D7.7 Brand-specific influenza vaccine effectiveness in Europe Season 2019/20 REPORT

777363 - DRIVE

Development of robust and innovative vaccine effectiveness

WP7 - IVE studies

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TABLE OF CONTENTS

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.

The DRIVE platform is constantly expanding, and the 2019/20 season constitutes the network's third influenza season. Newly added sites included one hospital network in France and two hospitals in Spain.

Objectives

The main objectives were to estimate confounder-adjusted seasonal (1) **overall** and **brand-specific** and (2) **type-specific** IVE against laboratory-confirmed influenza stratified by setting (primary care, hospital-based or mixed setting in case the source of the cases cannot be obtained) and age group (6m - 17yr, 18 - 64yr, ≥ 65yr), by type of outcome: any laboratory-confirmed influenza; laboratory-confirmed influenza A, overall and by subtype (A(H1N1)pdm09, A(H3N2)); laboratory-confirmed influenza B, overall and by lineage (B/Victoria, B/Yamagata).

Methods

TND studies were conducted in primary care (four networks) and hospital settings (five individual hospitals and three hospital networks) in seven European countries. Swabs were collected from subjects presenting with influenza-like illness (ILI) in primary care setting or severe acute respiratory infection (SARI) in hospital setting. 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 (to exclude nosocomial infection).

One register-based cohort study was conducted at THL Finland, by linking five national registers through personal identifiers. The study population consisted of all registered Finnish residents aged 6m-6y and 65-100y. Cases with laboratory-confirmed influenza were identified from the National Infectious Diseases Register.

Data collected at the study sites was transferred to the DRIVE Research Server where it was analysed centrally by P95. Site-specific IVE was calculated using logistic regression (TND studies) or Poisson regression (cohort study). Estimates were stratified by age and adjusted for age, sex, and calendar time. Site-specific IVE estimates from the TND studies were pooled through random-effects meta-analysis. In the register-based cohort it was not possible to differentiate between primary care and hospital cases, therefore estimates were not pooled with the TND studies.

Results

Influenza epidemiology in DRIVE-represented European countries (2019/20): Influenza A(H1N1)pm09, A(H3N2) and B/Victoria co-circulated in Europe. The number of influenza A cases exceeded the number of influenza B cases at all TND sites (range 52.8% to 95.8%), except at the Italy CIRI GP site (42.9%). The highest proportion of influenza A compared to influenza B cases was found at Finland HUS (95.8%). Among influenza A cases with a known subtype, the most frequently identified subtype was A(H1N1)pdm09 at the sites in Finland, France and Spain (range 71.7% to 91.3%), and A(H3N2) at the sites in Austria, Italy and Romania (range 56.9% to 62.6%). Differences between the circulating influenza strains and the vaccine strains may have impacted IVE.

Number of subjects and person-years: The number of subjects in the TND studies and person-years in the register-based cohort study are shown in Table 1. Eight of the eleven vaccines licensed in Europe in 2019/20 were identified in the DRIVE dataset and for these vaccines IVE estimates were obtained.

Table 1. Number of subjects or person-years per study setting and age categories, 2019/20

TND	**6m - 17y**		**18 - 64y**		**≥ 65y**	
Setting	**Cases (%PV)**	**Controls (%PV)**	**Cases (%PV)**	**Controls (%PV)**	**Cases (%PV)**	**Controls (%PV)**
PC	1332 (5.8)	1038 (12.8)	838 (6.2)	1403 (9.6)	65 (55.4)	282 (61.3)
Hosp	661 (3.3)	731 (5.2)	331 (15.1)	726 (23.6)	304 (37.5)	1368 (56.1)

Register-based cohort	**6m - 6y**				**≥ 65y**			
Setting	**Vac (py)**	**Unvac (py)**	**Vac cases**	**Unvac cases**	**Vac (py)**	**Unvac (py)**	**Vac cases**	**Unvac cases**
Mixed	16374.7	84567.4	110	917	110497.5	300414.4	467	933

Hosp: hospital; PC: primary care; vac: vaccinated; PV: proportion of vaccinated; py: person years; unvac: unvaccinated; y: years

IVE estimates: Pooled TND – primary care: In the primary care setting, three confounder-adjusted pooled IVE estimate with a CI width of <40% were obtained. The IVE against any influenza in children 6m-17y was 64% (95%CI 44-80) for any vaccine (based on pooled data from 4 sites and including 2372 subjects of which 77 were vaccinated cases), 81% (95%CI 58-92) for Fluarix Tetra (based on pooled data from 3 sites and including 2131 subjects of which 11 were vaccinated cases) and 61% (95%CI 38-77) for Vaxigrip Tetra (based on pooled data from 3 sites and 2198 subjects of which 50 were vaccinated cases).

IVE estimates: Pooled TND – hospital: In the hospital setting, one confounder-adjusted pooled IVE estimate with a CI width of <40% was obtained. The IVE for any vaccine against influenza A in older adults ≥65y, based on pooled data from seven study sites and including 1567 subjects of which 99 were vaccinated cases, was 53% (95%CI 35-67).

IVE estimates: Register-based cohort: All IVE estimates against any influenza and influenza A from the Finland THL register-based cohort have a CI width of less than 40%. The IVE estimate of Fluenz Tetra is 64.3% (95%CI 53.5- 72.7) against influenza A and 80.4% (95%CI 55.4-91.4) against influenza B in children aged 2-6y. The IVE estimates of Vaxigrip Tetra are 70.6% (95%CI 56.1-80.4) against any influenza and 70.6% (95%CI 54.3; 81.0) against influenza A in children aged 6m-6y, and 28.5% (95%CI 19.8-36.2) against any influenza and 27.0% (95%CI 18.0-35.0) against influenza A in older adults aged ≥65y.

Discussion and conclusion

In the 2019/20 season, the DRIVE network has expanded from five to eight TND hospital sites, including one new country, in addition to the existing TND primary care sites and the register-based cohort. Eight of eleven brands licensed and marketed in Europe were captured in the DRIVE data. Precise brand-specific estimates were obtained from the register-based cohort for the two vaccine brands used in Finland. Four precise estimates were obtained for the primary objectives from the TND studies, up from three in the previous season, and included two brand-specific estimates. This was achieved despite the start of the COVID-19 pandemic during the influenza season and the subsequent lockdown measures which interfered with and capped the 2019-20 influenza circulation and impacted data collection. All precise estimates showed a protective effect with point estimates varying between 26% and 81%.

Improvements were made to the method and the reporting. The list of confounders considered was simplified based on post hoc analysis from the 2018/19 data (only including age, sex and date of symptom onset), consequently all TND study sites were able to collect data on all confounders. Results of all site-specific, pooled, and register-based analyses are available in a WebAnnex, which is in line with DRIVE long-term sustainability, as it is less resource intensive to report on the results and makes the project outcomes and data FAIR (Findable, Accessible, Interoperable, Reusable).

Recommendations

For the 2020/2021 season, efforts should be focused on increasing the sample size for the adult and older adult population in hospital setting, to advance towards obtaining more precise IVE estimates for these strata where vaccination can have most impact on morbidity and mortality. In addition, as influenza and SARS-CoV-2 are expected to co-circulate in the 2020/21 season, the TND protocol has been adapted to encompass some COVID-19 components in the operations data collection and analysis.

Milestones

	Expected date	Actual date
Start of surveillance period		
End of surveillance period	30.04.2020 (expected before study start)	28.02.2020 (main analysis), 30.04.2020 (sensitivity analysis)
Data received	5.06.2020	09.06.2020 (all sites uploaded data)
Data quality reports completed	11.06.2020	17.06.2020 (first version circulated to the sites)
Database freeze		14.08.2020
First IVE results available	26.06.2020	26.06.2020
Report submission to IMI	10.09.2020	10.09.2020

List of figures, tables, abbreviations

List of figures

List of tables

List of abbreviations and acronyms

aTIV	Adjuvanted trivalent influenza vaccine
BIVE	Italian Hospital Network
DRIVE	Development of Robust and Innovative Vaccine Effectiveness
CI	Confidence Interval
CIRI	Centro Interuniversitario di Ricerca sull'Influenza e sulle altre infezioni trasmissibili
COVID-19	Coronavirus disease 2019
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FISABIO	Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana
GDPR	General Data Protection Regulation
GP	General practitioner
GTPUH	Germans Trias i Pujol University Hospital
HUS	Helsinki University Hospital, Jorvi Hospital
ILI	Influenza-like illness
IMI	Innovative Medicines Initiative
INSERM	Institut national de la santé et de la recherche médicale
ISS	Istituto Superiore di Sanita
IVE	Influenza vaccine effectiveness
LAIV	Live attenuated influenza vaccine
LCI	Laboratory confirmed influenza
LNS	Laboratoire National de Santé
LPUH	La Paz University Hospital
m	Months
MUV	Medical University Vienna
NIID	National Institute for Infectious Disease "Prof. Dr. Matei Bals"
OR	Odds ratio
QCAC	Quality Control and Audit Committee
QIVc	Quadrivalent influenza vaccine cell-based
QIVe	Quadrivalent influenza vaccine egg-based
RCGP RSC	Royal College of General Practitioners Research and Surveillance Centre
IRR	Incidence rate ratio
RT-PCR	Reverse transcription polymerase chain reaction
SAP	Statistical analysis plan
SARI	Severe acute respiratory infection

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
THL	The Finnish Institute for Health and Welfare
TIV	Trivalent influenza vaccine cat
TIV-HD	Trivalent influenza vaccine high dose
TND	Test-negative design
UK	United Kingdom
VCM	Vaccine Composition Meeting
VE	Vaccine effectiveness
VHUH	Vall d'Hebron University Hospital
y	year

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 European Union (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 2018/19, five primary care based test-negative design (TND) studies, five hospital-based TND studies and one register-based cohort study were conducted in Europe to assess brand-specific seasons IVE by health care setting and age group [3]. The DRIVE network is still expanding. The study conducted in 2019/20 season builds upon tools and processes developed, and lessons learned in the previous two seasons.

Similar to 2018/19, the main objective of the 2019/20 season was to estimate brand-specific seasonal IVE in Europe by health care setting and age group. Site-specific IVE were calculated and estimates were pooled across sites. For the 2019/20 season, a parsimonious set of confounders (sex, age, date of symptom onset) will be used for the main analysis, as post-hoc analysis of the 2018/19 TND data showed that this performed equally well to a more extended set of confounders.

Due to the COVID-19 outbreak, the study period was limited to the time prior to widespread SARS-CoV-2 circulation in Europe (i.e. up to February 29, 2020). The COVID-19 outbreak affected influenza surveillance and data collection at the sites, and changed healthcare seeking behaviour. At some DRIVE sites, data collection stopped in early March; other sites continued to include patients in April with a common triage strategy and simultaneous tests for Influenza and SARS-CoV-2; and in others still, inclusion of influenza cases in DRIVE were conditional to SARS-CoV-2 negative test results. The lockdown measures imposed across Europe to prevent the spread of SARS-CoV-2 likely impacted influenza circulation too. The COVID-19 outbreak and its impact are described in more detail in the WebANNEX (COVID-19).

This Study Report lists the participating study sites, summarizes the methods used, and describes the IVE estimates obtained for the 2019/20 influenza season, as well as the challenges and proposed

recommendations for next season. Further details on the characteristics of the study sites and the methods used are available in the statistical analysis plan (SAP) (WebANNEX – SAP). The SAP has been registered in the ENCEPP register, registration number EUPAS35685.

1.1 WebAnnex

Additional results are available in the WebANNEX. The WebAnnex is accessible at: https://apps.p-95.com/drivewebapp/ (username: DRIVE_user; password: 6;40rv57P3Z85YC). An overview of the tables and figures available in the WebAnnex is given in ANNEXES.

2 Objectives

2.1 Primary objective

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

- any laboratory-confirmed influenza;
- laboratory-confirmed influenza A, overall and by subtype (A(H1N1)pdm09, A(H3N2));
- laboratory-confirmed influenza B, overall and by lineage (B Victoria, B Yamagata).

2.2 Secondary objective

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

- any laboratory-confirmed influenza;
- laboratory-confirmed influenza A, overall and by subtype (A(H1N1)pdm09, A(H3N2));
- laboratory-confirmed influenza B, overall and by lineage (B Victoria, B Yamagata).

The following vaccine types will be considered:

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

3 Methods

3.1 Study sites

For the 2019/20 season, data is available from four primary care-based TND studies, eight hospital-based TND studies (Table 1) and one register-based cohort. For details on the study sites see the SAP section 4.1 (WebANNEX – SAP).

Table 1. Primary care and hospital sites where TND studies were conducted, 2019/20

Country	Site name	Number of primary care physicians or hospitals where subjects are identified	New site for season 2019/20
Primary care			
Austria	Medical University Vienna (MUV), Austria	96	No
Italy	Centro Interuniversitario di Ricerca sull'Influenza e sulle altre infezioni trasmissibili (CIRI-GP)	35	No
Italy	Istituto Superiore di Sanita (ISS)	245	No
UK	Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) & University of Oxford (OX)	12	No
Hospital			
Finland	Helsinki University Hospital (HUS), Jorvi Hospital	1	No
France	Institut National de la Sante et de la Recherche Medicale (INSERM)	5	Yes
Italy	Italian Hospital Network (BIVE)	5	No
Romania	National Institute for Infectious Disease "Prof. Dr. Matei Balș", Bucharest	1	No
Spain	Vall d'Hebron University Hospital (VHUH), Barcelona	1	No
Spain	Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO)	4	No
Spain	Hospital Universitario La Paz (LPUH), Madrid	1	Yes
Spain	Hospital Universitario Germans Trias i Pujol (GTPUH), Badalona	1	Yes

3.2 Study design

The studies are based on the core protocols for TND studies and population-based database cohort studies [4] [5]. The study design of TND studies and the register-based cohort study are briefly described below. Further details including site specific exceptions are available from the SAP sections 5-14 (WebANNEX - SAP).

For the TND studies, patients with ILI or SARI were identified by the sites in primary care or hospital, respectively. ILI was defined by the ECDC case definition as an individual that presented with a sudden onset of symptoms AND at least one of four systemic symptoms (fever or feverishness, malaise, headache, myalgia) AND at least one of three respiratory symptoms (cough, sore throat, shortness of breath). SARI was defined by the IMOVE+ 2017/18 case definition as a hospitalized person with at least one systemic symptom (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 of three respiratory symptoms or signs (cough, sore throat, shortness of breath) at admission or within 48 hours of admission. Only patients with suspected infection were screened for SARI. Any exceptions are described in the SAP section 9 (WebANNEX - SAP).

Subjects presenting with ILI or SARI aged < 6 months at the time of symptom onset were excluded. Other exclusion criteria were a contraindication for influenza vaccine, a prior positive influenza test in the 2019/20 season, being institutionalized, and unwillingness to participate or to give consent. In addition, SARI patients who were previously hospitalized < 48 hours prior to SARI onset or with onset ≥ 48 hours after hospital admission were excluded (to exclude nosocomial infection). A respiratory specimen was taken for patients with ILI or SARI that was tested for influenza through molecular or antigen detection tests. Specimens taken 8 days or more after ILI/SARI onset were excluded. Information on covariates (at least: age, sex, date of onset) and vaccination status was collected. Cases and controls were classified as vaccinated if they received seasonal influenza vaccination > 14 days before ILI/SARI symptom onset and as unvaccinated if they did not receive seasonal influenza vaccination in the 2019/20 season. The way vaccination status, vaccine brand and vaccinatation data were ascertained at each site is described in the SAP section 11.2 (WebANNEX - SAP).

The start of the study period was defined as the first week of two consecutive weeks when influenza viruses were detected at the study site level (based on the data as provided to DRIVE), and the end as 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 February 29th 2020, whichever occurred first. The study period at site level is shown in Table 2.

Table 2. Dates of first and last swab and study period, by site, TND studies, 2019/20

Site	First swab	Last swab	Study period start	Study period end*
Primary care				
Austria MUV	9-11-2019	13-3-2020	20-11-2019	29-2-2020
Italy CIRI-GP	4-11-2019	13-3-2020	18-11-2019	29-2-2020
Italy ISS	24-10-2019	7-4-2020	11-11-2019	29-2-2020
UK RCGP RSC	4-11-2019	12-3-2020	12-11-2019	27-2-2020
Hospital				
Finland HUS	1-12-2019	29-4-2020	26-11-2019	29-2-2020
France INSERM	11-12-2019	16-3-2020	16-12-2019	29-2-2020
Italy CIRI-BIVE	12-11-2019	15-4-2020	18-11-2019	29-2-2020
Romania NIID	19-11-2019	16-3-2020	26-11-2019	29-2-2020
Spain FISABIO	9-12-2019	13-3-2020	4-12-2019	29-2-2020
Spain GTPUH	21-12-2019	12-3-2020	20-12-2019	29-2-2020
Spain LPUH	18-1-2020	24-2-2020	16-1-2020	2-2-2020
Spain VHUH	22-11-2019	16-3-2020	21-11-2019	29-2-2020

*In a sensitivity analysis the study period was extended to April 30, 2020.

The register-based cohort was conducted in Finland among children (6m - 6y) and elderly (65 - 100y) by linking five national registers through personal identifiers. The cohort consisted of individuals registered in the Population Information System. Laboratory-confirmed influenza cases were identified through the National Infectious Diseases Register and vaccination status was retrieved from the National Vaccination Register. Information on covariates was retrieved from the Register of Primary Health Care Visits and the Care Register for Health Care. Subjects with presumably incomplete vaccination records in 2019/20 and 2018/19 were excluded[1]. The study period was defined a priori from week 40/2019 to February 29th 2020.

3.3 Statistical methods

The statistical methods are briefly described below. Further details are available from the SAP section 15 (WebANNEX - SAP).

For the TND studies, individual-level data were transferred from the study sites to the GDPR-compliant DRIVE Research Server. Site-specific crude and confounder-adjusted IVE and 95% confidence intervals were estimated as VE = (1 – OR) x 100%, where *OR* denotes the odds ratio, comparing the odds of vaccination among influenza-positive study participants to the odds of vaccination among influenza-negative study

[1] Completeness of vaccination data is routinely monitored every month for each health care center; only HCCs meeting the criterion for data completeness for all the months covered by the observation period of interest are included [6] Baum U, Sundman J, Jääskeläinen S, Nohynek H, Puumalainen T, Jokinen J. Establishing and maintaining the National Vaccination register in Finland. Eurosurveillance. 2017;22:30520.

participants. Confounder-adjusted IVE estimates were derived from logistic regression models. Complete case analysis was performed. Site-specific IVE estimates were pooled through random-effects meta-analysis.

For the register-based cohort study, aggregated data were transferred from the study site to the DRIVE Research Server. As it concerns an open cohort, the unit of measure are person-years. Site-specific semi-crude (adjusted only for calendar time) and confounder-adjusted IVE and 95% confidence intervals were estimated as VE = (1 – IRR) x 100%, where *IRR* denotes the incidence rate ratio comparing the influenza incidence among the vaccinated subjects to the influenza incidence among the unvaccinated subjects. Confounder-adjusted IVE estimates were derived from Poisson regression models. Estimates obtained from the register-based cohort study were not pooled with the TND studies as it was not possible to differentiate between primary care and hospital cases.

A parsimonious set of confounders was used (age, sex, date of symptom onset), similar to Lane et al. [7]. Based on a post-hoc analysis of the 2018/19 TND data, it has been shown that this parsimonious confounder-adjustment performs equally well. A major advantage of parsimonious confounder-adjustment is that the fewer records need to be discarded from the analysis due to missing covariate information.

The main analysis considered in this study is a pooled analysis. The VE estimates from the different TND studies are pooled by use of a random effects meta-analysis. Further details are given in SAP section 15 (WebANNEX - SAP).

Five sensitivity analyses were considered. First, an analysis considering partially vaccinated subjects as 1) unvaccinated and 2) vaccinated was performed. Second, for the TND studies, a sensitivity analysis was conducted excluding subjects with a respiratory specimen taken ≥ 4 days after ILI/SARI onset. Third, for the pooled estimates, any studies that are both outlying and influential were included in the meta-analysis. Fourth, an analysis with the study period extended to April 30th was considered. Fifth, a model including all available confounders was analysed. See the WebANNEX (Add. Confounders) for a site-specific overview of the covariates that were adjusted for in the analyses.

All data management and statistical analyses were conducted in R version 3.6.2. GitHub was used for version control. For each site, a data quality report (describing data quality checks and corrections, an attrition diagram, and a summary of data retained for analysis) was produced centrally. The reports for each site are presented in (WebANNEX - Data Quality Report).

3.4 Quality control

Procedures for quality control are described in the SAP section 19 (WebANNEX - SAP). The findings and conclusions of the Quality Control and Audit Committee (QCAC) will be made available in a separate report.

3.5 Ethics

Each local study was approved by national, regional or institutional ethics committees, as appropriate. In the case of ISS, the study was submitted to the ethics committee for information, but approval was not required as the study is nested in the National Influenza Surveillance Scheme. Similarly, for the Finnish register-based cohort study, an ethical evaluation was not mandatory, however an evaluation from an institutional ethical review group was requested.

3.6 Deviations from protocol or SAP

Deviations from the local protocols are described in the local study reports (WebANNEX – Local Study Reports). Local protocols are available upon request from info@drive-eu.org.
The following deviations from the SAP took place:

- Spain LPUH recruited patients with ILI and patients with SARI from the emergency department. Only SARI patients were included in the analysis, ILI patients were excluded as ILI patients seeking care at the emergency department may not be comparable to ILI patients seeking care in the primary care setting..
- No information on influenza A subtypes or B lineage was available for Spain LPUH.
- No data from LNS Luxembourg was included as approval from the National Research Ethical was not obtained in time.
- The sensitivity analysis regarding partially vaccinated subjects was included for all sites irrespective of whether the 5% cut-off was met (in the WebAnnex).

4 Results

4.1 Influenza vaccines in Europe, 2019/20

4.1.1 Vaccine recommendations

National or regional vaccine recommendations by target group and recommendations for the use of specific vaccines types are summarized in the WebANNEX (Vaccine Recommendations).

4.1.2 Vaccine indications

Twelve influenza vaccines were licensed in the EU for the season 2019/20. Details on vaccine characteristics, the approved age indication and, for each age group, the sites that reported the vaccine brand in the 2019/20 studies are listed in Table 3. Eight of the vaccines were reported in the DRIVE dataset.

Table 3. Vaccine characteristics and age indications by vaccine brand, 2019/20

Vaccine brand	Manufacturer	Valency	Inactivated or live-attenuated	Non-adjuvanted or adjuvanted	Egg- or cell-based	Non-high or high dose	Approved age indication	Countries (Sites if >1 in the country) in which the vaccine brand was observed*		
								6m - 17y	18 - 64y	≥ 65y
Afluria	Seqirus	3	Inactivated	Non-adjuvanted	Egg	Non-high	≥5y	-	-	-
Agrippal	Seqirus	3	Inactivated	Non-adjuvanted	Egg	Non-high	≥6m	Italy [1], Spain [2,3]	Spain [2,3,4]	Spain [4]
Fluad	Seqirus	3	Inactivated	Adjuvanted	Egg	Non-high	≥65y	-	-	Italy [5,6], Spain [2,3,4,7]
Fluarix Tetra	GSK	4	Inactivated	Non-adjuvanted	Egg	Non-high	≥6m	Italy [1,6]	Italy [1,5,6]	Italy [5,6]
Flucelvax Tetra	Seqirus	4	Inactivated	Non-adjuvanted	Cell	Non-high	≥9y	Italy [1]	Spain [7], UK	Austria, Spain [7]
Fluenz Tetra	AstraZeneca	4	Live	Non-adjuvanted	Egg	Non-high	≥2y to 18y	Finland [8] Romania, UK	-	-
Influvac	Abbott	3	Inactivated	Non-adjuvanted	Egg	Non-high	≥6m	-	-	France.
Influvac Tetra	Abbott	4	Inactivated	Non-adjuvanted	Egg	Non-high	≥3y	Italy [1], Romania.	UK, Romania, France.	France, Romania
Vaxigrip	Sanofi Pasteur	3	Inactivated	Non-adjuvanted	Egg	Non-high	≥6m	-	-	-
Vaxigrip Tetra	Sanofi Pasteur	4	Inactivated	Non-adjuvanted	Egg	Non-high	≥6m	Austria, Finland [8], Italy [1,5,6], Romania	Finland [9], France, Italy [5,6], Romania	Finland [8,9], France, Italy [5,6] .
TIV High Dose	Sanofi Pasteur	3	Inactivated	Non-adjuvanted	Egg	High	≥65y	-	-	-

*and for which sufficient data was available to calculate a site-specific brand-specific estimate for the relevant age group

[1] CIRI-GP, [2] GTPUH, [3] VHUH, [4] LPUH, [5] CIRI-BIVE, [6] ISS, [7] FISABIO, [8] THL, [9] HUS

GSK: GlaxoSmithKline; m: months; QIV: quadrivalent influenza vaccine; TIV: trivalent influenza vaccine; UK: United Kingdom; y: years

4.1.3 Composition of influenza vaccines

The 2019/20 Northern hemisphere trivalent vaccines contained the following strains [8]:

- an A/Brisbane/02/2018 (H1N1)pdm09-like virus;
- an A/Kansas/14/2017 (H3N2)-like virus;
- a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage); and

Quadrivalent vaccines contained additionally:

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

4.2 Influenza epidemiology in Europe, 2019/20

4.2.1 Influenza epidemiology in Europe and vaccine match

In the European Region, the influenza activity began earlier compared to the previous season and the positivity rate of 10% was exceeded in 47/2019 and returned to baseline in week 13/2020 [9]. Compared to the previous five seasons, the only season in which the 10% threshold was crossed earlier by one week was in the 2016/17 season.

The peak was observed in week 05/2020 (Figure 1), reaching a maximum positivity rate of 55%. The peak phase with positivity levels above 50% lasted for just two weeks, 05/2020 and 06/2020. After that, reporting in subsequent weeks has been affected by the COVID-19 pandemic. In the previous influenza season, the influenza positivity rate exceeded 50% for six weeks.

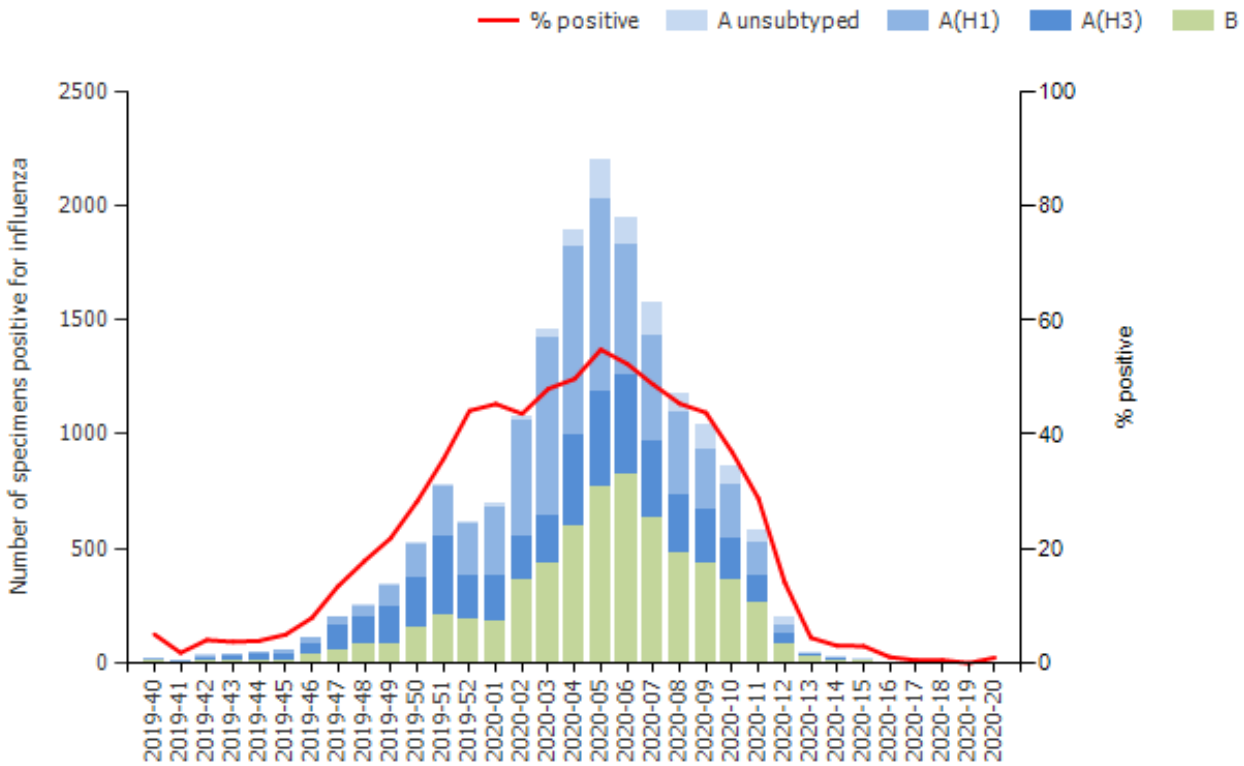


Figure 1. Distribution of virus types and subtypes and percentage positive over time, from sentinel surveillance in the European Region, 2019/20. Source: Flu News Europe [9]

Both influenza A and B types co-circulated in Europe, with patterns of dominant type and A subtypes among the countries (Figure 2). There was an early circulation of A(H3N2) followed by increased proportions of A(H1N1)pdm09 and B/Victoria viruses later in the season. A(H1N1)pdm09 has acquired three additional substitutions (N129D, D187A and Q189E related to the 6B.1A5A clade) that had an impact on virus antigenicity and as a consequence may have also impacted VE . Regarding A(H3) viruses, two H3N2 lineages with different antigenicity have co-circulated in Europe (3C.3a and 3C.2a1b) (personal communication Bruno Lina). Of the circulating B viruses, the majority belonged to the B/Victoria lineage (triple deleted).

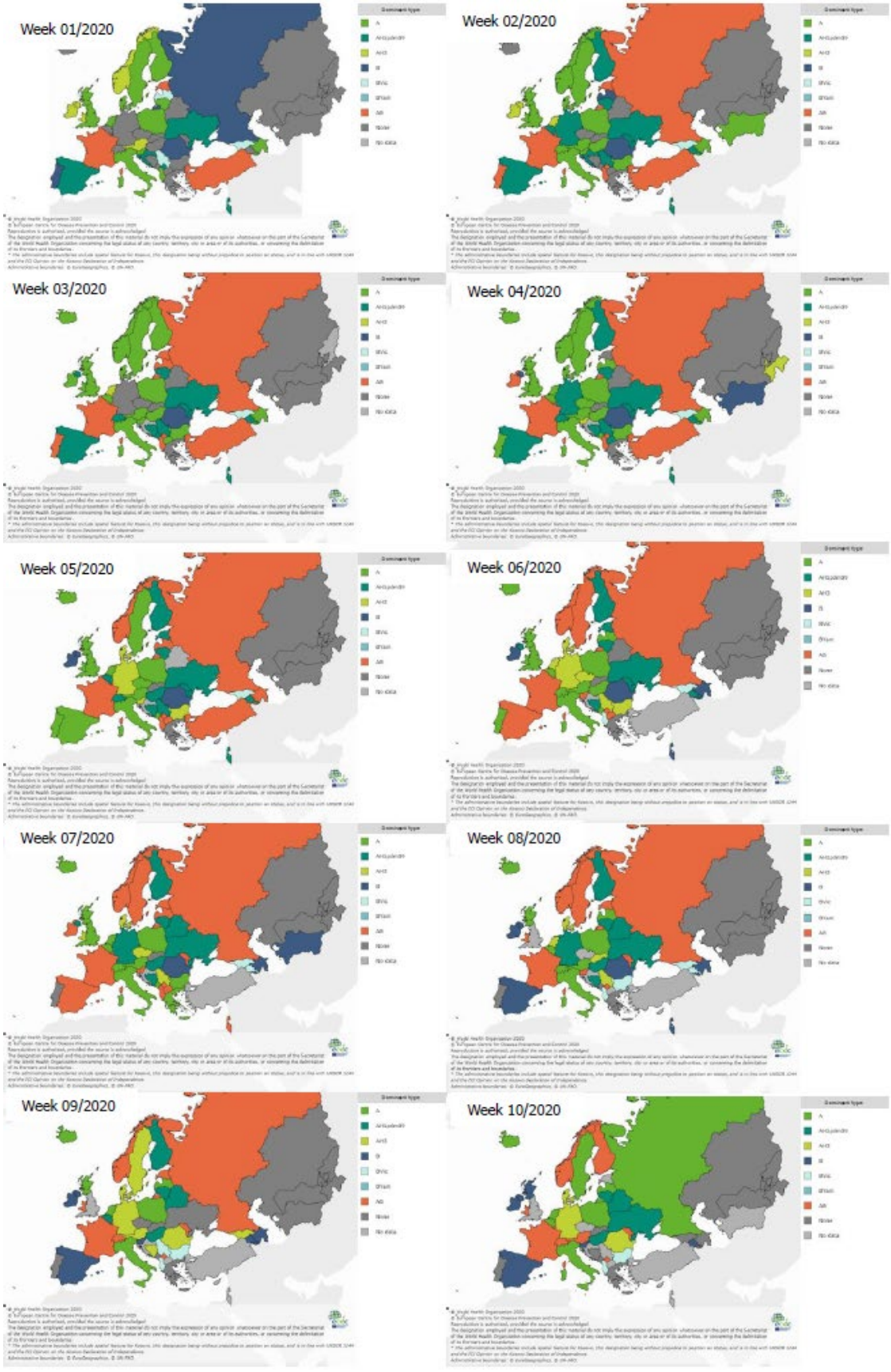


Figure 2. Pattern of circulation of the influenza viruses in Europe, by week. Source: ECDC [10]

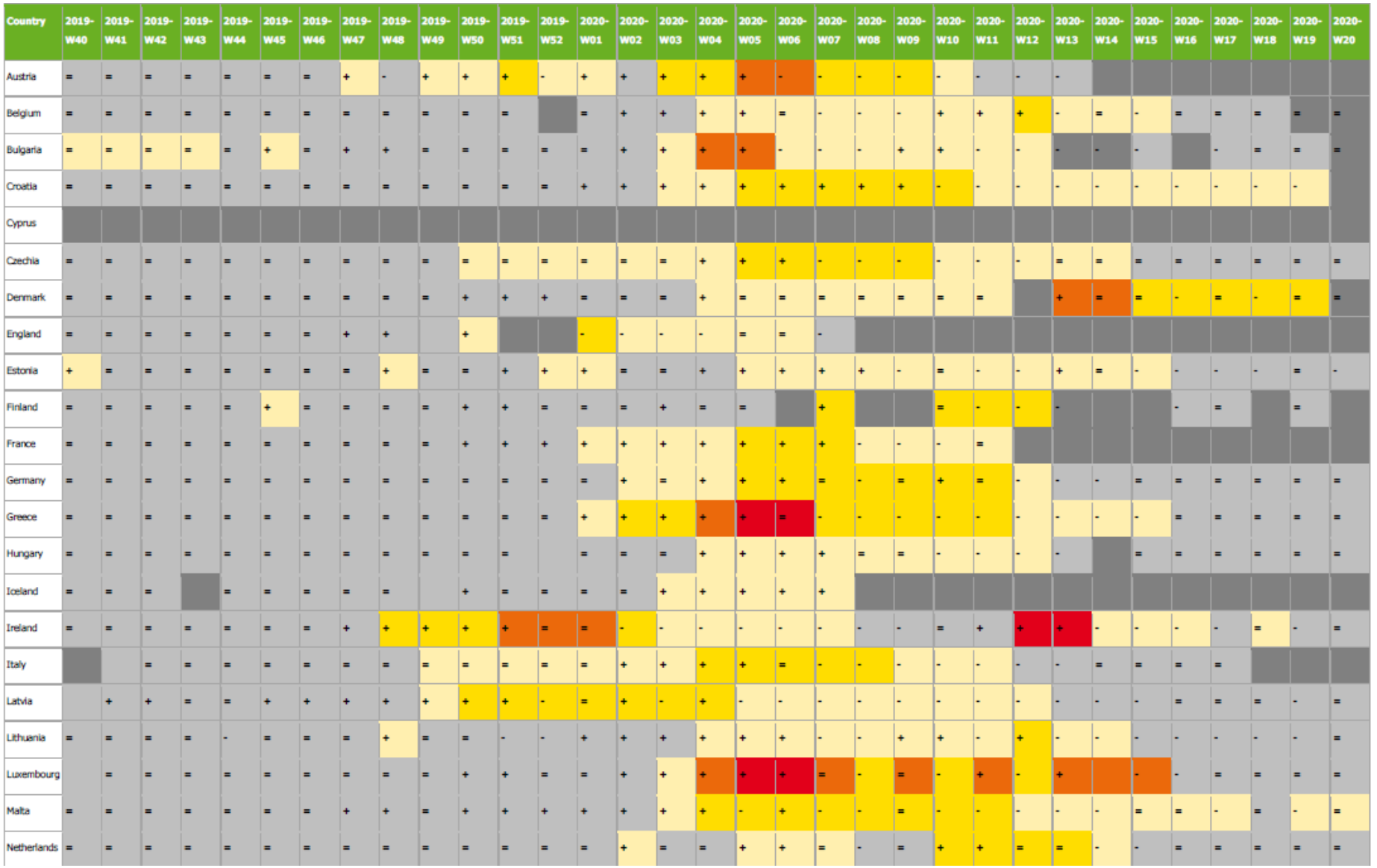
Based on these information, the substitutions observed in A(H1N1)pdm09 viruses have led to a reduction in vaccine effectiveness, and required a change in the vaccine composition to adapt the vaccine to this antigenic change. This switch to the 6B.5A5A clade with A/Guangdong-Maonan/SWL1536/2019 (egg-based) or A/Hawaii/70/2019 (H1N1)pdm09-like (cell-based) as prototypes was proposed during the Vaccine Composition Meeting (VCM) in February.

Regarding A(H3N2), it has been showed that post vaccination human serum panels raised against 3C.3a viruses recognise 3C.2a1b viruses somewhat less well. As a consequence, patients vaccinated with the A/Kansas/14/17 virus and exposed to 3C.2a1b viruses were less protected, leading to a measurable reduced vaccine effectiveness.

For the B viruses, there were no changes in the B/Yamagata lineage, but these viruses were barely circulating during this winter. The vast majority of the circulating B viruses belonged to the B/Victoria lineage. However, the circulating strains harboured a triple deletion in the HA, leading to antigenic differences as compared to the vaccine strain (B/Colorado6/2017) that had a double deletion. As a consequence of this mismatch, the VE was likely to be decreased, and a change was proposed in the VCM with a switch to the B/Washington/02/2019 triple deleted strain.

In Europe overall influenza activity remained low in most countries, but started to increase sharply in several countries from mid to late January (Figure 3). Until week 49/2019, the United Kingdom (Northern Ireland) reported medium intensity activity and five countries (Finland, Latvia, Portugal and the United Kingdom (UK) [Northern Ireland and Scotland]) reported geographically widespread influenza activity.

The circulation of the SARS-CoV-2 associated to the different measures taken during the first weeks of March (weeks 10, 11 and 12) Europe-wide had an impact on the epidemiology of the influenza viruses, reducing their circulation very rapidly. In addition, some community-based networks stopped their surveillance when the lockdowns were implemented.



Country	2019-W40	2019-W41	2019-W42	2019-W43	2019-W44	2019-W45	2019-W46	2019-W47	2019-W48	2019-W49	2019-W50	2019-W51	2019-W52	2020-W01	2020-W02	2020-W03	2020-W04	2020-W05	2020-W06	2020-W07	2020-W08	2020-W09	2020-W10	2020-W11	2020-W12	2020-W13	2020-W14	2020-W15	2020-W16	2020-W17	2020-W18	2020-W19	2020-W20
Austria	=	=	=	=	=	=	=	+	-	+	+	+	-	+	+	+	+	+	-	-	-	-	-	-	-	-						
Belgium	=	=	=	=	=	=	=	=	=	=	=	=		=	+	+	+	+	=	-	-	-	+	+	+	-	=	-	=	=	=	=	=
Bulgaria	=	=	=	=	=	+	=	+	+	=	=	=	=	=	+	+	+	+	-	-	-	+	+	-	-	-	-	-		-	=	=	=
Croatia	=	=	=	=	=	=	=	=	=	=	=	=	=	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	
Cyprus																																	
Czechia	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	=	+	+	+	-	-	-	-	-	-	=	=	=	=	=	=	=	=
Denmark	=	=	=	=	=	=	=	=	=	=	+	+	+	=	=	=	+	=	=	=	=	=	=	=		+	=	=	-	=	-	=	=
England	=	=	=	=	=	=	=	+	+		+			-	-	-	-	=	=	-													
Estonia	+	=	=	=	=	=	=	=	+	=	=	+	+	+	=	=	+	+	+	+	+	-	=	-	-	+	=	-	-	-	-	=	-
Finland	=	=	=	=	=	+	=	=	=	=	+	+	=	=	=	+	=	=		+			=	-	-	-			-	=		=	
France	=	=	=	=	=	=	=	=	=	=	+	+	+	+	+	+	+	+	+	+	-	-	-	=									
Germany	=	=	=	=	=	=	=	=	=	=	=	=	=	=	+	=	+	+	+	=	-	=	+	=	-	-	-	=	=	=	=	=	=
Greece	=	=	=	=	=	=	=	=	=	=	=	=	=	+	+	+	+	+	=	-	-	-	-	-	-	-	-	-	=	=	=	=	=
Hungary	=	=	=	=	=	=	=	=	=	=	=	=		=	=	=	+	+	+	+	=	=	-	-	-	-			=	=	=	=	=
Iceland	=	=	=		=	=	=	=	=		+	=	=	=	=	+	+	+	+	+													
Ireland	=	=	=	=	=	=	=	+	+	+	+	+	=	=	-	-	-	-	-	-	-	-	=	+	+	+	-	-	-	-	=	-	=
Italy			=	=	=	=	=	=	=	=	=	=	=	=	+	+	+	+	=	-	-	-	-	-	-	-	=	=	=				
Latvia		+	+	=	=	+	+	+	+	+	+	+	-	=	+	-	+	-	-	-	-	-	-	-	-	-	-	-	=	=	=	-	=
Lithuania	=	=	=	=	-	=	=	=	+	=	=	-	-	+	+	+	+	+	+	-	-	+	+	-	+	-	-	-	-	-	-	-	=
Luxembourg		=	=	=	=	=	=	=	=	=	+	+	=	=	+	+	+	+	+	=	-	=	-	+	-	+		-	=	=	=	=	=
Malta	=	=	=	=	=	=	=	+	+	=	+	+	+	+	+	+	+	-	+	-	-	=	-	-	-	-	-	=	=	-	=	-	=
Netherlands	=	=	=	=	=	=	=	=	=	=	=	=	=	=	+	=	=	+	+	=	-	=	+	+	=	=	-	-	=	=	=	=	=

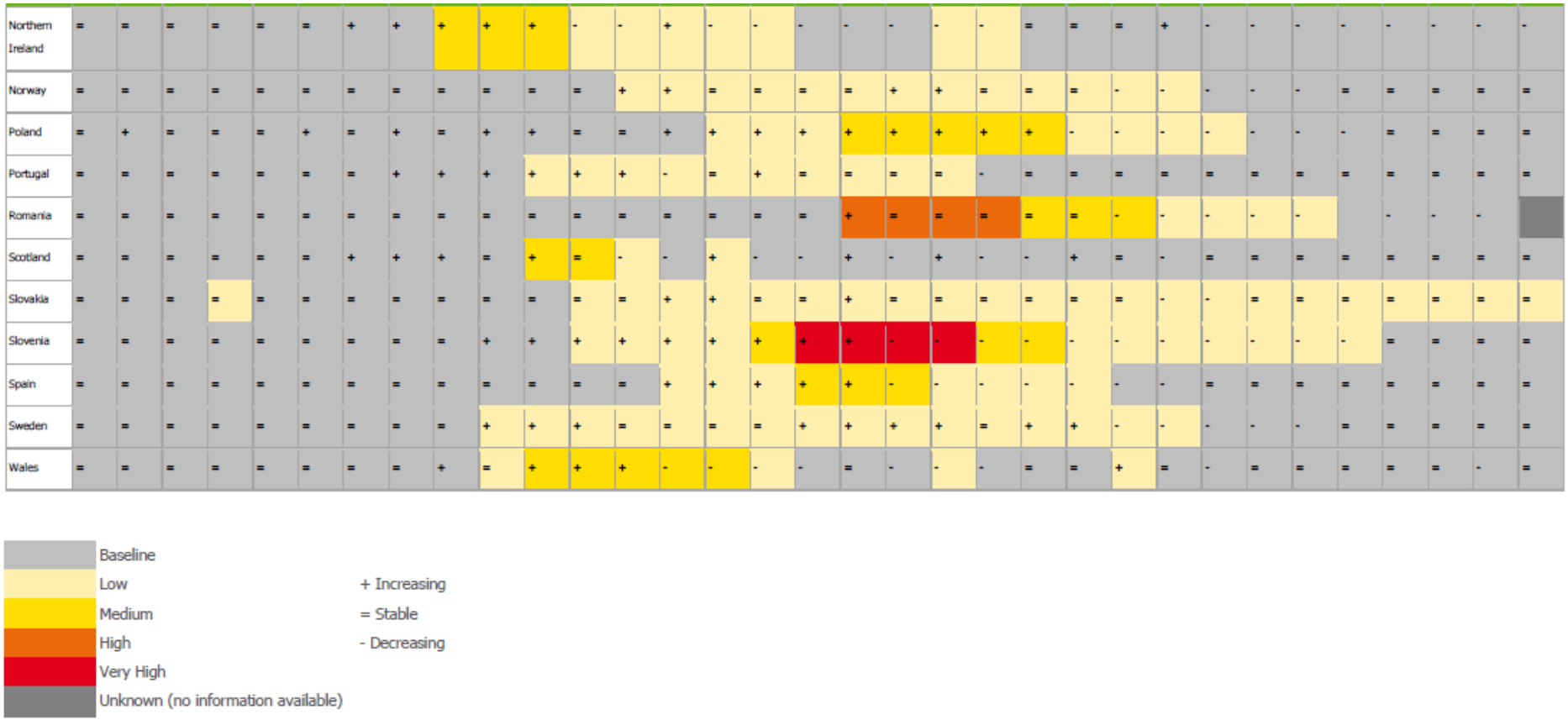


Figure 3. Intensity of influenza activity by country over time, 2019/20 Source: ECDC Annual epidemiological report [10] The levels of intensity were defined as follows: Baseline or below epidemic threshold: ILI or ARI rates that are very low and at levels usually seen throughout the inter-epidemic period. 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.

4.2.2 Influenza epidemiology by site

Table 4 describes the epidemic period, the peak, and the number of influenza cases by type and subtype in the DRIVE dataset for each site. The number of influenza A cases exceeded the number of influenza B cases at all TND sites (range 52.8% to 95.8%), except at the Italy CIRI GP site (42.9%). The highest proportion of influenza A compared to influenza B cases was found at Finland HUS (95.8%). Among influenza A cases with a known subtype, the most frequently identified subtype was A(H1N1)pdm09 at the sites in Finland, France and Spain (range 71.7% to 91.3%), and A(H3N2) at the sites in Austria, Italy and Romania (range 56.9% to 62.6%). In each of the countries, most influenza B cases were of the B/Victoria lineage.

Additional information on influenza epidemiology in countries of participating sites can be found in the local study reports (WebANNEX – Local Study Reports).

Table 4. Influenza epidemiology and influenza cases in the DRIVE dataset, 2019/20

	Epidemic period (week)	Peak (week 2020)	All influenza cases N	Influenza A n (% of total)	Influenza A(H1N1)pmd09 n (% of A with known subtype)	Influenza A(H3N2) n (% of A with known subtype)	Influenza B n (% of total)	Influenza B/Victoria n (%of B with known lineage)	Influenza B/Yamagata n (%of B with known lineage)
Austria									
MUV	3-14/2020	6	779	634 (81%)	273 (43%)	361 (57%)	145 (19%)	145 (100%)	0 (0%)
Finland									
HUS	3-12/2020	9	24	23 (96%)	21 (91%)	2 (9%)	1 (4%)	1 (100%)	0 (0%)
THL	3-12/2020	9							
France									
INSERM	2-11/2020	5-8	81	63 (78%)	42 (81%)	10 (19%)	18 (22%)	2 (67%)	1 (33%)
Italy									
CIRI-IT GP	49/2019-12/2020	5	513	220 (43%)	82 (37%)	137 (63%)	293 (57%)	212 (90%)	23 (10%)
CIRI-IT BIVE	49/2019-12/2020	5	473	355 (75%)	135 (41%)	194 (59%)	118 (25%)	52 (98%)	1 (2%)
ISS	46/2019-17/2020	5	862	481 (56%)	180 (40%)	267 (60%)	381 (44%)	147 (100%)	0 (0%)
Romania									
NIID	47/2019-11/2020	5	405	214 (53%)	77 (41%)	110 (59%)	191 (47%)	181 (100%)	0 (0%)
Spain									
FISABIO	50/2019-11/2020	5-6	60	54 (90%)	41 (89%)	5 (11%)	6 (10%)	6 (100%)	0 (0%)
GTPUH	52/2019-11/2020	6	85	72 (85%)	38 (72%)	15 (28%)	13 (15%)	7 (100%)	0 (0%)
LPUH	48/2019-10/2020	5	22	18 (82%)	9 (100%)	0 (0%)	4 (18%)	3 (100%)	0 (0%)
VHUH	3-11/2020	5	146	110 (75%)	74 (85%)	13 (15%)	36 (25%)	28 (100%)	0 (0%)
UK									
RCGP RSC	51/2019	1	81	63 (78%)	-	-	18 (22%)	-	-

4.3 Descriptive analysis

For the TND studies, 2235 cases and 2729 controls were included in the analysis in the primary care setting and 1296 cases and 2826 controls in the hospital setting (Table 5). The results of the data pre-processing by site (number of individual records received, number of records retained after excluding records that were not ILI/SARI or did not have a laboratory sample, number of records retained for analysis) including the attrition diagrams are described in the WebANNEX (Data Processing). For the register-based cohort study, aggregated data on 126872.2 vaccinated and 384981.8 unvaccinated person-years were received and included in the analysis (Table 6).

Table 5. Number of subjects per study setting and age categories, TND studies, 2019/20

TND	6m - 17y		18 - 64y		≥ 65y	
Setting	Cases (%PV)	Controls (%PV)	Cases (%PV)	Controls (%PV)	Cases (%PV)	Controls (%PV)
PC	1332 (5.8)	1038 (12.8)	838 (6.2)	1403 (9.6)	65 (55.4)	282 (61.3)
Hosp	661 (3.3)	731 (5.2)	331 (15.1)	726 (23.6)	304 (37.5)	1368 (56.1)

Hosp: hospital; PC: primary care; vac: vaccinated; PV: proportion of vaccinated; unvac: unvaccinated; y: years

Table 6. Number of vaccinated and unvaccinated person-years and influenza cases by age category, register-based cohort study, 2019/20

Register-based cohort *Setting*	6m - 6y				≥ 65y			
	Vac (py)	Unvac (py)	Vac cases	Unvac cases	Vac (py)	Unvac (py)	Vac cases	Unvac cases
Mixed	16374.7	84567.4	110	917	110497.5	300414.4	467	933

m: months; py: person years; y: years

4.3.1 Test-negative design studies

4.3.1.1 Test-negative design studies: primary care setting

For the combined data of the primary care TND studies (included in the primary analysis), 1332 cases and 1038 controls were included for children 6m-17y, 838 vs. 1403 for adults 18-64y, and 65 vs. 282 for those aged ≥65y. The majority of older adults ≥65y were female (55.3%), suffered from at least 1 chronic condition (73.8%) and were vaccinated with influenza in the current season (60.2%), mostly with Fluad, Fluarix Tetra and Vaxigrip Tetra (Table 9 and Figure 6). Of all adults aged 18-64y in primary care settings, 52.3% were female and 24.1% had at least 1 chronic condition. Among enrolled children 6m-17y and adults aged 18-64y, 8.9% and 8.3%,

respectively, were vaccinated with influenza in the current season. The vaccine brand used among these age groups were mostly Fluarix Tetra and Vaxigrip Tetra (Table 7 and Table 8). Among all vaccinated patients in primary care TND studies, the vaccine types used were primarily trivalent adjuvanted influenza and quadrivalent inactivated egg-based influenza vaccines. Graphical summaries of primary care settings and site-specific brand distribution are provided in Figure 4-Figure 6. The distribution of the controls and laboratory-confirmed influenza infections (by type and subtype/lineage) stratified by age group (6m-17y, 18-64 y, ≥65y) over time is given in Figure 3, showing a much lower influenza B proportion reported among older adults with laboratory-confirmed influenza this season. The percentage of subjects that tested positive for influenza over time is shown in Figure 5. Site-specific population characteristics, distribution of ILI/SARI over time, distribution of covariates and setting-specific population characteristics for each vaccine exposure are provided in the WebANNEX. All primary care TND studies used an unmatched design.

Table 7. Study population characteristics, 6m - 17y, primary care TND studies, 2019/20

Characteristic	All n (%)	Cases n (%)							Controls
		All	A	A/H1N1	A/H3N2	B	B Vict	B Yam	n (%)
Total	2370	1332	705	198	459	627	395	19	1038
Sex									
Female	1140 (48.1)	646 (48.5)	359 (50.9)	102 (51.5)	228 (49.7)	287 (45.8)	175 (44.3)	7 (36.8)	494 (47.5)
Male	1230 (51.9)	686 (51.5)	346 (49.1)	96 (48.5)	231 (50.3)	340 (54.2)	220 (55.7)	12 (63.2)	544 (52.4)
At least 1 chronic condition									
Yes	167 (7.0)	94 (7.1)	53 (7.5)	15 (7.6)	31 (6.8)	41 (6.5)	22 (5.6)	0 (0.0)	73 (7.0)
No	2188 (92.3)	1231 (92.4)	645 (91.5)	181 (91.4)	423 (92.2)	586 (93.5)	373 (94.4)	19 (100.0)	957 (92.2)
Unknown	15 (0.6)	7 (0.5)	7 (1.0)	2 (1.0)	5 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.8)
Pregnancy*									
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	672 (58.9)	393 (60.8)	238 (66.3)	67 (65.7)	154 (67.5)	155 (54.0)	117 (66.9)	7 (100.0)	279 (56.5)
Unknown	468 (41.1)	253 (39.2)	121 (33.7)	35 (34.3)	74 (32.5)	132 (46.0)	58 (33.1)	0 (0.0)	215 (43.5)
Number of GP visits in the previous 12 months									
0	270 (11.4)	147 (11.0)	67 (9.5)	15 (7.6)	49 (10.7)	80 (12.8)	35 (8.9)	9 (47.4)	123 (11.8)
1 - 5	1127 (47.5)	635 (47.7)	255 (36.2)	74 (37.4)	165 (35.9)	380 (60.6)	218 (55.2)	10 (52.6)	492 (47.3)
> 5	210 (8.9)	100 (7.5)	41 (5.8)	14 (7.1)	27 (5.9)	59 (9.4)	43 (10.9)	0 (0.0)	110 (10.6)
Unknown	763 (32.2)	450 (33.8)	342 (48.5)	95 (48.0)	218 (47.5)	108 (17.2)	99 (25.1)	0 (0.0)	313 (30.2)
Number of hospitalizations in the previous 12 months									
0	1476 (62.2)	809 (60.7)	345 (48.9)	90 (45.5)	237 (51.6)	464 (74.0)	259 (65.6)	19 (100.0)	667 (64.1)
1 - 2	35 (1.5)	21 (1.6)	11 (1.6)	4 (2.0)	7 (1.5)	10 (1.6)	1 (0.3)	0 (0.0)	14 (1.3)
> 2	5 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.5)
Unknown	854 (36.0)	502 (37.7)	349 (49.5)	104 (52.5)	215 (46.8)	153 (24.4)	135 (34.2)	0 (0.0)	352 (33.9)
Influenza vaccination status in current season									
Vaccinated	210 (8.9)	77 (5.8)	42 (6.0)	12 (6.1)	27 (5.9)	35 (5.6)	25 (6.3)	0 (0.0)	133 (12.8)
Vaccine brand									

Characteristic		All n (%)	Cases n (%)							Controls
			All	A	A/H1N1	A/H3N2	B	B Vict	B Yam	n (%)
	Agrippal	9 (0.4)	4 (0.3)	2 (0.3)	0 (0.0)	2 (0.4)	2 (0.3)	2 (0.5)	0 (0.0)	5 (0.5)
	Fluad	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Fluarix Tetra	50 (2.1)	11 (0.8)	9 (1.3)	5 (2.5)	4 (0.9)	2 (0.3)	2 (0.5)	0 (0.0)	39 (3.8)
	Flucelvax Tetra	7 (0.3)	3 (0.2)	1 (0.1)	0 (0.0)	1 (0.2)	2 (0.3)	1 (0.3)	0 (0.0)	4 (0.4)
	Fluenz Tetra	16 (0.7)	3 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	13 (1.2)
	Influvac	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Influvac Tetra	7 (0.3)	4 (0.3)	1 (0.1)	0 (0.0)	1 (0.2)	3 (0.5)	3 (0.8)	0 (0.0)	3 (0.3)
	Vaxigrip Tetra	117 (4.9)	50 (3.8)	27 (3.8)	7 (3.5)	19 (4.1)	23 (3.7)	16 (4.1)	0 (0.0)	67 (6.4)
	Unknown	3 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.3)	0 (0.0)	2 (0.2)
	Vaccine type									
	aTIV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	LAIV	16 (0.7)	3 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	13 (1.2)
	QIVc	7 (0.3)	3 (0.2)	1 (0.1)	0 (0.0)	1 (0.2)	2 (0.3)	1 (0.3)	0 (0.0)	4 (0.4)
	QIVe	174 (7.3)	65 (4.9)	37 (5.2)	12 (6.1)	24 (5.2)	28 (4.5)	21 (5.3)	0 (0.0)	109 (10.5)
	TIV	10 (0.4)	5 (0.4)	2 (0.3)	0 (0.0)	2 (0.4)	3 (0.5)	2 (0.5)	0 (0.0)	5 (0.5)
	Unknown	3 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.3)	0 (0.0)	2 (0.2)
	Unvaccinated	2160 (91.1)	1255 (94.2)	663 (94.0)	186 (93.9)	432 (94.1)	592 (94.4)	370 (93.7)	19 (100.0)	905 (87.0)
Study site										
	CIRI-GP	698 (29.4)	397 (29.8)	142 (20.1)	37 (18.7)	104 (22.7)	255 (40.7)	183 (46.3)	19 (100.0)	301 (28.9)
	ISS	938 (39.5)	502 (37.7)	229 (32.5)	66 (33.3)	145 (31.6)	273 (43.5)	119 (30.1)	0 (0.0)	436 (41.9)
	MUV	637 (26.9)	398 (29.9)	305 (43.3)	95 (48.0)	210 (45.8)	93 (14.8)	93 (23.5)	0 (0.0)	239 (23.0)
	RCGP RSC	97 (4.1)	35 (2.6)	29 (4.1)	0 (0.0)	0 (0.0)	6 (1.0)	0 (0.0)	0 (0.0)	62 (6.0)

*presented for females only

Site-specific population characteristics, site-specific distribution of ILI/SARI over time and site-specific distribution of covariates and setting-specific population characteristics for each vaccine exposure are provided in the WebANNEX.

Table 8. Study population characteristics, 18 - 64y, primary care TND studies, 2019/20

Characteristic	All n (%)	Cases n (%)							Controls
		All	A	A/H1N1	A/H3N2	B	B Vict	B Yam	n (%)
Total	2241	838	637	323	269	201	105	4	1403
Sex									
Female	1172 (52.3)	399 (47.6)	307 (48.2)	140 (43.3)	142 (52.8)	92 (45.8)	50 (47.6)	4 (100.0)	773 (55.1)
Male	1069 (47.7)	439 (52.4)	330 (51.8)	183 (56.7)	127 (47.2)	109 (54.2)	55 (52.4)	0 (0.0)	630 (44.9)
At least 1 chronic condition									
Yes	541 (24.1)	162 (19.3)	127 (19.9)	65 (20.1)	55 (20.4)	35 (17.4)	19 (18.1)	1 (25.0)	379 (27.0)
No	1668 (74.4)	661 (78.9)	499 (78.3)	249 (77.1)	212 (78.8)	162 (80.6)	82 (78.1)	3 (75.0)	1007 (71.8)
Unknown	32 (1.4)	15 (1.8)	11 (1.7)	9 (2.8)	2 (0.7)	4 (2.0)	4 (3.8)	0 (0.0)	17 (1.2)
Pregnancy*									
Yes	16 (1.4)	9 (2.3)	7 (2.3)	3 (2.1)	4 (2.8)	2 (2.2)	2 (4.0)	0 (0.0)	7 (0.9)
No	662 (56.3)	204 (51.1)	165 (53.7)	76 (54.3)	75 (52.8)	39 (42.4)	29 (58.0)	4 (100.0)	458 (59.0)
Unknown	497 (42.3)	186 (46.6)	135 (44.0)	61 (43.6)	63 (44.4)	51 (55.4)	19 (38.0)	0 (0.0)	311 (40.1)
Number of GP visits in the previous 12 months									
0	356 (15.9)	130 (15.5)	83 (13.0)	41 (12.7)	40 (14.9)	47 (23.4)	14 (13.3)	1 (25.0)	226 (16.1)
1 - 5	845 (37.7)	274 (32.7)	188 (29.5)	100 (31.0)	77 (28.6)	86 (42.8)	37 (35.2)	3 (75.0)	571 (40.7)
> 5	109 (4.9)	25 (3.0)	24 (3.8)	9 (2.8)	15 (5.6)	1 (0.5)	0 (0.0)	0 (0.0)	84 (6.0)
Unknown	931 (41.5)	409 (48.8)	342 (53.7)	173 (53.6)	137 (50.9)	67 (33.3)	54 (51.4)	0 (0.0)	522 (37.2)
Number of hospitalizations in the previous 12 months									
0	1325 (59.1)	424 (50.6)	291 (45.7)	149 (46.1)	128 (47.6)	133 (66.2)	51 (48.6)	4 (100.0)	901 (64.2)
1 - 2	46 (2.1)	10 (1.2)	5 (0.8)	2 (0.6)	3 (1.1)	5 (2.5)	2 (1.9)	0 (0.0)	36 (2.6)
> 2	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Unknown	868 (38.7)	404 (48.2)	341 (53.5)	172 (53.3)	138 (51.3)	63 (31.3)	52 (49.5)	0 (0.0)	464 (33.0)
Influenza vaccination status in current season									
Vaccinated	187 (8.3)	52 (6.2)	45 (7.1)	28 (8.7)	13 (4.8)	7 (3.5)	2 (1.9)	1 (25.0)	135 (9.6)

Characteristic	All n (%)	Cases n (%)							Controls
		All	A	A/H1N1	A/H3N2	B	B Vict	B Yam	n (%)
Vaccine brand									
Agrippal	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Fluad	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fluarix Tetra	53 (2.4)	10 (1.2)	8 (1.3)	6 (1.9)	2 (0.7)	2 (1.0)	1 (1.0)	1 (25.0)	43 (3.1)
Flucelvax Tetra	21 (0.9)	4 (0.5)	4 (0.6)	2 (0.6)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	17 (1.2)
Fluenz Tetra	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Influvac	1 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Influvac Tetra	13 (0.6)	6 (0.7)	6 (0.9)	5 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.5)
Vaxigrip Tetra	90 (4.0)	29 (3.5)	24 (3.8)	15 (4.6)	9 (3.3)	5 (2.5)	1 (1.0)	0 (0.0)	61 (4.3)
Unknown	7 (0.3)	2 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.4)
Vaccine type									
aTIV	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.3)
LAIV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
QIVc	21 (0.9)	4 (0.5)	4 (0.6)	2 (0.6)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	17 (1.2)
QIVe	156 (6.9)	45 (5.4)	38 (6.0)	26 (8.0)	11 (4.1)	7 (3.5)	2 (1.9)	1 (25.0)	111 (7.9)
TIV	3 (0.1)	1 (0.1)	1 (0.2)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Unknown	7 (0.3)	2 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.4)
Unvaccinated	2054 (91.7)	786 (93.8)	592 (92.9)	295 (91.3)	256 (95.2)	194 (96.5)	103 (98.1)	3 (75.0)	1268 (90.4)
Study site									
CIRI_GP	524 (23.3)	106 (12.6)	70 (11.0)	44 (13.6)	26 (9.7)	36 (17.9)	27 (25.7)	4 (100.0)	418 (29.7)
ISS	863 (38.4)	330 (39.4)	228 (35.8)	108 (33.4)	106 (39.4)	102 (50.7)	26 (24.8)	0 (0.0)	533 (37.9)
MUV	673 (30.0)	360 (43.0)	308 (48.4)	171 (52.9)	137 (50.9)	52 (25.9)	52 (49.5)	0 (0.0)	313 (22.2)
RCGP RSC	185 (8.2)	42 (5.0)	31 (4.9)	0 (0.0)	0 (0.0)	11 (5.5)	0 (0.0)	0 (0.0)	143 (10.2)

*presented for females only

Site-specific population characteristics, site-specific distribution of ILI/SARI over time and site-specific distribution of covariates and setting-specific population characteristics for each vaccine exposure are provided in the WebANNEX.

Table 9. Study population characteristics, ≥ 65, primary care TND studies, 2019/20

Characteristic	All n (%)	Cases n (%)							Controls
		All	A	A/H1N1	A/H3N2	B	B Vict	B Yam	n (%)
Total	347	65	56	14	37	9	4	0 (0.0)	282
Sex									
Female	192 (55.3)	37 (56.9)	31 (55.4)	9 (64.3)	19 (51.4)	6 (66.7)	2 (50.0)	0 (0.0)	155 (55.0)
Male	155 (44.7)	28 (43.1)	25 (44.6)	5 (35.7)	18 (48.6)	3 (33.3)	2 (50.0)	0 (0.0)	127 (45.0)
At least 1 chronic condition									
Yes	256 (73.8)	39 (60.0)	32 (57.1)	6 (42.9)	24 (64.9)	7 (77.8)	3 (75.0)	0 (0.0)	217 (77.0)
No	89 (25.6)	24 (36.9)	22 (39.3)	6 (42.9)	13 (35.1)	2 (22.2)	1 (25.0)	0 (0.0)	65 (23.0)
Unknown	2 (0.6)	2 (3.1)	2 (3.6)	2 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of GP visits in the previous 12 months									
0	18 (5.2)	3 (4.6)	2 (3.6)	0 (0.0)	2 (5.4)	1 (11.1)	1 (25.0)	0 (0.0)	15 (5.3)
1 - 5	146 (42.1)	22 (33.8)	17 (30.4)	4 (28.6)	11 (29.7)	5 (55.6)	3 (75.0)	0 (0.0)	124 (44.0)
> 5	75 (21.6)	15 (23.1)	13 (23.2)	3 (21.4)	10 (27.0)	2 (22.2)	0 (0.0)	0 (0.0)	60 (21.3)
Unknown	108 (31.1)	25 (38.5)	24 (42.9)	7 (50.0)	14 (37.8)	1 (11.1)	0 (0.0)	0 (0.0)	83 (29.4)
Number of hospitalizations in the previous 12 months									
0	231 (66.6)	35 (53.8)	28 (50.0)	6 (42.9)	20 (54.1)	7 (77.8)	3 (75.0)	0 (0.0)	196 (69.5)
1 - 2	30 (8.6)	4 (6.2)	3 (5.4)	1 (7.1)	2 (5.4)	1 (11.1)	1 (25.0)	0 (0.0)	26 (9.2)
> 2	3 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)
Unknown	83 (23.9)	26 (40.0)	25 (44.6)	7 (50.0)	15 (40.5)	1 (11.1)	0 (0.0)	0 (0.0)	57 (20.2)
Influenza vaccination status in current season									
Vaccinated	209 (60.2)	36 (55.4)	31 (55.4)	6 (42.9)	21 (56.8)	5 (55.6)	2 (50.0)	0 (0.0)	173 (61.3)
Vaccine brand									
Agrippal	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)
Fluad	88 (25.4)	17 (26.2)	15 (26.8)	2 (14.3)	10 (27.0)	2 (22.2)	0 (0.0)	0 (0.0)	71 (25.2)
Fluarix Tetra	52 (15.0)	6 (9.2)	5 (8.9)	0 (0.0)	4 (10.8)	1 (11.1)	1 (25.0)	0 (0.0)	46 (16.3)
Flucelvax Tetra	6 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.1)
Fluenz Tetra	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Influvac	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Characteristic		All n (%)	Cases n (%)							Controls
			All	A	A/H1N1	A/H3N2	B	B Vict	B Yam	n (%)
	Influvac Tetra	10 (2.9)	3 (4.6)	2 (3.6)	2 (14.3)	0 (0.0)	1 (11.1)	1 (25.0)	0 (0.0)	7 (2.5)
	Vaxigrip Tetra	46 (13.3)	9 (13.8)	8 (14.3)	1 (7.1)	7 (18.9)	1 (11.1)	0 (0.0)	0 (0.0)	37 (13.1)
	Unknown	5 (1.4)	1 (1.5)	1 (1.8)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)
	Vaccine type									
	aTIV	88 (25.4)	17 (26.2)	15 (26.8)	2 (14.3)	10 (27.0)	2 (22.2)	0 (0.0)	0 (0.0)	71 (25.2)
	LAIV	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	QIVc	6 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.1)
	QIVe	108 (31.1)	18 (27.7)	15 (26.8)	3 (21.4)	11 (29.7)	3 (33.3)	2 (50.0)	0 (0.0)	90 (31.9)
	TIV	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)
	Unknown	5 (1.4)	1 (1.5)	1 (1.8)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)
	Unvaccinated	138 (39.8)	29 (44.6)	25 (44.6)	8 (57.1)	16 (43.2)	4 (44.4)	2 (50.0)	0 (0.0)	109 (38.7)
Study site										
	CIRI-GP	146 (42.1)	10 (15.4)	8 (14.3)	1 (7.1)	7 (18.9)	2 (22.2)	2 (50.0)	0 (0.0)	136 (48.2)
	ISS	119 (34.3)	30 (46.2)	24 (42.9)	6 (42.9)	16 (43.2)	6 (66.7)	2 (50.0)	0 (0.0)	89 (31.6)
	MUV	47 (13.5)	21 (32.3)	21 (37.5)	7 (50.0)	14 (37.8)	0 (0.0)	0 (0.0)	0 (0.0)	26 (9.2)
	RCGP RSC	35 (10.1)	4 (6.2)	3 (5.4)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	31 (11.0)

Site-specific population characteristics, site-specific distribution of ILI/SARI over time and site-specific distribution of covariates and setting-specific population characteristics for each vaccine exposure are provided in the WebANNEX.

4.3.1.2 Test-negative design studies: hospital setting

For the combined data hospital-based TND studies (included in the primary analysis), 661 cases and 731 controls were included for children 6m-17y, 331 vs. 726 for adults 18-64y, and 304 vs. 1368 for those aged ≥65y. Of all older adults ≥65y, 91.7% suffered from at least 1 chronic condition, 54.2% were male and 52.7% were vaccinated with influenza in the current season, mostly with Fluad, Vaxigrip Tetra and Flucelvax (Table 12 and Figure 6). The majority of hospitalised adults aged 18-64y were female and had at least 1 chronic condition (51.8% and 62.6%). Children 6m-17y and adults 18-64y were less likely to be vaccinated compared to older adults, 4.3% and 20.9%, respectively (Table 10 and Table 11). The vaccine types used among all age groups were primarily trivalent adjuvanted, quadrivalent inactivated egg-based, and quadrivalent inactivated cell-based influenza vaccines. Graphical summaries of hospital-based studies and site-specific brand distribution are provided in Figure 4-Figure 6. The distribution of the controls and laboratory-confirmed influenza infections (by type and subtype/lineage) stratified by age group (6m-17y, 18-64 y, ≥65y) over time is given in Figure 4, showing a much lower influenza B proportion reported among older adults with laboratory-confirmed influenza this season. The percentage of subjects that tested positive for influenza over time is shown in Figure 5. Comparing the number of vaccinated subjects and distribution of vaccine brands of the hospital based TND studies 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 Agrippal was mainly collected in hospital based studies, Fluarix Tetra in primary care based studies, and was restricted geographically). Site-specific population characteristics, distribution of ILI/SARI over time, distribution of covariates and setting-specific population characteristics for each vaccine exposure are provided in the WebANNEX. For Spain VHUH and Spain GTPUH, the data collection followed a matched 1:1 case-control design, where information on exposure and covariates was obtained only for controls that could be matched to a case by epidemiological week (same or adjacent week) and age group (6m–17y, 18-64y, and 65-74 and 75+y). Additionally, Spain GTPUH matched for sex. All other studies used an unmatched design.

Table 10. Study population characteristics, 6m - 17y, hospital TND studies, 2019/20

Characteristic	All n (%)	Cases n (%)							Controls
		All	A	A/H1N1	A/H3N2	B	B Vict	B Yam	n (%)
Total	1392	661	382	132	213	281	208	0	731
Sex									
Female	621 (44.6)	295 (44.6)	166 (43.5)	52 (39.4)	93 (43.7)	130 (46.3)	92 (44.2)	0 (0)	326 (44.6)
Male	771 (55.3)	366 (55.4)	216 (56.5)	80 (60.6)	120 (56.3)	151 (53.7)	116 (55.8)	0 (0.0)	405 (55.3)
At least 1 chronic condition									
Yes	191 (13.7)	103 (15.6)	56 (14.7)	16 (12.1)	32 (15.0)	48 (17.1)	29 (13.9)	0 (0.0)	88 (12.0)
No	1201 (86.3)	558 (84.4)	326 (85.3)	116 (87.9)	181 (85.0)	233 (82.9)	179 (86.1)	0 (0)	643 (88.0)
Pregnancy*									
Yes	3 (0.5)	3 (1.0)	2 (1.2)	0 (0.0)	1 (1.1)	1 (0.8)	1 (1.1)	0 (0.0)	0 (0.0)
No	139 (22.3)	83 (28.1)	34 (20.5)	12 (23.1)	15 (16.1)	50 (38.5)	45 (48.9)	0 (0.0)	56 (17.1)
Unknown	480 (77.2)	209 (70.8)	130 (78.3)	40 (76.9)	77 (82.8)	79 (60.8)	46 (50.0)	0 (0.0)	271 (82.9)
Number of GP visits in the previous 12 months									
0	49 (3.5)	38 (5.7)	15 (3.9)	4 (3.0)	9 (4.2)	23 (8.2)	10 (4.8)	0 (0.0)	11 (1.5)
1 - 5	209 (15.0)	117 (17.7)	58 (15.2)	14 (10.6)	27 (12.7)	59 (21.0)	13 (6.2)	0 (0.0)	92 (12.6)
> 5	38 (2.7)	14 (2.1)	10 (2.6)	2 (1.5)	3 (1.4)	4 (1.4)	3 (1.4)	0 (0.0)	24 (3.3)
Unknown	1096 (78.7)	492 (74.4)	299 (78.3)	112 (84.8)	174 (81.7)	195 (69.4)	182 (87.5)	0 (0)	604 (82.6)
Number of hospitalizations in the previous 12 months									
0	381 (27.4)	225 (34.0)	118 (30.9)	42 (31.8)	62 (29.1)	108 (38.4)	102 (49.0)	0 (0)	156 (21.3)
1 - 2	248 (17.8)	136 (20.6)	70 (18.3)	31 (23.5)	34 (16.0)	66 (23.5)	55 (26.4)	0 (0.0)	112 (15.3)
> 2	66 (4.7)	35 (5.3)	10 (2.6)	4 (3.0)	5 (2.3)	26 (9.3)	17 (8.2)	0 (0.0)	31 (4.2)
Unknown	697 (50.1)	265 (40.1)	184 (48.2)	55 (41.7)	112 (52.6)	81 (28.8)	34 (16.3)	0 (0.0)	432 (59.0)
Influenza vaccination status in current season									
Vaccinated	60 (4.3)	22 (3.3)	18 (4.7)	3 (2.3)	12 (5.6)	4 (1.4)	4 (1.9)	0 (0)	38 (5.2)

Characteristic		All n (%)	Cases n (%)							Controls
			All	A	A/H1N1	A/H3N2	B	B Vict	B Yam	n (%)
	Vaccine brand									
	Agrippal	10 (0.7)	4 (0.6)	2 (0.5)	1 (0.8)	1 (0.5)	2 (0.7)	2 (1.0)	0 (0.0)	6 (0.8)
	Fluad	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Fluarix Tetra	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Flucelvax Tetra	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Fluenz Tetra	2 (0.1)	1 (0.2)	1 (0.3)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0)	1 (0.1)
	Influvac	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Influvac Tetra	4 (0.3)	2 (0.3)	2 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
	Vaxigrip Tetra	40 (2.9)	14 (2.1)	12 (3.1)	2 (1.5)	9 (4.2)	2 (0.7)	2 (1.0)	0 (0.0)	26 (3.6)
	Unknown	1 (0.1)	1 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Vaccine type									
	aTIV	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	LAIV	2 (0.1)	1 (0.2)	1 (0.3)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0)	1 (0.1)
	QIVc	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	QIVe	45 (3.2)	16 (2.4)	14 (3.7)	2 (1.5)	10 (4.7)	2 (0.7)	2 (1.0)	0 (0.0)	29 (4.0)
	TIV	10 (0.7)	4 (0.6)	2 (0.5)	1 (0.8)	1 (0.5)	2 (0.7)	2 (1.0)	0 (0.0)	6 (0.8)
	Unknown	1 (0.1)	1 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Unvaccinated	1332 (95.6)	639 (96.7)	364 (95.3)	129 (97.7)	201 (94.4)	277 (98.6)	204 (98.1)	0 (0.0)	693 (94.7)
Study site										
	CIRI-BIVE	771 (55.3)	311 (47.0)	205 (53.7)	61 (46.2)	127 (59.6)	106 (37.7)	43 (20.7)	0 (0.0)	460 (62.8)
	FISABIO	19 (1.4)	3 (0.5)	1 (0.3)	1 (0.8)	0 (0.0)	2 (0.7)	2 (1.0)	0 (0.0)	16 (2.2)
	GTPUH	25 (1.8)	12 (1.8)	9 (2.4)	1 (0.8)	1 (0.5)	3 (1.1)	2 (1.0)	0 (0.0)	13 (1.8)
	HUS	-	-	-	-	-	-	-	-	-
	INSERM	-	-	-	-	-	-	-	-	-

Characteristic	All n (%)	Cases n (%)							Controls
		All	A	A/H1N1	A/H3N2	B	B Vict	B Yam	n (%)
LPUH	-	-	-	-	-	-	-	-	-
NIID	499 (35.8)	296 (44.8)	145 (38.0)	54 (40.9)	80 (37.6)	153 (54.4)	148 (71.2)	0 (0)	203 (27.8)
VHUH	78 (5.6)	39 (5.9)	22 (5.8)	15 (11.4)	5 (2.3)	17 (6.0)	13 (6.2)	0 (0.0)	39 (5.3)

*presented for females only

Site-specific population characteristics, site-specific distribution of ILI/SARI over time and site-specific distribution of covariates and setting-specific population characteristics for each vaccine exposure are provided in the WebANNEX.

Table 11. Study population characteristics, 18 - 64y, hospital TND studies, 2019/20

Characteristic	All n (%)	Cases n (%)							Controls
		All	A	A/H1N1	A/H3N2	B	B Vict	B Yam	n (%)
Total	1057	331	256	154	56	75	55	0	726
Sex									
Female	548 (51.8)	176 (53.2)	122 (47.7)	70 (45.5)	30 (53.6)	54 (72.0)	39 (70.9)	0 (0.0)	372 (51.2)
Male	509 (48.2)	155 (46.8)	134 (52.3)	84 (54.5)	26 (46.4)	21 (28.0)	16 (29.1)	0 (0.0)	354 (48.8)
At least 1 chronic condition									
Yes	662 (62.6)	207 (62.5)	175 (68.4)	112 (72.7)	34 (60.7)	32 (42.7)	19 (34.5)	0 (0.0)	455 (62.7)
No	394 (37.3)	124 (37.5)	81 (31.6)	42 (27.3)	22 (39.3)	43 (57.3)	36 (65.5)	0 (0.0)	270 (37.2)
Unknown	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pregnancy*									
Yes	25 (4.6)	15 (8.5)	9 (7.4)	4 (5.7)	2 (6.7)	6 (11.1)	4 (10.3)	0 (0.0)	10 (2.7)
No	397 (72.4)	134 (76.1)	93 (76.2)	55 (78.6)	19 (63.3)	41 (75.9)	29 (74.4)	0 (0.0)	263 (70.7)
Unknown	126 (23.0)	27 (15.3)	20 (16.4)	11 (15.7)	9 (30.0)	7 (13.0)	6 (15.4)	0 (0.0)	99 (26.6)
Number of GP visits									
In the previous 12 months									
0	64 (6.1)	16 (4.8)	13 (5.1)	9 (5.8)	3 (5.4)	3 (4.0)	2 (3.6)	0 (0.0)	48 (6.6)
1 - 5	81 (7.7)	24 (7.3)	18 (7.0)	8 (5.2)	3 (5.4)	6 (8.0)	4 (7.3)	0 (0.0)	57 (7.9)
> 5	32 (3.0)	20 (6.0)	17 (6.6)	12 (7.8)	2 (3.6)	3 (4.0)	2 (3.6)	0 (0.0)	12 (1.7)

Characteristic	All n (%)	Cases n (%)							Controls
		All	A	A/H1N1	A/H3N2	B	B Vict	B Yam	n (%)
*In the previous 3 months***									
0	45 (4.3)	19 (5.7)	14 (5.5)	10 (6.5)	0 (0.0)	5 (6.7)	1 (1.8)	0 (0.0)	26 (3.6)
1 - 2	49 (4.6)	10 (3.0)	9 (3.5)	7 (4.5)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	39 (5.4)
> 2	39 (3.7)	8 (2.4)	5 (2.0)	4 (2.6)	1 (1.8)	3 (4.0)	0 (0.0)	0 (0.0)	31 (4.3)
Unknown	747 (70.7)	234 (70.7)	180 (70.3)	104 (67.5)	47 (83.9)	54 (72.0)	46 (83.6)	0 (0.0)	513 (70.7)
Number of hospitalizations in the previous 12 months									
0	501 (47.4)	158 (47.7)	115 (44.9)	68 (44.2)	22 (39.3)	43 (57.3)	32 (58.2)	0 (0.0)	343 (47.2)
1 - 2	275 (26.0)	104 (31.4)	83 (32.4)	51 (33.1)	16 (28.6)	21 (28.0)	15 (27.3)	0 (0.0)	171 (23.6)
> 2	63 (6.0)	13 (3.9)	11 (4.3)	8 (5.2)	1 (1.8)	2 (2.7)	1 (1.8)	0 (0.0)	50 (6.9)
Unknown	218 (20.6)	56 (16.9)	47 (18.4)	27 (17.5)	17 (30.4)	9 (12.0)	7 (12.7)	0 (0.0)	162 (22.3)
Influenza vaccination status in current season									
Vaccinated	221 (20.9)	50 (15.1)	37 (14.5)	21 (13.6)	9 (16.1)	13 (17.3)	9 (16.4)	0 (0.0)	171 (23.6)
Vaccine brand									
Agrippal	43 (4.1)	14 (4.2)	12 (4.7)	5 (3.2)	1 (1.8)	2 (2.7)	2 (3.6)	0 (0.0)	29 (4.0)
Fluad	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Fluarix Tetra	19 (1.8)	4 (1.2)	4 (1.6)	2 (1.3)	2 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	15 (2.1)
Flucelvax Tetra	45 (4.3)	3 (0.9)	2 (0.8)	1 (0.6)	1 (1.8)	1 (1.3)	1 (1.8)	0 (0.0)	42 (5.8)
Fluenz Tetra	-	-	-	-	-	-	-	-	-
Influvac	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Influvac Tetra	37 (3.5)	11 (3.3)	6 (2.3)	4 (2.6)	2 (3.6)	5 (6.7)	2 (3.6)	0 (0.0)	26 (3.6)
Vaxigrip Tetra	72 (6.8)	18 (5.4)	13 (5.1)	9 (5.8)	3 (5.4)	5 (6.7)	4 (7.3)	0 (0.0)	54 (7.4)
Unknown	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Vaccine type									

Characteristic		All n (%)	Cases n (%)							Controls
			All	A	A/H1N1	A/H3N2	B	B Vict	B Yam	n (%)
	aTIV	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
	LAIV	-	-	-	-	-	-	-	-	-
	QIVc	45 (4.3)	3 (0.9)	2 (0.8)	1 (0.6)	1 (1.8)	1 (1.3)	1 (1.8)	0 (0.0)	42 (5.8)
	QIVe	128 (12.1)	33 (10.0)	23 (9.0)	15 (9.7)	7 (12.5)	10 (13.3)	6 (10.9)	0 (0.0)	95 (13.1)
	TIV	45 (4.3)	14 (4.2)	12 (4.7)	5 (3.2)	1 (1.8)	2 (2.7)	2 (3.6)	0 (0.0)	31 (4.3)
	Unknown	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Unvaccinated	836 (79.1)	281 (84.9)	219 (85.5)	133 (86.4)	47 (83.9)	62 (82.7)	46 (83.6)	0 (0.0)	555 (76.4)
Study site										
	CIRI-BIVE	296 (28.0)	73 (22.1)	64 (25.0)	36 (23.4)	23 (41.1)	9 (12.0)	7 (12.7)	0 (0.0)	223 (30.7)
	FISABIO	157 (14.9)	20 (6.0)	18 (7.0)	14 (9.1)	1 (1.8)	2 (2.7)	2 (3.6)	0 (0.0)	137 (18.9)
	GTPUH	68 (6.4)	32 (9.7)	25 (9.8)	17 (11.0)	3 (5.4)	7 (9.3)	4 (7.3)	0 (0.0)	36 (5.0)
	HUS	56 (5.3)	15 (4.5)	14 (5.5)	14 (9.1)	0 (0.0)	1 (1.3)	1 (1.8)	0 (0.0)	41 (5.6)
	INSERM	134 (12.7)	37 (11.2)	28 (10.9)	21 (13.6)	1 (1.8)	9 (12.0)	1 (1.8)	0 (0.0)	97 (13.4)
	LPUH	15 (1.4)	11 (3.3)	9 (3.5)	6 (3.9)	0 (0.0)	2 (2.7)	2 (3.6)	0 (0.0)	4 (0.6)
	NIID	221 (20.9)	84 (25.4)	50 (19.5)	16 (10.4)	23 (41.1)	34 (45.3)	30 (54.5)	0 (0.0)	137 (18.9)
	VHUH	110 (10.4)	59 (17.8)	48 (18.8)	30 (19.5)	5 (8.9)	11 (14.7)	8 (14.5)	0 (0.0)	51 (7.0)

*presented for females only

**for INSERM, only the number of GP visits in the previous 3 months was available. This variable was categorized as “0”, “1 to 2” and “more than 2”.

Site-specific population characteristics, site-specific distribution of ILI/SARI over time and site-specific distribution of covariates and setting-specific population characteristics for each vaccine exposure are provided in the WebANNEX.

Table 12. Study population characteristics, ≥ 65y, hospital TND studies, 2019/20

Characteristic	All n (%)	Cases n (%)							Controls
		All	A	A/H1N1	A/H3N2	B	B Vict	B Yam	n (%)
Total	1672	304	271	151	80	34	18	2	1368
Sex									
Female	765 (45.8)	147	127 (46.9)	70 (46.4)	37 (46.2)	21 (61.8)	10 (55.6)	0 (0.0)	618 (45.2)
Male	907 (54.2)	157	144 (53.1)	81 (53.6)	43 (53.8)	13 (38.2)	8 (44.4)	2 (100.0)	750 (54.8)
At least 1 chronic condition									
Yes	1534 (91.7)	285	255 (94.1)	144	74 (92.5)	31 (91.2)	15 (83.3)	2 (100.0)	1249 (91.3)
No	138 (8.3)	19 (6.2)	16 (5.9)	7 (4.6)	6 (7.5)	3 (8.8)	3 (16.7)	0 (0.0)	119 (8.7)
Number of GP visits									
*In the previous 12 months**									
0	121 (7.2)	19 (6.2)	17 (6.3)	6 (4.0)	10 (12.5)	2 (5.9)	1 (5.6)	1 (50.0)	102 (7.5)
1 - 5	201 (12.0)	28 (9.2)	27 (10.0)	12 (7.9)	6 (7.5)	1 (2.9)	0 (0.0)	0 (0.0)	173 (12.6)
> 5	100 (6.0)	33 (10.9)	31 (11.4)	18 (11.9)	9 (11.2)	3 (8.8)	1 (5.6)	0 (0.0)	67 (4.9)
*In the previous 3 months**									
0	40 (2.4)	11 (3.6)	8 (3.0)	4 (2.6)	2 (2.5)	3 (8.8)	1 (5.6)	0 (0.0)	29 (2.1)
1 - 2	114 (6.8)	25 (8.2)	20 (7.4)	13 (8.6)	5 (6.2)	5 (14.7)	0 (0.0)	1 (50.0)	89 (6.5)
> 2	89 (5.3)	8 (2.6)	7 (2.6)	4 (2.6)	2 (2.5)	1 (2.9)	0 (0.0)	0 (0.0)	81 (5.9)
Unknown	1007 (60.2)	180	161 (59.4)	94 (62.3)	46 (57.5)	19 (55.9)	15 (83.3)	0 (0.0)	827 (60.5)
Number of hospitalizations in the previous 12 months									
0	830 (49.6)	153 (50.3)	136 (50.2)	79 (52.3)	35 (43.8)	18 (52.9)	7 (38.9)	2 (100.0)	677 (49.5)
1 - 2	496 (29.7)	80 (26.3)	69 (25.5)	41 (27.2)	15 (18.8)	11 (32.4)	7 (38.9)	0 (0.0)	416 (30.4)
> 2	134 (8.0)	17 (5.6)	15 (5.5)	6 (4.0)	5 (6.2)	2 (5.9)	2 (11.1)	0 (0.0)	117 (8.6)
Unknown	212 (12.7)	54 (17.8)	51 (18.8)	25 (16.6)	25 (31.2)	3 (8.8)	2 (11.1)	0 (0.0)	158 (11.5)
Influenza vaccination status in current season									

Characteristic		All n (%)	Cases n (%)							Controls
			All	A	A/H1N1	A/H3N2	B	B Vict	B Yam	n (%)
Vaccinated		881 (52.7)	114 (37.5)	103 (38.0)	60 (39.7)	27 (33.8)	11 (32.4)	3 (16.7)	2 (100.0)	767 (56.1)
Vaccine brand										
	Agrippal	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
	Fluad	432 (25.8)	63 (20.7)	59 (21.8)	34 (22.5)	15 (18.8)	4 (11.8)	3 (16.7)	1 (50.0)	369 (27.0)
	Fluarix Tetra	68 (4.1)	5 (1.6)	5 (1.8)	5 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	63 (4.6)
	Flucelvax Tetra	124 (7.4)	8 (2.6)	8 (3.0)	5 (3.3)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	116 (8.5)
	Fluenz Tetra	-	-	-	-	-	-	-	-	-
	Influvac	10 (0.6)	2 (0.7)	1 (0.4)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	8 (0.6)
	Influvac Tetra	76 (4.5)	9 (3.0)	8 (3.0)	3 (2.0)	3 (3.8)	1 (2.9)	0 (0.0)	1 (50.0)	67 (4.9)
	Vaxigrip Tetra	168 (10.0)	26 (8.6)	21 (7.7)	12 (7.9)	8 (10.0)	5 (14.7)	0 (0.0)	0 (0.0)	142 (10.4)
	Unknown	2 (0.1)	1 (0.3)	1 (0.4)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Vaccine type										
	aTIV	432 (25.8)	63 (20.7)	59 (21.8)	34 (22.5)	15 (18.8)	4 (11.8)	3 (16.7)	1 (50.0)	369 (27.0)
	LAIV	-	-	-	-	-	-	-	-	-
	QIVc	124 (7.4)	8 (2.6)	8 (3.0)	5 (3.3)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	116 (8.5)
	QIVe	312 (18.7)	40 (13.2)	34 (12.5)	20 (13.2)	11 (13.8)	6 (17.6)	0 (0.0)	1 (50.0)	272 (19.9)
	TIV	11 (0.7)	2 (0.7)	1 (0.4)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	9 (0.7)
	Unknown	2 (0.1)	1 (0.3)	1 (0.4)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Unvaccinated		791 (47.3)	190 (62.5)	168 (62.0)	91 (60.3)	53 (66.2)	23 (67.6)	15 (83.3)	0 (0.0)	601 (43.9)
Study site										
CIRI-BIVE		583 (34.9)	89 (29.3)	86 (31.7)	38 (25.2)	44 (55.0)	3 (8.8)	2 (11.1)	1 (50.0)	494 (36.1)

Characteristic	All n (%)	Cases n (%)							Controls
		All	A	A/H1N1	A/H3N2	B	B Vict	B Yam	n (%)
FISABIO	486 (29.1)	37 (12.2)	35 (12.9)	26 (17.2)	4 (5.0)	2 (5.9)	2 (11.1)	0 (0.0)	449 (32.8)
GTPUH	89 (5.3)	41 (13.5)	38 (14.0)	20 (13.2)	11 (13.8)	4 (11.8)	1 (5.6)	0 (0.0)	48 (3.5)
HUS	69 (4.1)	9 (3.0)	9 (3.3)	7 (4.6)	2 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	60 (4.4)
INSERM	246 (14.7)	44 (14.5)	35 (12.9)	21 (13.9)	9 (11.2)	9 (26.5)	1 (5.6)	1 (50.0)	202 (14.8)
LPUH	21 (1.3)	11 (3.6)	9 (3.3)	3 (2.0)	0 (0.0)	2 (5.9)	1 (5.6)	0 (0.0)	10 (0.7)
NIID	78 (4.7)	25 (8.2)	19 (7.0)	7 (4.6)	7 (8.8)	6 (17.6)	4 (22.2)	0 (0.0)	53 (3.9)
VHUH	100 (6.0)	48 (15.8)	40 (14.8)	29 (19.2)	3 (3.8)	8 (23.5)	7 (38.9)	0 (0.0)	52 (3.8)

*for INSERM, only the number of GP visits in the previous 3 months was available. This variable was categorized as “0”, “1 to 2” and “more than 2”.

Site-specific population characteristics, site-specific distribution of ILI/SARI over time and site-specific distribution of covariates and setting-specific population characteristics for each vaccine exposure are provided in the WebANNEX.

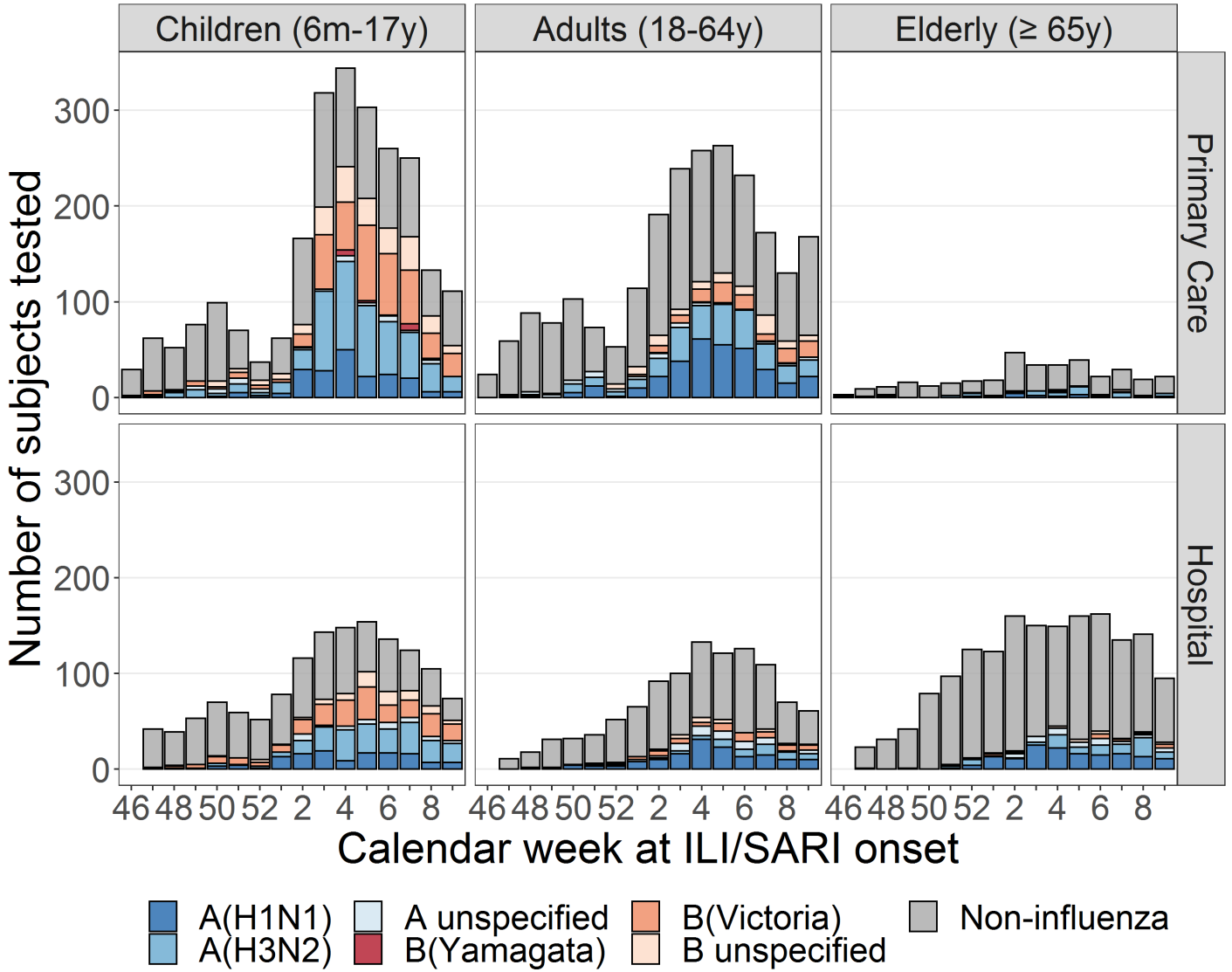


Figure 4. Distribution of ILI/SARI cases over time; TND studies, 2019/20

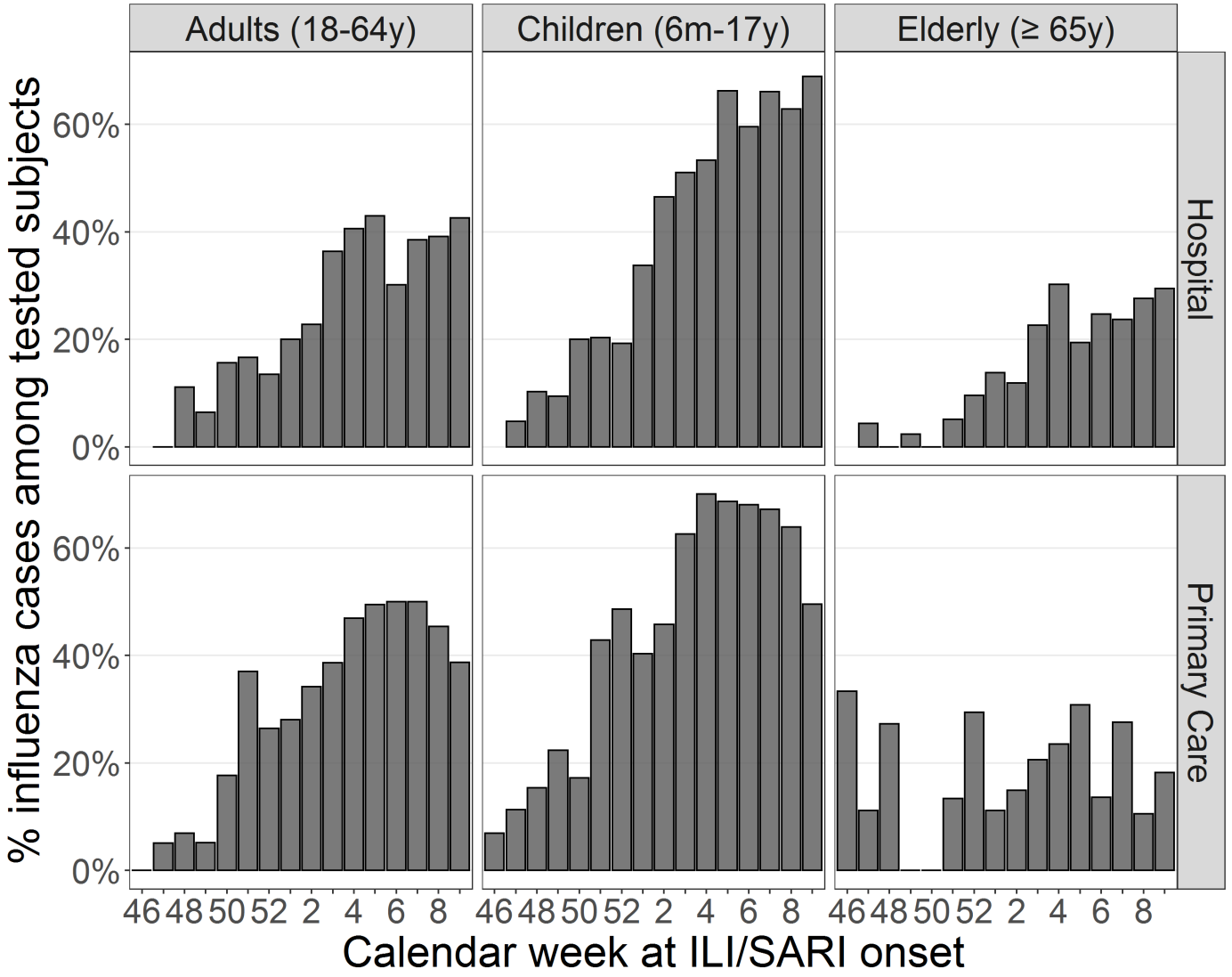
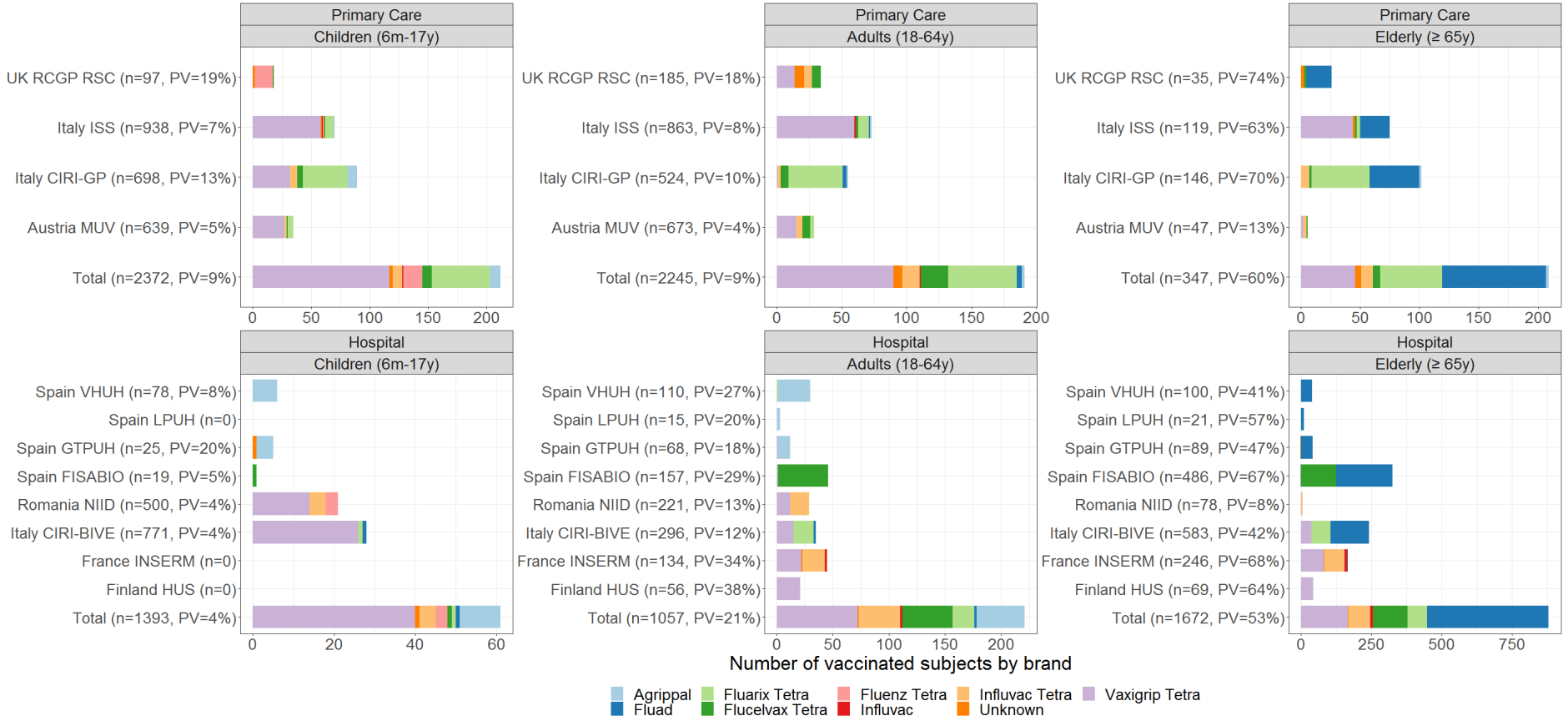


Figure 5. Distribution of percentage of influenza cases among tested ILI/SARI subjects over time, TND studies, 2019/20



PV: proportion vaccinated; y: years

Figure 6. Number of vaccinated subjects among enrolled subjects and distribution of vaccine brands; TND studies, 2019/20

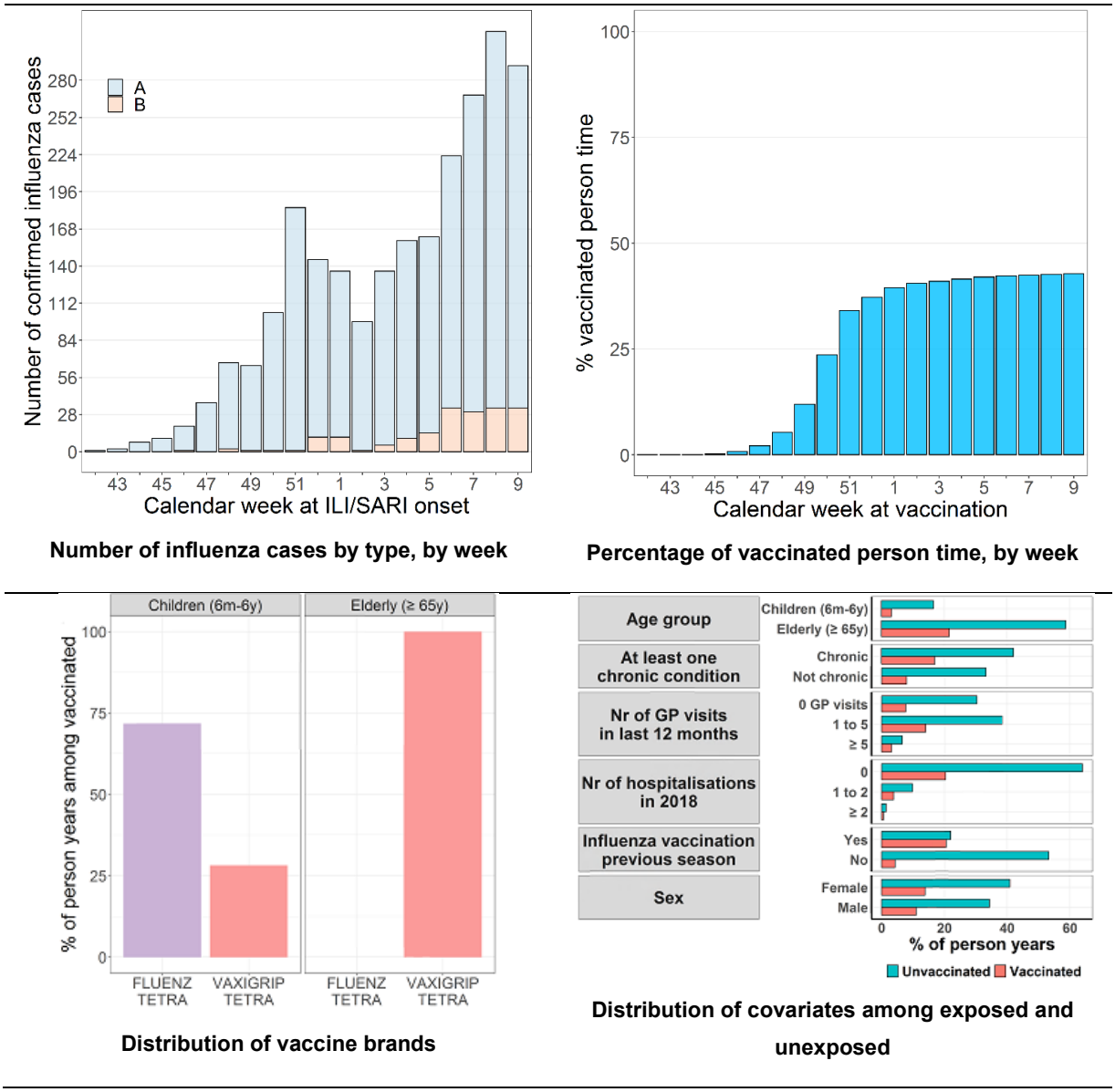
4.3.2 Register-based cohort study, Finland

The Finland THL register-based cohort includes children 6m-6y (100,942 person years) and older adults 65-100y (410,911 person years). Tabular and graphical summaries of the data are provided in Table 13 and Figure 7. The season was dominated by influenza virus A (Figure 7, top left). The vaccine brands used were Fluenz Tetra (for children 2-6 years of age) and Vaxigrip Tetra (all ages) (Figure 7, bottom left). Similar to the 2018/19 season, older adults, persons with at least one chronic condition and persons vaccinated with influenza in the previous season were more likely to be vaccinated compared to their counterparts (Figure 7, bottom right).

Table 13. Study population characteristics, Finland THL register-based cohort study, 2019/20

Characteristic	6m - 6y				≥ 65y			
	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
Total	110	16,375	917	84,567	467	110,497	933	300,414
Sex								
female	42	8043	409	41,224	247	62,683	518	167,943
male	68	8331	508	43,344	220	47814	415	132471
At least 1 chronic condition								
Yes	10	1659	98	7415	439	84,809	819	207,684
No	100	14,715	819	77,153	28	25,688	114	92,730
Number of primary care visits in the previous 12 months								
0	41	6117	324	32,120	91	33,020	289	123,156
1 - 5	61	9458	522	48,192	259	62,187	480	148,183
> 5	8	799	71	4255	117	15,290	164	29,075
Number of hospitalizations in 2018								
0	98	15102	833	78,764	270	89,365	576	248,566
1 -2	9	1185	74	5509	162	18,311	287	44,882
> 2	3	87	10	294	35	2821	70	6966
Influenza vaccination status in previous season								
Vaccinated	70	11,683	96	17,107	371	93,229	236	95,348
Unvaccinated	40	4691	821	67,460	96	17,269	697	205,067
Vaccine brand								
Any	110	16,375	-	-	467	110,497	-	-
Vaxigrip Tetra	25	4044	-	-	451	108,124	-	-
Fluenz Tetra	64	10,276	-	-	-	-	-	-

Population characteristics for each vaccine exposure are provided in the WebAnnex.



Number of influenza cases by type, by week

Percentage of vaccinated person time, by week

Distribution of vaccine brands

Distribution of covariates among exposed and unexposed

Figure 7. Data visualizations, Finland THL register-based cohort study, 2019/20.

4.4 Primary objective: overall IVE and IVE by brand

4.4.1 Test-negative design studies

The IVE estimates for each primary care TND study separately are given in the WebANNEX.

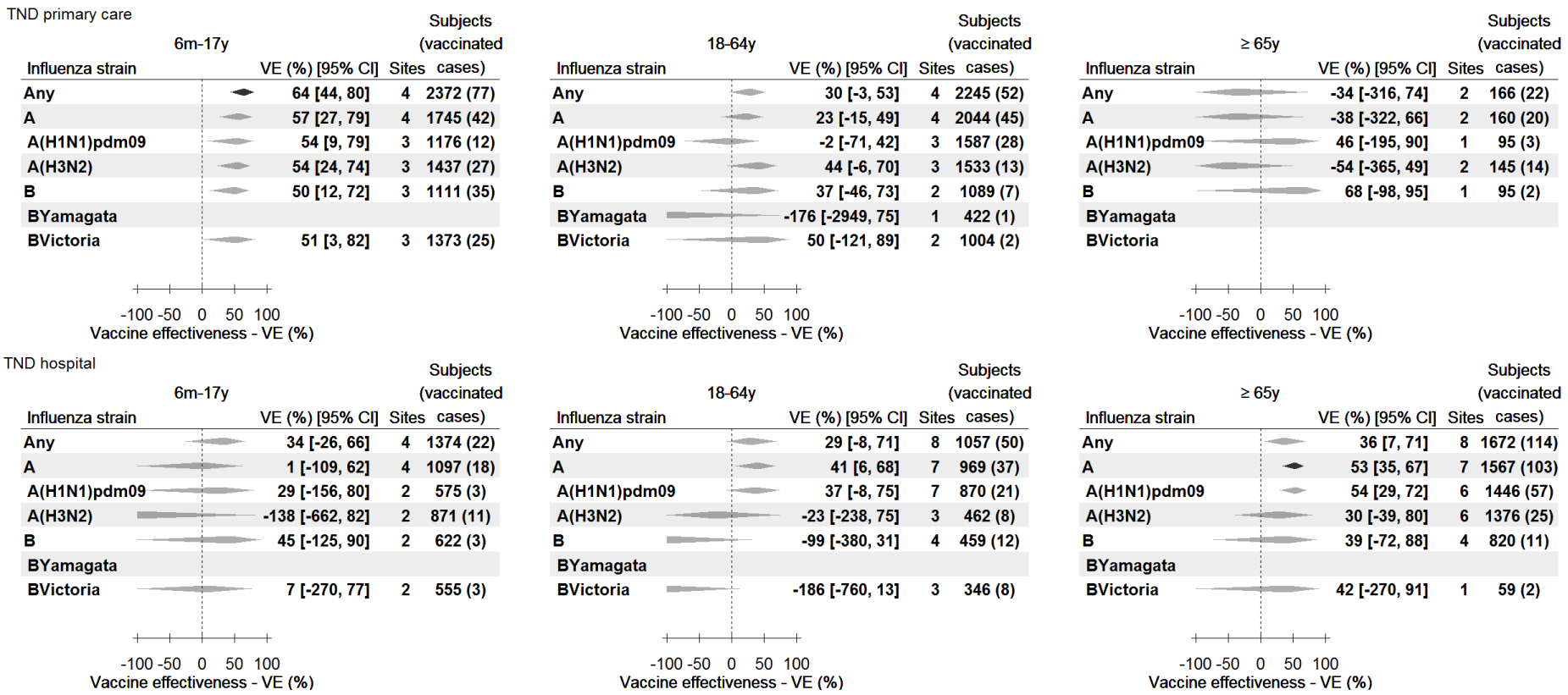
4.4.1.1 Pooled analysis

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 Figure 8 to Figure 16. Wide confidence intervals

(with a confidence interval width > 40%) are colored light grey to emphasise that estimates with wide confidence intervals are not considered precise. 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.

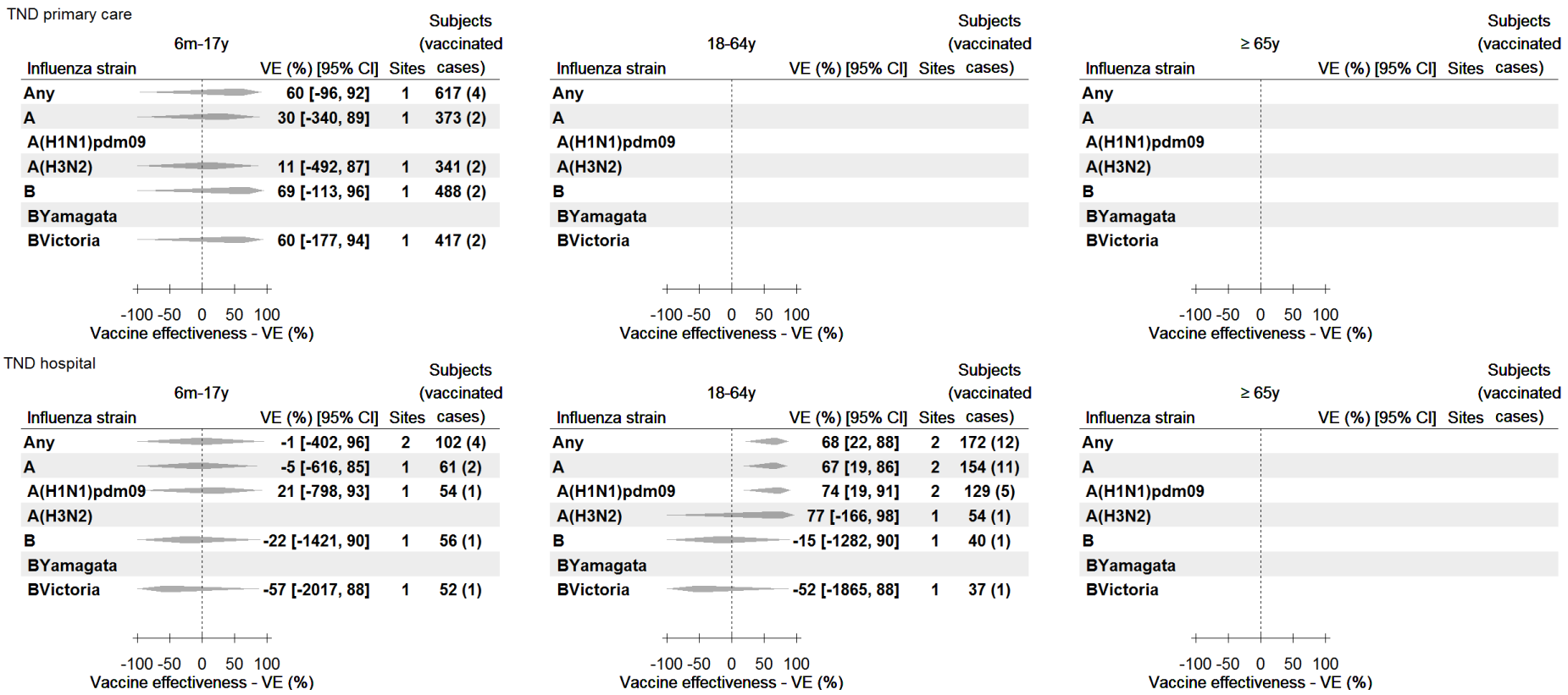
Four estimates with a narrow confidence interval are available. For children 6m-17y in the primary care setting, IVE against any flu was 64% (95%CI 44-80) for any vaccine, 81% (95%CI 58-92) for Fluarix Tetra and 61% (95%CI 38-77) for Vaxigrip Tetra. In the hospital setting, the IVE estimate for any vaccine against influenza A in those aged ≥65y was 53% (95%CI 35-67).

Figures with pooled crude IVE estimates and tables with pooled crude and pooled adjusted IVE estimates are provided in the WebANNEX. To aid the interpretation of the pooled estimates, the corresponding forest plots with the site-specific estimates are also provided in the WebANNEX.



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

Figure 8. Any influenza vaccine: pooled confounder-adjusted (age, sex and calendar time) influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2019/20

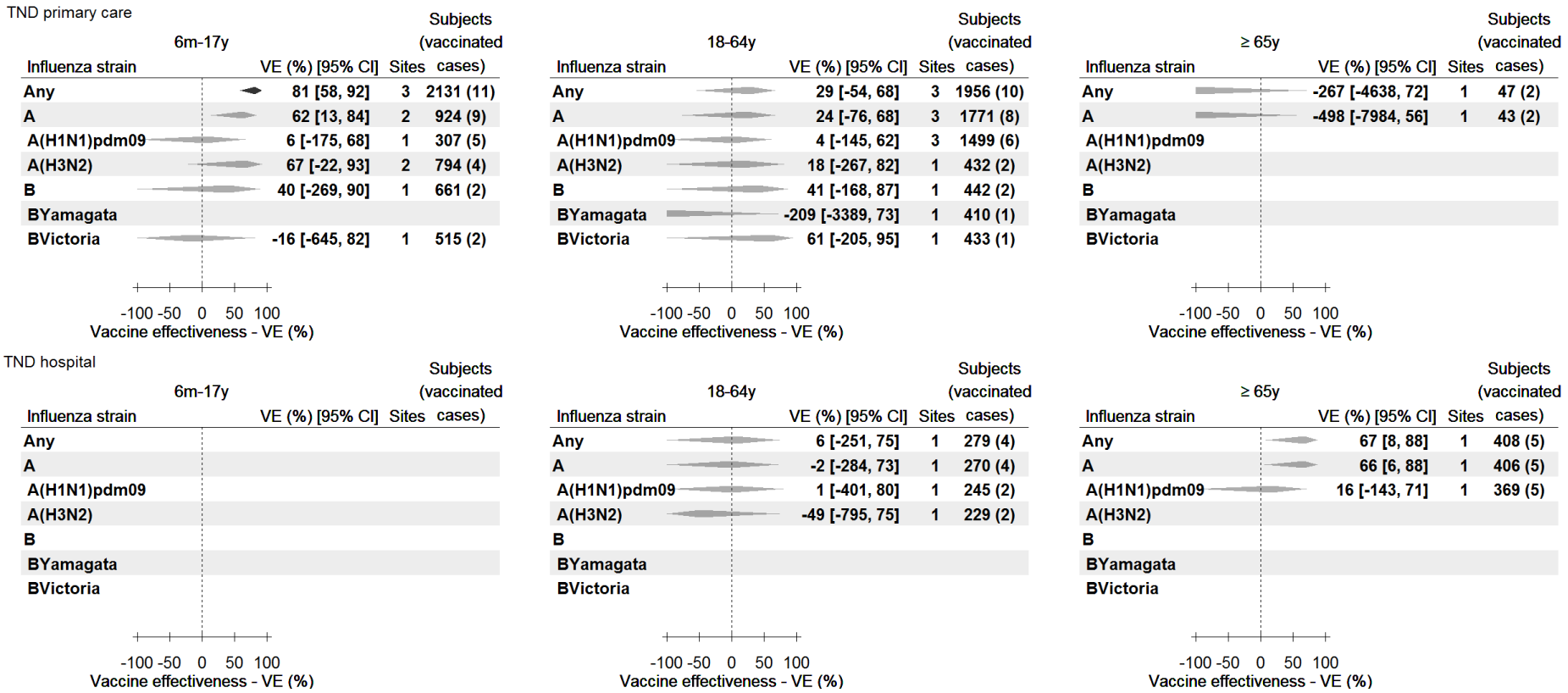


Dark grey diamond: precise results (width of CI < 40%). Light grey diamond: non-precise results.

Figure 9. Agrippal (Seqirus): pooled confounder-adjusted (age, sex and calendar time) influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2019/20

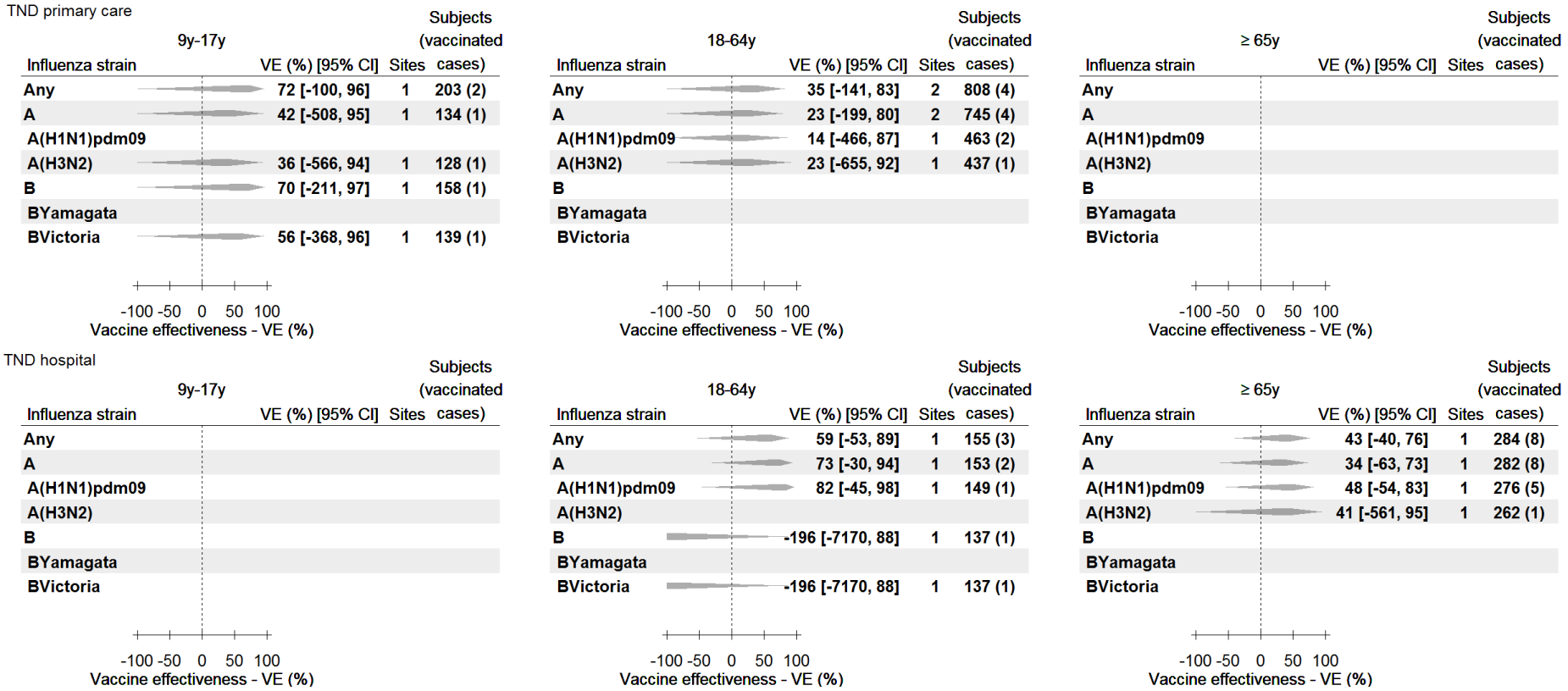
Dark grey diamond: precise results (width of CI < 40%). Light grey diamond: non-precise results.

Figure 10. Fluad (Seqirus): pooled confounder-adjusted (age, sex and calendar time) influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2019/20



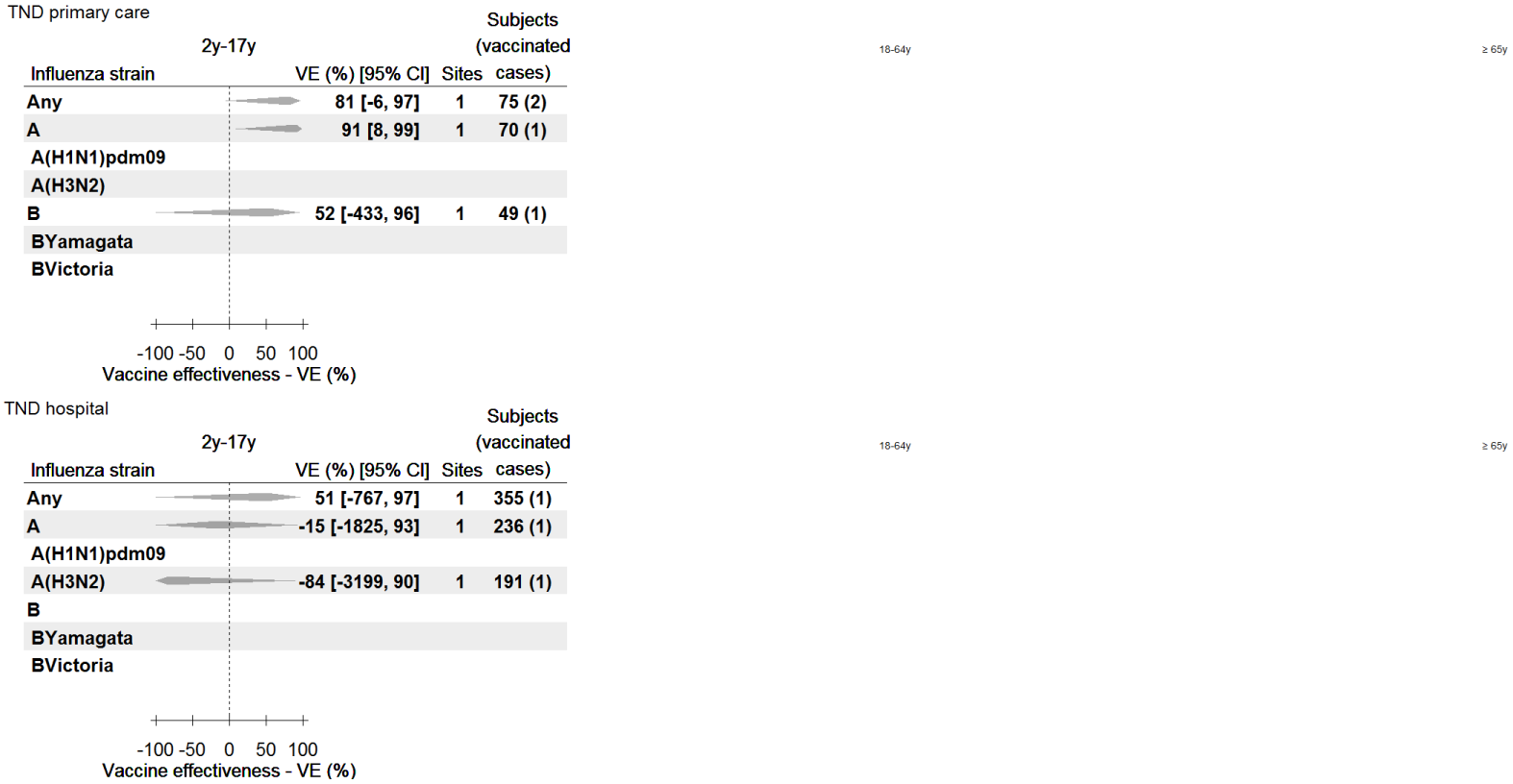
Dark grey diamond: precise results (width of CI < 40%). Light grey diamond: non-precise results.

Figure 11. Fluarix Tetra (GlaxoSmithKline): pooled confounder-adjusted (age, sex and calendar time) influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2019/20



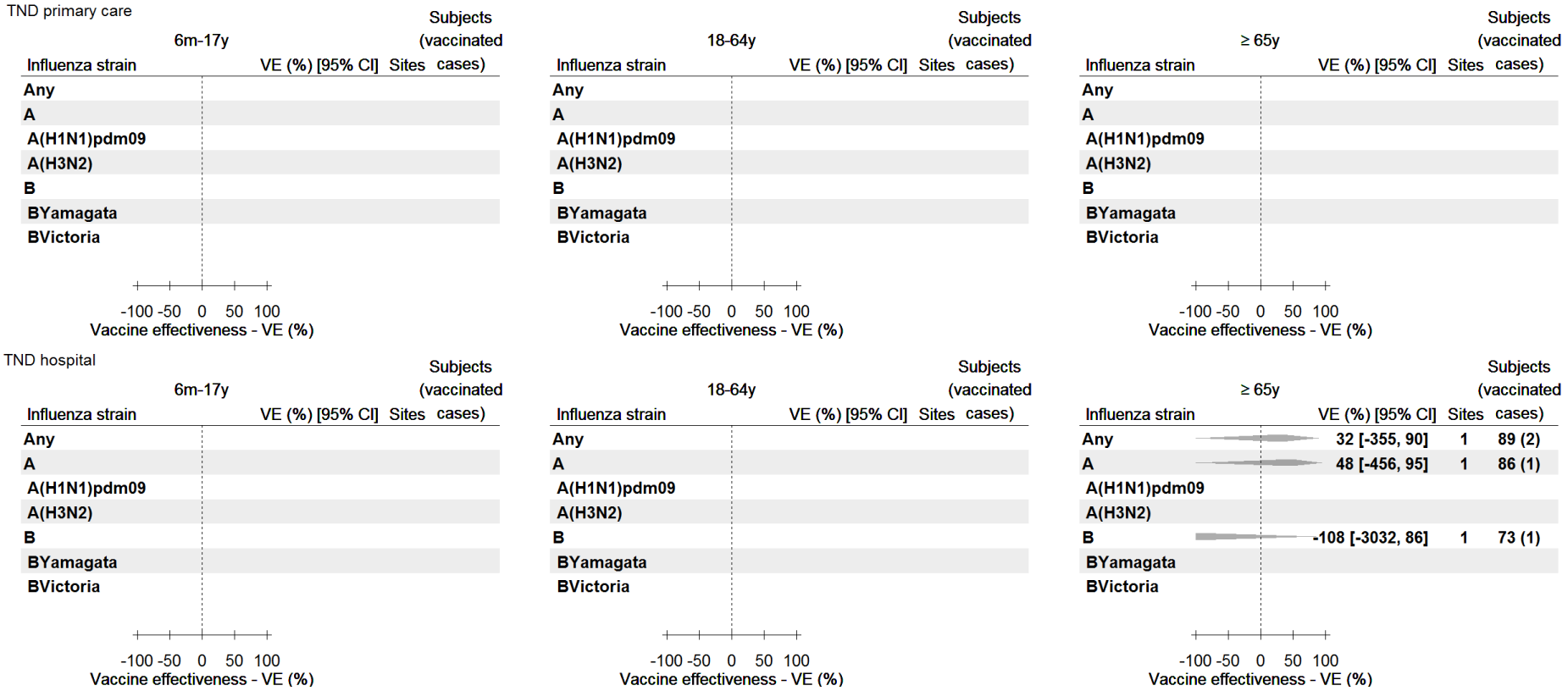
Dark grey diamond: precise results (width of CI < 40%). Light grey diamond: non-precise results.

Figure 12. Flucelvax Tetra (Seqirus): pooled confounder-adjusted (age, sex and calendar time) influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2019/20



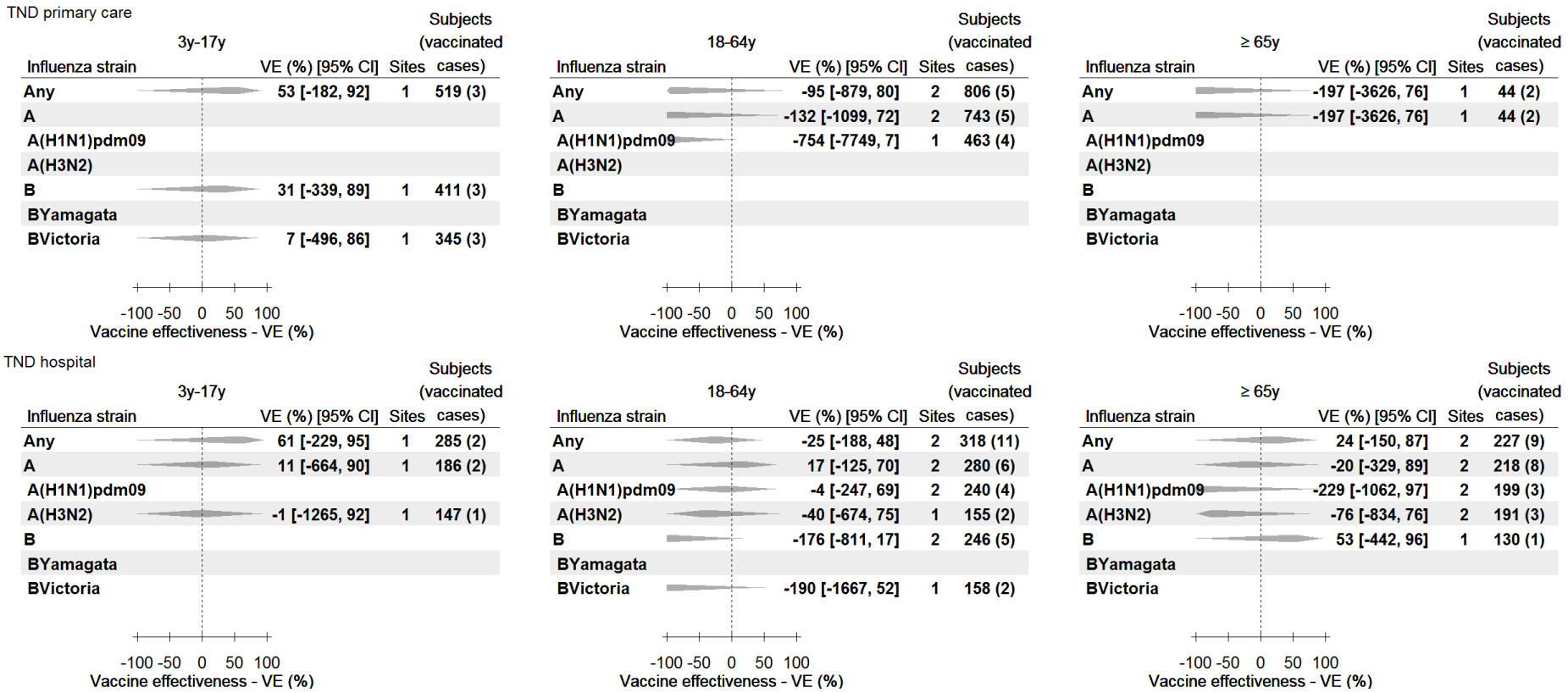
Dark grey diamond: precise results (width of CI < 40%). Light grey diamond: non-precise results. Only children aged 2-17y are considered to reflect the age group for which the vaccine is licensed.

Figure 13. Fluenz Tetra (AstraZeneca): pooled confounder-adjusted (age, sex and calendar time) influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2019/20



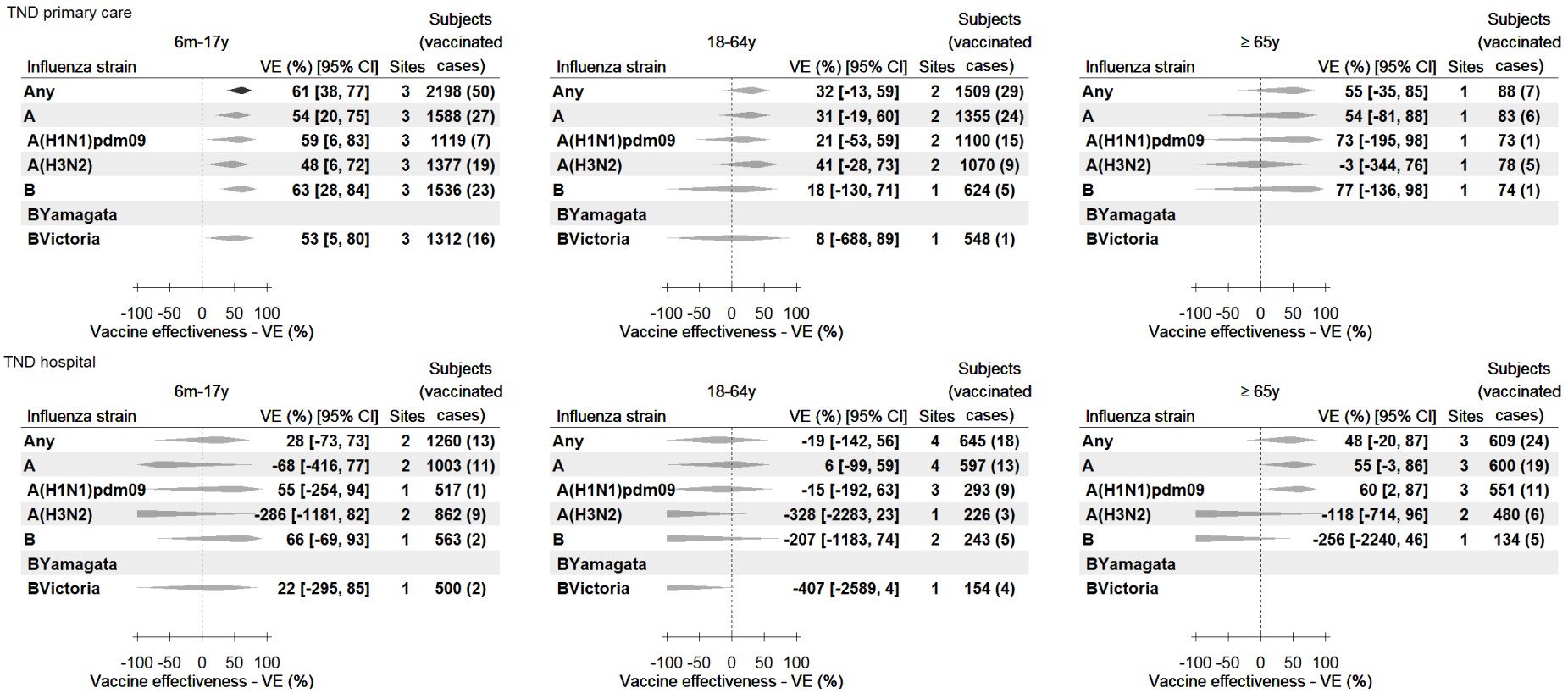
Dark grey diamond: precise results (width of CI < 40%). Light grey diamond: non-precise results.

Figure 14. Influvac (Abbott): pooled confounder-adjusted (age, sex and calendar time) influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2019/20



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

Figure 15. Influvac Tetra (Abbott): pooled confounder-adjusted (age, sex and calendar time) influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2019/20



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

Figure 16. Vaxigrip Tetra (Sanofi Pasteur): pooled confounder-adjusted (age, sex and calendar time) influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2019/20

4.4.1.2 Sensitivity analysis: partially vaccinated

In this sensitivity analysis, partially vaccinated subjects were included in the analysis, and were either all considered vaccinated or all unvaccinated. The results are similar to the main analysis. The full results of the sensitivity analysis are presented in the WebANNEX (SA partially vaccinated; SA partially unvaccinated).

4.4.1.3 Sensitivity analysis: time between ILI/SARI onset and swab

In this sensitivity analysis, respiratory specimens taken ≥ 4 days after ILI/SARI onset were excluded. This affected the estimates obtained (though not in a consistent direction) and resulted in an increase in the width of the CIs. The full results of the sensitivity analysis are presented in the WebANNEX (SA Swab Time).

4.4.1.4 Sensitivity analysis: outlying and influential analysis

In this sensitivity analysis, any studies that were both outlying and influential were included in the meta-analysis. Table 14 shows which site-specific IVE estimates were both outlying and influential and the pooled IVE obtained when this estimate is included in the meta-analysis.

Table 14. Influential and outlying studies and their adjusted IVE estimates, 2019/20

Site	Influenza A Adjusted VE [95%CI]	Influenza A(H1n1)pdm09 Adjusted VE [95%CI]	Influenza B
PC; 6M-17Y			
Any vaccine			
CIRI GP			85 [70; 92]
Pooled (SA)			63 [33; 84]
Pooled (main analysis)			50 [12; 72]
HOSPITAL; ≥65Y			
Any vaccine			
Romania NIID	-648 [-4797; -14]	-891 [-8934; -9]	
Pooled	25 [-8; 71]	12 [-29; 77]	
Pooled (main analysis)	53 [35; 67]	54 [29; 72]	

CI: confidence interval; m: months; PC: primary care; SA: sensitivity analysis; VE: vaccine effectiveness; y: years

The full results of the sensitivity analysis are presented in the WebANNEX (SA: outlying and influential).

4.4.1.5 Sensitivity analysis: extended study period

Due to the COVID-19 outbreak a number of sites had to end the data collection earlier than planned. The study period for the main analysis has therefore been shortened to February 29, 2020. COVID-19 epidemiology in Europe, the impact of COVID-19 on influenza surveillance among DRIVE sites for 2019/2020 season, and on implemented policies and lockdown measures across EU countries are described in the WebANNEX (COVID-19).

In this sensitivity analysis, the study period was extended to April 30, 2020. At the site level, the end of the study period was still defined as the week prior to the first of two consecutive weeks when no influenza viruses are detected. The number of subjects tested by week for the extended study period is shown in Figure

17. All local study periods effectively ended before April 30, as no more influenza positive tests were reported after week 12.

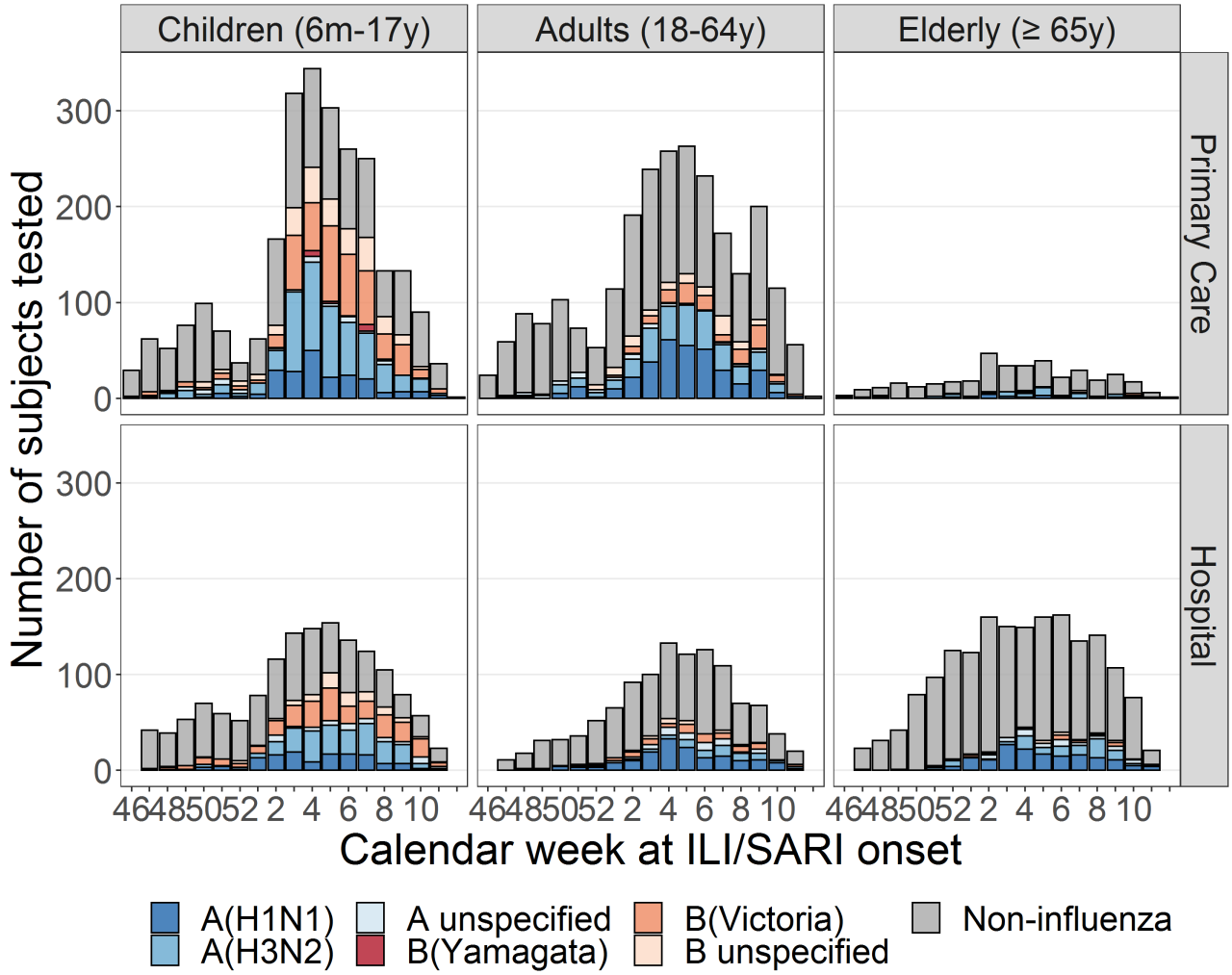


Figure 17. Distribution of ILI/SARI cases over time, until April 30; TND studies, 2019/20

The estimates with a CI width of <40% in the main analysis were similar in the sensitivity analysis. Furthermore, two additional estimates with a CI width of <40% were obtained: for older adults ≥65y in hospital setting, IVE for any vaccine against influenza A was 54% (95%CI 32-70), and IVE for Fluad against any influenza was 52% (95%CI 29-68). The full results of the sensitivity analysis with the extended study period (up to April 30, 2020) are presented in the WebANNEX (SA Full Season).

4.4.1.6 Sensitivity analysis: extended confounder adjustment

In this sensitivity analysis, an extended set of confounders was used, that included sex, a smooth function of age, a smooth function of calendar time, pregnancy, presence of at least one chronic condition and number of GP visits/hospitalizations. The number of subjected included in this analysis was reduced compared to the main analysis. The precise estimates in the main analysis are similar in this meta-analysis. Point estimates were impacted (though not in a consistent direction). The full results of the sensitivity analysis are presented in the WebANNEX (SA Additional Confounders).

4.4.2 Register-based cohort study

All IVE estimates against any influenza and influenza A from the Finland THL register-based cohort have a CI width of less than 40% (Table 15). The IVE estimate of Fluenz Tetra is 64.3 (95%CI 53.5- 72.7) against influenza A and in 80.4 (95%CI 55.4-91.4) against influenza B in children aged 2-6y. The IVE estimates of Vaxigrip Tetra against influenza A are 70.6 (95%CI 54.3; 81.0) in children aged 6m-6y and 27.0 (95%CI 18.0-35.0) in older adults aged ≥65y.

Estimates for any virus subtype/lineage include in the vaccine are not available for this data.

Table 15. Confounder-adjusted influenza vaccine effectiveness of any vaccine and by vaccine brand against any influenza, influenza A and influenza B, Finland THL register-based cohort, 2019/20

	Any influenza VE [95%CI]	A VE [95%CI]	B VE [95%CI]
6m - 6y			
Any vaccine	66.3 [58.8; 72.4]	63.4 [54.9; 70.4]	75.9 [57.3; 86.4]
Vaccine brand			
Vaxigrip Tetra	70.6 [56.1; 80.4]	70.6 [54.3; 81.0]	64.4 [11.6; 85.6]
Fluenz Tetra*	67.7 [58.3; 75.0]	64.3 [53.5; 72.7]	80.4 [55.4; 91.4]
≥ 65y			
Any vaccine	27.7 [19.1; 35.4]	26.4 [17.5; 34.4]	63.6 [23.5; 82.7]
Vaccine brand			
Vaxigrip Tetra	28.5 [19.8; 36.2]	27.0 [18.0; 35.0]	66.9 [27.9; 84.8]

*only children 2y – 6y

Influenza vaccine effectiveness estimates adjusted only for calendar time for the THL register-based cohort study are given in the WebANNEX. These semi-crude IVE estimates are similar to the confounder-adjusted IVE estimates.

4.5 Secondary objective: influenza vaccine effectiveness by type

Vaccine type specific IVE estimates were calculated only for vaccine types for which a minimum of two brands were available, i.e.QIVe and TIV.

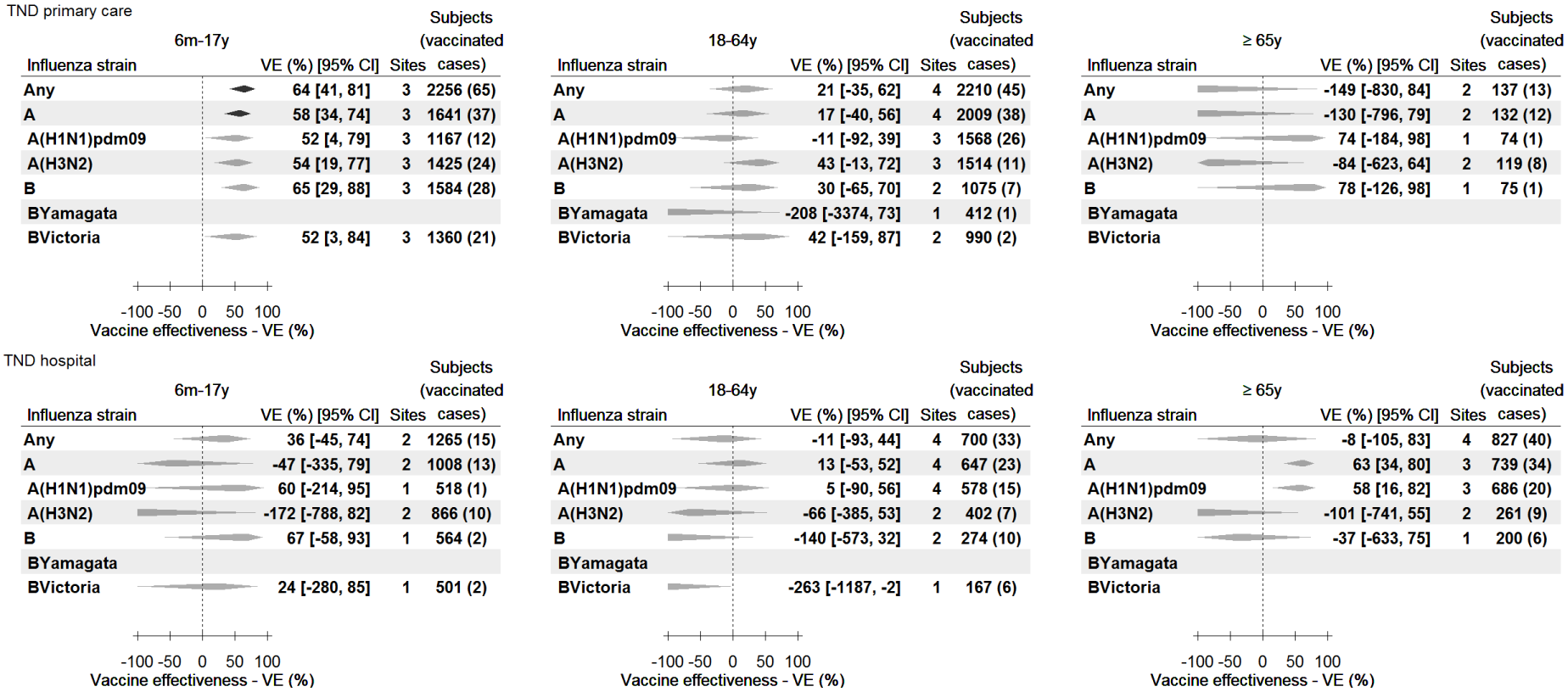
4.5.1 Test-negative design studies

The IVE estimates for each primary care TND study separately are given in the WebANNEX.

4.5.1.1 Pooled analysis

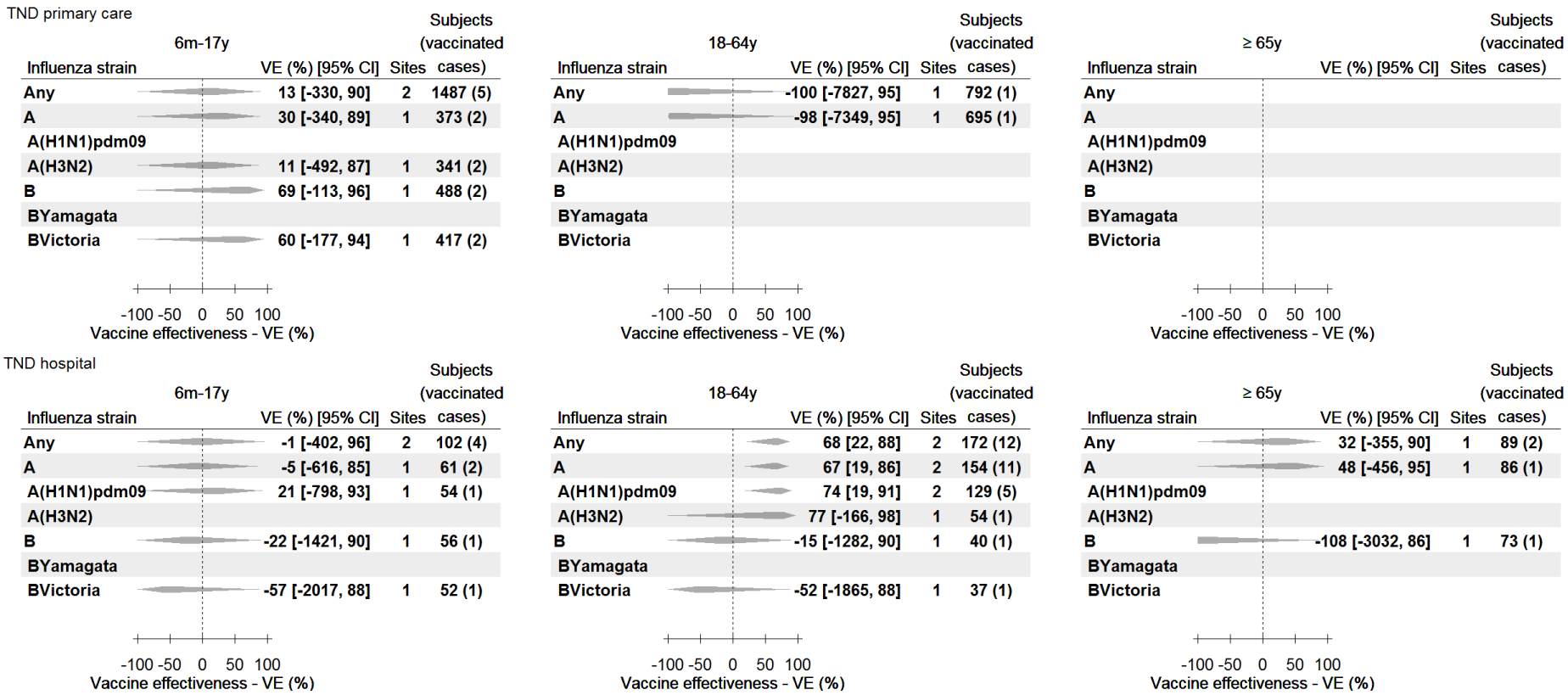
The pooled confounder-adjusted IVE estimates by vaccine type stratified by age group and healthcare setting are provided in Figure 18 (for QIVe) and Figure 19 (for TIV). Wide CI (with a CI width > 40%) are colored light grey to emphasise that estimates with wide confidence intervals are not considered precise.

For QIVe, two estimates had a CI width of <40%. For children 6m-17y in primary care setting, IVE against any influenza was 64% (95%CI 41-81) and IVE against influenza A was 58% (95%CI 34-74). None of the estimates for TIV had a CI width of <40%. All the pooled crude and adjusted influenza vaccine effectiveness estimates by vaccine type are provided in the WebANNEX.



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

Figure 18. Quadrivalent inactivated egg-based influenza vaccines: pooled confounder-adjusted (age, sex and calendar time) influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2019/20



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

Figure 19. Trivalent non-adjuvanted influenza vaccines: pooled confounder-adjusted (age, sex and calendar time) influenza vaccine effectiveness against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2019/20

4.5.2 Register-based cohort study, Finland

Only one vaccine brand per vaccine type was available.

5 Discussion

In the 2019/20 season, the DRIVE network encompassed twelve TND study sites, up from nine in the previous season, and one register-based cohort. Of the three hospital sites that joined, one is located in a country that was not previously represented (France). Data from 9079 subjects, of which 3531 were cases, were analyzed in the TND studies, and 511,854 person-years were included in the register-based cohort. Four precise estimates were obtained for the primary objectives from the TND studies, up from three in the previous season, and this included two precise brand-specific estimates, for Vaxigrip Tetra and Fluarix Tetra. One strength of the DRIVE network is that estimates from individual TND sites (none of which were precise) are pooled to increase precision. Additionally, estimates from the THL register-based cohort were precise. All precise estimates showed a protective effect, with point estimates varying between 26% and 81%.

The 2019/20 influenza season in Europe was characterized by co-circulation of influenza A A(H1N1)pdm09 and A(H3N2) and to a lesser extent B/Victoria. This was reflected in the TND studies, where influenza A was the dominant type (65.3% of all influenza), and both A(H1N1)pdm09 (46.4% of A with known subtype) and A(H3N2) (53.9% of A with known subtype) were identified. The peak of reported cases was reached in week 5 2020. Differences between the circulating influenza A(H1N1)pdm09, A(H3N2) and B/Vicotria strains and the vaccine strains may have impacted IVE.

5.1 Estimation of IVE for any vaccine

In the 2019/20 season, point estimates for pooled TND IVE estimates for any vaccine against any influenza ranged from -34 to 64% in the primary care setting and from 29% to 36% in the hospital setting. The pooled TND IVE estimates for any vaccine with a width of <40% were 64% (95%CI 44-80) against any influenza among children in primary care and 53% (95%CI 35-67) against influenza A in hospitalized patients ≥65y. IVE estimates from the Finland THL register-based cohort for any vaccine against any influenza was 66.3% (95%CI 58.8-72.5) in children 6m-6y and 27.7% (95%CI 19.1-35.4) in older adults ≥65y. 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 populations ≥65y from the register-based cohort and TND studies are more comparable than the respective children populations. Nevertheless, the point estimates for any vaccine

against any influenza in children (aged 6m-17y in the primary care TND studies and aged 6m-6y in the register-based cohort study) are very similar.

Another European network estimated interim IVE based on data from multiple study sites until January 29, 2020 [11]. The DRIVE estimates for any influenza in children in primary care are similar to the IVE estimates from the EU I-MOVE multi-country network (64% (95% CI 16-85)) [11]. Another IVE estimate obtained from primary care setting in Denmark was 95% (95% CI: 67 to 99) [11]. The DRIVE estimate for influenza A in hospitalized patients ≥65y is also in line with interim estimates from two study sites in Europe, where IVE was reported as 37% (95%CI 19-50) and 62% (95%CI 41-76) [11].

In the United States, interim IVE against outpatient medically-attended influenza of any type among children 6m-17y from the U.S. Flu VE Network was 55% (95%CI 42-65) [12]. The proportion of influenza type and subtype viruses differed from Europe. The majority of viruses were influenza B viruses (65% of influenza with known type) and few A(H3N2) viruses were identified (3% of A with known subtype).

5.2 Estimation of brand-specific IVE

Eleven influenza vaccine brands were licensed and marketed in the European Union (EU) in the 2019/20 season: Of the eleven brands, brand-specific estimates for eight vaccines were obtained (Agrippal, Fluad, Fluarix Tetra, Flucelvax Tetra, Fluenz Tetra, Influvac, Influvac Tetra, Vaxigrip Tetra).This included estimates for all quadrivalent vaccines for all approved age indications; whereas no estimates were reported for three of the six trivalent vaccines. This difference reflects the current transition to quadrivalent influenza vaccines in Europe. In light of this transition and the arrival of new vaccine types (such as cell-based and high dose influenza vaccines), a strong network is key to capture an increasing number of brands.

Precise estimates were obtained for Fluarix Tetra in children (TND studies), Vaxigrip Tetra in children (TND studies and THL register-based cohort) and in older adults ≥65y (THL register-based cohort), and for Fluenz Tetra (THL register-based cohort).

Reporting brand-specific estimates is unique to DRIVE, and no other studies were found that reported brand-specific estimates.

Public Health England has calculated type-specific IVE estimates for vaccines aTIV, LAIV, QIVc and QIVe; a single brand is available for the first three types listed, although the brands are not reported in their publication. The PHE estimates are 16.2 (-58.7-55.7) for aTIV in those aged ≥65y; 45.4% (12.6-65.9) for LAIV in children 2-17y; 63.9% (26.9-82.2) and 31.7 (-81.5-74.3) for QIVc in adults 18-64y and older adults aged ≥65y, respectively, and 38.9% (-4.5-64.3) for QIVe in adults 18-64y [13]. The confidence intervals of these estimates are wide and overlap with the confidence intervals of the respective DRIVE TND primary care estimates.

5.3 Precision

Multiple factors affect the precision of estimates, such as sample size, vaccine coverage, and the influenza attack rate, but also the true VE, test sensitivity and specificity, statistical methods, the variance of site-specific VE estimates etc. DRIVE is making efforts to increase sample size. However, many of the other factors (and in particular influenza attack rate) cannot be controlled. We recognize that defining estimates as precise when the absolute width of the CI is <40% is arbitrary. This was done to help with the interpretation of the vast number of estimates obtained in the study.

5.4 COVID-19

The COVID-19 pandemic and subsequently lockdown measures interfered with and capped the 2019-20 influenza circulation and impacted data collection. Therefore, the study period for the main analysis was truncated at February 29, 2020. This was two months earlier than originally expected, consequently fewer ILI and SARI subjects were included hampering options to obtain more precise brand-specific VE estimates. In the sensitivity analysis that included date up to April 30th, two additional precise brand-specific VE estimates were obtained.

The COVID-19 is likely to significantly impact the 2020-21 season, both in terms of epidemiology, as measures that prevent SARS-CoV-2 transmission can prevent transmission of other respiratory viruses, as in terms of data collection, as healthcare seeking and testing pathways have been adapted in many countries (e.g. influenza testing conditional to a negative SARS-CoV-2 test, parallel testing, etc). A good understanding of the latter at all DRIVE sites will be important to accurately describe the study population.

5.5 Parsimonious confounder adjustment

Using a simplified approach to adjust for confounding and with that defining a minimum confounder adjustment, we aim to avoid discarding data due to missing values, permit participation of sites who have limited data on confounders, and avoid potential over-adjustment based on the results of the ad-hoc analysis conducted in season 1018/19. However, the tradeoff of this simplified adjustment is that residual confounding may be present in the VE estimates and limitations may apply to their interpretation. For sites that are able to collect a larger set of confounding variables we will continue to do so to permit the conduct of sensitivity analysis which will help to understand the potential and the extent of the effects of the simplified adjustment.

5.6 Strenghts and limitations

Improvements to the analyses and reporting of results compared to the 2018/19 season

- The list of confounders considered was simplified based on post hoc analysis from the 2018/19 data. All TND study sites were able to collect data on confounders adjusted for in the main analysis (age, sex, date of onset).
- Reporting of DRIVE results was improved compared to the previous seasons. A mock report was developed and agreed upon between the partners prior to the availability of the study results and readability of figures was improved. Furthermore, a WebANNEX was developed which enables easier access to the full results (all site-specific and pooled analyses) to support data interpretation and improves the speed of report, as the report is more concise. Importantly, this also makes the project more sustainable for the future, as it is less resource intensive to report on the results, and makes the project outcomes and data FAIR (Findable, Accessible, Interoperable, Reusable) [14].

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 matching of controls.
- In the THL register based cohort, the swabbing is not “active” but based on routine physicians' assessment.

6 Conclusions

- DRIVE provided the first precise brand-specific IVE estimates in season 2019-2020.
- The number of precise estimates was increased compared to the 2018/19 season despite the mild influenza season and the shortening of the season due to the COVID-19 outbreak, which reflects network growth.
- The DRIVE network has expanded from five to eight TND hospital sites, including one new country, in addition to the existing TND primary care sites and the register-based cohort.
- Eight out of eleven brands licensed and marketed in Europe were captured in the DRIVE data. Due to the transition to QIV, the total number of subjects exposed to the conventional TIV vaccines was low,

however two precise brand-specific estimates were obtained for the QIVe vaccines Fluarix Tetra and Vaxigrip Tetra.

6.1 Recommendations

- An approach focused on the older age groups, in which a relatively high vaccine coverage is observed and where vaccination can have most impact on morbidity and mortality, combined with the hospital setting, where the proportion of older age groups is higher than in primary care, would increase the efficiency and feasibility of the network and is consistent with most influenza vaccine recommendations applicable in Europe. This would also enhance the homogeneity across sites, better permitting to pool the data from different sites in a given season. However, the tradeoff is that the coverage of some vaccine brands is low in the older age groups, the data won't be representative for the licensed age indication of all influenza vaccines and may not encompass exposure to all vaccine brands available in EU. In addition, the hospital setting is likely to reflect protection against more severe illness. The call for tenders for the 2020/21 season focused on the adults and older adult population in hospital setting. It is noted that national and regional public health institutes in Europe are still encouraged to join DRIVE, regardless of age groups covered and regardless of whether they have access to primary care or hospital data.
- Influenza and SARS-CoV-2 are expected to co-circulate in the 2020/21 season and DRIVE needs to account for this co-circulation in the operations' data collection and analysis. The COVID-19 and influenza testing strategy at the sites has to be understood, ideally all ILI and SARI patients would be tested for both viruses. In addition, the generic protocol for TND studies has been adapted to encompass some COVID-19 components in the operations data collection and analysis, more specifically to estimate COVID-19 impact on IVE and to compare clinical and laboratory features of COVID-19 and influenza cases at the time of hospital admission.

7 Funding

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8 Study team

The study team is described in the SAP (WebANNEX – SAP).

9 ANNEXES

The WebAnnex is accessible at: https://apps.p-95.com/drivewebapp/ (username: DRIVE_user; password: 6;40rv57P3Z85YC). The results of all the analyses are available there. In addition, the following documents are accessible:

- Statistical analysis plan
- COVID-19 (Impact of COVID-19; Lockdown policies and healthcare seeking behavior; SARS-Cov-2 epidemiology in Europe)
- Local study protocols (including deviations from protocol, if any)
- National or regional vaccine recommendations

WebAnnex hierarchy

- **TND site-specific analyses**
    - Main analysis / all sensitivity analyses
        - Descriptive
            - Histogram of covariates
                - By age group
            - Histogram of cumulative number of vaccinations over time
                - By ge group
            - Histogram of infections over time
                - By age group
            - Vaccination plot
                - By age group
            - Table of outcome by covariates
        - VE adjusted / VE crude
            - Site_adjusted/crude_IVE
        - Data quality report
- **TND pooled analyses**
    - Main analysis / all sensitivity analyses
        - Descriptive
            - Influenza over time
                - By setting and age group
            - Vaccination plot
                - By setting and age group
            - Table of outcomes by covariate
                - By setting and age group
            - Table of vaccine type by covariate
                - By setting and age group

        - VE adjuvated / VE crude
            - Pooled VE
                - Any vaccine / all vaccine brands / vaccine type
                    - Vaccine_clean *(→multipanel plots)*
                    - Vaccine_setting_age group *(→ forest plots for each estimates in the multipanel plots)*
                    - resultsClean *(→ IVE results in table format including 2x2 tables)*
            - Outlying and influential (excluded from main analysis)
- **Register-based cohort**
    - Descriptive
        - Histogram of covariates THLCohort
        - Histogram of Cumulative number of vaccinations over time THLCohort
        - Histogram of infections over time THLCohort
        - Vaccine brands
        - Table of outcome by covariates
            - Age group
    - VE results
        - THL_Adjusted_IVE_Report
        - THL_Crude_IVE_Report
- **Additional documents**
    - Data processing *(→ info on the number of records retained during the data processing)*
    - COVID-19: SARS-Cov2 Epidemiology in Europe 2019/2020
    - COVID-19: Impact of COVID-19 on influenza surveillance 2019/20
    - COVID-19: policies and lockdown measures, and healthcare seeking behavior 2019/20
    - Vaccine recommendations: target groups and vaccine types
    - Vaccine recommendations: webpage *(→ references for the vaccine recommendations)*
    - Local Study Reports 2019/20
    - Statistical Analysis Plan 2019/20

10 References

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