D7.8 Brand-specific influenza vaccine effectiveness in Europe Season 2020/21 REPORT

777363 – DRIVE
Development of Robust and Innovative Vaccine Effectiveness

WP7 – IVE studies

Study registered in ENCEPP (EUPAS40875).

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1. Document History

Version	Date	Description
V1.0	June 15 2021	First draft circulated to WP7 and DRIVE sites
V2.0	July 5 2021	Second draft incorporating feedback from WP7 and DRIVE sites, additionally including data from two sites (RJCUH and Iceland), data on number of SARS-CoV-2 positive subjects, and minor corrections.
V3.0	August 19 2021	Final report incorporating EFPIA and ISC comments.

2. List of figures

3. List of tables

4. List of acronyms and abbreviations

aTIV	Adjuvanted trivalent influenza vaccine
BIVE	Italian Hospital Network
CI	Confidence Interval
CIRI-IT	Centro Interuniversitario di Ricerca sull'Influenza e sulle altre infezioni trasmissibili Italy
COVID-19	Coronavirus disease 2019
DRIVE	Development of Robust and Innovative Vaccine Effectiveness
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
EL	Directorate of Health - Embætti landlæknis
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
ILI	Influenza-like illness
IMI	Innovative Medicines Initiative
INSERM	Institut national de la santé et de la recherche médicale
IRR	Incidence rate ratio
ISS	Istituto Superiore di Sanità
IVE	Influenza vaccine effectiveness
HUVH	Vall d'Hebron University Hospital
LAIV	Live attenuated influenza vaccine
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
QIVr	Quadrivalent influenza vaccine recombinant
RCGP RSC	Royal College of General Practitioners Research and Surveillance Centre
IRR	Incidence rate ratio
RJCUH	Rey Juan Carlos University Hospital

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
SOP	Standard Operating Procedure
SUH	Salamanca University Hospital
TGUH	Girona Josep Trueta University Hospital
THL	The Finnish Institute for Health and Welfare
TIV	Trivalent influenza vaccine
TIV-HD	Trivalent influenza vaccine high dose
TND	Test-negative design
UK	United Kingdom
VE	Vaccine effectiveness
y	year

5. Milestones

	Expected date	Actual date
Start of surveillance period	October/November 2020	September/December 2020
End of surveillance period	April 30 2021	April 30 2021/May 16 2021
First subject enrolled (TND studies)	n/a	October 2 2020
Last subject enrolled (TND studies)	n/a	April 30 2021
First data upload by site	May 1-9	April 30 2021 - XX
Final data upload by site	May 28 2021	May 5 - June 21 2021
Data quality reports completed	May 28 2021	July 2 2021
Database freeze		
First IVE results available	June 15 2021	June 15 2021
Analysis archived		
Report submission to IMI	September 1 2021	

n/a: not applicable

6. Executive summary

Background

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

DRIVE has successfully set up a strong and efficient data collection platform through a network of independent study sites across Europe (Figure E1), establishing a quality control, IT and pooled analysis infrastructure alongside with an appropriate governance. In DRIVE, data from several independently operating national or regional study sites is analysed jointly to increase geographical coverage and sample size for brand-specific IVE estimates. The 2020/21 season is the network's fourth influenza season. DRIVE platform is still expanding despite the challenges posed by the COVID-19 pandemic and the lack of influenza circulation in Europe in the 2020/21 season.

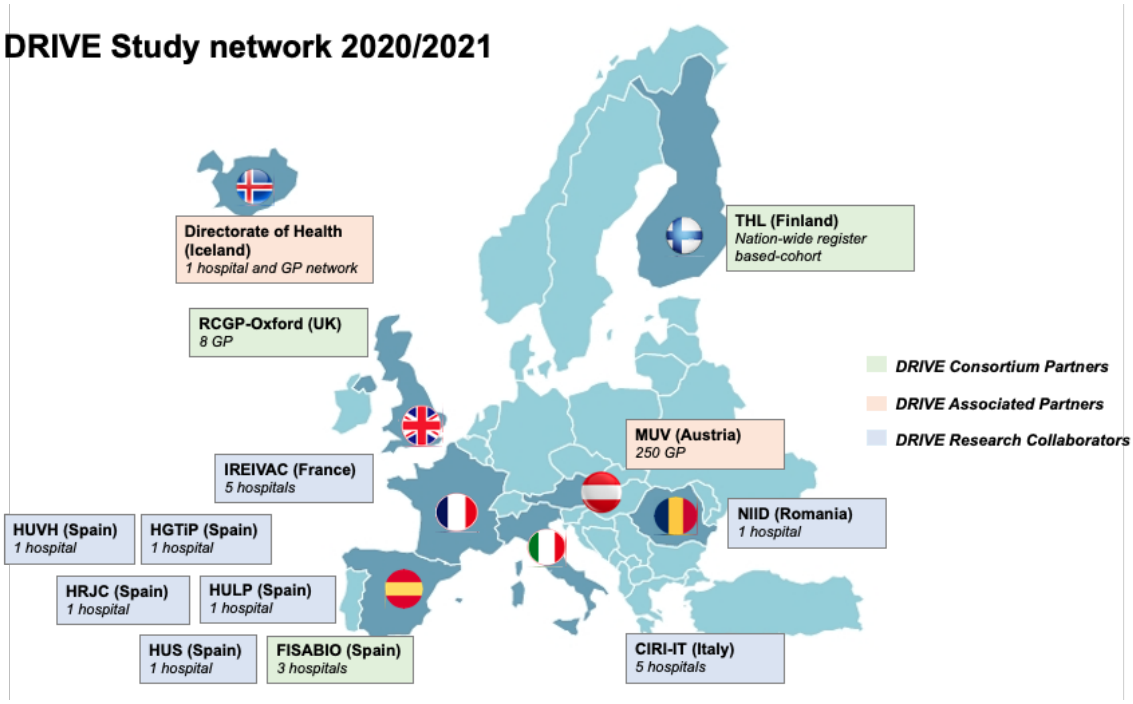


Figure E1. DRIVE Study network for season 2020-21. The DRIVE network is composed of (1) 13 independent study sites across Europe that conduct Test negative design (TND) prospective studies (which include a total of 20 hospitals and more than 250 GPs) and (2) a nation-wide register-based cohort study in Finland. Three

new TND study sites joined the DRIVE network (Iceland Directorate of Health joined as Associated Partners and 2 new study sites in Spain).

Objectives

The objectives were to estimate season (1) **overall**, **brand-specific** and (2) **type-specific** IVE against laboratory-confirmed influenza stratified by setting (primary care, hospital-based) and age group (6 months (m) – 17 years (y), 18-64y, ≥65y), by type of outcome: any laboratory-confirmed influenza, influenza A and A subtypes, influenza B and B lineage. An exploratory objective was to describe clinical signs and symptoms as well as laboratory features at hospital admission, among COVID-19 cases as compared to influenza cases.

Methods

TND studies

For the 2020-21 season, TND studies were conducted in primary care (3 networks) and hospital settings (7 individual hospitals and 3 hospital networks). Swabs were collected from subjects presenting with influenza-like illness (ILI, ECDC case definition) in the primary care setting and with severe acute respiratory infection (SARI) (IMOVE+ 2017/18 case definition) in the hospital setting (except for one hospital network where an alternative case definition was used). Swabs were tested for influenza using RT-PCR. The study population consisted of non-institutionalized subjects ≥6 months of age, with no contraindication for influenza vaccination, no prior positive influenza test in the same season, and with a swab taken < 8 days after ILI/SARI onset. In hospital settings, subjects hospitalized <48h prior to symptom onset or with symptom onset ≥48h after hospital admission were excluded. Vaccine brand was collected for vaccinated subjects. Due to the COVID-19 pandemic waves during the 2020/21 season and the lack of influenza circulation, only 5 (50%) of 10 hospital sites tested all SARI patients for influenza as influenza testing was limited e.g. to those testing negative for SARS-CoV-2 or was performed at clinician's discretion.

Register-based cohort

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. The case definition was laboratory-confirmed influenza, as registered in the National Infectious Diseases Register. Using the Care Register for Health Care, it was possible to identify laboratory-confirmed influenza cases who were hospitalized for any reason starting (or ongoing) on the day of laboratory confirmation. However, the Care Register for Health Care does not cover the full Finnish population, the percent covered is not known by THL.

Statistical methods

Data collected at the study sites was transferred to the DRIVE Research Server where it was analysed centrally by P95. The statistical analysis plan is registered at ENCEPP (EUPAS40875). Due to the historically low circulation of influenza, samples size calculations were performed (and described in the SAP), and IVE would

only be calculated if a pre-established minimum number of vaccinated influenza cases would be available at any single study site. In case this analysis is performed for a certain setting and age group all the other analyses applying to this population will also be performed.

Table E1. *Vaccination coverage among control subjects and control:case ratio observed in the DRIVE data from the 2019/2020 season and the number of vaccinated influenza cases required to perform the analyses in the 2020/21 season.*

	Primary care			**Hospital setting**		
	6m-17yr	**18-64yr**	**≥65yr**	**6m-17yr**	**18-64yr**	**≥65yr**
Observed coverage among the controls	13%	10%	61%	5%	23%	56%
Control:case ratio	0.8	1.7	4.3	1.1	2.2	4.5
Number of exposed influenza cases required for performing the analysis	7	5	9	7	6	9

IVE estimation: TND studies

Not applicable for the season 2020/2021 as the threshold for sample size defined in the SAP was not met (see Table E1 and E3).

IVE estimation: Register-based cohort study

For the register-based cohort, 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 *RR* denotes the relative ratio, comparing relative risk, 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.

Results

Overall, 7026 subjects from the TND sites (Table E2) and 857 thousand person-years from the register-based cohort (Table E3) were included in the analyses for the 2020/21 influenza season. The level of influenza circulation was historically low and remained at inter-seasonal levels, following measures to contain SARS-CoV-2 infection. Only a total of 5 influenza cases were reported from the TND studies (from Austria, Italy, Romania and Spain), and 25 in the Finnish register-based cohort study.

Table E2. *Number of subjects per study setting and age categories, TND studies, 2020/21*

TND	**6m-17y**		**18-64y**		**≥ 65y**	
Setting	**Cases (%PV)**	**Controls (%PV)**	**Cases (%PV)**	**Controls (%PV)**	**Cases (%PV)**	**Controls (%PV)**

PC	1 (0)	462 (11)	0 (0)	1547 (8)	0 (0)	251 (25)
Hosp	2 (50)	845 (5)	0 (0)	1801 (15)	2 (50)	2115 (42)

Hosp: hospital; m: months; PC: primary care; PV: proportion of vaccinated; y: years

Table E3. *Number of vaccinated and unvaccinated person-years and influenza cases by age category, register-based cohort study, 2020/21*

Register-based cohort Setting	**6m - 6y**				**≥65y**			
	Vac (py)	**Unvac (py)**	**Vac cases**	**Unvac cases**	**Vac (py)**	**Unvac (py)**	**Vac cases**	**Unvac cases**
Mixed	42,059	135,933	5	3	254,393	424,710	11	6
Hospital	42,059	135,933	2	1	254,393	424,710	3	1

m: months; py: person years; unvac: unvaccinated; vac: vaccinated; y: years

Influenza vaccines 2020/2021 season

Seven of the nine vaccines licensed in Europe the European Union (EU)/European Economic Area (EEA)/UK in 2020/21 were identified in the DRIVE dataset (Table E4).

Table E4. *Vaccine characteristics age indications of vaccines licensed and marketed in EU/EEA/UK, by vaccine brand, 2020/21*

Vaccine brand	**Manufacturer**	**Countries (Sites if >1 in the country) in which the vaccine brand was observed in the DRIVE dataset**		
		6m - 17y	18 - 64y	≥ 65y
Afluria Tetra	Seqirus	-	-	-
Agrippal	Seqirus	-	Spain [1]	Spain [1, 2]
Fluad	Seqirus	n/a	n/a	Austria, Italy, Spain [1-5], UK
Fluarix Tetra	GSK	-	Italy, Spain [3]	Iceland [6], Italy, Spain [3]
Flucelvax Tetra	Seqirus	-	Austria, Italy, Spain [1]	Austria, Italy, Spain [1]
Fluenz Tetra	AstraZeneca	Austria, Finland	-	-
Influvac Tetra	Abbott	-	Austria, France, Iceland [6,7], Spain [1], Romania	Austria, France, Iceland [6,7], Romania
TIV High Dose	Sanofi Pasteur	n/a	-	-
Vaxigrip Tetra	Sanofi Pasteur	Austria, Finland, Iceland [6,7], Romania	Austria, France, Iceland [6,7], Italy, Romania, Spain [4], UK	Austria, Finland, France, Iceland [6,7], Italy, Romania

[1] FISABIO, [2] LPUH , [3] HUVH, [4] SUH, [5] RJCUH, [6] EL Hospital, [7] EL GP,

-: vaccine licensed for age group but vaccine brand not observed in DRIVE dataset; GSK: GlaxoSmithKline; m: months; n/a: not applicable because vaccine not licensed for age group; QIV: quadrivalent influenza vaccine; TIV: trivalent influenza vaccine; UK: United Kingdom; y: years

Descriptive analyses

The highest proportion vaccinated was observed in the control group for the oldest age group (25% in primary care setting and 42% in hospital setting).), compared to adults 18-64y (8% and 15%) and children 6m-17y (11% and 5%). The most frequently reported vaccine brand in all age groups was Vaxigrip Tetra, followed by Fluenz Tetra among subjects 6m-17y, Influvac Tetra among subjects 18-64y and Fluad among subjects ≥65y. Overall an increase in proportion vaccinated with influenza in controls compared to the previous two seasons was observed. The proportion of vaccinated controls more than double at Austria MUV in the 6m-17y age group, it increased by 3-25 percentage points at 5 of 7 sites in the 18-64y age group, and it increased by 2-37 percentage points at 4 of 6 sites in the ≥65y age group.

IVE estimates: TND studies

The pre-established minimum number of vaccinated influenza cases was not met at any TND site, therefore IVE was not calculated.

IVE estimates: Register-based cohort study

IVE estimates against laboratory-confirmed influenza in any setting (Table E5) and in the hospital setting (Table E6) were computed, however due to the low number of influenza cases, estimates were imprecise.

Table E5. *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, mixed setting, 2020/21*

	Any influenza **VE [95%CI]**	**A** **VE [95%CI]**	**B** **VE [95%CI]**
Mixed setting			
≥ 65y			
Any vaccine	-122.3 [-524.5, 20.9]	-676.7 [-7793.1 ,23.6]	-41.9 [-353.3, 55.6]
Vaccine brand*			
Vaxigrip Tetra	-124 [-529.4, 20.3]	-683.7 [-7872.8, 23]	-43 [-356.6, 55.2]

*In Finland, Vaxigrip Tetra was the only influenza vaccine offered by the national vaccination programme for adults ≥65y in season 2020/21.

Table E6. *Confounder-adjusted influenza vaccine effectiveness of any vaccine and by vaccine brand against any influenza, Finland THL register-based cohort, hospital setting, 2020/21*

	Any influenza **VE [95%CI]**

Hospital setting	
≥ 65y	
Any vaccine	-521.7 [-7186.5, 46.9]
Vaxigrip Tetra	-527.9 [-7271, 46.5]

Discussion

The season was marked by the near-absence of influenza circulation in Europe. Consequently, no brand-specific or overall IVE estimates could be obtained for the TND studies, and IVE estimates were produced only for the Finnish cohort study. However, the latter could not be interpreted due to large confidence intervals although the magnitude of all IVE estimates suggested there may not have been any protection against any influenza and influenza A/B among patients ≥ 65y. Nevertheless, DRIVE has conducted a descriptive analysis of the data collected by the DRIVE study sites during the 2020/21 season.

Nine influenza vaccine brands were marketed in the EU/EEA/UK in the 2020/21 season. DRIVE dataset has captured 7 out of these 9 marketed brands, demonstrating DRIVE's ability to gather information on the majority of influenza vaccine brands across Europe. Overall, an increase in influenza vaccination coverage among controls compared to the previous two seasons was noted.

At the primary care sites, testing for SARS-CoV-2 and influenza in patients presenting with ILI was done simultaneously. However, modifications in influenza testing of SARI patients in the hospital setting were observed, and influenza testing of these patients was not complete.

Several **limitations** have been described for the DRIVE study during the 2020/21 season:

- There was little to no influenza circulation in Europe in the season 2020/21
- Consequently, IVE (including brand-specific IVE) could not be estimated from the TND studies. The IVE estimations for the Finnish register-based cohort study were very imprecise and therefore not informative.
- Similarly, the exploratory comparison of signs and symptoms between subjects with COVID-19 vs. influenza did not inform on any differences between the two diseases.

Due to the COVID-19 waves and the (near) absence of influenza circulation (making influenza an unlikely diagnosis), not all hospitalized SARI cases were tested for influenza, as influenza testing was limited e.g. to those testing negative for SARS-CoV-2 or at clinician's discretion. However, even if all SARI patients at those study sites had been tested, it is unlikely the threshold for performing IVE analyses for the TND studies would have been met this season.

On the other hand, it is important to also highlight the **strengths** of the DRIVE study:

- Despite the COVID-19 pandemic and the lack of influenza circulation in the 2020/21 season, the DRIVE network welcomed two additional hospitals in Spain, and onboarded the Iceland Directorate of Health

in the TND studies. DRIVE has created a solid study network despite the challenges and shift of attention to COVID-19.

- Seven of the nine licensed and marketed influenza vaccines in Europe were captured in the DRIVE dataset.
- In the Finnish register-based cohort study, in the 2020/21 season, it was possible to identify influenza cases that were admitted to hospital from the Care Register for Health Care, although this does not cover the full population and an unknown percentage of hospitalized influenza cases may therefore be missed. In previous seasons, it was not possible to differentiate influenza cases by setting. This will allow to estimate IVE against hospitalized laboratory-confirmed influenza in future seasons.
- 2x2 tables showing the number of cases and controls by vaccination status have been created for each exposure, thereby increasing the granularity of the reported results.
- The lessons learnt from DRIVE, especially during the past two years, highly marked by the COVID-19 pandemic, have greatly contributed to the development of a COVID-19 vaccine effectiveness platform: COVIDRIVE. COVIDRIVE has been established by several of the DRIVE consortium partners and will conduct COVID-19 vaccine effectiveness studies leveraging the infrastructure and study sites network built in DRIVE.

As Influenza and SARS-CoV-2 are expected to co-circulate in the season 2021/22, DRIVE will continue investigating influenza VE as well as to collect data on the COVID-19 impact and vaccination in participating countries.

7. Background

According to the European Centre for Disease Prevention and Control (ECDC), seasonal influenza affects 4–50 million European citizens each year and is associated with the death of 15,000–70,000 European citizens, exerting a significant human, economic and healthcare burden [1]. Together with hygiene, vaccination is considered the best action to protect against influenza, however, vaccines performance varies between influenza seasons. This performance is affected by the type of viruses strains actually circulating compared to the ones included in the vaccine, the technology of the vaccine and/or an individual's immune response (modulated by age and/or other individual characteristics and history). The above factors make the single estimation of an average influenza vaccine effectiveness a challenge.

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 [2].

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. Public health institutes can join DRIVE as associate partners, contributing data for any age group in the primary care or hospital setting. Other sites can join DRIVE through the annual call for tenders. For the 2020/21 call for tenders, it was decided to focus resources on sites that could collect data in the adult and older adult population in the hospital setting, in order to enhance data available for the strata containing the population most vulnerable for influenza and with the highest influenza vaccine coverage.

DRIVE's main objective in its first pilot season (2017/2018) was to establish and test the feasibility of the new multi-country platform using a limited number of sites (5 study sites from 4 different countries). Although the influenza season was severe, precise IVE estimates were not obtained partially due to the limited number of participating study sites and consequently, limited sample size. However, DRIVE succeeded in setting up the IVE study platform in a challenging timeframe, including the IT infrastructure, the governance for conducting IVE studies and key processes such as data collection, DRIVE generic protocol implementation across the different sites, Standard Operating Procedures (SOPs) and statistical analyses.

For the 2018/2019 season, the network expanded from 5 to 13 sites from 7 different European countries. In particular, five primary care-based Test-Negative Design (TND) studies, five hospital-based TND studies and one register-based cohort study were conducted to assess brand-specific seasons IVE by health care setting

and age group. DRIVE protocols were further harmonized, the Statistical Analysis Plan (SAP) was improved and age-and setting-stratified IVE estimates were calculated [3]. As a result, DRIVE obtained precise brand-specific estimations from the register-based cohort study in Finland.

Furthermore, a post hoc analysis of the 2018/2019 data allowed the simplification of the list of confounders that was considered on the following season 2019/2020 main analysis. The parsimonious set of confounders (sex, age, date of symptom onset) was shown to generate comparable results to a more extended set of confounders. This facilitated the participation of study sites which have limited data on confounders during the 2019/20 season, and avoided potential over-adjustment.

In 2019/2020, DRIVE continued its expansion and included 13 sites from 8 different European countries. For the 2019/2020 season, 4 primary care-based TND studies, 8 hospital-based TND studies and one register-based cohort study were conducted. 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. The COVID-19 pandemic in March 2020 and the subsequent lockdown measures interfered with and capped an already mild influenza circulation and impacted health seeking behavior and the data collection within DRIVE study sites [4]. Despite all these challenges, precise brand-specific estimates were obtained from the pooled TND studies in DRIVE, in addition to those from the population-based cohort study [5].

The study conducted in 2020/21 season builds upon tools and process developed, and lessons learned in the previous three seasons. Thus, the call for tenders for the 2020/21 season focused on the adults and older adult population in hospital setting to increase the efficiency and feasibility of the network. Due to the historically low influenza circulation in the 2020/21 season, a threshold regarding the minimum number of vaccinated influenza cases that should be present in a stratum at site-level as pre-requisite to calculate IVE was described in the 2020/21 SAP. This threshold was not met for the TND studies. This Study Report summarizes the methods used and the results obtained for the 2020/21 influenza season, as well as the challenges and proposed recommendations for next season. For further details regarding the characteristics of the study sites and the methods used are available in the SAP, posted on the WebANNEX. The SAP has been registered in the ENCEPP register, registration number EUPAS40875.

Additional results are available in the WebANNEX. The WebAnnex is accessible at: https://apps.p-95.com/drivewebapp/. The hierarchy of the tables and figures in the WebANNEX is given in the section named ANNEXES as the end of this report.

8. Objectives

8.1. Primary objective

To estimate seasonal overall, age-specific (6m-17 years (y), 18-64 y, ≥65 y) and brand-specific IVE against medically attended (primary care/hospital) laboratory-confirmed influenza, 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).

8.2. Secondary objectives

To estimate seasonal vaccine-type IVE against laboratory-confirmed influenza 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 were considered, if available in the DRIVE dataset:

- trivalent inactivated vaccine (TIV)
- high-dose TIV
- high-dose QIV
- adjuvanted TIV (aTIV)
- adjuvanted QIV (aQIV)
- live attenuated quadrivalent egg-based vaccine (LAIV)
- quadrivalent inactivated egg-based vaccine (QIVe)
- quadrivalent inactivated cell-based vaccine (QIVc)
- quadrivalent inactivated recombinant vaccine (QIVr)

8.3. Exploratory objective

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

9. Methods

9.1. Study sites

For the 2020/21 season, data is available from three primary care-based TND studies, ten hospital-based TND studies (Table 1), and one register-based cohort. Three new TND study sites joined the study platform (two additional hospitals in Spain, and the Iceland Directorate of Health, contributing with hospital and primary care data. The hospital-based TND study from Romania (NIID) was conducted in a designated COVID-19 only hospital during the 2020/21; had there been any IVE analyses this site would only have been included in the sensitivity analysis only. The site has been included in the descriptive analyses. For details on the study sites see the SAP section 4.1 (WebANNEX – SAP). Finally, at the start of the season Italy ISS and Hospital Universitari de Girona Doctor Josep Trueta (TGUH) in Spain were expected to take part in the TND studies, however finally they did not (see section 9.626). Following difficulties in obtaining ethics approval in the 2019/20 season, Luxembourg's Laboratoire Nationale de Santé was no longer an associated partner of DRIVE in the 2020/21 season, and Jorvi Hospital (part of Helsinki University Hospital) in Finland did not reapply to the call for tender.

Table 1. Primary care and hospital sites where TND studies were conducted, 2020/21

Country	Site name	Number of primary care physicians or hospitals where subjects are identified	New site for season 2020/21
Primary care			
Austria	Medical University Vienna (MUV)	250	No
Iceland	Directorate of Health - Embætti landlæknis (EL GP)	TBC*	Yes
UK	Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) & University of Oxford	8	No
Hospital			
France	Institut National de la Santé et de la Recherche Médicale (INSERM)	5	No
Iceland	Directorate of Health - Embætti landlæknis (EL HOSP). Landspitali University Hospital.	1	Yes

Country	Site name	Number of primary care physicians or hospitals where subjects are identified	New site for season 2020/21
Italy	Italian Hospital Network coordinated by Centro Interuniversitario di Ricerca sull'Influenza e sulle altre infezioni trasmissibili Italy (CIRI-BIVE)	5	No
Romania	National Institute for Infectious Disease "Prof. Dr. Matei Balș" (NIID), Bucharest	1**	No
Spain	Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO)	3	No
Spain	Hospital Universitario Germans Trias i Pujol (GTPUH), Badalona	1	No
Spain	Hospital Universitario La Paz (LPUH), Madrid	1	No
Spain	Hospital Universitario Rey Juan Carlos (RJCUH), Móstoles	1	Yes
Spain	Hospital Universitario de Salamanca (SUH), Salamanca	1	Yes
Spain	Vall d'Hebron University Hospital (HUVH), Barcelona	1	No
Register-based cohort			
Finland	The Finnish Institute for Health and Welfare (THL)	All	No

*All samples sent to national reference laboratory. **COVID-19 hospital

9.2. Study design

The studies are based on the core generic protocols for TND studies and the Finnish register-based cohort study. 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).

9.2.1. Test-negative design studies

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 regarding the case definition are described in the SAP section 7.4 (WebANNEX - SAP).

Due to the COVID-19 pandemic waves during the 2020/21 season and the lack of influenza circulation, not all hospital sites tested all SARI patients for influenza (Table 2). In CIRI-IT BIVE, generally SARI patients were tested for influenza and SARS-CoV-2 simultaneously, however some differences existed between the hospitals in the network. In France INSERM, initially all SARI patients were tested for both influenza and SARS-CoV-2, however later in the season only SARS-CoV-2 negative patients were tested for influenza. Similarly, in Spain RJCUH, SARI patients were only tested for influenza if they tested negative for SARS-CoV-2 or at clinician's discretion. In Spain LPUH and GTPUH, SARI patients were tested at clinician's discretion, and additionally the microbiology department's influenza surveillance in hospitalized SARI patients was included. In Romania NIID, the SARI patients tested were either positive for SARS-CoV-2 (as it was a COVID-19 only hospital) or, rarely, tested for SARS-CoV-2 and influenza at the same time.

Table 2. Overview of influenza and COVID-19 sampling strategies used in TND studies, 2020/21

Site	Same swab used for COVID-19 and influenza test	Influenza testing	Matched controls
Primary care			
Austria MUV	Yes		No
Iceland EL GP	Yes		No
UK RCGP RSC	Yes		No
Hospital			
France INSERM	Initially yes; later no	SARI who were SARS-CoV-2 negative	No
Iceland EL HOSP	Yes		No
Italy CIRI-BIVE	Generally yes		No
Romania NIID	Generally no	Nearly all SARI were known SARS-CoV-2 positive (as it was a COVID-19 hospital)	No
Spain FISABIO	Yes		No
Spain GTPUH	No	At clinician's discretion; microbiology dept's influenza surveillance in hospitalized SARI	No
Spain HUVH	Yes		No

Spain LPUH	No	At clinician's discretion; microbiology dept's influenza surveillance in hospitalized SARI	No
Spain RJCUH		SARI who were SARS-CoV-2 negative; or at clinician's discretion	No
Spain SUH	Yes		Planned as per SAP, but finally not done.

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 2020/21 season, being institutionalized, and unwillingness to participate or to give consent., if applicable. 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. Subjects were tested for influenza and for SARS-CoV-2. 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 2020/21 season. The way vaccination status, vaccine brand and vaccination data were ascertained at each site is described in the SAP section 10.2 (WebANNEX - SAP).

The start of the study period for IVE analyses for the DRIVE studies is normally 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 April 30th 2021, whichever occurred first. However, due the near-absence of influenza and lack of influenza IVE analyses, the study period definition was not applied this season, and study period was not taken into account for the descriptive analyses. The dates of the first and last swabs at site level is shown in Table 3.

Table 3. Dates of first and last swab, by site, TND studies, 2020/21

Site	First swab	Last swab
Primary care		
Austria MUV	2-10-2020	26-3-2021
Iceland EL GP	28-9-2020	16-5-2021
UK RCGP RSC	18-10-2020	11-3-2021
Hospital		
France INSERM	23-12-2020	1-5-2021
Iceland EL HOSP	29-9-2020	16-5-2021

Site	First swab	Last swab
Italy CIRI-BIVE	13-11-2020	30-4-2021
Romania NIID	3-11-2020	30-4-2021
Spain FISABIO	12-12-2020	25-4-2021
Spain GTPUH	3-11-2020	30-4-2021
Spain HUVH	8-12-2020	22-4-2021
Spain LPUH	18-12-2020	30-4-2021
Spain RJCUH	9-12-2020	1-3-2021
Spain SUH	16-11-2020	26-4-2021

9.2.2. Register-based cohort study

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. Both primary care and hospital settings are covered. Hospitalization was defined as ≥24 hour stay in hospital and/or emergency room care for any reason starting or ongoing on the day of laboratory confirmation. The Care Register for Health Care does not cover the full Finnish population, the percent covered is not known by THL. Therefore, results are presented for 'mixed' and for 'hospital' setting. Subjects with presumably incomplete vaccination records in 2020/21 and 2019/20 were excluded[1]; as were FinFluHD trial participants. For the hospital setting, subjects with presumably incomplete hospital recorded in 2020/21 were also excluded. The study period was defined a priori from week 40/2020 to April 30th 2021.

9.3. Statistical methods

The statistical methods are briefly described below. Further details are available from the SAP section 15 (WebANNEX - SAP). All data management and statistical analyses were conducted in R version 4.0.3. 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 the WebANNEX.

9.3.1. Test-negative design studies

For the TND studies, individual-level data were transferred from the study sites to the GDPR-compliant DRIVE Research Server.

[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.

Sample size considerations were not foreseen at the time of protocol writing. As the flu activity was unusually low in the 2020/21 season, a threshold regarding the minimum number of exposed influenza cases required at site-level to perform the IVE analyses was defined (Table 4; see also section 14.2 of the 2020/21 SAP (WebANNEX - SAP)). This number was not met for any group or setting, consequently IVE was not estimated from the TND studies.

Table 4. Vaccination coverage among control subjects and control:case ratio observed in the DRIVE data from the 2019/2020 season and the number of vaccinated influenza cases required to perform the analyses in the 2020/21 season.

	Primary care			**Hospital setting**		
	6m-17yr	**18-64yr**	**≥65yr**	**6m-17yr**	**18-64yr**	**≥65yr**
Observed coverage among the controls	13%	10%	61%	5%	23%	56%
Control:case ratio	0.8	1.7	4.3	1.1	2.2	4.5
Number of exposed influenza cases required for performing the analysis	7	5	9	7	6	9

Descriptive analyses of ILI and SARI subjects were performed, as described in the SAP section 15 (WebANNEX - SAP). In addition, demographic and clinical signs and symptoms as well as laboratory features, around the point of admission, are described among hospitalized COVID-19 cases as compared to influenza cases, if any.

9.3.2. Register-based cohort study

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 is person-years. Site-specific semi-crude (adjusted only for calendar time) and confounder-adjusted IVE (adjusted for calendar week, age and sex) 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.

Three sensitivity analysis were performed. In the first sensitivity analysis, IVE was additionally adjusted for the confounder “at least one chronic condition”. In the second and third sensitivity analysis, IVE was additionally adjusted for the confounder “number of GP visits in the previous year” or “number of hospitalizations in the previous year”.

9.4. 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.

9.5. Ethics

Each local study was approved by national, regional or institutional ethics committees, as appropriate. Ethics submission process by sites participating did not encounter any particular issue regarding approval and submission and approval timings and all the studies were approved without the need of revision of the protocols, therefore the ethics committee clearance was given in due time for the DRIVE project data collection and analysis.

Overall, ethics committee clearance was required for all sites performing DRIVE IVE studies, with the exception of THL (Finland) and FISABIO (Spain). For the Finnish register-based cohort study, an ethical evaluation was not mandatory, however an evaluation from an institutional ethical review group was requested in 2016. On the other hand, FISABIO obtained approval for their influenza surveillance and VE network in 2009; and in 2011 updated and approved the protocol and since then only an annual renewal request is needed.

In several study sites, namely, RCGP RSC (UK), CIRI-BIVE (Italy), MUV (Austria), GTPUH (Spain), and HUVH (Spain), IVE studies were nested into the national or regional influenza surveillance systems. In the rest of study sites, studies were not nested into the national influenza surveillance system. Moreover, secondary data from pre-existing national routine administrative registers were used in THL. Written informed consent was obtained in two-thirds of cases; in the remaining third of study sites (i.e. THL, MUV, GTPUH, HVUH) informed consent was not needed, as the DRIVE study is nested into the national/regional influenza surveillance systems.

9.6. 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 protocol (not described in the SAP) took place:

- For RCGP RSC and EL, the date of symptom onset was not available, therefore the exclusion criterion “had the respiratory specimen taken ≥ 8 days after SARI onset” was not applied.

The following deviations from the SAP took place:

- For RCGP RSC and EL, the date of symptom onset was not available. For these two sites, swab date was used instead of date of symptom onset for all figures and analyses requiring symptom onset date.

- For 10 vaccinated subjects from INSERM and 78 vaccinated subjects from MUV, the month and year of vaccination were available but the day was not. For these subjects, the day of vaccination was imputed as the 1st or 15th of the month.
- Not all SARI patients in the hospital setting were tested for influenza, due to the lack of influenza circulation and the large number of COVID-19 patients. See also section 9.2.1.
- Hospital Universitari de Girona Doctor Josep Trueta (TGUH) in Girona, which was to form one DRIVE site together with HUVH, and the Italian Istituto Superiore di Sanità (ISS) did not provide data to DRIVE for the 2020/21 season. TGUH could not join for due to a legal issue in the contract between the two hospitals, which has been resolved for the 2021/22 season. ISS did not participate due to competing priorities as a result of the COVID-19 pandemic, however they are expected to participate again in the 2021/22 season.

10. Results

10.1. Influenza vaccines in Europe, 2020/21

10.1.1. 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). Due to the COVID-19 pandemic, several groups for whom influenza vaccination was not previously actively recommended have been include in the 2020/21 influenza recommendations, such as all children and adults 60-65y in Italy, adults aged 50-64y in England and adults 60-64y in Catalonia, Madrid and Salamanca. In Austria the recommendations did not change however the influenza vaccine was offered for free for the first time to children 6m-14y, adults ≥65y and to all inhabitants of Vienna.

10.1.2. Vaccine indications

Nine influenza vaccines were licensed and marketed in the EU/European Economic Area (EEA)/UK for the season 2020/21. In addition, three vaccines were exceptionally supplied under the United States license for the 2020/21 campaigns in the context of the COVID-19 epidemic. These were Fluad Tetra in Italy (Lombardy), Fluzone High Dose Quadrivalent in Austria, France and Italy, and Flublok Quadrivalent in the UK. These vaccines arrived later in the season (between October and December 2020).
Details on vaccine characteristics, the approved age indication and, for each age group, the sites that reported the vaccine brand in the 2020/21 studies are listed in Table 5, 7 of the 9 licensed and marketed vaccines were reported in the DRIVE dataset.

Table 5. Vaccine characteristics and age indications by vaccine brand, 2020/21

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

Vaccine brand	Manufacturer	Valency	Inactivated or live-attenuated	Non-adjuvanted or adjuvanted	Egg- or cell-based, or recombinant	Standard or high dose	Approved age indication	Countries (Sites if >1 in the country) in which the vaccine brand was observed in the DRIVE dataset		
								6m - 17y	18 - 64y	≥ 65y
									Romania, Spain [4], UK	
Vaccines exceptionally supplied under US license										
Fluad Tetra	Seqirus	4	Inactivated	Adjuvanted	Egg	Standard	≥65y	-	-	-
Flubok Quadrivalent	Sanofi Pasteur	4	Inactivated	Non-adjuvanted	Recombinant	Standard	≥18y	-	-	-
Fluzone High Dose Quadrivalent	Sanofi Pasteur	4	Inactivated	Non-adjuvanted	Egg	High	≥65y	-	-	Austria, France, Italy

[1] FISABIO, [2] LPUH , [3] HUVH, [4] SUH, [5] RJCUH, [6] EL HOSP, [7] EL GP,

-: vaccine licensed for age group but not reported in DRIVE dataset; GSK: GlaxoSmithKline; m: months; n/a: not applicable as vaccine is not licensed for age group; QIV: quadrivalent influenza vaccine; TIV: trivalent influenza vaccine; UK: United Kingdom; y: years

10.1.3. Composition of influenza vaccines

The strains contained in the 2020/21 Northern hemisphere egg-based and cell-based vaccines are described below [7]:

Egg-based vaccines:

- an A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09-like virus;
- an A/Hong Kong/2671/2019 (H3N2)-like virus;
- a B/Washington/02/2019 (B/Victoria lineage)-like virus; and
- a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage) (quadrivalent vaccines only)

Cell-based vaccines:

- an A/Hawaii/70/2019 (H1N1)pdm09-like virus;
- an A/Hong Kong/45/2019 (H3N2)-like virus;
- a B/Washington/02/2019 (B/Victoria lineage)-like virus; and
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus (quadrivalent vaccines only)

10.2. Influenza epidemiology in Europe, 2020/21

The non-pharmaceutical interventions put in place to contain COVID-19 transmission, such as face masks, social distancing and hand hygiene practices, were still highly efficacious in preventing influenza. In the European Region, the European Surveillance System (TESSy) reported a 99.5% drop in influenza detections compared to the previous influenza season and influenza activity remained at inter-seasonal levels [8].

10.2.1. Influenza epidemiology in Europe and vaccine match

As of week 20/2021 of the only 909 influenza detections across the WHO European Region reported to TESSy, The European Surveillance System, 52% were type A viruses and 48% were type B viruses. Virus A(H3N2) and virus A(H1N1)pdm09 were approximately equally represented. Only 16 B viruses were ascribed to a lineage, with 13 (81.3%) being B/Victoria lineage and 3 (18.7%) being B/Yamagata. The WHO had recommended the use of quadrivalent vaccines in the 2020-2021 northern hemisphere influenza season, and the recommended composition of the trivalent influenza vaccines included the B/Victoria lineage-like virus, therefore no mismatch was documented for this season for this strain.

10.2.2. Influenza epidemiology by site

In total, 5 influenza cases were reported in the DRIVE dataset in the TND studies. Table 6

Table 6 describes the number of influenza cases by type and subtype for each site.

Table 6. Influenza epidemiology and influenza cases in the DRIVE dataset, 2020/21

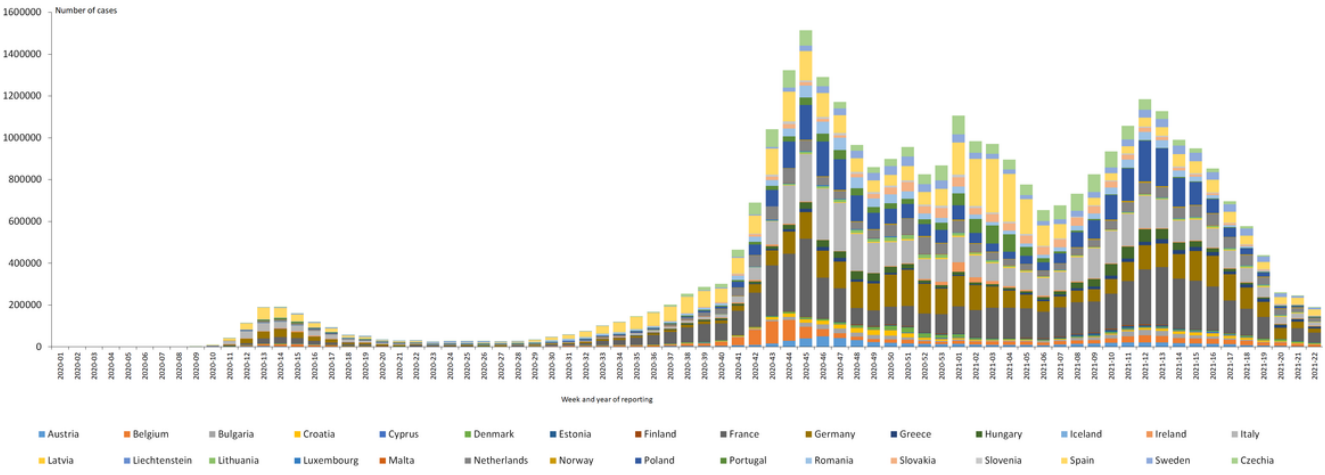
			Influenza type/subtype					
	Number of tested samples for influenza*	**All influenza cases**	**A n (% of total)**	**A(H1N1)pmd09 n (% of A with known subtype)**	**A(H3N2) n (% of A with known subtype)**	**B n (% of total)**	**B/Victoria (%of B with known lineage)**	**B/Yamagata (%of B with known lineage)**
Austria								
MUV	1449	1	0 (0)	-	-	1 (100)	1 (100)	0 (0)
France								
INSERM	511	0	-	-	-	-	-	-
Iceland								
EL GP	741	0	-	-	-	-	-	-
EL HOSP	2329	0	-	-	-	-	-	-
Italy								
CIRI BIVE	1349	2	1 (50)	1 (100)	0 (0)	1 (50)	NA	NA
Romania								
NIID	486	1	0 (0)	0	0	1 (100)	0	0
Spain								
FISABIO	81	1	1 (100)	0	0	0 (0)	-	-
GTPUH	113	0	-	-	-	-	-	-
HURJC	5	0	-	-	-	-	-	-
HUVH	39	0	-	-	-	-	-	-
LPUH	26	0	-	-	-	-	-	-
SUH	116	0	-	-	-	-	-	-
UK								
RCGP RSC	21	0	-	-	-	-	-	-

NA: not available; *i.e. number of subjects retained for analysis

10.2.3. COVID-19 in Europe

COVID-19, a disease caused by the SARS-CoV-2, was first identified in China in December 2019. By January 2020, isolated cases had appeared in some EU member states. On March 11th, 2020, the World Health Organization finally declared COVID-19 a global pandemic. The first pandemic wave in Europe was reported in March and April 2020. In the European region, the second pandemic wave peaked in week 45/2020, when the 14-day case notification rate for the EU/EEA and the UK, based on data collected by ECDC from official national sources from 31 countries, was 602.9 (country range: 49.5–1506.3) per 100,000 population [9]; another peak in COVID-19 incidence was observed between the end of 2020 and the beginning of 2021, when the 14-day case notification rate for the EU/EEA was 425 (country range: 48–1 513) per 100 000 population. The 4th pandemic wave peaked in the last week of March, week 12/2021, when 489 cases per 100,000 were notified (country range: 27-1,364) [10]. In Figure 1 the trend of COVID-19 laboratory confirmed cases by country is reported; it is noted that numbers are much affected by testing capacity and testing indications . As of June 10, 2021, EU/EEA countries have reported more than 32,000,000 COVID-19 cases and 725,000 deaths (representing 19% of all cases and 4.9% of all deaths reported worldwide) [11]. COVID-19 epidemiology by site is available in the local study reports.

Figure 1. Trend of the distribution of COVID-19 laboratory confirmed cases by country, 2020/21



Source: ECDC 2021 in accordance with the applied testing strategies and diagnostic capacities [12]

10.3. Descriptive analysis

For the TND studies, 1 case and 2260 controls were retained in the primary care setting and 4 cases and 4761 controls in the hospital setting (Table 7). 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 296,452 vaccinated and 560,643 unvaccinated person-years were received and included in the analysis (Table 8).

Table 7. Number of subjects per study setting and age categories, TND studies, 2020/21

TND	6m-17y		18-64y		≥ 65y	
Setting	Cases (%PV)	Controls (%PV)	Cases (%PV)	Controls (%PV)	Cases (%PV)	Controls (%PV)
PC	1 (0)	462 (11)	0 (0)	1547 (8)	0 (0)	251 (25)
Hosp	2 (50)	845 (5)	0 (0)	1801 (15)	2 (50)	2115 (42)

Hosp: hospital; m: months; PC: primary care; PV: proportion of vaccinated; y: years

Table 8. Number of vaccinated and unvaccinated person-years and influenza cases by age category, register-based cohort study, 2020/21

Register-based cohort Setting	6m - 6y				≥65y			
	Vac (py)	Unvac (py)	Vac cases	Unvac cases	Vac (py)	Unvac (py)	Vac cases	Unvac cases
Mixed	42,059	135,933	5	3	254,393	424,710	11	6
Hospital	42,059	135,933	2	1	254,393	424,710	3	1

m: months; py: person years; unvac: unvaccinated; vac: vaccinated; y: years

10.3.1. Test-negative design studies

For the combined data of the primary care TND studies, 1 case and 462 controls were included in the primary analysis for children 6m-17y, 0 vs. 1547 for adults 18-64y, and 0 vs. 251 for those aged ≥65y. For the combined data of the hospital TND studies, 2 cases and 845 controls were included in the primary analysis for children 6m-17y, 0 vs. 1801 for adults 18-64y, and 2 vs. 2115 for those aged ≥65y (Table 7). The attrition diagrams by

setting are shown in

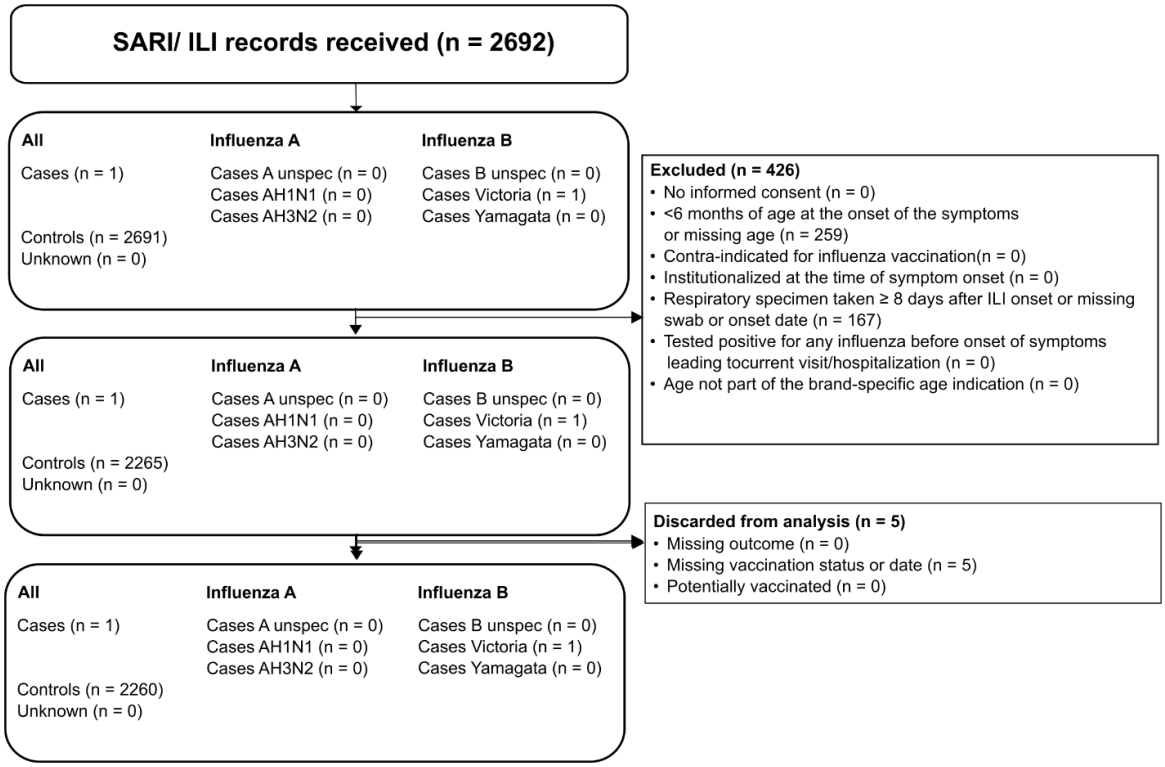


Figure 2 and

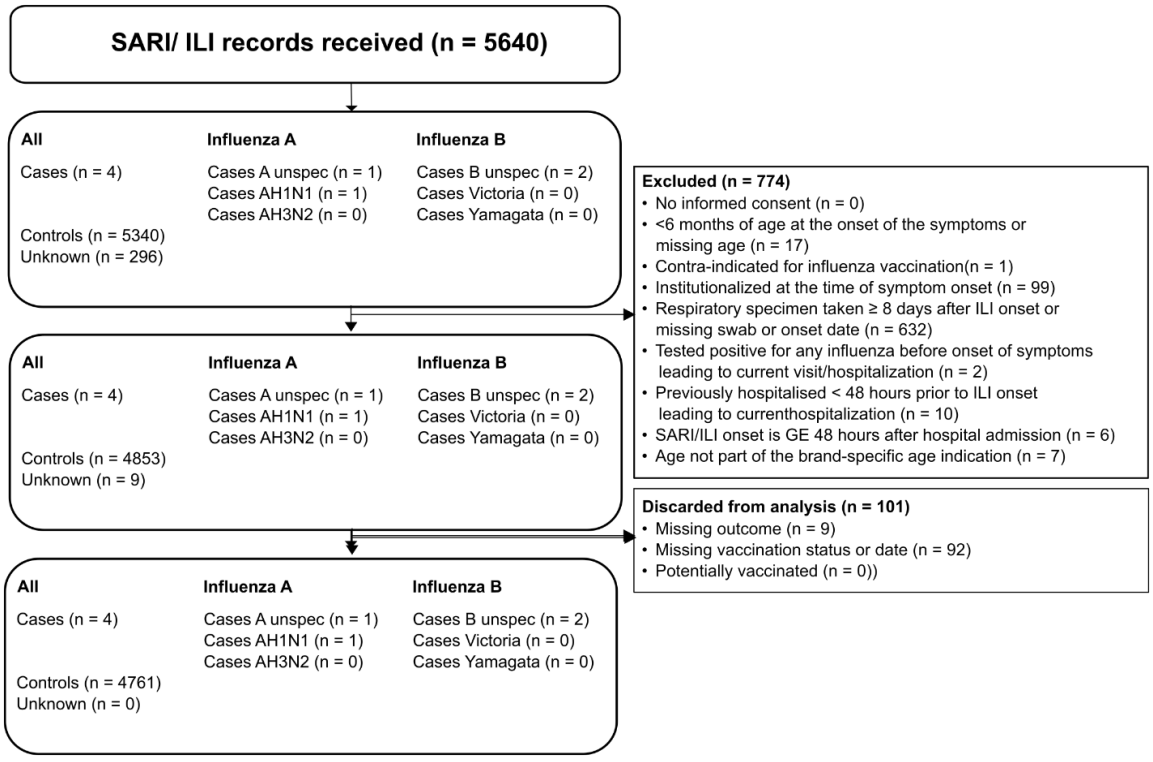


Figure 3. Attrition diagrams by site are available in the Data Quality Reports in the WebANNEX. At sites where at least one subject was excluded at the time of analysis because the swab was taken >7 days after symptom onset, the proportion of subjects excluded for this reason was generally higher than in the 2019/20 season

(Figure 4). The 2x2 tables showing the number of cases and controls by vaccination status are shown in Table 9 and Table 10. Site-specific 2x2 tables for each exposure/age group combination are presented in the WebANNEX.

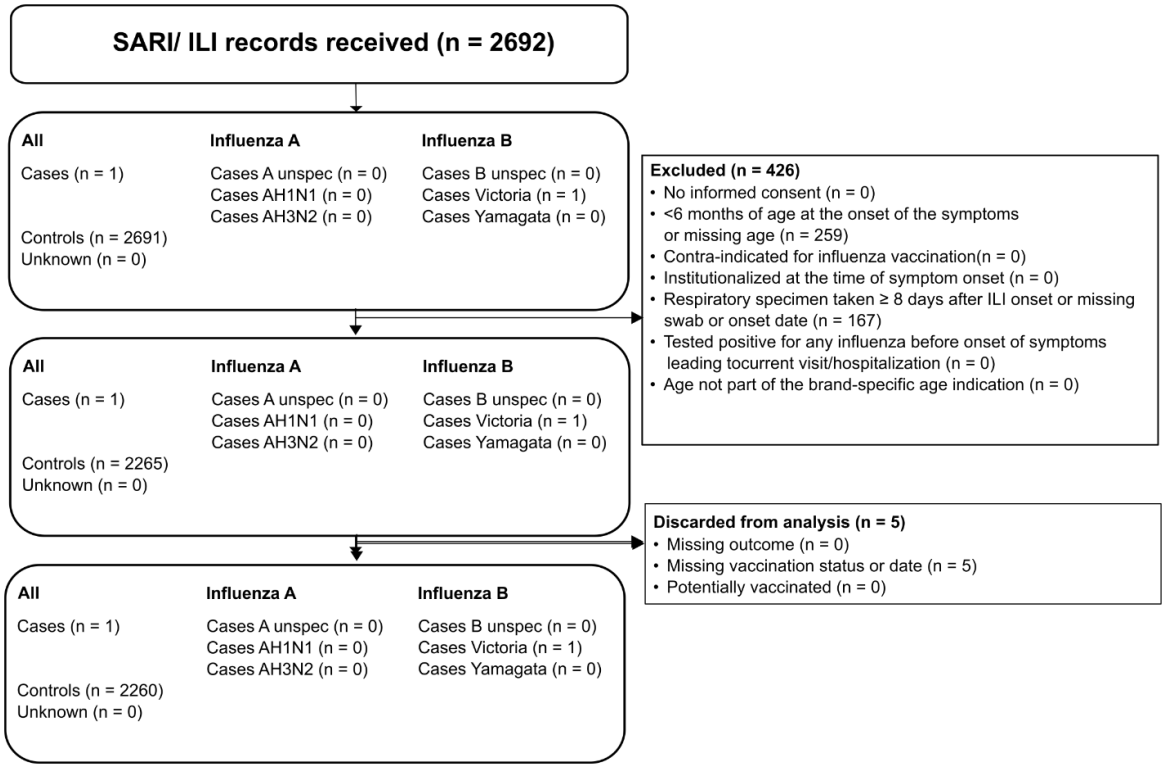


Figure 2. Attrition diagram primary care TND studies, pooled analysis, 2020/21. The 259 samples excluded due to age <6 months or missing age were all subjects from Austria MUV excluded because of missing data of birth.

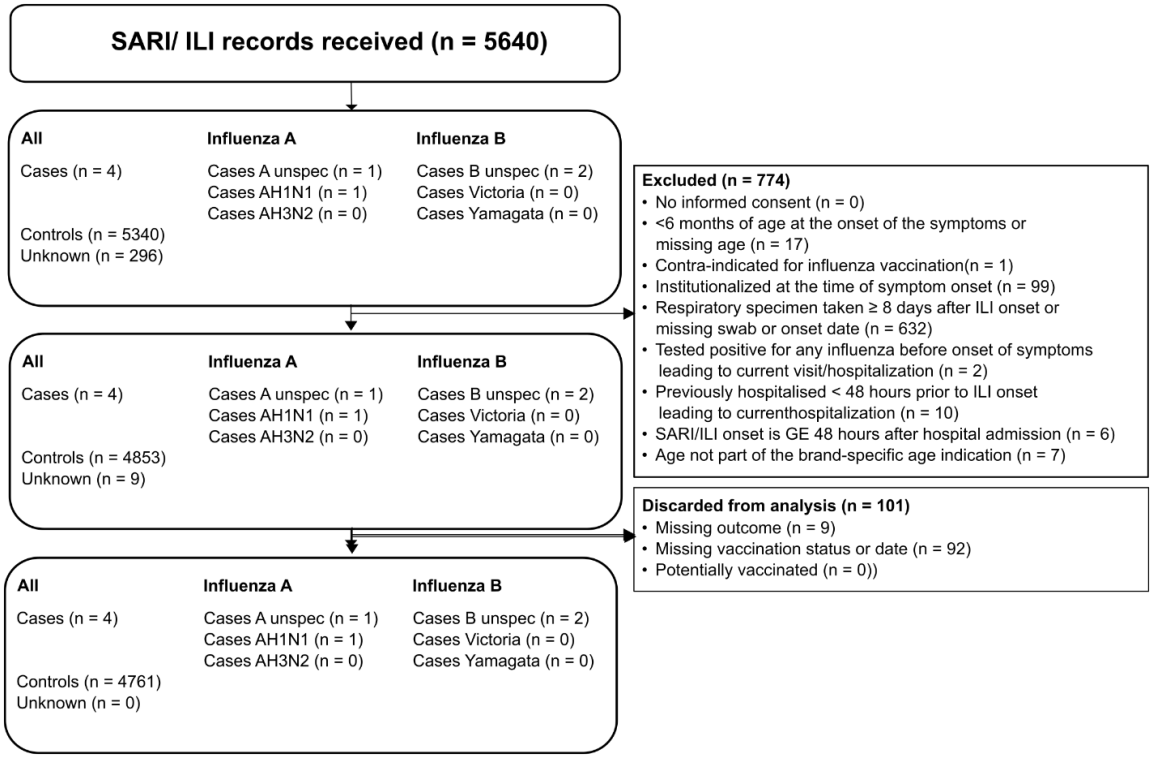


Figure 3. Attrition diagram hospital TND studies, pooled analysis, 2020/21

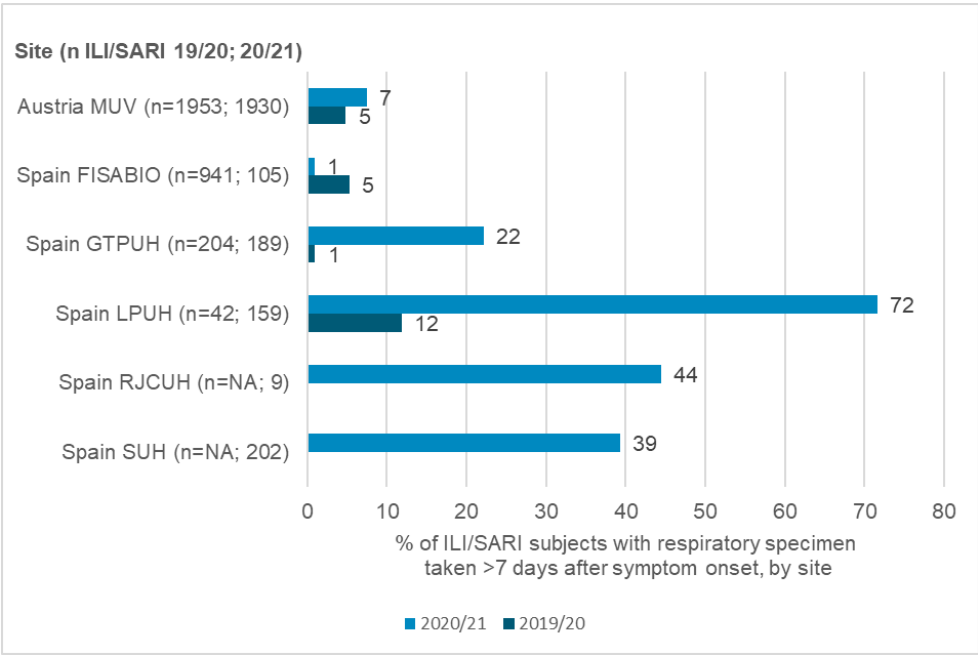


Figure 4. Percentage of ILI/SARI subjects excluded due to the respiratory specimen being taken >7 days after symptom onset, among sites with at least one subjects excluded for this reason at the time of analysis.

Table 9. Number of cases and controls by exposure status, primary care TND studies, 2020/21.

Analysis	Age group	All, n	Cases	Controls	Vaccinated cases, n (% among cases)	Non-vaccinated cases, n (% among cases)	Vaccinated controls, n (% among controls)	Non-vaccinated controls, n (% among controls)
Any vaccine								
	6m-17y	463	1	462	0 (0)	1 (100)	51 (11)	411 (89)
	18-64y	1547	0	1547	0 (0)	0 (0)	129 (8)	1418 (92)
	≥65y	251	0	251	0 (0)	0 (0)	64 (25)	187 (75)
Vaccine brand								
Fluad								
	≥65y	197	0	197	0 (0)	0 (0)	10 (5)	187 (95)
Flucelvax Tetra								
	18-64y	1429	0	1429	0 (0)	0 (0)	11 (1)	1418 (99)
	≥65y	188	0	188	0 (0)	0 (0)	1 (1)	187 (99)
Fluenz Tetra								
	6m-17y	430	1	429	0 (0)	1 (100)	18 (4)	411 (96)
Fluzone High Dose Quadrivalent								
	≥65y	195	0	195	0 (0)	0 (0)	8 (4)	187 (96)
Influvac Tetra								
	18-64y	1454	0	1454	0 (0)	0 (0)	36 (2)	1418 (98)
	≥65y	201	0	201	0 (0)	0 (0)	14 (7)	187 (93)
Vaxigrip Tetra								
	6m-17y	444	1	443	0 (0)	1 (100)	32 (7)	411 (93)
	18-64y	1499	0	1499	0 (0)	0 (0)	81 (5)	1418 (95)
	≥65y	218	0	218	0 (0)	0 (0)	31 (14)	187 (86)

Table 10. Number of cases and controls by exposure status, hospital TND studies, 2020/21

Analysis	Age group	All, n	Cases	Controls	Vaccinated cases, n (% among cases)	Non-vaccinated cases, n (% among cases)	Vaccinated controls, n (% among controls)	Non-vaccinated controls, n (% among controls)
Any vaccine								
	6m-17y	847	2	845	1 (50)	1 (50)	44 (5)	801 (95)
	18-64y	1801	0	1801	0 (0)	0 (0)	267 (15)	1534 (85)
	≥65y	2117	2	2115	1 (50)	1 (50)	898 (42)	1217 (58)
Vaccine brand								
Fluad								
	≥65y	1553	1	1552	0 (0)	1 (100)	335 (22)	1217 (78)
Fluarix Tetra								
	18-64y	1550	0	1550	0 (0)	0 (0)	16 (1)	1534 (99)
	≥65y	1226	2	1224	1 (50)	1 (50)	7 (1)	1217 (99)
Flucelvax Tetra								
	18-64y	1555	0	1555	0 (0)	0 (0)	21 (1)	1534 (99)
Influvac Tetra								
	18-64y	1560	0	1560	0 (0)	0 (0)	26 (2)	1534 (98)
	≥65y	1305	1	1304	0 (0)	1 (0)	87 (7)	1217 (93)
Vaxigrip Tetra								
	6m-17y	843	2	841	1 (50)	1 (50)	40 (5)	801 (95)
	18-64y	1721	0	1721	0 (0)	0 (0)	187 (11)	1534 (89)
	≥65y	1649	1	1648	0 (0)	1 (100)	431 (26)	1217 (74)

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 5. The percentage of subjects that tested positive for influenza over time is shown in Figure 6. Site-specific figures are shown in the WebANNEX.

The number of vaccinated subjects among enrolled subjects and the distribution of vaccine brands is shown in Figure 7. The highest proportion vaccinated was observed in the oldest age group (25% in primary care setting and 42% in hospital setting) compared to adults 18-64y (8% and 15%) and children 6m-17y (11% and 5%). The most frequently reported vaccine brands in all age groups was Vaxigrip Tetra, followed by Fluenz Tetra Fluenz Tetra among subjects 6m-17y, Influvac Tetra among subjects 18-64y and Fluad among subjects ≥65y. The most frequently reported vaccine brand

The proportion of vaccinatedcontrols from 2018/19 to 2020/21 by site is shown in Figure 8 to Figue 10. Only controls from January onwards (i.e. after the main vaccination campaigns) are included in this analysis, and only proportions with a denominator of at least 15 controls are shown. In the 6m-17y age group, the proportion of vaccinatedcontrols doubled from 10% in 2019/20 to 21% in 2020/21 at Austria MUV. In the 18-64y age group, the proportion of vaccinated controls increased by 3-25 percentage points at Austria MUV, Italy CIRI-BIVE, Spain FISABIO, GTPUH, and HUVH; and decreased at France INSERM, and Romania NIID. In the ≥65y age group, the proportion of vaccinated controlswas 2-37 percentage points higher than in the previous two seasons at Austria MUV, Italy CIRI-BIVE, Spain FISABIO and LPUH, and lower at France INSERM; whereas it was unchanged at Romania NIID. Proportion vaccinated by brand, by site and by setting, is shown in the WebANNEX.

Site-specific and pooled population characteristics for each exposure/age group combination by outcome and by case-control and vaccination status are presented in the WebANNEX.

All primary care TND studies used an unmatched design for data collection. At the hospital site Spain SUH, the data collection followed a matched 1:2 or 1:3 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 65-74y and 75+y). All other hospital studies used an unmatched design.

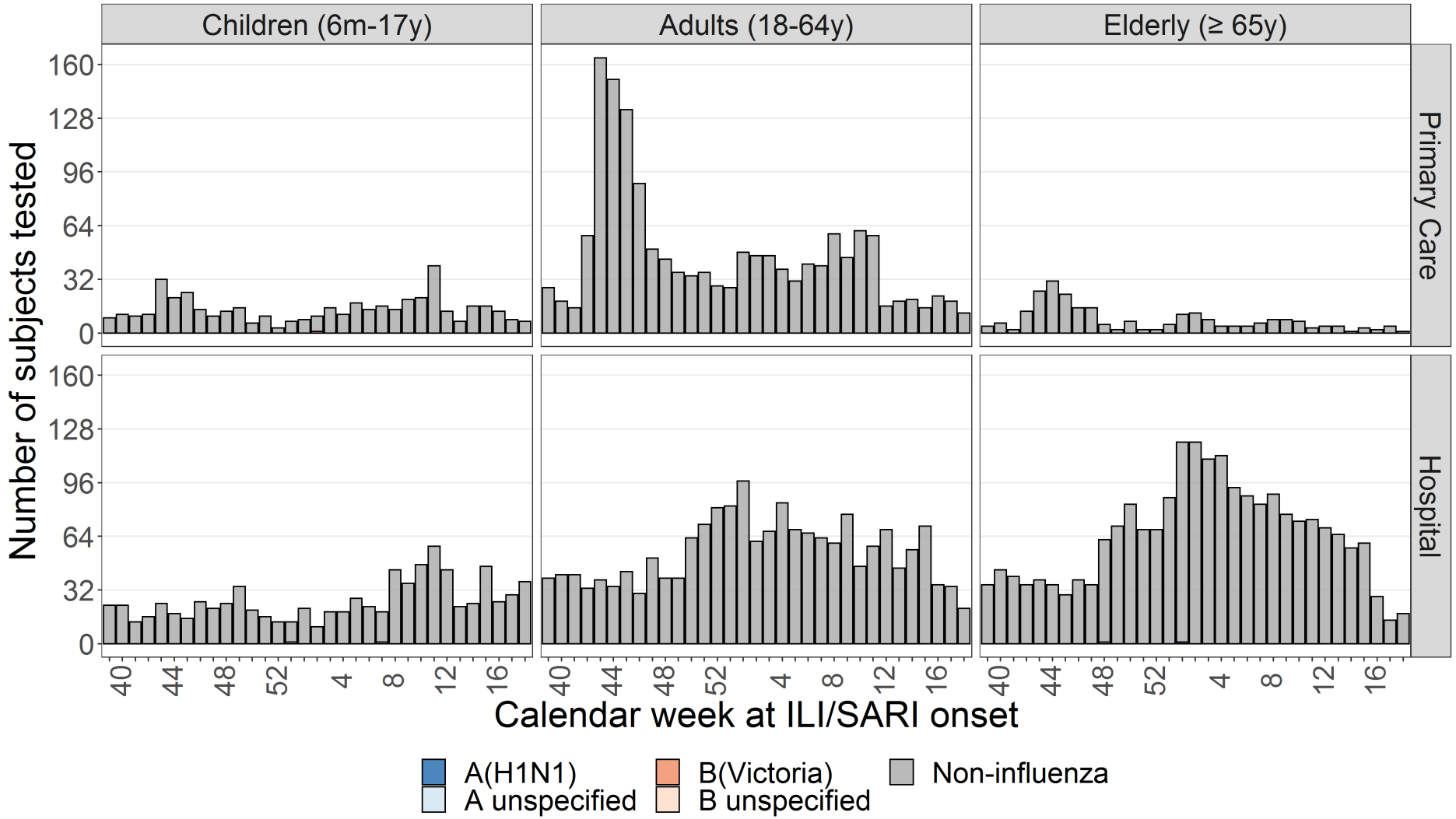


Figure 5. Distribution of ILI/SARI cases over time; TND studies, 2020/21

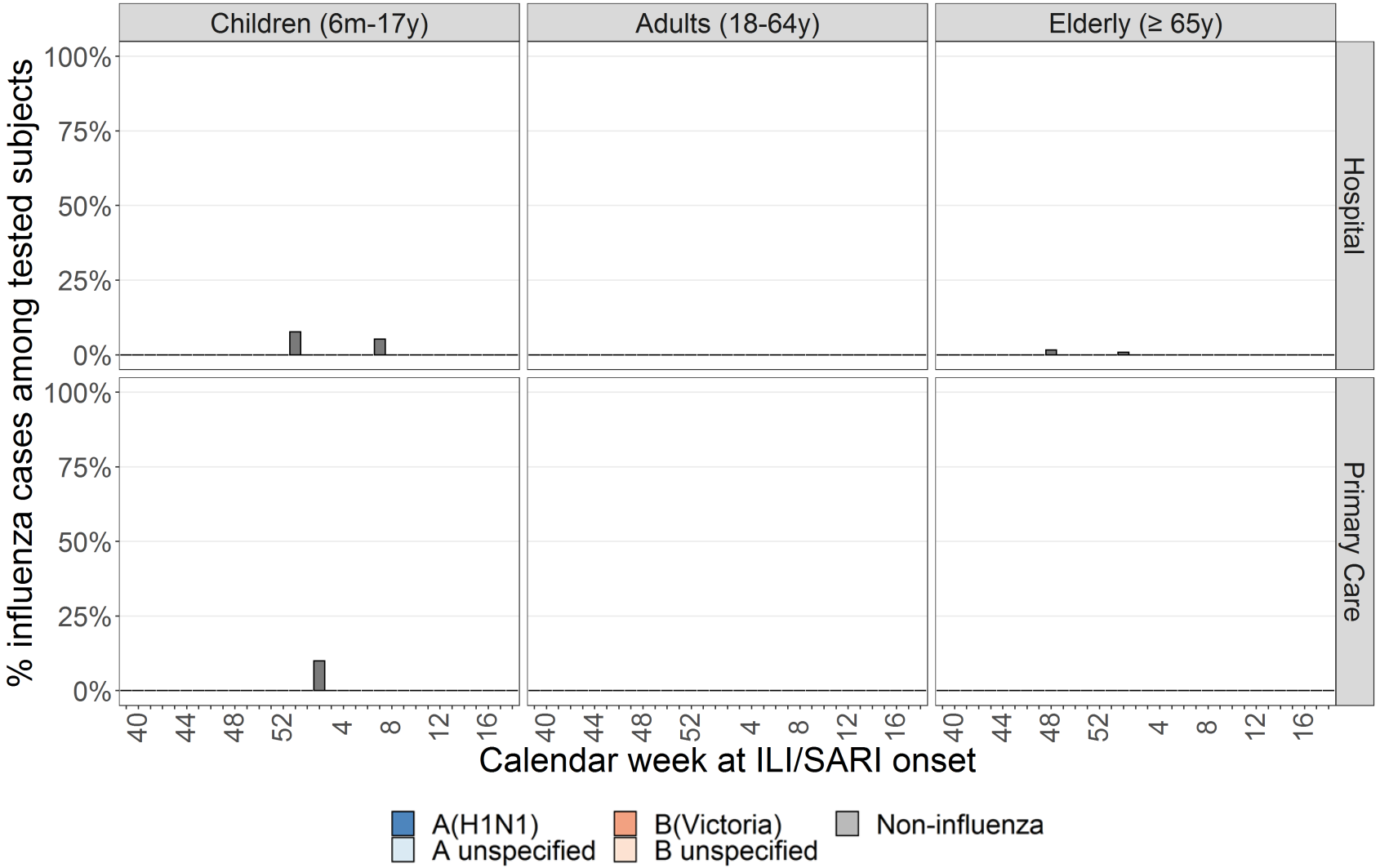
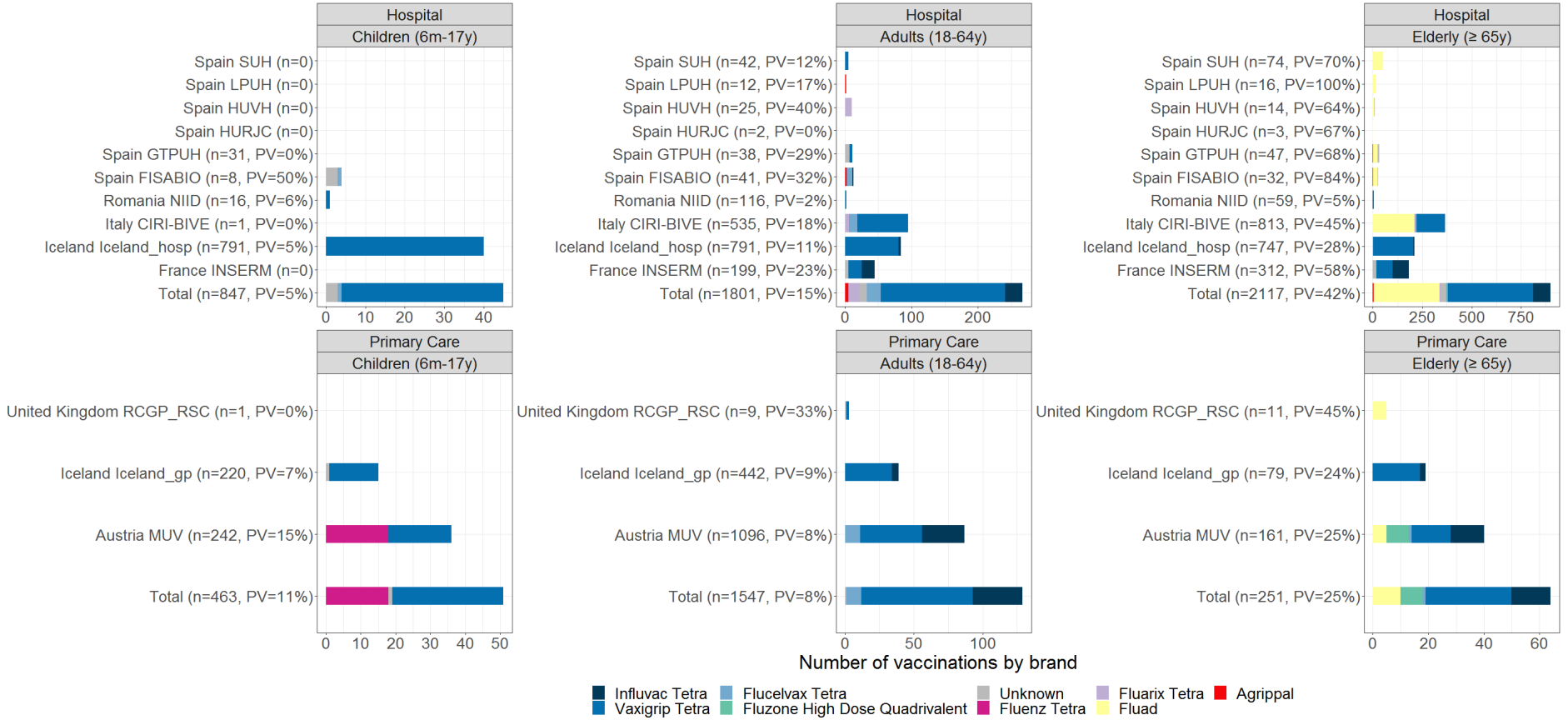


Figure 6. Distribution of percentage of influenza cases among tested ILI/SARI subjects over time, TND studies, 2020/21



PV: proportion vaccinated; m: months; y: years

Figure 7. Number of vaccinated subjects among enrolled subjects and distribution of vaccine brands; TND studies, 2020/21

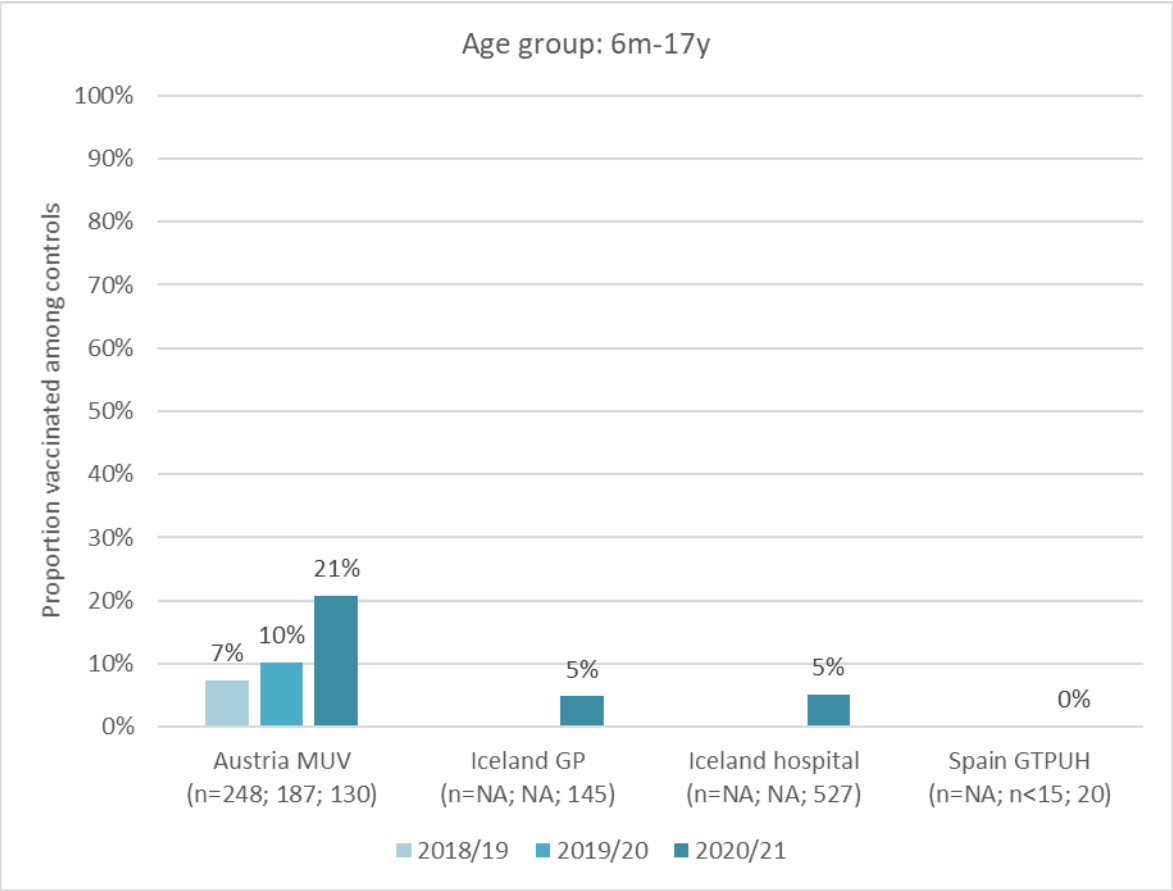


Figure 8. Overall proportion vaccinated by site among controls enrolled between January and the end of the study period, 6m - 17y, TND studies, seasons 2018-19 to 2020-21. n: number of controls for each site. n<15: data not shown because of small number of controls. NA: not applicable (no DRIVE partnering).

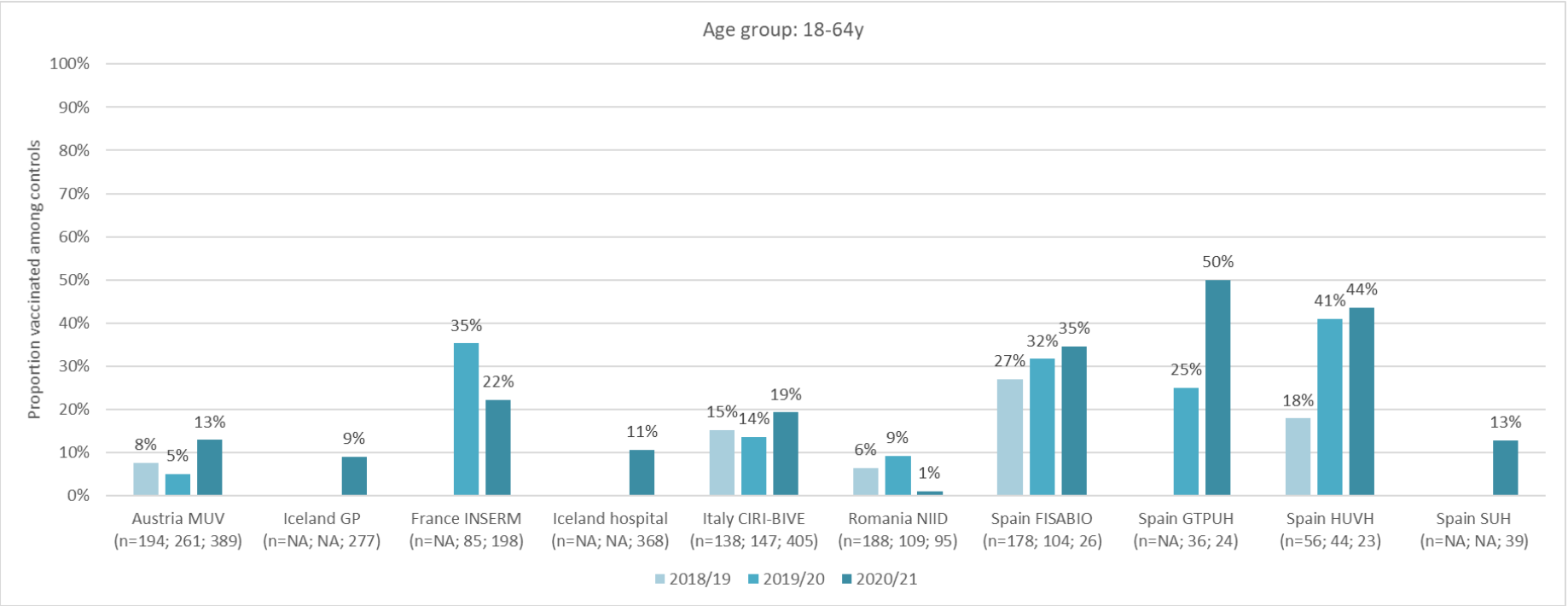
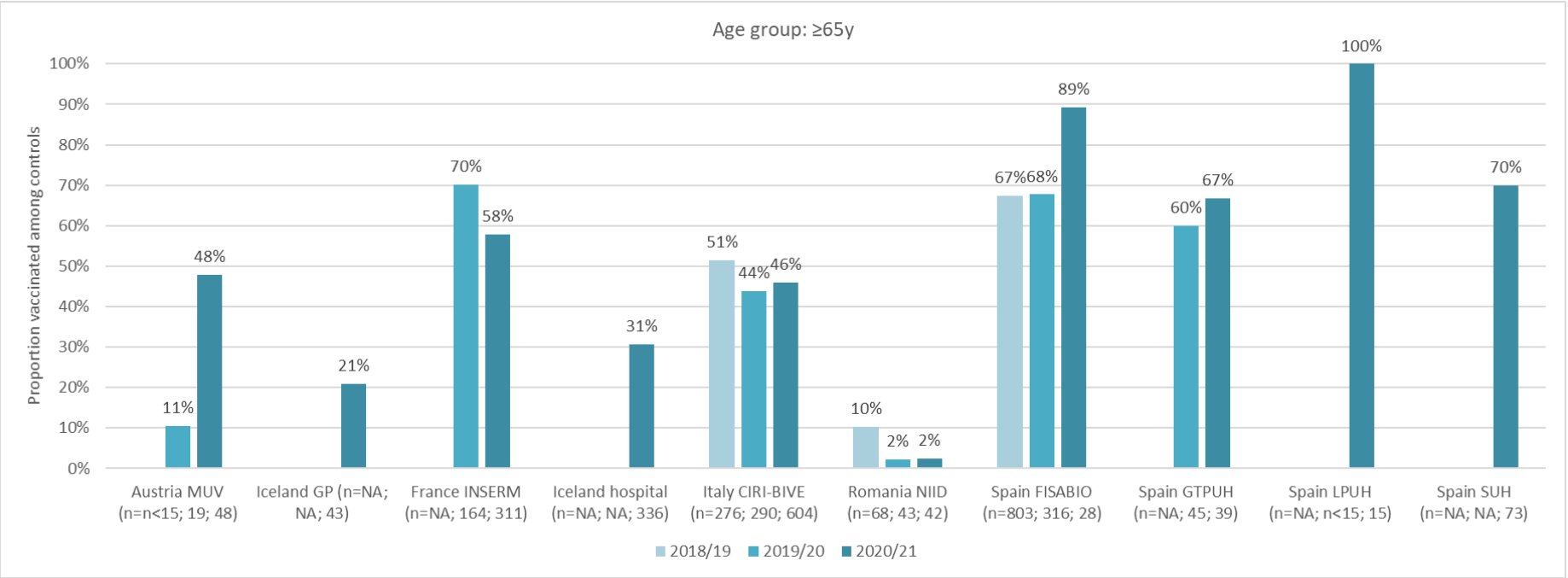


Figure 9. Overall proportion vaccinated by site among controls enrolled between January and the end of the study period, 18 - 64y, TND studies, seasons 2018-19 to 2020-21. n: number of controls by season. NA: not applicable (no DRIVE partnering).



Figue 10. Overall proportion vaccinated by site among controls enrolled between January and the end of the study period, 65y, TND studies, seasons 2018-19 to 2020-21. n: number of controls by season. n<15: data not shown because of small number of controls. NA: not applicable (no DRIVE partnering).

The percentage of cases and controls with a positive SARS-CoV-2 test (among those tested for SARS-CoV-2 is shown in Table 11. The proportion of subjects with SARS-CoV-2 was highest among adults (ranging from 26% to 36%). Corresponding tables by site are available in the WebANNEX.

Table 11. SARS-CoV-2 positivity among enrolled subjects with known SARS-CoV-2 status, TND hospital studies, 2020/21

	Cases	**SARS-CoV-2 positive cases (% of total cases)**	**Controls**	**SARS-CoV-2 positive controls (% of total controls)**
Primary care				
6m-17y	1	0 (0)	462	46 (10)
18-64y	0	-	1547	398 (26)
≥65y	0	-	251	86 (34)
Hospital				
6m-17y	2	1 (50)	845	18 (2)
18-64y	0	-	1801	598 (33)
≥65y	2	1 (50)	2115	755 (36)

10.3.2. Register-based cohort study, Finland

The Finland THL register-based cohort includes children 6m-6y (177,992 person years) and older adults 65-100y (679,103 person years). Tabular and graphical summaries of the data are provided in

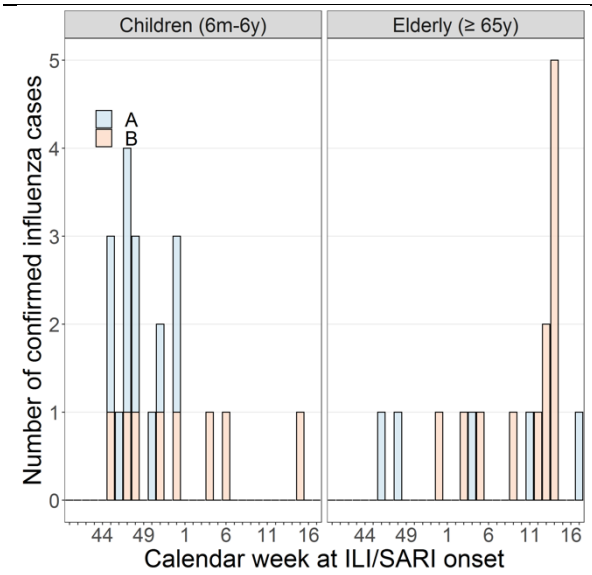
Table 12 and Figure 11. Very little influenza virus circulation was observed (Figure 11, top left). The vaccine brands used were Fluenz Tetra and Vaxigrip Tetra in children, and Vaxigrip Tetra in adults ≥65y (Figure 11, bottom left). Key covariates are shown (Figure 11, bottom right).

Population characteristics for each exposure, and for influenza in the hospital setting, are provided in the WebANNEX.

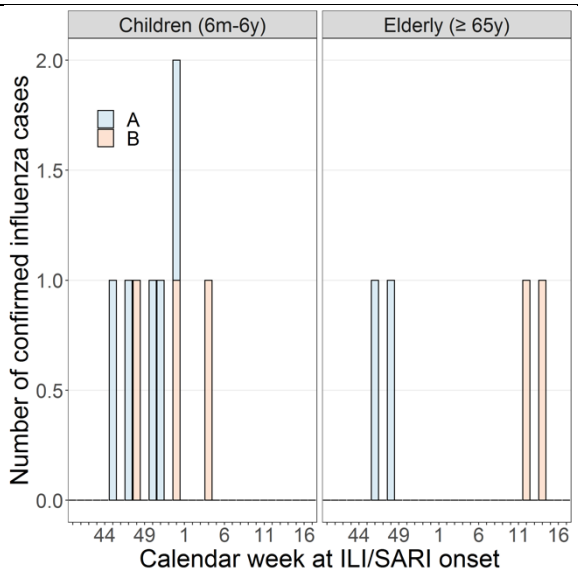
Table 12. Number of influenza infections and person-years by vaccination status and exposure, Finland THL register-based cohort study, 2020/21

Analysis	Age group	Vaccinated			Unvaccinated		
		Number of influenza infections	Number of hospitalized influenza infections*	Person years	Number of influenza infections	Number of hospitalized influenza infections*	Person years
Any vaccine							
	6m-6y	5	2	42,059	3	1	135,933
	≥65y	11	3	254,393	6	1	424,710
Vaxigrip Tetra							
	6m-6y	0	0	8,364	3	1	135,933
	≥65y	11		252,456	6		424,710
Fluenz Tetra							
	2y-6y	5	2	33,481	1	1	114,052

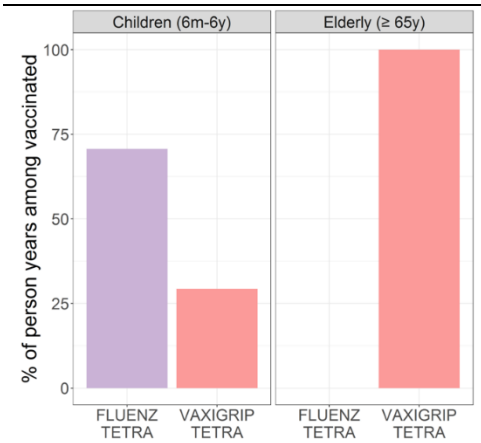
*Registered in the Care Register for Health Care only



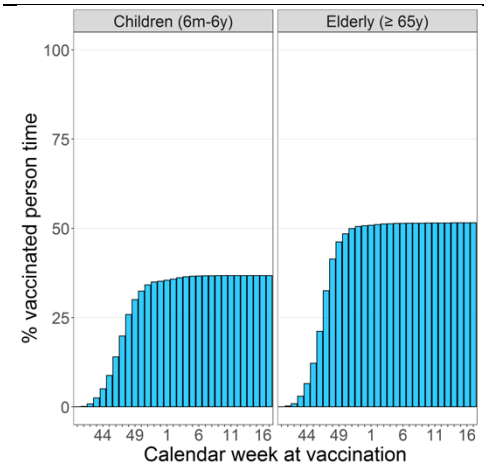
Number of influenza cases by type, mixed setting, by week



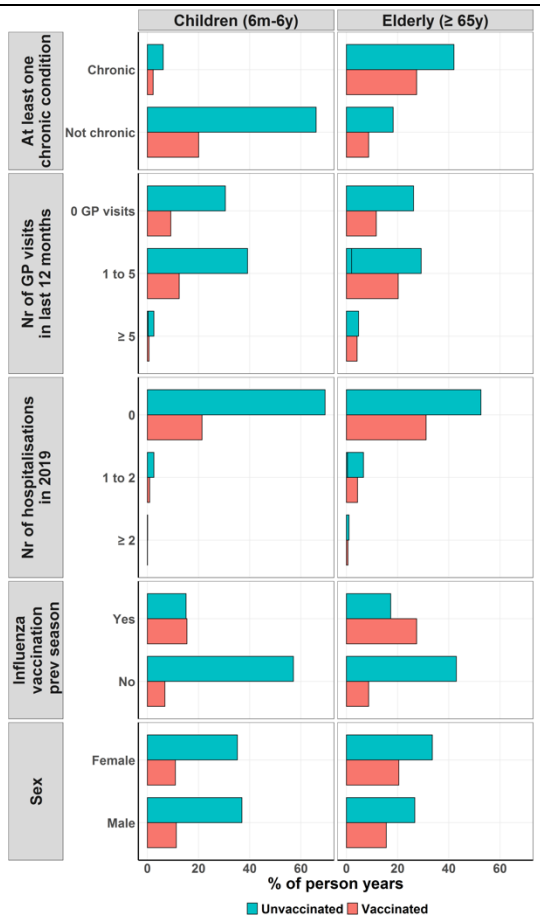
Number of influenza cases by type, hospital setting, by week



Distribution of vaccine brands



Percentage of vaccinated person time, by week



Distribution of covariates among exposed and unexposed

Figure 11. Data visualizations, Finland THL register-based cohort study, 2020/21

10.4. Primary objective: overall IVE and IVE by brand

10.4.1. Test-negative design studies

Overall and brand-specific IVE were not estimated from the TND studies in 2020/21.

10.4.2. Register-based cohort study

For the 6m-6y age group, no IVE estimates are presented as due to the scarcity of events the IVE could not be estimated. For the ≥65y age group, IVE estimates against influenza in any setting are shown in Table 13, and estimates against influenza in the hospital setting in Table 14. IVE point estimates ranged from -41.9 to -124 suggesting no protective effect against any influenza or influenza A/B, however, it is noted CI estimate are very wide leading to non-interpretable estimates. Estimates for any virus subtype/lineage included in the vaccine are not available for this data, and for influenza in the hospital setting the number of vaccinated cases was too low to stratify by influenza A and B.

Table 13. 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, mixed setting, 2020/21

	Any influenza **VE [95%CI]**	**A** **VE [95%CI]**	**B** **VE [95%CI]**
Mixed setting			
≥ 65y			
Any vaccine	-122.3 [-524.5, 20.9]	-676.7 [-7793.1 ,23.6]	-41.9 [-353.3, 55.6]
Vaccine brand*			
Vaxigrip Tetra	-124 [-529.4, 20.3]	-683.7 [-7872.8, 23]	-43 [-356.6, 55.2]

*In Finland, Vaxigrip Tetra was the only influenza vaccine offered by the national vaccination programme for adults ≥65y in season 2020/21.

Table 14. Confounder-adjusted influenza vaccine effectiveness of any vaccine and by vaccine brand against any influenza, Finland THL register-based cohort, hospital setting, 2020/21

	Any influenza **VE [95%CI]**
Hospital setting	
≥ 65y	
Any vaccine	-521.7 [-7186.5, 46.9]

	Any influenza VE [95%CI]
Vaxigrip Tetra	-527.9 [-7271, 46.5]

Influenza vaccine effectiveness estimates adjusted only for calendar week for the THL register-based cohort study are given in the WebANNEX.

Sensitivity analysis: extended confounder adjustment

In the sensitivity analyses, the estimates were adjusted for additional confounders, namely (1) number of GP visits in the previous year, or (2) number of hospitalizations in the previous year, or (3) presence of at least once chronic condition. IVE estimates were similar to those from the main analysis. The full results of the sensitivity analysis are presented in the WebANNEX. These analyses were performed as per SAP 2020/21, but given the confidence intervals in the primary analysis these sensitivity analyses are not to be considered informative.

10.5. 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. As a single vaccine brand was used in the age group ≥65y in Finland, no IVE estimates by type were calculated.

10.6. Exploratory objective: comparison of COVID-19 and influenza cases

As nearly no influenza hospitalizations were observed (Table 15), a comparison between the demographic and clinical characteristics of COVID-19 vs. influenza patients could not be performed.

Table 15. Clinical signs and symptoms around the point of admission among hospitalized influenza and hospitalized COVID-19 cases, TND hospital studies, 2020/21.

	18-64y			**≥65y**		
	COVID-19 n (%)	**Any Influenza n (%)**	**Co-infections n (%)**	**COVID-19 n (%)**	**Any Influenza n (%)**	**Co-infections n (%)**
Total	598	0	0	755	2	1
Age (median, IQR)	53, 13	–	–	76, 12	81.5, 8.5	73, 0
Sex (male)	362 (61)	–	–	425 (56)	1 (50)	1 (100)
At least one chronic underlying condition	363 (61)	–	–	652 (86)	1 (50)	0 (0)
Day at admission since symptom onset (median, IQR)	4, 3	–	–	4, 4	2.5, 3.5	6, 0
Fever	475 (80)	–	–	530 (71)	2 (100)	1 (100)
Headache	178 (30)	–	–	88 (12)	1 (50)	1 (100)
Myalgia	174 (29)	–	–	116 (15)	2 (100)	1 (100)
Fatigue/Malaise	265 (47)	–	–	359 (51)	2 (100)	1 (100)
Sudden onset of symptoms	283 (48)	–	–	274 (37)	1 (50)	0 (0)
Cough	415 (70)	–	–	379 (50)	0 (0)	0 (0)
Difficulty breathing	408 (69)	–	–	606 (81)	1 (50)	1 (100)
Sore throat	77 (13)	–	–	54 (7)	2 (100)	1 (100)
Deterioration of general condition	194 (37)	–	–	260 (42)	0 (0)	0 (0)
Pneumonia	370 (83)	–	–	565 (85)	1 (50)	1 (100)
Anosmia	104 (18)	–	–	51 (7)	1 (50)	1 (100)
Ageusia	84 (14)	–	–	54 (7)	1 (50)	1 (100)

IQR: interquartile range; y: years

11. Discussion

DRIVE faced its fourth influenza season with the uncertainties posed by the COVID-19 pandemic and the unforeseen changes in the influenza circulation patterns. A study network involving 13 research sites in 8 European countries, covering 24 hospitals and more than 500 general practitioners worked together to collect the data necessary for the DRIVE studies and adapt to the particularities of the season 2020/21.

The dramatic drop in the number of influenza cases detected in DRIVE dataset is in line with the observations during the influenza season in the Southern hemisphere and Northern hemisphere in 2020 and 2021. The non-pharmaceutical measures to contain SARS-CoV-2 infection, including physical distancing or the use of face masks, as well as the regional and national lockdowns, had a huge impact on the influenza circulation worldwide [13].

In a season marked by the absence of influenza circulation in Europe, the objectives of DRIVE for the 2020/21 season have only been partially fulfilled, as insufficient lab-confirmed influenza cases were recruited in DRIVE dataset. Thus, no brand-specific or overall IVE estimates could be obtained for the TND studies, and only overall IVE estimates for the Finnish cohort study were produced. However, the latter could not be interpreted due to large confidence intervals. Nevertheless, DRIVE has conducted a descriptive analysis of the data collected by the DRIVE study sites during the 2020/21 season.

Nine influenza vaccine brands were marketed in the EU/EEA/UK in the 2020/21 season. DRIVE dataset has captured 7 out of these 9 marketed brands, demonstrating DRIVE's ability to gather information on multiple influenza vaccine brands across Europe. The brands that were not captured are Afluria Tetra (Seqirus), and TIV High Dose (Sanofi Pasteur). Afluria Tetra was only marketed in Germany, a country not included in DRIVE. TIV High Dose was marketed in the UK but was not commissioned nor reimbursed by the NHS [14].

Overall, an increase in influenza vaccination coverage among controls compared to the previous two seasons was noted. Whilst acknowledging that controls are not fully comparable in profile to controls from previous season (as a substantial proportion tested positive for SARS-CoV-2, which was not circulating in prior seasons; and neither are controls necessarily fully representative of the general population (as they are presenting with ILI/SARI during a season with many contact restrictions in place), this trend was also observed at the regional/national level in numerous countries. Reasons for this included more active vaccination campaigns aimed at reducing influenza burden to save healthcare resources for COVID-19 care (e.g. through increased communication, and in Catalonia new mass vaccination sites in public buildings); more media attention for influenza vaccination, and a heightened awareness of epidemics among the general public. In addition, in Austria, where the largest relative increase in the proportion of vaccinated controlswas noted despite the overall proportion still being low, the influenza vaccine was offered for free for the first time to children 6m-14y, adults ≥65y and to all inhabitants of Vienna. The demand for influenza vaccines was higher than foreseen in some countries, resulting in vaccine shortages (e.g. Iceland, Romania), prioritiziation of those at highest risk (e.g. Finland, UK), and also in the use of additional influenza vaccines under the US license, such as Fluzone High

Dose Quadrivalent in Austria, France and Italy. Similarly, in Finland, the demand for pneumococcal vaccination for children also increased.

The decrease in proportion vaccinated observed among controls in for France INSERM can be partially though not fully explained by the exclusion of a relatively high number of subjects from the analysis due to missing vaccination status or date (including these subjects would lead to a vaccination coverage among controls of 25% among adults 18-64y and 62% among adults ≥65y). At the national level, vaccination coverage in France increased by 8% compared to 2019/20 [15].

We note that although data on vaccination was complete at the majority of the sites, vaccination date was either missing or incomplete for 13.1% enrolled subjects at INSERM and 4.7% enrolled subjects at MUV. Subjects with an incomplete vaccination date (missing 'day') were retained in the data set with an imputed day of vaccination. Subjects with a missing vaccination date were discarded from the analysis. In the absence of IVE analyses based on the TND studies this season, the impact of the above is minimal. However, it is noted imputation can lead to misclassification of vaccination status when ILI/SARI occurs in the same month as the vaccination, and that discarding subjects with missing vaccination date artificially lowers the proportion of vaccinated subjects. Therefore, the COVID-19–related work overload and impact of safety measures i.e. in the management of suspected and confirmed patients with COVID-19 admitted to hospital may explain the observed deviations. Therefore, we stress the importance of collecting complete data on vaccination.

Despite the setbacks created by the COVID-19 pandemic, DRIVE study sites continued their standard DRIVE data collection during the 2020/21 influenza season. Only minor issues with study start were raised at sites where the start date of the data collection was linked to a minimum number of influenza cases (e.g. national epidemic threshold or the DRIVE protocol's definition of the start of the study period ("first week of two consecutive weeks when influenza viruses were detected at the study site level"). Sites were advised to start data collection on January 1st 2021 if they had not already done so by that date.

At the primary care sites, testing for SARS-CoV-2 and influenza in patients presenting with ILI was done simultaneously. However, modifications in influenza testing of SARI patients were observed, especially during the third pandemic wave in Europe (January-March 2021). At some sites, all SARI patients admitted to the hospital were still tested for both SARS-CoV-2 and influenza simultaneously. In other sites, patients admitted to the hospitals were first tested for SARS-CoV-2, and directed to COVID-19 or non-COVID-19 wards depending on the outcome, and testing for influenza was only done for SARS-CoV-2 negative patients or at discretion of the clinician. The proportion of subjects excluded at the time of analysis because the swab for influenza testing was taken >7 days after the onset of symptom was higher than in previous years (at sites where at least one subject was excluded for this reason at the time of analysis). This can be explained by the change in the clinical pathway, and by the fact that many COVID-19 patients, for whom the median duration of symptoms at hospital admission is typically longer than for influenza (10 vs. 3 days) [16], were included in the study.

Several **limitations** have been described for the DRIVE study during the 2020/21 season:

- There was little to no influenza circulation in Europe in the season 2020/21– only 5 lab-confirmed influenza cases were observed from the TND studies and 25 from the register-based cohort study.
- Consequently, IVE (including brand-specific IVE) could not be estimated from the TND studies. The IVE estimations for the Finnish register-based cohort study were very imprecise and therefore not informative.
- Similarly, the exploratory comparison of signs and symptoms between subjects with COVID-19 vs. influenza did not inform on any differences between the two diseases.
- Due to the COVID-19 waves and the (near) absence of influenza circulation (making influenza an unlikely diagnosis), not all hospitalized SARI cases were tested for influenza, as influenza testing was limited e.g. to those testing negative for SARS-CoV-2 or at clinician's discretion. However, even if all SARI patients at those study sites had been tested, it is unlikely the threshold for performing IVE analyses for the TND studies would have been met this season.

On the other hand, it is important to also highlight the **strengths** of the DRIVE study:

- Despite the COVID-19 pandemic and the lack of influenza circulation in the 2020/21 season, the DRIVE network welcomed two additional hospitals in Spain, and onboarded the Iceland Directorate of Health in the TND studies. DRIVE has created a solid study network despite the challenges and shift of attention to COVID-19.
- Seven of the nine licensed and marketed influenza vaccines in Europe were captured in the DRIVE dataset.
- In the Finnish register-based cohort study, in the 2020/21 season, it was possible to identify of influenza cases that were admitted to hospital from the Care Register for Health Care, although this does not cover the full population and an unknown percentage of hospitalized influenza cases may therefore be missed. In previous seasons, it was not possible to differentiate influenza cases by setting. This will allow to estimate IVE against hospitalized laboratory-confirmed influenza in future seasons.
- 2x2 tables showing the number of cases and controls by vaccination status have been created for each exposure, thereby increasing the granularity of the reported results.
- The WebANNEX has been improved by adding the option to export the tables, by copying them or downloading them as CSV, Excel or PDF-file.
- The lessons learnt from DRIVE, especially during the past two years, highly marked by the COVID-19 pandemic, have greatly contributed to the development of a COVID-19 vaccine effectiveness platform: COVIDRIVE (website to be added). COVIDRIVE has been established by several of the DRIVE consortium partners and will conduct COVID-19 vaccine effectiveness studies leveraging the infrastructure and study sites network built in DRIVE.

12. Conclusions

- The very low influenza circulation in Europe in the 2020/21 season did not allow to obtain IVE estimates for the TND studies and only very imprecise IVE estimates were obtained for the ≥65y age group for the Finnish cohort study.
- DRIVE continued its study conduct through the 2020/21 influenza season and the sites kept their data collection for DRIVE with some modifications in patients triage and testing strategies due to the COVID-19 pandemic.
- DRIVE study network will be facing the 2021/2022 season as the final season under IMI umbrella.

13. Funding

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

14. Study team

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

15. References

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16. ANNEXES

The WebAnnex is accessible at: https://apps.p-95.com/drivewebapp/. The results of all the analyses are available there. In addition, the following documents are accessible:

- Data processing (number of records retained during the data processing)
- Vaccine recommendations
- Study teams 2020/21
- Local Study Reports 2020/21
- Statistical Analysis Plan 2020/21
- All R scripts related to the workflow (excluding site-specific cleaning scripts)

WebAnnex hierarchy

- TND site-specific analyses:
    - Site
        - Analysis: Descriptive analysis
            - Type: Histogram of covariates

- Age group
- Type: Histogram of cumulative number of vaccinations over time
  - Age group
- Type: Histogram of infections over time
  - Age group
- Type: Histogram of influenza positivity rate over time
  - Age group
- Type: Vaccine brands
  - Age group
- Type: Table covid cases
- Type: Table of study population characteristics - by outcome
  - Age group
- Type: Table of study population characteristics - by strain
  - Age group
- Type: Table of study population characteristics - by exposure
  - Age group
    - Exposure

- Analysis: Exploratory analysis
- Analysis: Data quality report

- TND pooled analyses
  - Main analysis: Descriptive
    - Type: Any Vaccine
      - Type: Influenza over time (Figure 5)
      - Type: Influenza positivity over time (Figure 6)
      - Type: Vaccination distribution (Figure 7)
      - Type: Histogram of covariates SETTING/AGE
      - Type: Brand-specific coverage among controls
      - Type: Case-control by analysis SETTING *(2x2 tables for each age/ exposure combination)* (Table 9, Table 10)
      - Type: case-control overview (Table 7)
      - Type: Descriptive table by outcome exposure combination SETTING AGE (*Study population characteristics by case/control and vaccination status)*
      - Type: Descriptive table by strain SETTING AGE *(Study population characteristics by influenza any/type/subtype or lienage)*
      - Type: Coverage among controls
      - Type: Epidemiology data (
      - Table 6)
      - Type: Table covid cases (Table 11)
    - Type: Exposure-specific

- Descriptive table by outcome exposure combination SETTING AGE EXPOSURE
  - Exposure
- Descriptive table by strain SETTING AGE EXPOSURE
  - Exposure
-

- Exploratory analyses
  - Type: Symptom data (Table 15)
    - Descriptive table of symptoms among influenza and covid-19 cases

- Register-based cohort
  - Analysis: Descriptive
    - Number of vaccinated and unvaccinated person-years and influenza cases SETTING (Figure 11)
    - Histogram of covariates THLCohort SETTING (Figure 11)
    - Histogram of Cumulative number of vaccinations over time SETTING (Figure 11)
    - Histogram of infections over time THLCohort SETTING (Figure 11)
    - Vaccine brands SETTING
    - Table of study population characteristics AGE SETTING
  - Analysis: Main analysis
    - THL Adjusted IVE hospital setting
    - THL Adjusted IVE mixed setting
  - Analysis: Sensitivity Analysis N Hosp
    - THL Adj. Hosp. IVE Report
    - THL Adj. IVE Report
  - Analysis: Sensitivity Analysis Chronic
    - THL Adj. Hosp. IVE Report
    - THL Adj. IVE Report
  - Analysis: Sensitivity Analysis GP Visit
    - THL Adj. Hosp. IVE Report
    - THL Adj. IVE Report

Quality Control & Audit Committee Annual Report Season 2020/2021

DRIVE

Development of Robust and Innovative Vaccine Effectiveness

QCAC – Quality Control & Audit Committee

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Delivery date	28 September 2021

Description of Work	**Version**	**Date**
	0.4	28 September 2021

Document History

Version	**Date**	**Description**
V0.1	22 Apr 2021	First version for QCAC / SC meeting
V0.2	11 Jun 2021	Second QCAC draft report
V0.3	15 Sep 2021	Third QCAC draft report sent for review
V0.4	28 Sep 2021	Fourth QCAC draft report sent to SC for review

List of abbreviations

DMP	Data Management Plan
DMR	Data Management Report
DQR	Data Quality Report
DRIVE	Development of Robust and Innovative Vaccines
ESSA	Electronic Study Support Application
QC	Quality Control
QCAC	Quality Control and Audit Committee
SAP	Statistical Analysis Plan
SC	Steering Committee
WP	Work Package

1. Summary

This is a summary of QCAC activities covering the 2020/2021 season which summarises the improvements incorporated from the 2019/2020 season and the activities planned for 2020/2021.

The QCAC evaluation performed in prior seasons was conducted in order to determine whether there were any limitations from a quality perspective which may have impacted quality of the study conduct, data reporting and the pooled analysis. The previous evaluations focused on study conduct which incorporated compliance with regulatory requirements, quality of data collected from study sites, availability of procedures describing these processes, maintenance of documentation and data reporting including the key deliverables generated by P95 and the pooled analysis. The evaluation was focused on quality management systems and was not an assessment of the scientific integrity of the sites' study design and analysis and interpretation of the study results.

Due to the participating sites focus on the COVID-19 pandemic and the low levels of circulating influenza in 2020/2021, QCAC planned activities as listed in the 2020/2021 Workplan were restricted as detailed below.

- Review of Site Quality Management Questionnaire (designed to perform evaluations of study site's quality and feasibility) developed by WP3. As per SC's recommendation, only new participating sites for the 2020/2021 season (three sites) were to be requested to complete the Site Quality Management Questionnaires. However because of the low circulation of influenza in Europe and the very limited data collected from sites during the 2020-21 season (no IVE), the SC along with the QCAC decided to postpone the evaluation of the new sites for the beginning of the next season in sept-oct 2021.
- Because no pooled analysis were done for 2020-21 season, QCAC did not have to review related P95 processes.

The key recommendation from the 2019/2020 QCAC annual report was for an independent evaluation of P95 processes to be carried out by a Data Management / Programming/ Biostatistics expert (independent from DRIVE and P95) with a focus on the set-up of the software (ESSA), data transfer processes, generation of the datasets/listings and pooled analysis. The SC and P95 have agreed for an audit to be conducted. The auditor who is currently undergoing selection by QCAC, will review the following:

- Data management including but not limited to DMP, data integrity, data transfer, data QC, data storage, data privacy and archiving.
- Statistical analysis including but not limited to SAP, mock report and tables, conduct of analysis, QC of analysis, documentation and archiving.
- IT infrastructure linked to data collection/data process including but not limited to the ESSA characteristics, data privacy, secured data transfer and storage, "Disaster Recovery Plan" to ensure remote access to files/system and ensure business continuity, documentation and archiving.

The season was marked by the near-absence of influenza circulation in Europe. Consequently, it was decided that QCAC routine activities as per the Workplan were of limited value to conduct for the 2020/2021 season and the focus was for the independent evaluation of P95 which is currently planned for Q4 2021.