (54.4)	1 (50.0)	0 (0.0)	1 (100.0)	1836 (53.4)
At least 1 chronic condition									
Yes	3158 (64.7)	880 (61.1)	401 (52.1)	379 (72.3)	100 (68.0)	0 (0.0)	0 (0.0)	0 (0.0)	2277 (66.2)
No	1726 (35.3)	560 (38.9)	368 (47.9)	145 (27.7)	47 (32.0)	2 (100.0)	1 (100.0)	1 (100.0)	1163 (33.8)
Pregnancy									
Yes	25 (1.1)	17 (2.4)	6 (0.8)	7 (1.3)	4 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.5)
No	1423 (61.7)	407 (58.2)	419 (54.5)	345 (65.8)	107 (72.8)	0 (0.0)	0 (0.0)	0 (0.0)	1015 (63.3)
Unknown	857 (37.2)	275 (39.3)	344 (44.7)	172 (32.8)	36 (24.5)	1 (100.0)	1 (100.0)	1 (100.0)	581 (36.2)
Number of hospitalizations in the previous 12 months									
0	2311 (47.3)	697 (48.4)	349 (45.4)	268 (51.1)	80 (54.4)	1 (50.0)	1 (100.0)	0 (0.0)	1611 (46.8)
1-2	1086 (22.2)	279 (19.4)	132 (17.2)	114 (21.8)	33 (22.4)	0 (0.0)	0 (0.0)	0 (0.0)	807 (23.5)
>2	337 (6.9)	100 (6.9)	48 (6.2)	33 (6.3)	19 (12.9)	0 (0.0)	0 (0.0)	0 (0.0)	237 (6.9)
Unknown	1150 (23.5)	364 (25.3)	240 (31.2)	109 (20.8)	15 (10.2)	1 (50.0)	0 (0.0)	1 (100.0)	785 (22.8)
Influenza vaccination status in previous season									
Vaccinated	1502 (30.8)	337 (23.4)	107 (13.9)	197 (37.6)	33 (22.4)	0 (0.0)	0 (0.0)	0 (0.0)	1165 (33.9)
Unvaccinated	3154 (64.6)	1044 (72.5)	628 (81.7)	305 (58.2)	111 (75.5)	2 (100.0)	1 (100.0)	1 (100.0)	2106 (61.2)
Unknown	228 (4.7)	59 (4.1)	34 (4.4)	22 (4.2)	3 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	169 (4.9)
Influenza vaccination status in current season									
Vaccinated	1530 (31.3)	333 (23.1)	108 (14.0)	194 (37.0)	31 (21.1)	0 (0.0)	0 (0.0)	0 (0.0)	1197 (34.8)
Agrippal	69 (1.4)	37 (2.6)	12 (1.6)	24 (4.6)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	32 (0.9)

Characteristic	All N(%)	Cases N (%)							Controls N (%)
	all	A	A/H1N1	A/H3N2	A Unspecified	B	B Vict	B Yam	
Fluad	620 (12.7)	144 (10.0)	45 (5.9)	80 (15.3)	19 (12.9)	0 (0.0)	0 (0.0)	0 (0.0)	476 (13.8)
Fluarix Tetra	68 (1.4)	9 (0.6)	4 (0.5)	4 (0.8)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	59 (1.7)
Influvac Tetra	478 (9.8)	68 (4.7)	21 (2.7)	37 (7.1)	10 (6.8)	0 (0.0)	0 (0.0)	0 (0.0)	410 (11.9)
Vaxigrip Tetra	216 (4.4)	58 (4.0)	22 (2.9)	36 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	158 (4.6)
Unvaccinated	3354 (68.7)	1107 (76.9)	661 (86.0)	330 (63.0)	116 (78.9)	2 (100.0)	1 (100.0)	1 (100.0)	2243 (65.2)
Study site									
HUS Finland HUS	274 (5.6)	70 (4.9)	27 (3.5)	43 (8.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	204 (5.9)
Italy BIVE	1598 (32.7)	487 (33.8)	298 (38.8)	157 (30.0)	32 (21.8)	1 (50.0)	0 (0.0)	1 (100.0)	1110 (32.3)
Romania NIID	1027 (21.0)	427 (29.7)	251 (32.6)	123 (23.5)	53 (36.1)	1 (50.0)	1 (100.0)	0 (0.0)	597 (17.4)
Spain VHUH	465 (9.5)	233 (16.2)	123 (16.0)	95 (18.1)	15 (10.2)	0 (0.0)	0 (0.0)	0 (0.0)	232 (6.7)
Spain FISABIO	1520 (31.1)	223 (15.5)	70 (9.1)	106 (20.2)	47 (32.0)	0 (0.0)	0 (0.0)	0 (0.0)	1297 (37.7)
Total	4884	1440	769	524	147	2	1	1	3440

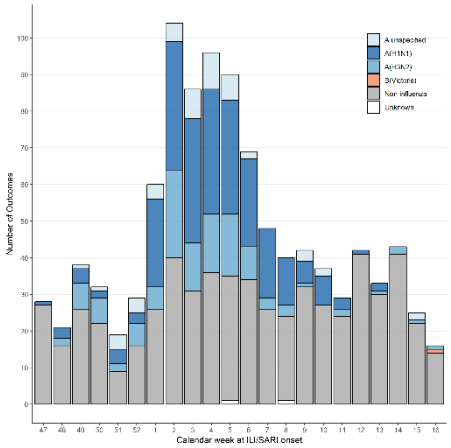
*Not all sites provide information on all the individual chronic conditions. See Table 8.



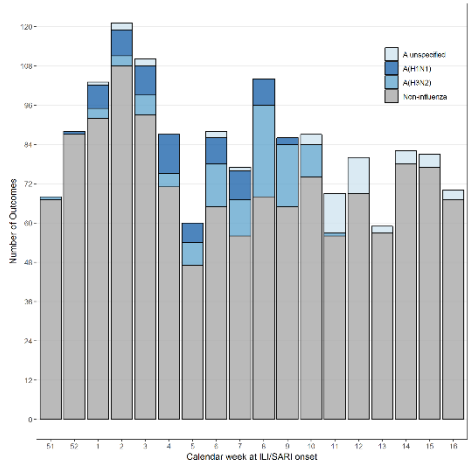
Finland HUS



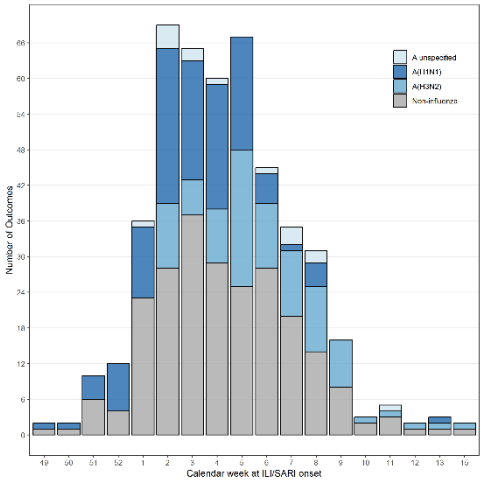
Italy BIVE



Romania NIID

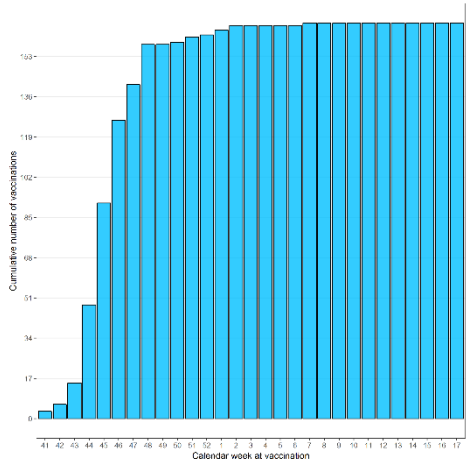


Spain FISABIO

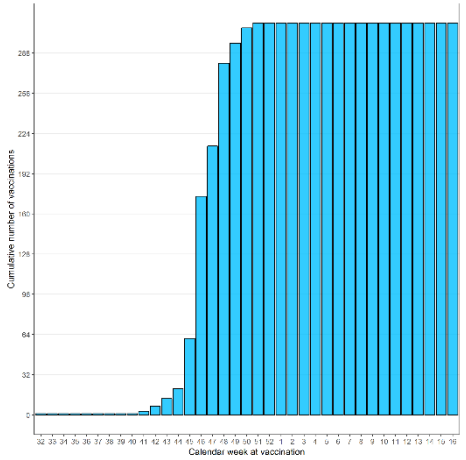


Spain HUVH

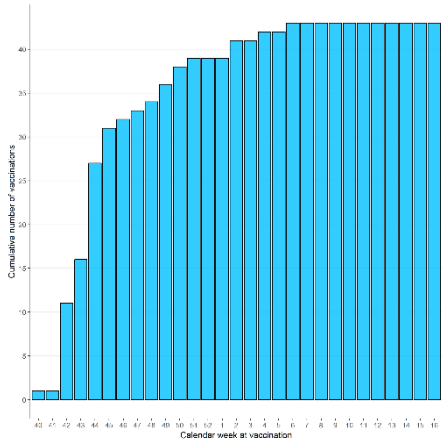
Figure 8. Distribution of SARI cases (all sites except FISABIO) and acute hospitalizations or influenza-like illness (FISABIO) over time; hospital TND studies, 2018/19



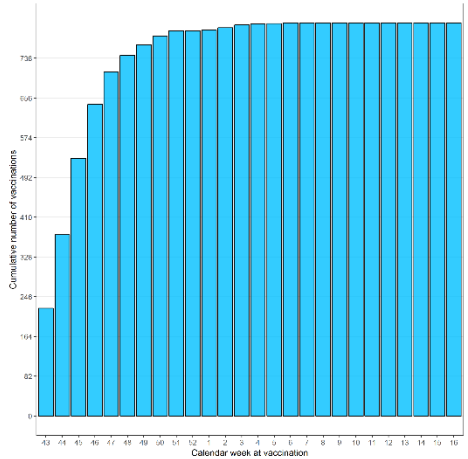
Finland HUS



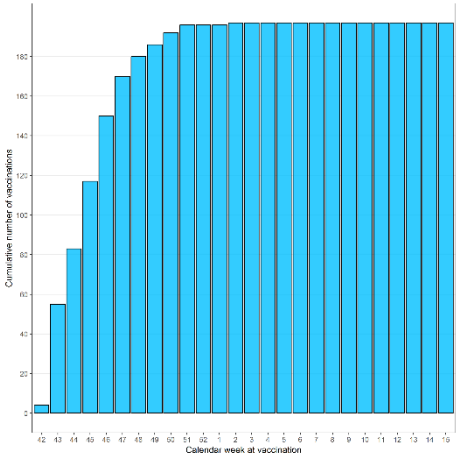
Italy BIVE



Romania NIID

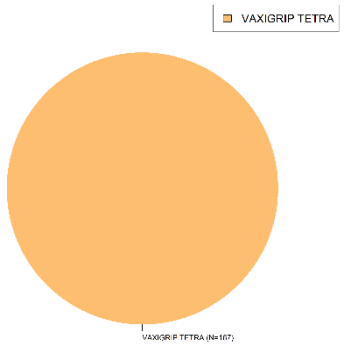


Spain FISABIO

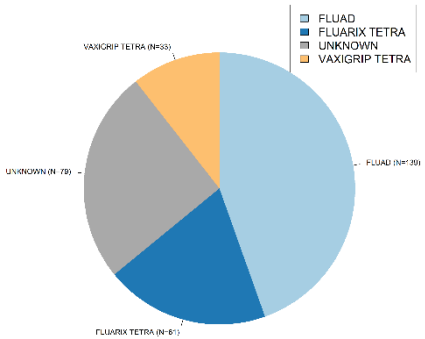


Spain HUVH

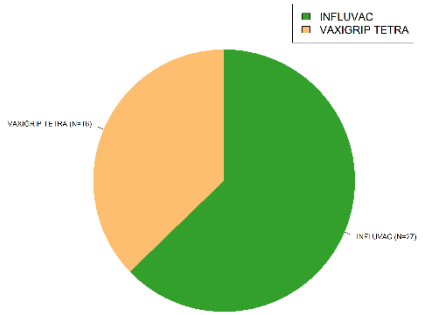
Figure 9. Cumulative number of vaccinations over time; hospital TND studies, 2018/19



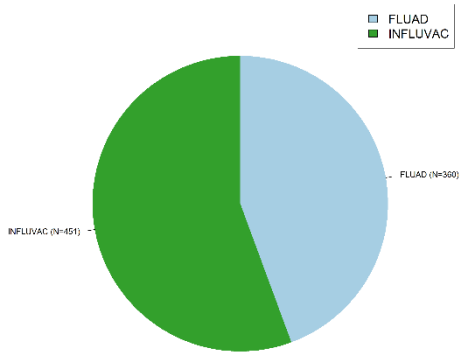
Finland HUS



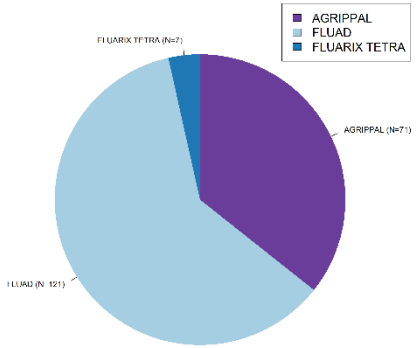
Italy BIVE



Romania NIID

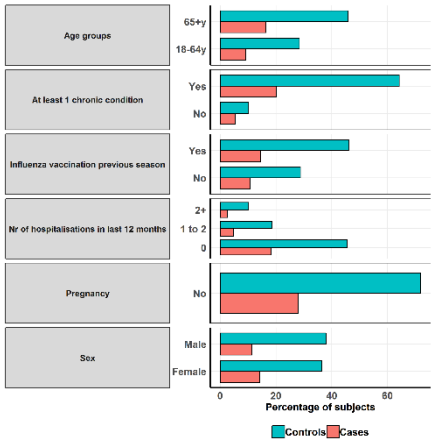


Spain FISABIO

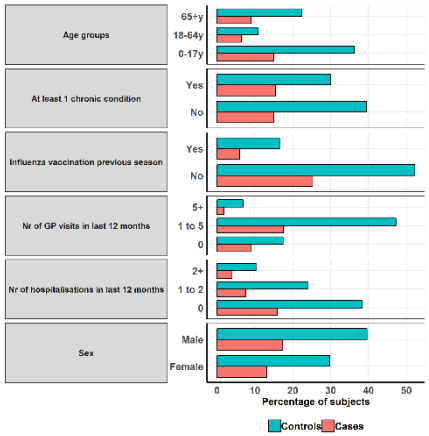


Spain HUVH

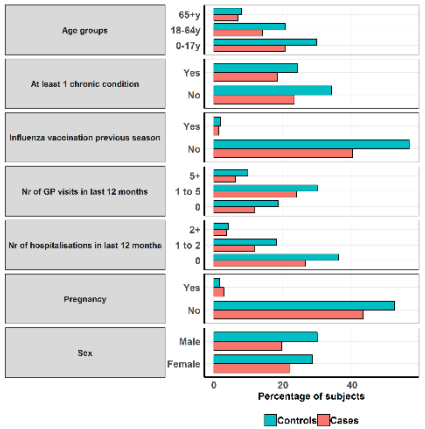
Figure 10. Distribution of vaccine brands; hospital TND studies, 2018/19



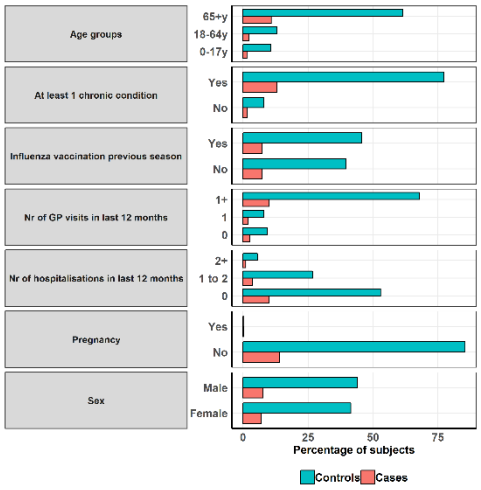
Finland HUS



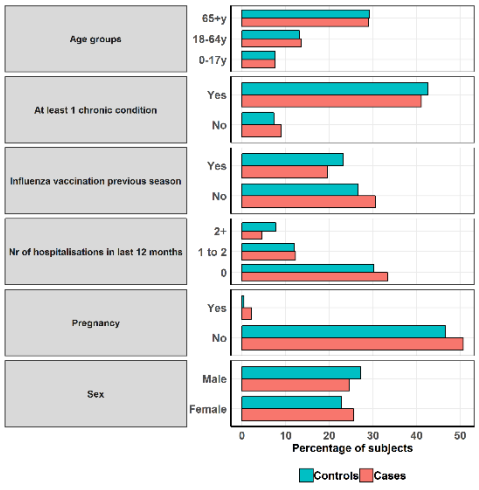
Italy BIVE



Romania NIID



Spain FISABIO



Spain HUVH

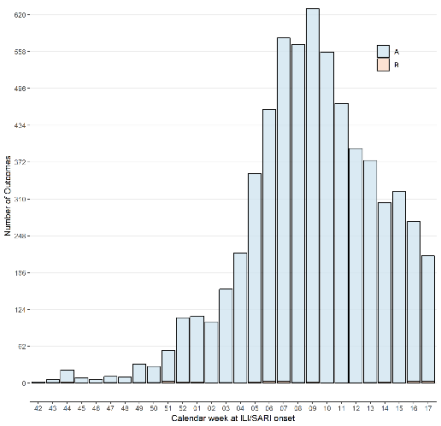
Figure 11. Distribution of covariates; hospital TND studies, 2018/19.

4.3.3 Register-based cohort study, Finland

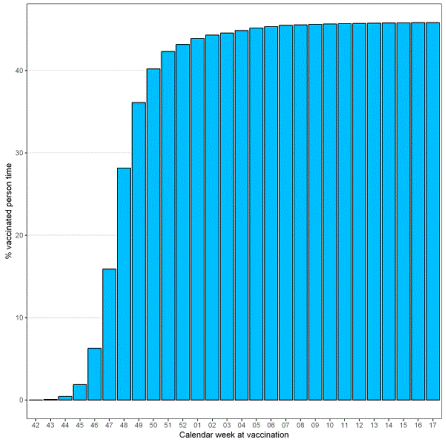
The Finland THL register-based cohort includes children 6m-6y (168020.7 person years) and elderly 65-100 y (600394.9 person years).Tabular and graphical summaries of the data are provided in Table 15 and Figure 12. Almost no influenza B was observed this season (Figure 12, top left). The vaccine brands used were either Fluenz tetra (for children 2-6 years of age) or Vaxigrip Tetra (all ages) (Figure 12, bottom left). Elderly, persons with at least 1 chronic condition and persons vaccinated with influenza in the previous season were more likely vaccinated compared to their counterparts (Figure 12, bottom right).

Table 15. Study population characteristics, Finland THL register-based cohort study, 2018/19

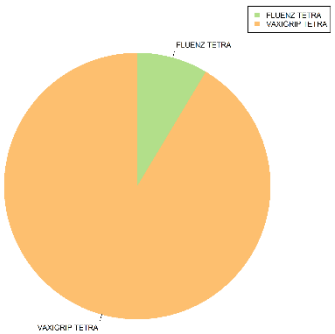
Characteristic	6m – 6y				65+ y			
	Vaccinated		Unvaccinated		Vaccinated		Unvaccinated	
	Number of influenza infections	Person years	Number of influenza infections	Person years	Number of influenza infections	Person years	Number of influenza infections	Person years
Sex								
female	145	18460	643	63694	1013	133121	1437	204275
male	198	19321	848	66546	961	103177	1134	159822
At least 1 chronic condition								
Yes	281	33990	1329	118910	151	58558	300	118430
No	62	3791	162	11330	1823	177740	2271	245667
Number of primary care visits in the previous 12 months								
0	111	13609	553	49723	459	71764	912	156856
1-5	212	22509	856	74560	1080	133063	1244	173780
>5	20	1662	82	5958	435	31471	415	33462
Number of hospitalizations in the previous 12 months								
0	305	34764	1363	121737	1240	193179	1635	300577
1-2	36	2797	111	8048	563	37827	730	54864
>2	2	219	17	455	171	5291	206	8656
Influenza vaccination status in previous season								
Vaccinated	172	16989	1399	116134	376	42967	2062	283058
Unvaccinated	171	20792	92	14106	1598	193330	509	81040
Total	343	37781	1491	130240	1974	236298	2571	364097



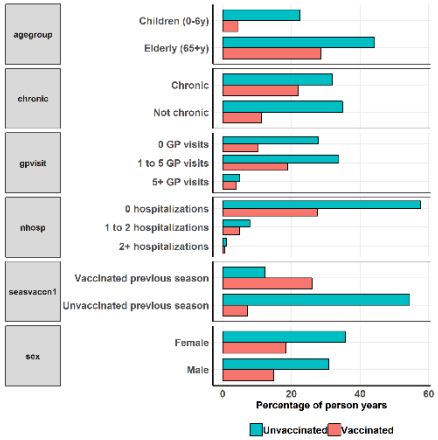
Influenza cases over time



Number of vaccinations over time



Distribution of vaccine brands



Distribution of covariates

Figure 12. Data visualizations, Finland THL register-based cohort study, 2018/19.

4.3.4 Clinical cohorts

Descriptive data of the clinical cohorts is presented in ANNEX 11.

4.4 Primary objective: influenza vaccine effectiveness by brand

4.4.1 Site-specific estimates

4.4.1.1 Test-negative design studies: primary care setting

The total number of primary care TND studies for which specific confounder-adjusted estimates were obtained are summarized in Table 16 (for any influenza and any vaccine type influenza) and Table 17 (for influenza A/H1N1 and A/H3N2). These tables also present the lowest and highest observed IVE estimates by type of estimate. No estimates for influenza B are presented in these summary tables as influenza B was virtually not circulating this year. All site-specific influenza estimates, both crude and confounder-adjusted, are given in ANNEX 12 for each TND site separately. The number of studies providing specific IVE estimates was low. Estimates of IVE of any influenza vaccine in the elderly were obtained most, with this estimate being obtained for 4 different study sites.

Table 16. Summary of the site-specific confounder-adjusted influenza vaccine effectiveness against any influenza and against any virus subtype or lineage included in the vaccine (number of studies, minimum and maximum estimate), primary care TND studies, 2018/19

	Any influenza				Any virus subtype or lineage included in vaccine			
	N estimates	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**	**N estimates**	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**
6m-17 y								
Any vaccine	3	1965 (54)	29 [-18,57]	89 [7,99]	0	0		
Vaccine brand								
Agrippal	1	347 (7)	-41 [-630,73]	-41 [-630,73]	1	346 (7)	-41 [-631,73]	-41 [-631,73]
Influvac	0	0			0	0		
Fluarix Tetra	2	1488 (35)	0 [-85,46]	67 [2,89]	0	0		
Influvac Tetra	0	0			0	0		
Vaxigrip Tetra	2	1514 (12)	-65 [-1821,86]	58 [5,82]	0	0		
Fluad	0	0			0	0		
Fluenz Tetra	1	36 (3)	-65 [-1872,86]	-65 [-1872,86]	0	0		
18-64 y								
Any vaccine	4	2036 (69)	38 [1,61]	92 [-77,100]	0	0		
Vaccine brand								
Agrippal	1	918 (1)	17 [-1314,95]	17 [-1314,95]	1	918 (1)	17 [-1314,95]	17 [-1314,95]
Influvac	0	0			0	0		
Fluarix Tetra	3	1861 (34)	-1 [-135,56]	64 [-374,97]	0	0		
Influvac Tetra	1	408 (1)	60 [-422,97]	60 [-422,97]	0	0		
Vaxigrip Tetra	3	1463 (29)	31 [-1173,96]	90 [-97,100]	0	0		
Fluad	0	0			0	0		
Fluenz Tetra	0	0			0	0		
65+ y								
Any vaccine	2	368 (82)	-6 [-115,47]	60 [-28,87]	0	0		
Vaccine brand								
Agrippal	0	0			0	0		
Influvac	0	0			0	0		

	Any influenza				Any virus subtype or lineage included in vaccine			
	N estimates	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**	**N estimates**	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**
Fluarix Tetra	2	240 (30)	7 [-330,80]	68 [-11,90]	0	0		
Influvac Tetra	0	0			0	0		
Vaxigrip Tetra	1	115 (25)	-1 [-142,58]	-1 [-142,58]	0	0		
Fluad	2	197 (25)	-48 [-5749,96]	-25 [-198,48]	2	197 (25)	-48 [-5749,96]	-25 [-198,48]
Fluenz Tetra	0	0			0	0		

Table 17. Summary of the site-specific confounder-adjusted influenza vaccine effectiveness against A/H1N1 and A/H3N2 (number of studies, minimum and maximum estimate), primary care TND studies, 2018/19

	A/H1N1				A/H3N2			
	N estimates	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**	**N estimates**	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**
6m-17 y								
Any vaccine	3	1482 (12)	73 [36,89]	83 [-35,98]	2	1183 (41)	-11 [-98,38]	50 [-58,84]
Vaccine brand								
Agrippal	1	238 (1)	59 [-510,97]	59 [-510,97]	1	272 (5)	-73 [-1346,79]	-73 [-1346,79]
Influvac	0	0			0	0		
Fluarix Tetra	2	1069 (8)	54 [-31,84]	80 [1,96]	2	1142 (27)	-33 [-172,35]	51 [-82,87]
Influvac Tetra	0	0			0	0		
Vaxigrip Tetra	2	1167 (3)	-73 [-1922,85]	87 [42,97]	1	829 (9)	12 [-126,65]	12 [-126,65]
Fluad	0	0			0	0		
Fluenz Tetra	0	0			0	0		
18-64 y								
Any vaccine	3	1626 (25)	39 [-11,66]	80 [-26,97]	3	1485 (41)	35 [-18,64]	73 [-159,97]
Vaccine brand								
Agrippal	1	752 (1)	-128 [-4820,89]	-128 [-4820,89]	0	0		
Influvac	0	0			0	0		
Fluarix Tetra	2	1195 (11)	-36 [-261,49]	72 [-41,95]	3	1396 (22)	-24 [-1844,92]	58 [-53,89]
Influvac Tetra	1	346 (1)	41 [-644,95]	41 [-644,95]	0	0		
Vaxigrip Tetra	2	1150 (11)	37 [-1071,97]	50 [-9,77]	1	726 (16)	25 [-50,63]	25 [-50,63]
Fluad	0	0			0	0		
Fluenz Tetra	0	0			0	0		
65+ y								

Any vaccine	2	286 (25)	7 [-140,64]	69 [-148,96]	2	325 (56)	-6 [-157,56]	56 [-63,88]
Vaccine brand								
Agrippal	0	0			0	0		
Influvac	0	0			0	0		
Fluarix Tetra	2	191	58 [-986,98]	90 [-35,99]	2	217	35 [-334,90]	57 [-60,88]
Influvac Tetra	0	0			0	0		
Vaxigrip Tetra	1	83 (5)	52 [-102,89]	52 [-102,89]	1	98 (20)	-45 [-293,47]	-45 [-293,47]
Fluad	1	89 (12)	-110 [-571,34]	-110 [-571,34]	1	85 (8)	24 [-139,76]	24 [-139,76]
Fluenz Tetra	0	0			0	0		

4.4.1.2 Test-negative design studies: hospital setting

The total number of hospital TND studies for which specific confounder-adjusted estimates were obtained are summarized in Table 18 (for any influenza and any vaccine type influenza) and Table 19 (for influenza A/H1N1 and A/H3N2). All site-specific influenza estimates, both crude and confounder-adjusted, are given in ANNEX 12 for each TND site separately. The number of studies providing specific IVE estimates was low. Estimates of IVE of any influenza vaccine in the 18-64y old and the elderly were obtained most, with these estimates being obtained for 5 different study sites.

Table 18. Summary of the site-specific confounder-adjusted influenza vaccine effectiveness against any influenza and any virus subtype or lineage included in the vaccine (number of studies, minimum and maximum estimate), hospital TND studies, 2018/19

	Any influenza				Any virus subtype or lineage included in vaccine			
	N estimates	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**	**N estimates**	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**
6m-17 y								
Any vaccine	3	1408 (16)	14 [-120,66]	88 [23,98]	0	0		
Vaccine brand								
Agrippal	1	69 (5)	86 [9,98]	86 [9,98]	1	69 (5)	86 [9,98]	86 [9,98]
Influvac	0	0			0	0		
Fluarix Tetra	1	811 (5)	52 [-64,86]	52 [-64,86]	0	0		
Influvac Tetra	0	0			0	0		
Vaxigrip Tetra	2	1317 (5)	-228 [-1844,45]	66 [-822,99]	0	0		
Fluad	0	0			0	0		
Fluenz Tetra	0	0			0	0		
18-64 y								
Any vaccine	5	1095 (50)	-17 [-490,77]	71 [4,91]	0	0		
Vaccine brand								
Agrippal	1	120 (12)	-13 [-228,61]	-13 [-228,61]	1	120 (12)	-13 [-228,61]	-13 [-228,61]
Influvac	2	576 (14)	-10 [-610,83]	69 [-2,91]	2	574 (14)	-8 [-596,83]	69 [-2,91]
Fluarix Tetra	2	346 (3)	30 [-344,89]	63 [-739,98]	0	0		
Influvac Tetra	0	0			0	0		
Vaxigrip Tetra	3	692 (15)	-9 [-1148,91]	53 [-74,87]	0	0		
Fluad	0	0			0	0		
Fluenz Tetra	0	0			0	0		
65+ y								
Any vaccine	5	2194 (267)	8 [-759,90]	34 [-2,57]	0	0		
Vaccine brand								

	Any influenza				Any virus subtype or lineage included in vaccine			
	N estimates	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**	**N estimates**	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**
Agrippal	1	148 (20)	-31 [-192,42]	-31 [-192,42]	1	148 (20)	-31 [-192,42]	-31 [-192,42]
Influvac	2	869 (54)	8 [-759,90]	25 [-28,56]	2	896 (54)	8 [-759,90]	25 [-28,56]
Fluarix Tetra	1	292 (1)	92 [40,99]	92 [40,99]	0	0		
Influvac Tetra	0	0			0	0		
Vaxigrip Tetra	2	442 (38)	-142 [-737,30]	25 [-69,66]	0	0		
Fluad	3	1351 (141)	6 [-57,43]	34 [-12,61]	3	1351 (141)	6 [-57,43]	34 [-12,61]
Fluenz Tetra	0	0			0	0		

Table 19. Summary of the site-specific confounder-adjusted influenza vaccine effectiveness against A/H1N1 and A/H3N2 (number of studies, minimum and maximum estimate), hospital TND studies, 2018/19

	A/H1N1				A/H3N2			
	N estimates	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**	**N sites**	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**
6m-17 y								
Any vaccine	2	799 (8)	-12 [-222,61]	94 [26,100]	1	643 (3)	50 [-145,90]	50 [-145,90]
Vaccine brand								
Agrippal	1	57 (1)	94 [21,100]	94 [21,100]	0	0		
Influvac	0	0			0	0		
Fluarix Tetra	1	733 (3)	42 [-156,87]	42 [-156,87]	1	638 (2)	58 [-160,93]	58 [-160,93]
Influvac Tetra	0	0			0	0		
Vaxigrip Tetra	1	722 (3)	-286 [-2375,40]	-286 [-2375,40]	1	359 (1)	-80 [-6001,95]	-80 [-6001,95]
Fluad	0	0			0	0		
Fluenz Tetra	0	0			0	0		
18-64 y								
Any vaccine	4	653 (16)	35 [-143,83]	80 [-15,97]	4	579 (20)	-223 [-1203,20]	58 [-208,94]
Vaccine brand								
Agrippal	1	99 (6)	19 [-212,79]	19 [-212,79]	1	76 (6)	-218 [-1234,24]	-218 [-1234,24]
Influvac	2	485 (4)	52 [-1171,98]	63 [-135,94]	2	452 (8)	-100 [-1532,75]	58 [-213,94]
Fluarix Tetra	1	218 (1)	26 [-818,94]	26 [-818,94]	1	171 (1)	1 [-1108,92]	1 [-1108,92]
Influvac Tetra	0	0			0	0		
Vaxigrip Tetra	2	314 (5)	47 [-129,88]	80 [-15,97]	3	505 (8)	-34 [-2318,93]	53 [-330,95]
Fluad	0	0			0	0		
Fluenz Tetra	0	0			0	0		
65+ y								
Any vaccine	4	1734 (77)	9 [-254,77]	51 [4,75]	4	1802 (158)	-56 [-207,20]	25 [-93,71]
Vaccine brand								

	A/H1N1				A/H3N2			
	N estimates	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**	**N sites**	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**
Agrippal	1	108 (5)	37 [-106,81]	37 [-106,81]	1	102 (14)	-156 [-580,4]	-156 [-580,4]
Influvac	2	780 (17)	20 [-103,68]	58 [-547,97]	2	790 (29)	-215 [-4597,79]	8 [-93,56]
Fluarix Tetra	0	0			1	240 (1)	83 [-38,98]	83 [-38,98]
Influvac Tetra	0	0			0	0		
Vaxigrip Tetra	2	364 (12)	-87 [-995,68]	9 [-254,77]	2	374 (26)	-377 [-2344,7]	25 [-93,71]
Fluad	3	1143 (45)	-19 [-138,40]	53 [-37,84]	3	1157 (77)	-37 [-180,33]	36 [-28,68]
Fluenz Tetra	0	0			0	0		

4.4.1.3 Register-based cohort study, Finland

All IVE estimates against any influenza and influenza A from the Finland THL register-based cohort are robust, defined as having a CI width of less than 40% (Table 20). The IVE estimate of Fluenz Tetra against influenza A is 35.7 (95%CI 24.4-45.3) in children aged 6m-6y. The IVE estimates of Vaxigrip against influenza A are 54 (95%CI 43.6-62.4) in children aged 6m-6y and 30.4 (95%CI 24.8-35.5) in the elderly 65+y.

Estimates for any virus subtype/lineage include in the vaccine are not available for this data. No estimates for influenza B are presented here as influenza B was virtually not circulating this year. These estimates, along with the crude influenza vaccine effectiveness estimates for the THL register-based are given in ANNEX 12. The confounder adjusted IVE estimates were substantially higher compared to the crude estimates.

Table 20. Site-specific confounder-adjusted influenza vaccine effectiveness against any influenza and influenza A, Finland THL register-based cohort, 2018/19

	Any influenza VE [95%CI]	A VE [95%CI]
6m-6y		
Any vaccine	44[36,51]	44.3[36.3,51.3]
Vaccine brand		
Vaxigrip Tetra	53.7[43.3,62.2]	54[43.6,62.4]
Fluenz Tetra	35.5[24.1,45.1]	35.7[24.4,45.3]
65+y		
Any vaccine	30.3[24.8,35.4]	30.4[24.8,35.5]
Vaccine brand		
Vaxigrip Tetra	30.3[24.8,35.4]	30.4[24.8,35.5]

4.4.2 Pooled estimates

4.4.2.1 Main analysis

The pooled confounder-adjusted IVE estimates for every exposure of interest (any vaccine, by brand) stratified by age group and healthcare setting are provided in Dark grey diamond: robust results (width of CI <40%). Light grey diamond: non-robust results.-Dark grey diamond: robust results (width of CI <40%). Light grey diamond: non-robust results.

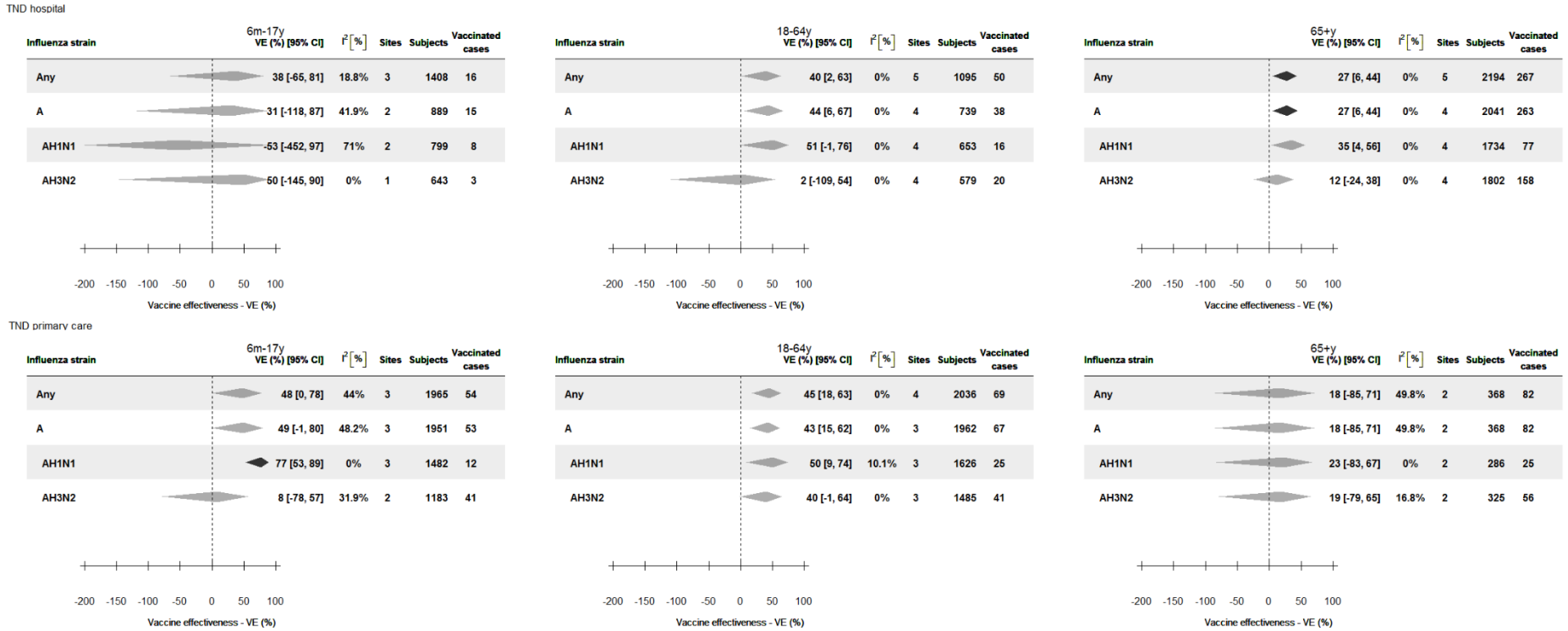
Figure 20. Wide confidence intervals (with a confidence interval width > 40%) are colored light grey to emphasise that estimates with wide confidence intervals are not considered robust. Forest plots without estimates indicate that no data was available for that specific age group and setting. Blank squares indicate that the vaccine brand is not indicated for use in that specific age group. The pooled crude IVE estimates are provided in ANNEX 13, all pooled adjusted IVE estimates (including for influenza B) are provided in ANNEX 14. To aid the interpretation of the pooled estimates, the corresponding forest plots with the site-specific estimates are provided in the ANNEX 13 for the crude estimates and ANNEX 14 for the confounder-adjusted estimates.

An overview of the brands for which estimates are available is given in Table 21. For children aged 6m-17y, IVE estimates are available for 4 brands in primary care setting and 3 brands in hospital setting; for adults 18-64y 4 brands in primary care setting and 4 brands in hospital setting; and for elderly 65+y 2 brands in primary care setting and 5 brands in hospital setting.

Three robust IVE estimates were available. The IVE estimate for any vaccine against any influenza and influenza A in elderly 65+y in hospital setting was estimated at 28 % (95%CI 7-44). The IVE estimate for any vaccine against A/H1N1 in primary care in children aged 6m-17y was 77 % (95%CI 53-89). No robust brand-specific IVE estimates were obtained.

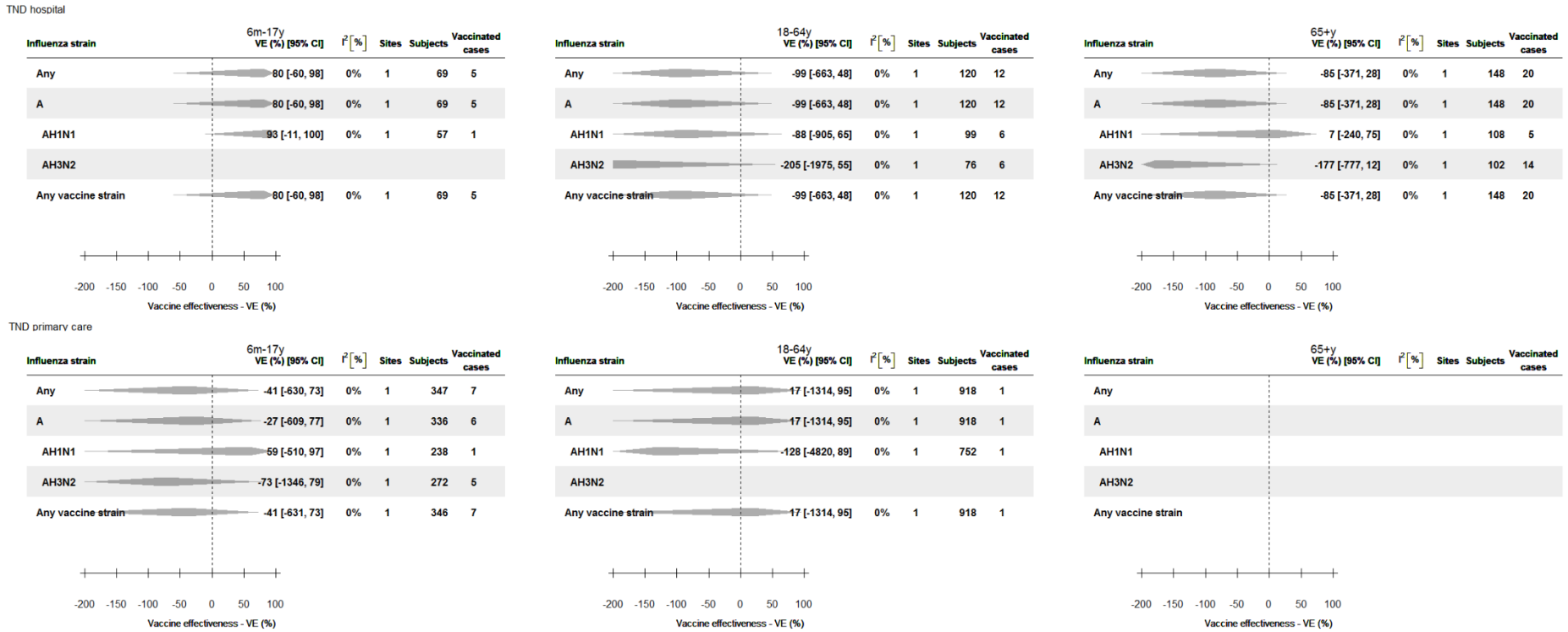
Table 21. Overview of number of sites that contribute data to the pooled IVE estimates for primary objectives, by setting, vaccine brand and age, 2018/19

	Age group		
	6m-17y	**18-64y**	**65+y**
Primary care			
Any vaccine	3	4	2
Vaccine brand			
Agrippal	1	1	No data
Fluad	Not licensed	Not licensed	2
Fluarix Tetra	2	3	2
Fluenz Tetra	1	Not licensed	Not licensed
Influvac	No data	No data	No data
Influvac Tetra	No data	1	No data
Vaxigrip Tetra	2	3	1
Hospital			
Any vaccine	3	5	5
Vaccine brand			
Agrippal	1	1	1
Fluad	Not licensed	Not licensed	3
Fluarix Tetra	1	2	1
Fluenz Tetra	No data	Not licensed	Not licensed
Influvac	No data	2	2
Influvac Tetra	No data	No data	No data
Vaxigrip Tetra	2	3	2



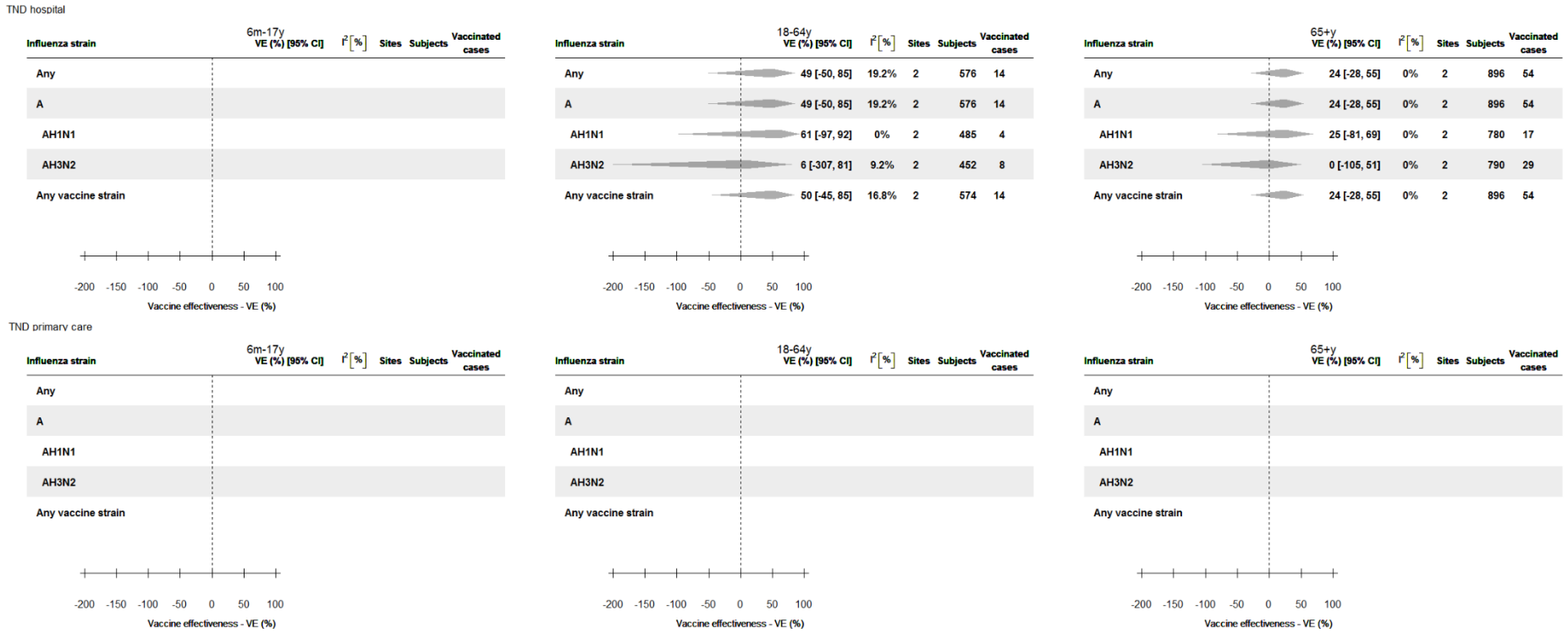
Dark grey diamond: robust results (width of CI <40%). Light grey diamond: non-robust results.

Figure 13. Any influenza vaccine: pooled confounder-adjusted influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2018/19



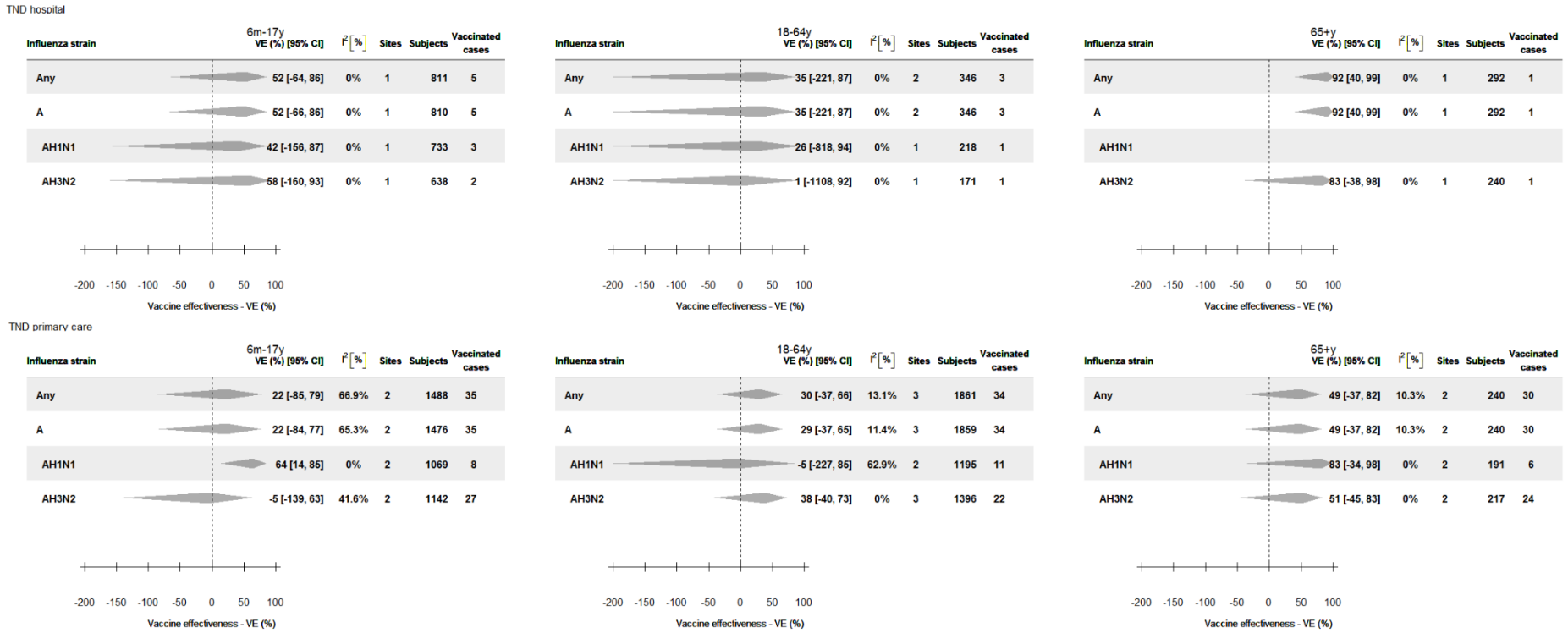
Dark grey diamond: robust results (width of CI <40%). Light grey diamond: non-robust results.

Figure 14. Agrippal (Seqirus): pooled confounder-adjusted influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2018/19



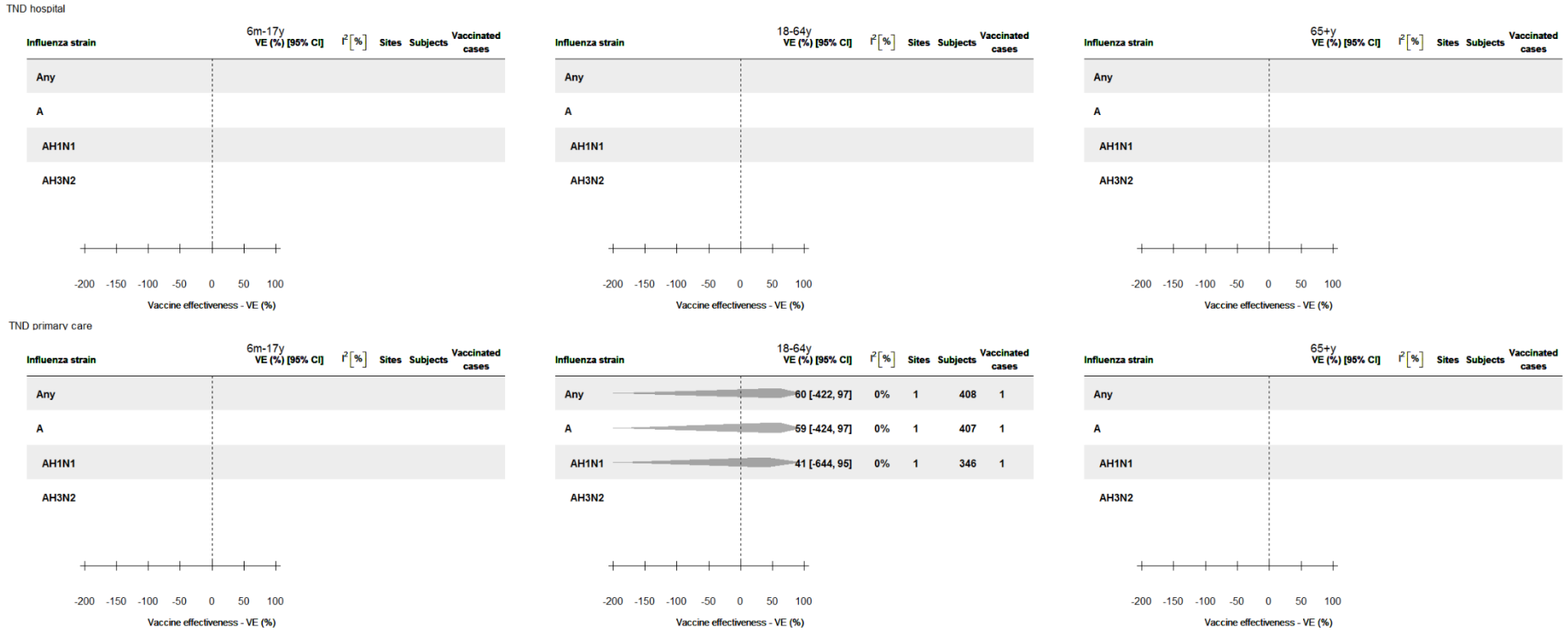
Dark grey diamond: robust results (width of CI <40%). Light grey diamond: non-robust results.

Figure 15. Influvac (Abbott Biologicals): pooled confounder-adjusted brand-specific influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2018/19.



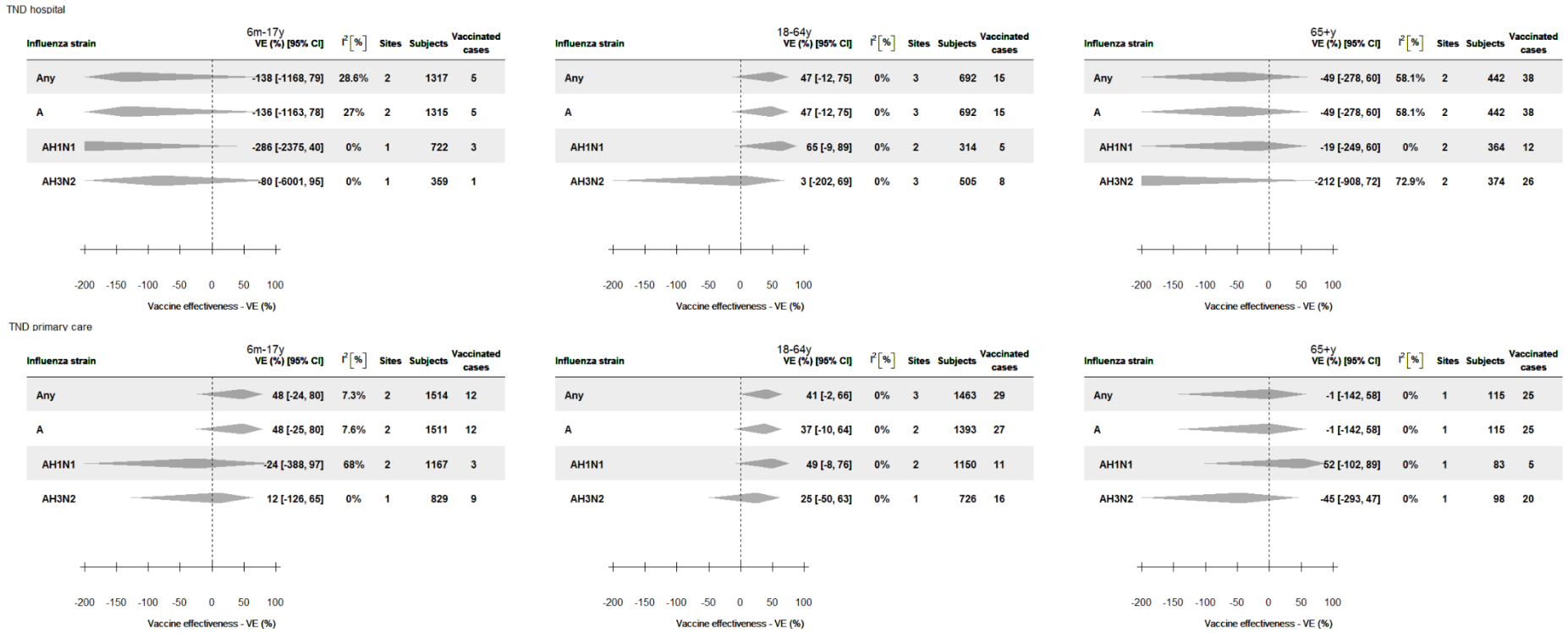
Dark grey diamond: robust results (width of CI <40%). Light grey diamond: non-robust results.

Figure 16. Fluarix Tetra (GlaxoSmithKline): pooled confounder-adjusted brand-specific influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2018/19



Dark grey diamond: robust results (width of CI <40%). Light grey diamond: non-robust results.

Figure 17. Influvac Tetra (Abbot Biologicals): pooled confounder-adjusted brand-specific influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2018/19



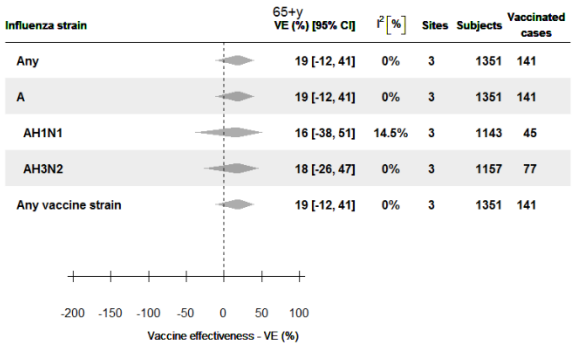
Dark grey diamond: robust results (width of CI <40%). Light grey diamond: non-robust results.

Figure 18. Vaxigrip Tetra (Sanofi Pasteur): pooled confounder-adjusted brand-specific influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2018/19

TND hospital

6m-17y

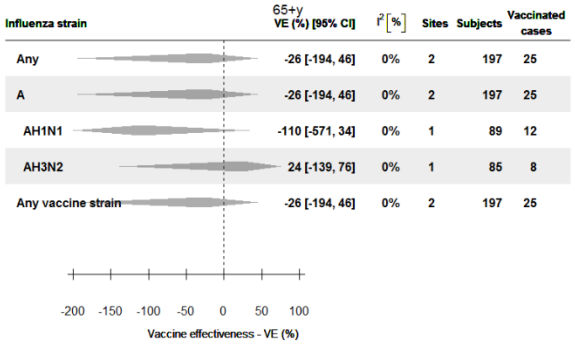
18-64y



TND primary care

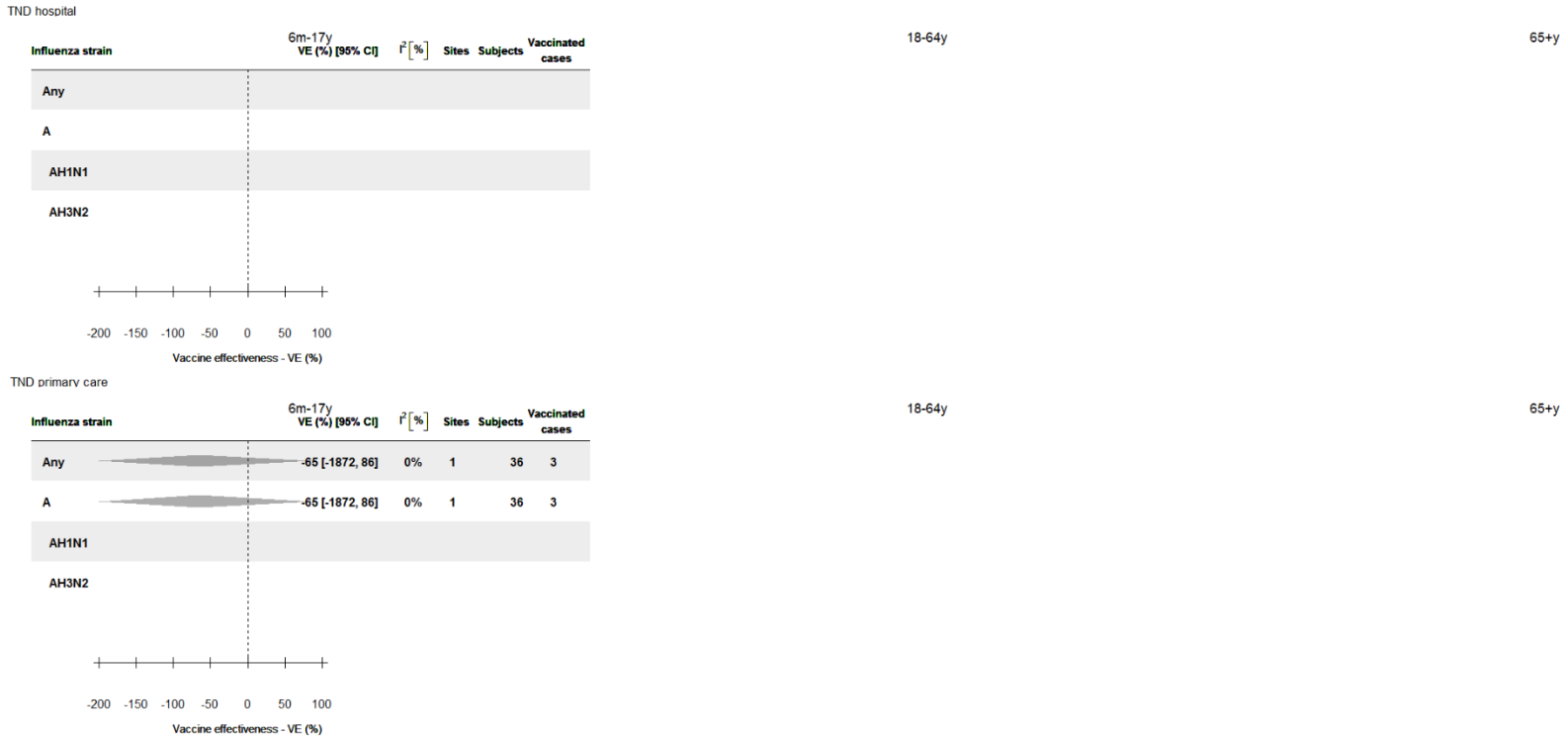
6m-17y

18-64y



Dark grey diamond: robust results (width of CI <40%). Light grey diamond: non-robust results.

Figure 19. Fluad (Seqirus): pooled confounder-adjusted brand-specific influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2018/19



Dark grey diamond: robust results (width of CI <40%). Light grey diamond: non-robust results.

Figure 20. Fluenz Tetra (AstraZeneca): pooled confounder-adjusted brand-specific influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2018/19

4.4.2.2 Sensitivity analysis: outlying/influential analysis

In the meta analyses of the crude IVE of Fluarix Tetra against any influenza, A, and A/H3N2 for 6m-17y old subjects in the primary care setting two studies were excluded due to their corresponding VE estimates being flagged as outlying/influential. The estimates are shown in Table 22. Given that these were the two only studies in this scenario, and both were excluded due to being outlying/influential, no pooled estimates were obtained for the IVE of Fluarix Tetra against any influenza, A, and A/H3N2. The same happened for the quadrivalent inactivated vaccine type IVE (Table 22). No outlying/influential studies were reported for the meta analyses of the confounder-adjusted IVE estimates.

Table 22. Influential/outlying studies and their crude IVE estimates for 6m-17y old subjects in the primary care setting.

Site	Any influenza Crude VE [95%CI]	A Crude VE [95%CI]	AH3N2 Crude VE [95%CI]
Fluarix Tetra			
Italy CIRI-IT	75 [44, 90]	73 [40,89]	74 [32,93]
Italy ISS	-12 [-97,36]	-12 [-97,35]	-78 [-223,1]
Pooled	Not available	Not available	Not available
Quadrivalent inactivated			
Italy CIRI-IT	Not outlying/influential	Not outlying/influential	75 [37,93]
Italy ISS	11 [-40,44]	11 [-40,43]	-42 [-130,13]
Pooled	77 [49, 90]	69 [40, 84]	Not available

4.4.2.3 Sensitivity analysis: partially/recently vaccinated subjects

Only 40 out of the 9,352 subjects (0.43%) from the combined TND data were partially or recently vaccinated. This small number is negligible and hence, this sensitivity analysis was not performed.

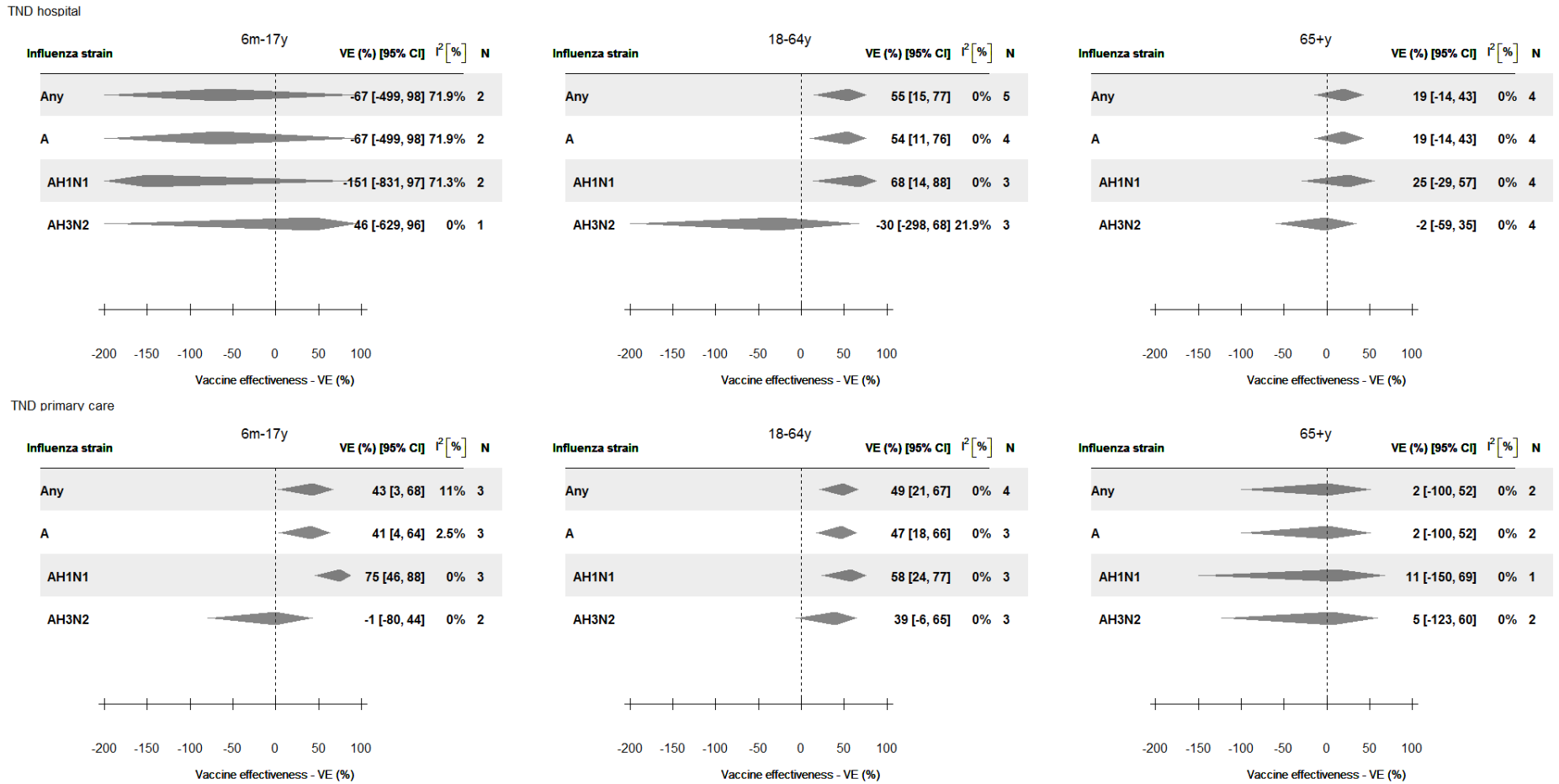
4.4.2.4 Sensitivity analysis: time lag between disease onset and swab

Subjects were excluded when the respiratory specimen was taken ≥ 4 days after ILI/SARI onset. The pooled confounder-adjusted IVE estimates for any influenza vaccine is given in Dark grey diamond: robust results (width of CI <40%). Light grey diamond: non-robust results.

Figure 21. The estimates by influenza vaccine brand and vaccine type are given in ANNEX 15. The results for the sensitivity analysis are in the same line as the ones for the main analysis. The CI of the sensitivity analysis results are wider as less ILI-cases were kept when requiring a shorter period between symptom onset and swab collection.

4.4.2.5 Sensitivity analysis: inclusion of Luxembourg LNS data

Results of sensitivity analysis including data from Luxembourg LNS are given in ANNEX 16 . Only Fluarix Tetra was used at this site. Upon inclusion of the Luxembourg LNS data, the pooled IVE point estimates for Fluarix Tetra decreased for A/H3N2 in 18-64y and 65+y and increased for A/H1N1 in 18-64y. None of the estimates were robust.



Dark grey diamond: robust results (width of CI <40%). Light grey diamond: non-robust results.

Figure 21. Any influenza vaccine: Sensitivity analysis (respiratory specimen ≥ 4 days after ILI/SARI excluded); pooled confounder-adjusted influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2018/19

4.5 Secondary objective: influenza vaccine effectiveness by type

4.5.1 Site-specific estimates

Vaccine type specific IVE estimates were calculated only for vaccine types for which a minimum of two brands were available, being the trivalent non-adjuvanted and quadrivalent inactivated vaccines. No estimates for trivalent adjuvanted and quadrivalent live attenuated vaccine were calculated as only one brand for each of these vaccine types (Fluad and Fluenz Tetra, respectively) was available in Europe in 2018/19.

4.5.1.1 Test-negative design studies: primary care setting

The confounder-adjusted IVE estimates against influenza types are summarized in Table 23 (for any influenza and any vaccine type influenza) and Table 24 (for influenza A/H1N1 and A/H3N2). The corresponding crude and confounder-adjusted IVE estimates for each primary care TND study separately are given in ANNEX 12.

Table 23. Summary of the site-specific confounder-adjusted influenza vaccine effectiveness against any and any vaccine type influenza (number of studies, minimum and maximum estimate), primary care TND studies, 2018/19

	Any influenza				Any virus subtype or lineage included in vaccine			
	N estimates	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**	**N estimates**	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**
6m-17 y								
Vaccine type								
Trivalent non-adjuvanted	1	347 (7)	-41 [-630,73]	-41 [-630,73]	1	346 (7)	-41 [-631,73]	-41 [-631,73]
Quadrivalent inactivated	3	1942 (47)	26 [-22,56]	71 [15,90]				
18-64 y								
Vaccine type								
Trivalent non-adjuvanted	1	918 (1)	17 [-1314,95]	17 [-1314,95]	1	918 (1)	17 [-1314,95]	17 [-1314,95]
Quadrivalent inactivated	4	2009 (64)	28 [-18,56]	90 [-97,100]				
65+ y								
Vaccine type								
Trivalent non-adjuvanted	0	0			0	0		
Quadrivalent inactivated	2	294 (55)	-3 [-136,55]	68 [-11,90]				

Table 24. Summary of the site-specific confounder-adjusted influenza vaccine effectiveness against A/H1N1 and A/H3N2 influenza (number of studies, minimum and maximum estimate), primary care based TND, 2018/19

	A/H1N1				A/H3N2			
	N sites	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**	**N sites**	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**
6m-17 y								
Vaccine type								
Trivalent non-adjuvanted	1	238 (1)	59 [-510,97]	59 [-510,97]	1	272 (5)	-73 [-1346,79]	-73 [-1346,79]
Quadrivalent inactivated	3	1465 (11)	56 [-284,95]	82 [15,96]	2	1171 (36)	-16 [-109,35]	57 [-58,88]
18-64 y								
Vaccine type								
Trivalent non-adjuvanted	1	752 (1)	-128 [-4820,89]	-128 [-4820,89]	0	0		
Quadrivalent inactivated	3	1605 (23)	29 [-32,62]	76 [-60,96]	3	1463 (38)	24 [-42,59]	61 [-293,96]
65+ y								
Vaccine type								
Trivalent non-adjuvanted	0	0			0	0		
Quadrivalent inactivated	2	225 (11)	50 [-82,86]	90 [-35,99]	2	266 (44)	-33 [-251,50]	57 [-60,88]

4.5.1.2 Test-negative design studies: hospital setting

The confounder-adjusted estimates of influenza vaccine effectiveness against influenza types are summarized in Table 25 (for any influenza and any vaccine type influenza) and

Table 26 (for influenza A/H1N1 and A/H3N2. The crude and confounder-adjusted influenza vaccine effectiveness estimates for each primary care TND study separately are given in ANNEX 12.

Table 25. Summary of the site-specific confounder-adjusted influenza vaccine effectiveness against any and any vaccine type influenza (number of studies, minimum and maximum estimate), hospital based TND, 2018/19

	Any influenza				Any virus subtype or lineage included in vaccine			
	N sites	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**	**N sites**	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**
6m-17 y								
Vaccine type								
Trivalent non-adjuvanted	1	69 (5)	86 [9,98]	86 [9,98]	1	69 (5)	86 [9,98]	86 [9,98]
Quadrivalent inactivated	2	1335 (10)	12 [-134,67]	66 [-822,99]				
18-64 y								
Vaccine type								
Trivalent non-adjuvanted	3	696 (26)	-13 [-228,61]	69 [-2,91]	3	694 (26)	-13 [-228,61]	69 [-2,91]
Quadrivalent inactivated	4	803 (18)	-9 [-1148,91]	63 [-739,98]				
65+ y								
Vaccine type								
Trivalent non-adjuvanted	3	1044 (74)	-31 [-192,42]	25 [-28,56]	3	1044 (74)	-31 [-192,42]	25 [-28,56]
Quadrivalent inactivated	2	476 (39)	25 [-69,66]	54 [-14,81]				

Table 26. Summary of the site-specific confounder-adjusted influenza vaccine effectiveness against A/H1N1 and A/H3N2 influenza (number of studies, minimum and maximum estimate), hospital based TND, 2018/19

	A/H1N1				A/H3N2			
	N sites	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**	**N sites**	**Total N subjects (n vaccinated influenza cases)**	**Min VE (95%CI)**	**Max VE (95%CI)**
6m-17 y								
Vaccine type								
Trivalent non-adjuvanted	1	57 (1)	94 [21,100]	94 [21,100]	0	0		
Quadrivalent inactivated	1	738 (6)	-17 [-254,62]	-17 [-254,62]	2	1000 (4)	-80 [-6001,95]	42 [-196,88]
18-64 y								
Vaccine type								
Trivalent non-adjuvanted	3	584 (10)	19 [-212,79]	63 [-135,94]	3	528 (14)	-218 [-1234,24]	58 [-213,94]
Quadrivalent inactivated	2	322 (6)	42 [-113,84]	80 [-15,97]	3	513 (9)	-34 [-2318,93]	35 [-247,88]
65+ y								
Vaccine type								
Trivalent non-adjuvanted	3	888 (22)	20 [-103,68]	58 [-547,97]	3	892 (43)	-215 [-4597,79]	8 [-93,56]
Quadrivalent inactivated	2	397 (12)	9 [-254,77]	66 [-57,93]	2	408 (27)	25 [-93,71]	31 [-112,77]

4.5.1.3 Register-based cohort study, Finland

Only Vaxigrip Tetra and Fluenz Tetra were used in Finland, both vaccine brands belonging to a different vaccine type. Hence, no vaccine type specific IVE estimates were calculated.

4.5.2 Pooled estimates

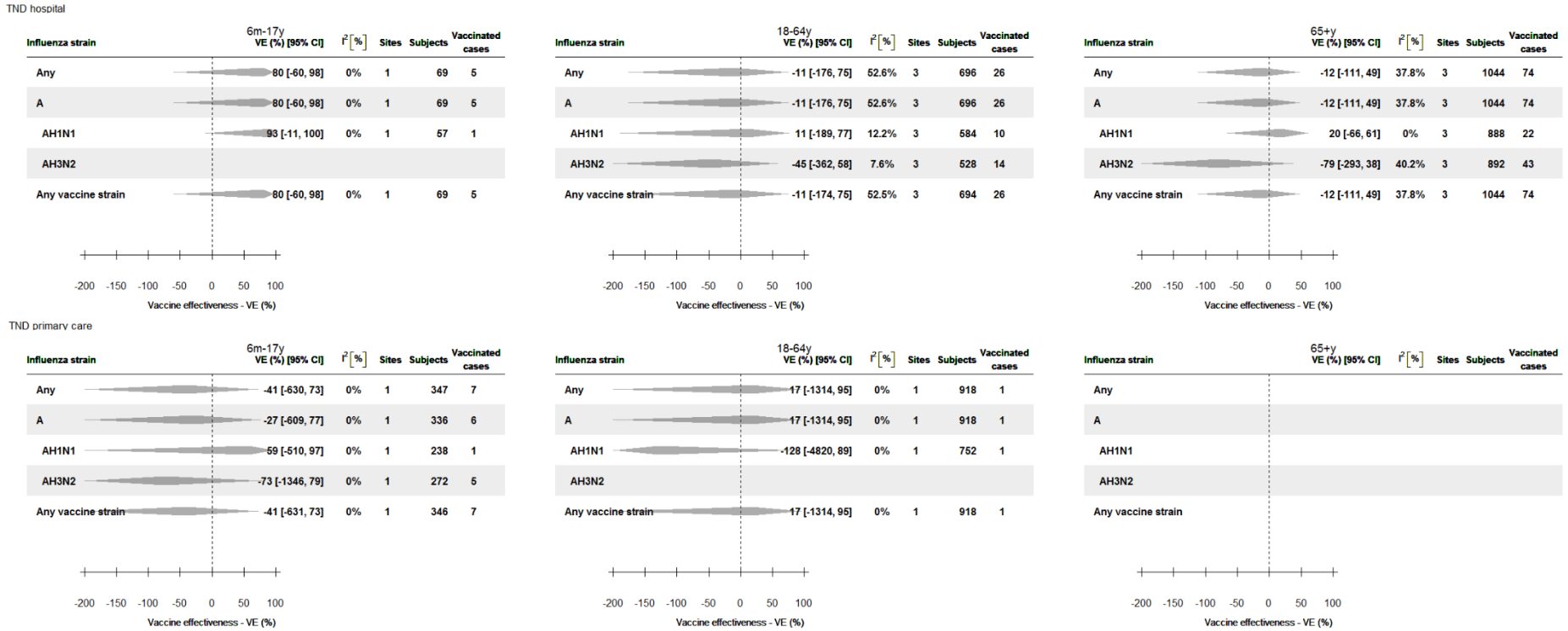
The pooled confounder-adjusted IVE estimates for both vaccine types (trivalent non-adjuvanted and quadrivalent inactivated vaccine) stratified by age group and healthcare setting are provided in Dark grey diamond: robust results (width of CI <40%). Light grey diamond: non-robust results.
Figure 22 and Dark grey diamond: robust results (width of CI <40%). Light grey diamond: non-robust results.
Figure 23. The pooled crude influenza vaccine effectiveness estimates are provided in ANNEX 17 To aid the interpretation of the pooled estimates, the corresponding forest plots with the site-specific estimates are provided in ANNEX 17 for the crude estimates and ANNEX 18 for the confounder-adjusted estimates.

For trivalent non-adjuvanted vaccines IVE estimates are available for all age groups in hospital setting, and for children 6m-17y and adults 18-64y in primary care setting. For quadrivalent inactivated vaccines IVE estimates are available for all age groups and both health care settings (Table 27). No robust IVE estimates were obtained (Dark grey diamond: robust results (width of CI <40%). Light grey diamond: non-robust results.
Figure 22 and Dark grey diamond: robust results (width of CI <40%). Light grey diamond: non-robust results.
Figure 23).

Table 27. Overview of number of sites that contribute data to the pooled estimates for the secondary objectives, by setting, vaccine brand and age, 2018/19

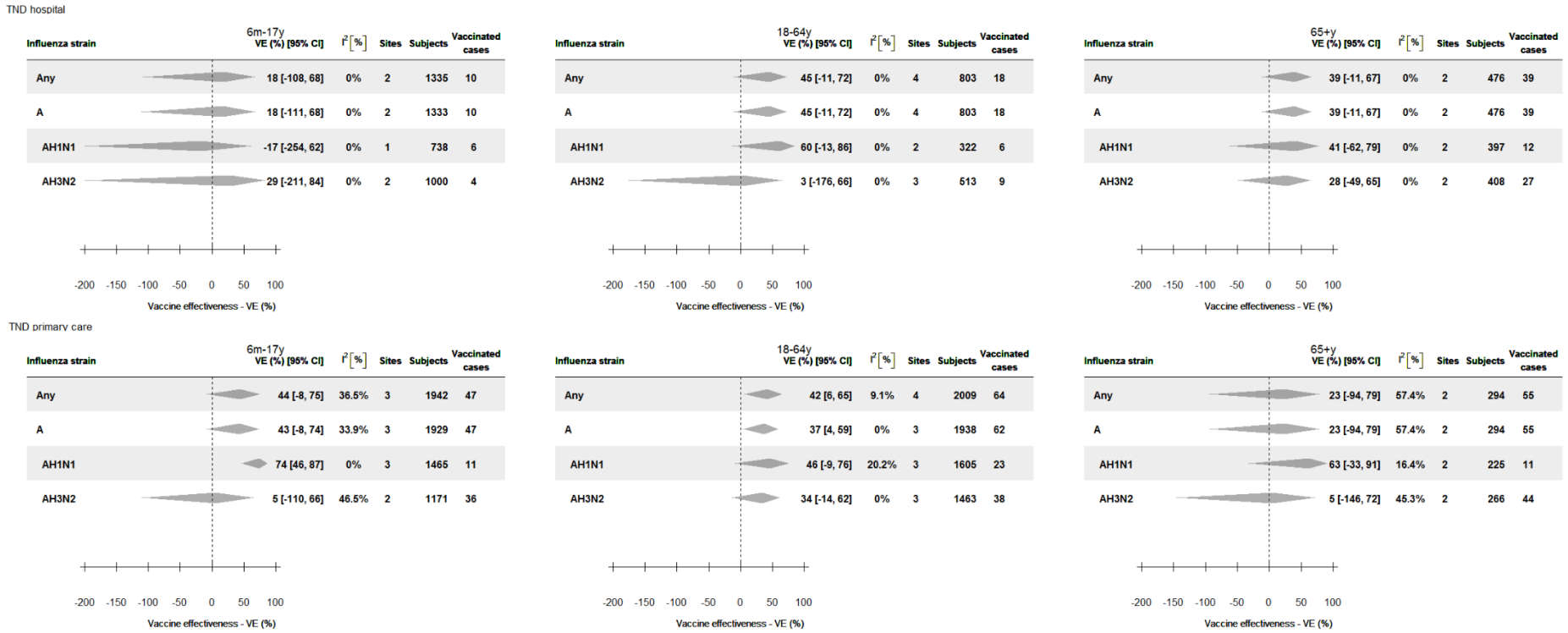
	Age group		
	6m-17y	**18-64y**	**65+y**
Primary care			
Trivalent non-adjuvanted	1	1	No
Trivalent adjuvanted	Not applicable(1)	Not applicable(1)	Not applicable(1)
Quadrivalent live attenuated	Not applicable(2)	Not applicable(2)	Not applicable(2)
Quadrivalent inactivated	3	4	2
Hospital			
Trivalent non-adjuvanted	1	3	3
Trivalent adjuvanted	Not applicable(1)	Not applicable(1)	Not applicable(1)
Quadrivalent live attenuated	Not applicable(2)	Not applicable(2)	Not applicable(2)
Quadrivalent inactivated	2	4	2

(1)only Fluad for this vaccine type, (2)only Fluenz Tetra for this vaccine type



Dark grey diamond: robust results (width of CI <40%). Light grey diamond: non-robust results.

Figure 22. Trivalent non-adjuvanted vaccines: pooled confounder-adjusted influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2018/19



Dark grey diamond: robust results (width of CI <40%). Light grey diamond: non-robust results.

Figure 23. Quadrivalent inactivated vaccines: pooled confounder-adjusted influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2018/19

4.6 Exploratory objective: influenza vaccine effectiveness by risk group

Results for exploratory objectives are described in ANNEX 19 and ANNEX 20.

5 Discussion

The 2018/19 influenza season in Europe was characterized by co-circulation of influenza A/H1N1pmd09 and A/H3N2, with little to no circulation of influenza B. There was a good match between the vaccine virus and the circulating viruses for A/H1N1 but not for A/H3N2. The season was mild compared to the 2017/18 season.

5.1 Estimation of IVE for any vaccine

In the 2018/19 season, the pooled TND IVE estimate for any vaccine against A/H1N1 in children aged 6m-17y in primary care setting was very good, at 77% (95%CI 53-89), whereas the TND IVE estimate for any vaccine against any influenza and influenza A in elderly 65+y in hospital setting was low, at 28% (95%CI 7-44). For elderly 65+y in hospital setting, IVE against A/H1N1 was moderate but vaccination provided little protection for A/H3N2; this may be partially explained by the good vaccine match against H1N1 and poor match for A/H3N2. However, circulation of H3N2 varied greatly between the different study sites. The width of the 95% confidence intervals for estimates in other strata was >40% and were therefore not considered robust.

The IVE estimate from the Finland THL register-based cohort for any vaccine against influenza and influenza A in children aged 6m-6y was moderate, at 44% (95%CI 36-51), and low for elderly 65+y, at 30% (95%CI 25-35). This data includes influenza cases from both primary care and hospital setting and were therefore not pooled with the TND studies. Finland has a general child vaccine recommendation whereas the countries where the TND studies took place do not (except UK), therefore the elderly populations from the register-based cohort and TND studies are more comparable than the respective children populations. The IVE estimates in the elderly from the TND studies and the register-based cohort are comparable.

Another European network network estimated interim IVE based on data until January 2019 [18]. In primary care setting, IVE estimates were between 39% (95% CI: -23 to 69) and 75% (95% CI: 27 to 91) in adults 18-64y (n=2) and 0% (95% CI: - 61 to 38) in elderly 65+y (n=1). Provisional end-of-season estimates against any influenza from the UK are 44% (95%CI 21 to 61) in adults 18-64 y and 50% (95%CI -14 to 78) in elderly 65+y [15].

Interim IVE estimates from the European network in hospital setting were 49% (95% CI: 13 to 70) in adults aged 18–64y (n=1) and 29% (95% CI: - 75 to 71) to 37% (95% CI: 3 to 60) in elderly aged 65+y(n=2). The DRIVE TND IVE estimate for elderly 65+y in hospital setting is in line with the corresponding interim IVE estimates from this network.

Ten influenza vaccine brands were licensed in the European Union in the 2018/19 season: Abbott: Influvac, Influvac Tetra; AstraZeneca: Fluenz Tetra; GlaxoSmithKline: Fluarix Tetra; Sanofi: TIV High Dose, Vaxigrip, Vaxigrip Tetra; Seqirus: Afluria, Agrippal, Fluad).

None of the TND brand-specific IVE estimates were sufficiently robust. Non-robust pooled brand-specific IVE estimates from the TND studies were available for the following 7 brands: Agrippal, Influvac, Fluarix Tetra, Influvac Tetra, Vaxigrip Tetra, Fluad, Fluenz Tetra. IVE estimates in children aged 6m-17y were available for 4 brands (4 in primary care setting, 3 in hospital setting), 5 brands in adults 18-64y (4 in primary care setting, 4 in hospital setting), and 5 brands in elderly aged 65+y (3 in primary care setting, 5 in hospital setting). No IVE estimates from the TND studies were available for Influvac and Influvac Tetra in children 6m-17y, and Influvac Tetra in elderly 65+y.

Brand-specific IVE estimates for Fluenz Tetra and Vaxigrip Tetra were available from the THL register-based cohort study. The IVE of Fluenz Tetra against any influenza in children aged 2-6y was estimated at 36% (95%CI 24-45). This is in line with the provisional end-of-season estimate for LAIV in children in primary care in UK, 48% (95%CI 0 to 78) [15]. For Vaxigrip Tetra, the IVE was estimated at 54% (95%CI 43-62) in children aged 6m-6y and 30% (95%CI 25-35) in elderly 65+y.

5.2 Estimation of type-specific IVE

No robust type-specific IVE estimates were obtained from the TND studies. As only one type of inactivated quadrivalent and live attenuated quadrivalent influenza vaccine were used, no type-specific estimates were calculated for the THL register-based cohort study.

5.3 Estimation of IVE from clinical cohort studies

- No robust IVE estimates were obtained from the pregnancy cohort and from the healthcare worker cohort.
- EMA guidance encourages the assessment of IVE in specific risk groups [1]. Therefore, a clinical pregnancy cohort and a clinical healthcare cohort were followed during the 2018/19 season.
- The follow-up of the pregnancy cohort was resource intensive, as ca. 700 enrolled women were called weekly for the duration of 4 months. In the healthcare workers cohort reminders were sent by email or text message.
- Higher sample sizes are needed to obtain a similar precision as TND.
- Populations of the clinical cohort studies were different from the general population as included in the TND studies and the Finnish register-based cohort study. As such, it was decided to not pool the results from the clinical cohort studies with the results from the other studies.

5.3.1 Healthcare worker cohort

Negative IVE estimates were observed in the healthcare worker cohort. As with all observational studies, this cohort study was susceptible to confounding due to differences in vaccinated and unvaccinated subjects. For example, differences in occupational risk of exposure (between nurses, clinicians and administrative staff) can be substantial and can overwhelm a true vaccine effect, however this information was not collected and could not be used to adjust the analysis.

Specifically, in this cohort, it is likely there was underreporting of ILI symptoms. Follow-up consisted of a weekly reminder SMS and/or email sent to all enrolled subjects. It was assumed that those that did not reply to the weekly reminders had no ILI symptoms and this likely led to an underreporting of ILI cases. There was likely more underreporting in the unvaccinated subjects, as the percentage of subjects with a laboratory-confirmed influenza negative swab among all enrolled subjects was much higher (8.9%) in the vaccinated group than in the unvaccinated group (3.9%). The data were re-analysed post hoc as a nested TND case-control study. The IVE estimates were higher than for the cohort analysis, which further supports the hypothesis of differential misclassification. Taken together, these results explain the negative IVE estimates observed despite efforts to actively follow-up on all study participants. This type of bias is akin to health-seeking behaviour bias.

5.4 Limitations

5.4.1 Limitations related to the data

It was not possible to distinguish between influenza cases from primary care and hospital settings in the Finland THL register-based cohort study. Consequently, it was decided to not pool this data with the TND studies.

Whilst the influenza type was available for all included datasets, subtype and lineage was not available for influenza cases from the Finland THL register-based cohort and the UK RCGP RSC TND primary care study.

All TND studies included in the main analysis closely followed the generic TND study protocol. However, the study sites were still different in several aspects, including the sampling strategy and covariates available for adjustment.

For some sites, the information on covariates was limited or incompletely provided, resulting in discarding of these subjects for analysis. When the % percentage of missingness was too high (>10%) for a specific confounder, it was decided to not adjust for that confounder to avoid a too big loss of data. This happened for pregnancy (Romania NIID), vaccination status in previous season (Finland HUS; Italy BIVE) and number of

hospitalizations or GP visits (Italy BIVE). 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. A careful trade-off between inclusion of possible confounder information and the risk of losing records and having data of sufficient quality must be made. Influenza vaccination status in previous status warrants studies of its own.

Luxembourg LNS came on board in June 2019. Consequently, 2018/19 data collection was not fully in line with the DRIVE generic protocol. However, this provided opportunities to flag improvements required for next year’s data collection. This data was included as a post hoc sensitivity analysis.

5.4.2 Limitations related to small sample size

Few robust estimates were obtained. This is in part because the influenza season was mild. However, obtaining sufficient sample for brand-specific IVE estimates is expected to be challenging also in more intense seasons than this year. Even for the primary objective estimating IVE for any vaccine, sample size was insufficient for most strata.

5.4.3 Limitations due to confounding by indication

Vaccination recommendations vary across countries, particularly regarding the vaccination of children and the recommendation of specific vaccine types. In Austria there is a general vaccine recommendation for the whole population, however vaccine uptake was very low (8.3%, based on number of doses distributed by manufacturers) [19]. In Finland and the UK, all children within certain age groups are recommended to receive influenza vaccination, compared to children with underlying conditions only elsewhere; consequently, vaccinated children in Finland and the UK are expected to, on average, be healthier. However, adjusting for chronic conditions in the analysis should address this difference. In Catalonia, QIV is only recommended at the hospital level for very high risk population, for other patients with underlying conditions TIV is recommended. Consequently, those receiving QIV in Catalonia are expected to be less healthy than those receiving QIV elsewhere. In Valencia (Spain), aTIV is recommended for persons aged 75+y, compared to 65+y elsewhere. In Italy, both aTIV and QIV are recommended in persons aged 65-74y and aTIV in 75+y. Therefore, on average, persons receiving aTIV in Valencia, and to a lesser extent in Italy, are expected to be older.

Study population characteristics by brand were compared for subjects 65+y included at study sites in Italy to explore confounding by indication. In most Italian regions, one brand of QIV and aTIV were available during the 2018/19 season. However, sample size was too small to draw conclusions (data not shown).

5.5 Experience and next steps

5.5.1 Improvements compared to the pilot season 2017/2018:

- Compared to the 2017/18 pilot season, seven new TND study sites and two clinical cohort sites participated.
- Prior to the start of data collection, site visits were conducted at four sites (Finland HUS , Austria MUV, Romania NIID , Greece UoA). These visits were valuable to understand the study setting and study flow. Several calls between the central DRIVE research team and the local investigators took place during the season.
- Some sites were able to improve the quality of the data provided in the 2018/19 season compared to the pilot 2017/18 season. For example, it was now possible to differentiate between cases from primary care and hospital settings, and the vaccine brands were available for the majority of ILI cases (compared to >50% missingness in 2017/18).
- The list of chronic conditions for the covariate 'presence of at least one chronic condition' was refined and definitions for individual chronic diseases were included to further harmonize the data collection across sites.
- Minimum data requirements for the clinical cohort studies were developed.
- The DRIVE ESSA was developed. The DRIVE ESSA enabled local investigators to upload their datasets in a secure environment, perform data quality checks, view (and share) visual summaries of their data, and securely upload their data to the central DRIVE Research Server for statistical analysis. To ensure familiarity with the data upload procedure and ESSA environment prior to the end-of-season data transfer, an interim data upload was performed by the sites.
- The DRIVE SAP was registered on ENCEPP (EUPAS29817).
- Many analytical scripts were pre-programmed prior to the receipt of data to speed up the analysis.
- The QCAC of DRIVE was formed and is composed of external quality control advisors.
- Data quality reports were centrally produced for each site, describing the results of the quality checks performed, data retained for analysis and graphical summaries of the data. Data was locked prior to the final analysis of the data.

5.5.2 Challenges

- No time was foreseen for the preparation of the data quality reports and potential data correction by the sites, as the decision to request data quality reports was taken by the QCAC mid-May.
- There was limited time for the analysis, despite the many pre-programmed scripts. This was due to large number and diversity of datasets received: 9 TNDs (of which 6 new sites), one register-based cohort using aggregated data, one clinical cohort with mother-baby link, and one healthcare worker cohort. The many differences in the cohort studies made it difficult to re-use the same code, requiring tailored analysis for each. This is a resource-intensive process and requires time.

- There is a very large amount of output, which was challenging to summarize well. Based on this season's report layout, efforts towards further automatic reporting should be made to facilitate reporting. This year only the appendices were automated.
- Due to the limited time, a full mock report defining the structure and all table shells was not developed. This will be developed in parallel with the SAP for the 2019/2020 season.

5.6 Conclusions

The primary objectives were not met in the 2018/19 season due to insufficient sample size per strata. Few robust IVE estimates were obtained, and outside the register-based cohort study, no robust brand-specific IVE estimates were obtained. Ways to increase sample size should be further explored for next season.

5.7 Recommendations

Increase in recruitment and/or further expansion of the DRIVE network is needed in order to be able to obtain robust brand specific IVE estimates. DRIVE is a five year project, so sustainability is an important consideration to take into account when exploring the different options to achieve enough sample size. Some of these options are:

- Expand the network with the incorporation of additional sites: although the network increased from 5 to 13 sites, there was not enough sample size in most strata. For 2019/20, an additional hospital network as well as 2 additional hospitals will join DRIVE. Focus should be on adding sites that can be pooled with the rest of sites rather than single site studies on special populations.
- Increase resources to existing sites, to increase the number of ILI recruited. Some sites, due to limited resources, only recruit a sample of the ILI, so there could be room to increase recruitment if adequate resources were in place to allow this.
- Generating robust age- and setting stratified brand-specific IVE data for all brands in Europe based solely on TND studies is unlikely to be feasible. The use of secondary data, such as register or other electronic healthcare databases, could be a potential sustainable solution to the problem of obtaining sufficient sample size and warrants further exploration, both in terms of additional secondary data sources and investing in the improvement of data availability from the THL study.
- Explore obtaining additional data via open data initiatives
- Review the minimum data requirements and the minimum set of confounders to adjust for (including method of adjustment), as well as the number of strata used for the analysis. This is important not only to increase sample size by avoiding discarding records with missing information, but also to reduce the workload at the sites. These minimum data requirements may be different for studies with primary data collection compared with those making use of secondary data, with less stringent requirements for secondary data. The THL register-based cohort was not able to differentiate cases from different healthcare settings, nor to provide influenza subtype/lineage data. However, they were the only site where robust brand-specific estimates were obtained.

6 References

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7 Other information

7.1 Funding

The DRIVE project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 777363. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.

7.2 Dissemination

This report will be made publicly available following submission to IMI. It is expected that these results will be submitted to a peer-reviewed journal and at least one conference. The dissemination plan will be developed in WP5.

8 Study team

The study team is described in ANNEX 21.

9 Reference documents

For this season, this study report has been developed using the following documents:

- DRIVE 2018/19 generic protocols (D7.1 and D7.2)
- DRIVE 2018/19 local study protocols
- DRIVE 2018/19 SAP (7.4)
- DRIVE data management plan (D4.2)
- Guideline for interpretation of IVE results (D4.6)

10 ANNEXES

ANNEX 1 – SAP

ANNEX 3 – Ethics

ANNEX 2 – Clinical cohort study characteristics and in-exclusion criteria

ANNEX 4 – Local reports (except RCGP and THL)

ANNEX 5 – Data quality reports

ANNEX 6 – Vaccine recommendation webpages

ANNEX 7 – Data pre-processing

ANNEX 8 – Attrition diagrams

ANNEX 9 – Site-specific population characteristics

ANNEX 10 – Study characteristics by age, setting and brand

ANNEX 11 – Clinical cohort descriptives

ANNEX 12 – Site-specific crude and adjusted IVE estimates

ANNEX 13 – Primary objectives crude IVE estimates

ANNEX 14 – Primary objectives adjusted IVE estimates

ANNEX 15 – Primary objectives sensitivity analyses (swab less than 4 days after disease onset)

ANNEX 16 – Primary objectives sensitivity analyses (including Luxembourg LNS data)

ANNEX 17 – Secondary objectives crude IVE estimates

ANNEX 18 – Secondary objectives adjusted IVE estimates

ANNEX 19 – Exploratory objectives

ANNEX 20 – Exploratory objectives adjusted IVE estimates risk groups

ANNEX 21 – Study team