IMI2 777363 – DRIVE

Development of Robust and Innovative Vaccine Effectiveness

WP7 – Framework for analysis and study report

D7.9 Brand-specific influenza vaccine effectiveness in Europe Season 2021/22 REPORT

Study registered in ENCEPP (EUPAS46888).

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Document History

Version	Date	Description
V1.0	May 25 2022	First draft circulated to WP7 and sites.

V2.0	May 30 2022	Second draft circulated to EFPIA and ISC. This draft includes an updated results based on a dataset from Spain HUVH-HUJT and a revised study period for Romania NIID; it also includes pooled VE results for Flucelvax Tetra.
V3.0	July 5 2022	This version addresses EFPIA and ISC feedback. The results have been updated, as Vaxigrip for HUVH-HUJT was changed to Vaxigrip Tetra, a cut-off at April 30 2022 was applied to the Italy ISS data, and more complete data was received from France I-REIVAC.

1.1 Table of Contents

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1.4 List of acronyms and abbreviations

aQIV	Adjuvanted quadrivalent influenza vaccine
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 GP	Directorate of Health - Embætti landlæknis, GP study
EL HOSP	Directorate of Health - Embætti landlæknis, Landspitali University Hospital
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
hdQIV	High-dose quadrivalent influenza vaccine
HUJT	Hospital Universitari de Girona Doctor Josep Trueta
HUVH-HUJT	Vall d'Hebron University Hospital - Hospital Universitari de Girona Doctor Josep Trueta
I-REIVAC	Innovative Clinical Research Network in Vaccinology
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 & University of Oxford
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
SOP	Standard Operating Procedure
SUH	Salamanca University Hospital
GTPUH	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

1.5 Milestones

	Expected date	Actual date
Start of surveillance period	October/November 2021	October/November 2021
End of surveillance period	April 30 2022	April 30 2022
First subject enrolled (TND studies)	n/a	September 1 2021
Last subject enrolled (TND studies)	n/a	April 29 2022
First data upload by site	May 2-10 2022	May 9 2022
Final data upload by site	May 20 2022	June 30 2022
Data quality reports completed	May 20 2022	June 9 2022
Database freeze	May 20 2022	June 30 2022
First IVE results available	May 20 2021	May 24 2022
Analysis archived	June 28 2022	June 30 2022
Report submission to IMI	September 1 2021	July 5 2022

n/a: not applicable

1.6 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, 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 at 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-authorisation effectiveness studies.

DRIVE has successfully set up an 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 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 2021/22 season is the network's fifth and last influenza season.

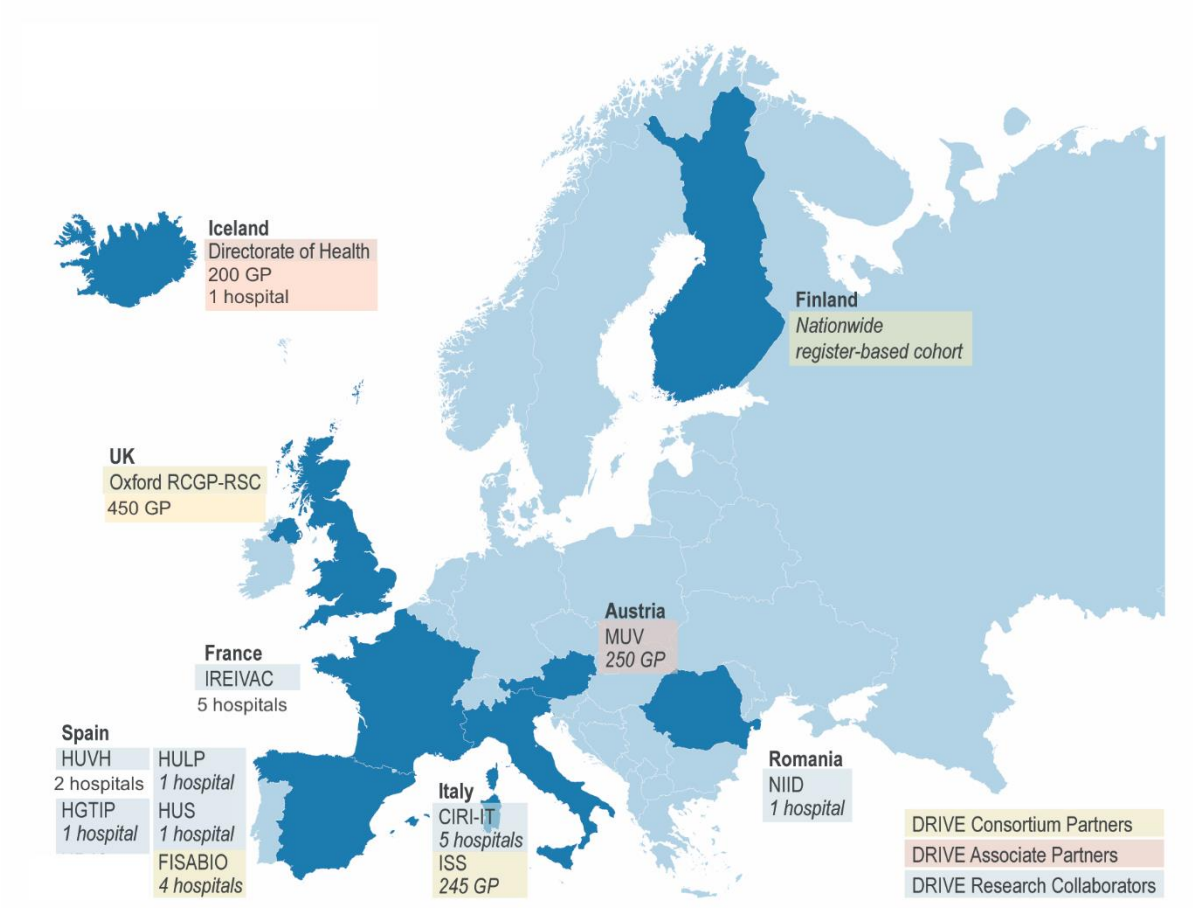


Figure E1. DRIVE Study network for season 2021-22. The DRIVE network is composed of (1) 12 independent study sites across seven European countries that conduct test-negative design (TND) prospective studies (which include a total of 21 hospitals and roughly 1145 GPs) and (2) a nationwide register-based cohort study

in Finland. No new sites joined the DRIVE network in 2021/22, although four new hospitals joined the existing DRIVE sites.

Objectives

The objectives are to estimate seasonal (1) **overall**, **brand-specific** and (2) **type-specific** IVE against laboratory-confirmed influenza stratified by setting (primary care, hospital-based) and age group (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. Exploratory objectives were to explore if SARS-CoV-2 co-infection or COVID-19 vaccination are effect modifiers of influenza infection and influenza vaccination and if COVID-19 vaccination is a confounder of IVE.

Methods

TND studies

In the 2021/22 season, TND studies were conducted in primary care (four networks) and hospital settings (five individual hospitals and four hospital networks) from eight different European countries. 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) (I-MOVE+ 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-institutionalised 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 hospitalised <48 hours prior to symptom onset or with symptom onset ≥48 hours after hospital admission were excluded. Vaccine brand was collected for vaccinated subjects.

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 hospitalised for any reason starting (or ongoing) on the day of laboratory confirmation.

Statistical methods

Data collected at the study sites were transferred to the DRIVE Research Server where they were analysed centrally by P95. The statistical analysis plan is registered at ENCEPP (EUPAS46888). Due to the historically low circulation of influenza, sample size calculations were performed (and described in the SAP), and IVE would only be calculated if a pre-established minimum number of influenza cases would be available in the pooled data, stratified by setting and age group (Table E1; Statistical Analysis Plan Table 15). In case this analysis is

performed for a certain setting and age group all the other analyses applying to this population would also be performed.

Table E1. *Vaccination coverage among TND control subjects and control:case ratio observed in the DRIVE data from the 2019/20 season and the number of influenza cases required to perform the analyses in the 2021/22 season. The required numbers were obtained assuming a power of 50% and an IVE of 60%, additional information can be found in the SAP.*

	Primary care			**Hospital setting**		
	6m-17yr	**18-64yr**	**≥65yr**	**6m-17yr**	**18-64yr**	**≥65yr**
Observed coverage among the controls in 2019/20	13%	10%	61%	5%	23%	56%
Control:case ratio	0.8	1.7	4.3	1.1	2.2	4.5
Number of influenza cases required for performing the analysis	155	102	24	155	45	18

IVE estimation: TND studies

Site-specific IVE was calculated using logistic regression. Estimates were stratified by age and adjusted for age, sex and calendar time (i.e. date of symptom onset). Site-specific IVE estimates from the TND studies were pooled through random-effects meta-analysis.

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 I*RR* is 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.

Results

Descriptive analyses

Overall, 411 cases and 2805 controls were retained for analysis in the TND primary care studies, and 628 cases and 2450 controls in the TND hospital studies (Table E2). The highest proportion of vaccinated controls was observed in the ≥65y age group (33% in primary care setting and 56% in hospital setting). The most frequently reported vaccine brands 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.

Table E2. *Number of cases and controls retained for analysis per study setting and age categories, TND studies, 2021/22*

TND	6m-17y		18-64y		≥ 65y	
Setting	Cases (%PV)	Controls (%PV)	Cases (%PV)	Controls (%PV)	Cases (%PV)	Controls (%PV)
PC	189 (11)	1106 (16)	181 (18)	1448 (13)	41 (41)	251 (33)
Hosp	211 (4)	589 (6)	206 (14)	677 (22)	211 (65)	1184 (56)

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

In the register-based cohort, 169,823 person-years were available for analysis in the age group 6m-6y and 666,799 person-years in the age group ≥65y (Table E3). Among vaccinated children both Fluenz Tetra and Vaxigrip Tetra were observed, whereas among older adults only Vaxigrip Tetra was observed.

Table E3. *Number of vaccinated and unvaccinated person-years and influenza cases by age category, register-based cohort study, 2021/22*

Register-based cohort	6m - 6y				≥65y			
Setting	Vac py (% of total py)	Unvac py (% of total py)	Vac cases	Unvac cases	Vac py (% of total py)	Unvac py (% of total py)	Vac cases	Unvac cases
Mixed	37508 (22)	132315 (78)	29	93	304570 (46)	362229 (54)	118	91
Hospital	37508 (22)	132315 (78)	8	17	304570 (46)	362229 (54)	51	41

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

Influenza vaccines 2021/2022 season

Eight of the 12 vaccines marketed in the European Union (EU)/European Economic Area (EEA)/UK in 2021/22 were identified in the DRIVE dataset (Table E4).

Table E4. *Sites in which the vaccine brand was observed in the DRIVE dataset, by age group, 2021/22*

Vaccine brand	Manufacturer	Sites in which the vaccine brand was observed in the DRIVE dataset		
		6m - 17y	18 - 64y	≥ 65y
Afluria Tetra	Seqirus	n/a	-	-
Chiroflu	Seqirus	-	-	-
Efluelda	Sanofi	n/a	MUV	CIRI-BIVE, GTPUH, HUVH-HUJT, I-REIVAC, MUV
Fluad	Seqirus	n/a	n/a	FISABIO, ISS, LPUH, SUH

Vaccine brand	Manufacturer	Sites in which the vaccine brand was observed in the DRIVE dataset		
		6m - 17y	18 - 64y	≥ 65y
Fluad Tetra	Seqirus	n/a	n/a	CIRI-BIVE, GTPUH, HUVH-HUJT, MUV, SUH
Fluarix Tetra	GSK	ISS, MUV	ISS, MUV	CIRI-BIVE, ISS, MUV
Flucelvax Tetra	Seqirus	-	CIRI-BIVE, FISABIO, MUV	CIRI-BIVE, FISABIO, MUV
Fluenz Tetra	AstraZeneca	ISS, MUV, THL	n/a	n/a
Influvac		-	-	-
Influvac Tetra	Abbott	FISABIO, MUV	FISABIO, GTPUH, HUVH-HUJT, I-REIVAC, MUV, NIID	EL HOSP, FISABIO, GTPUH, HUVH-HUJT, I-REIVAC, MUV
Supemtek	Sanofi	n/a	-	-
Vaxigrip Tetra	Sanofi	EL GP, EL HOSP, ISS, MUV, NIID, THL	CIRI-BIVE, EL GP, EL HOSP, HUVH-HUJT, I-REIVAC, ISS, LPUH, MUV, NIID, SUH	CIRI-BIVE, EL GP, EL HOSP, HUVH-HUJT, I-REIVAC, ISS, MUV, THL

-: 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; UK: United Kingdom; y: years

IVE estimates: TND studies

Results from the primary care and hospital TND studies in children, adults 18-64y and ≥65y are shown in Figure E2. In addition, brand-specific estimates were available for at least one age/setting stratum for Efluelda, Fluad, Fluad Tetra, Fluarix Tetra, Flucelvax Tetra, Fluenz Tetra, Influvac Tetra, and Vaxigrip Tetra.

In the 2021/22 season, point estimates for pooled TND IVE estimates for any vaccine against any influenza virus
ranged from 0 to 76% in the primary care setting and from -32% to 85% in the hospital setting. In the primary care setting, the IVE estimate for any vaccine against influenza A(H3N2) was estimated at 53% (95%CI -550 to 97) for children 6m-17y and 76% (95% CI 23 to 93) for those aged ≥65y. None of the estimates had a 95% CI width of <40% and most had wide to very wide confidence intervals. Several significant estimates were obtained. These estimates are among older adults in the primary care setting, with VE for any vaccine against any influenza of 76% (95%CI 23 to 93) and VE for Vaxigrip Tetra against any influenza of 81% (95%CI 22 to 95); and among children in the primary care setting with VE for Fluenz Tetra against any influenza of 64% (95%CI 25 to 83). In the hospital setting, the IVE estimate for any vaccine agains any influenza among adults was 82% (95% CI 12 to 97)

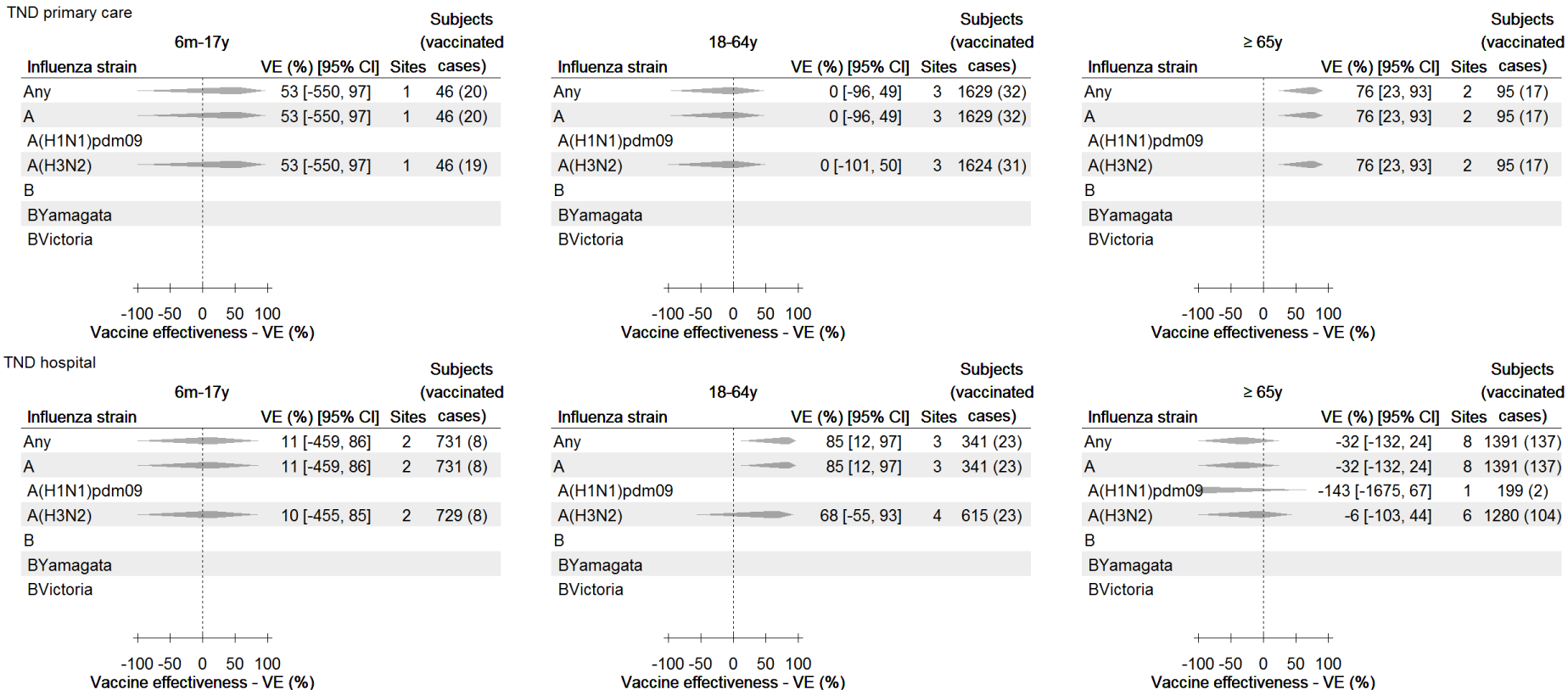


Figure E2. *Any influenza vaccine: pooled confounder-adjusted (age, sex and date of symptom onset) influenza vaccine effectiveness against laboratory-confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2021/22*

IVE estimates: Register-based cohort study

IVE estimates against influenza in any setting are shown in Table E5. VE against any laboratory-confirmed influenza in children was estimated at 23% (95%CI -17 to 50), with brand-specific estimates available for Vaxigrip Tetra (37% [95%CI -50 to 73] and Fluenz Tetra (25% [95%CI -21 to 53]). The VE estimate for influenza A was 38% (95%CI 1 to 62). VE for Vaxigrip Tetra against any laboratory-confirmed influenza in older adults was estimated at 15% (95%CI -11.9% to 35.7%) and was similar for influenza A. VE against inpatient influenza in older adults was estimated at 17% (95%CI -26% to 45%) and thus similar to the estimates from the mixed setting.

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 and hospital setting, 2021/22*

		Any influenza VE (95%CI)	**A VE (95%CI)**	**B VE (95%CI)**
Mixed setting				
6m-6y				
	Any vaccine	23.3 (-17.1, 49.7)	38.4 (1.1, 61.6)	-240.4 (-911, -14.6)
	Vaxigrip Tetra	36.9 (-50.1, 73.4)	53.9 (-30.3, 83.7)	-134.3 (-1133, 55.5)
	Fluenz Tetra (2-6y)	24.9 (-21.2, 53.4)	39.6 (-2.9, 64.5)	-322 (-1467.9, -13.6)
≥65y				
	Any vaccine	16.1 (-10.7, 36.4)	13.8 (-14.2, 34.9)	61.5 (-107.8, 92.9)
	Vaxigrip Tetra	15.2 (-11.9, 35.7)	12.9 (-15.4, 34.3)	61.1 (-109.7, 92.8)
Hospital setting				
6m-6y				
	Any vaccine	-13.8 (-169.1, 51.9)	-	-
	Vaxigrip Tetra	50.7 (-304.4, 94)	-	-
	Fluenz Tetra (2-6y)	-42.3 (-265.3, 44.6)		
≥65y				
	Any vaccine	17.1 (-25.9, 45.4)	-	-
	Vaxigrip Tetra	16.3 (-27.2, 44.9)	-	-

Discussion

The low influenza virus circulation observed during the 2021/22 season, partly due to the non-pharmaceutical interventions and lockdowns implemented to combat the COVID-19 pandemic, together with the shift of attention and resources from influenza to COVID-19, which resulted in no new study sites this season, has largely impacted this season DRIVE's study, preventing the generation of robust brand-specific IVE estimates. A late influenza epidemic in the months of March, April and May might have also impacted the study, as in some

European countries the influenza season was still ongoing when the data collection for the DRIVE study stopped at the end of April. Despite all the challenges, DRIVE has been able to generate brand-specific IVE estimates for eight of the 12 influenza vaccines currently marketed in Europe.

In the 2021/22 season, VE estimates for 8 vaccine brands were available from the **TND studies**. The number of brand-specific estimates was largest among older adults in the hospital setting (5 brands), followed by children in the primary care setting (4 brands), adults 18-64y in the hospital setting (3 brands) and two brands each for the other age/setting strata. For any vaccine, pooled confounder-adjusted estimates stratified by age group and settings had wide CIs (with 95% CI width > 40%). However, results suggested a VE against any influenza of >50% among older adults in the primary care setting and among adults in the hospital setting.

As the influenza season was still ongoing in Finland when the **register-based cohort study** was ended, the presented 2021/22 VE estimates are preliminary. Due to the small number of influenza cases, VE in children could not be estimated precisely. VE in older adults was less than 50% with CIs starting below 0%. Interestingly, the two different settings, hospital setting and mixed primary care and hospital setting, yielded similar results, although VE against severe disease is suspected to be higher than VE against infection. A different pattern was observed in the TND studies, with point estimates being higher among older adults in primary care than for those in hospital settings.

Limitations:

- DRIVE has not been able to reach the sample size required to produce precise brand-specific estimates due to the low influenza circulation in Europe and the inability to expand the study site network in the current context.
- The majority of the IVE estimates are therefore presenting very wide CIs and consequently have to be interpreted with caution
- The limited sample size has also prevented DRIVE from performing several sensitivity analyses

Strengths:

- Despite the COVID-19 pandemic and the low influenza circulation in the 2021/22 season, the DRIVE network was able to produce brand-specific IVE estimates for eight of the 12 marketed influenza vaccines in Europe. This, by itself, is a success. However, study power was insufficient for properly interpreting the estimates.
- DRIVE has created a solid study network composed of 21 hospitals, more than 1000 GP and a nationwide register from eight European countries despite the challenges raised by the COVID-19 pandemic, the PPP hesitancy and the shift of attention to COVID-19.
- Twelve influenza vaccine brands were marketed in the EU/EEA/UK in the 2020/21 season. The DRIVE dataset has captured 8 of these 12 brands, highlighting the ability of the study network to cover the variety of influenza vaccine brands administered in Europe.
- The lessons learnt from the DRIVE studies, especially during the past two years, have greatly contributed to the development of a COVID-19 vaccine effectiveness platform: COVIDRIVE

(https://covidrive.eu/). COVIDRIVE has been established by several of the DRIVE consortium partners and is conducting COVID-19 vaccine effectiveness studies since September 2021, leveraging the infrastructure and study sites network built in DRIVE.

2 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 health care burden [1]. Together with hygiene, vaccination is considered the best action to protect against influenza; however, vaccine performance varies between influenza seasons. This performance is affected by the type of circulating virus strains 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 (IVE) a challenge.

The DRIVE project is a public-private partnership aiming to build capacity in Europe for estimating brand-specific IVE. The DRIVE Project, which is funded by the Innovative Medicines Initiative (IMI), was initiated as a response to the changes for post-licensing requirements of influenza vaccines in Europe. The new guidance on influenza vaccines by the EMA came into effect at the beginning of 2017. This guidance states that the performance of influenza vaccines should no longer be assessed based on serological assays but on post-authorisation effectiveness studies [2].

DRIVE sought to establish a sufficiently sized network for robust, high-quality, brand-specific effectiveness estimates for all influenza vaccines used in the EU each season. In DRIVE, data from several independently operating national or regional study sites is analysed jointly to increase geographical coverage and sample size for brand-specific IVE estimates. 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. Since 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 to enhance data available for the strata containing the population most vulnerable to 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 (five study sites from four 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 five to 13 sites from seven 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 IVE seasons by health care setting and age group. DRIVE protocols were further harmonised, the Statistical Analysis Plan (SAP) was improved,

age- and site-specific IVE estimates were calculated, and estimates were pooled across settings[3]. As a result, DRIVE obtained precise brand-specific estimates 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's (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 having 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 eight different European countries. For the 2019/2020 season, four primary care-based TND studies, eight 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, impacted health care–seeking behaviour 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 register-based cohort study [5].

The study conducted in the 2020/21 season built upon tools and processes 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 the hospital setting to increase the efficiency and feasibility of the network. In the 2020/21, the circulation of influenza was historically low following non-pharmaceutical interventions to curb the transmission of COVID-19. The threshold in terms of minimum influenza cases for calculating IVE was not met for the TND studies. IVE was only estimated for the register-based cohort study.

This Study Report summarises the methods used and the results obtained for the 2021/22 influenza season, the final season of DRIVE under the IMI umbrella. 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 EUPAS46888.

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.

3 Objectives

3.1 Primary objective

To estimate seasonal overall, age-specific (6m-17 years (y), 18-64y, ≥65y) 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).

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

4 Methods

4.1 Study sites

For the 2021/22 season, data is available from four primary care-based TND studies, 9 hospital-based TND studies (Table 1), and one register-based cohort. The Iceland Directorate of Health contributed both GP and hospital data. No new TND study sites joined the study platform. However one additional hospital (HUJT) joined HUVH. As date of symptom onset was known upfront to be systematically unavailable at RCGPRSC-OX, data from this site was not included in the primary analysis and was only planned to be included in a sensitivity analysis. For details on the study sites see the SAP section 5.1 (WebANNEX – SAP).

Table 1. Primary care and hospital sites where TND studies were conducted, 2021/22

Country	Site name	Number of primary care physicians or hospitals where subjects are identified
Primary care		
Austria	Medical University Vienna (MUV)	250
Iceland	Directorate of–Health - Embætti landlæknis (EL GP)	Ca. 200*
Italy	Istituto Superiore di Sanità (ISS)	Ca. 245
UK	Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) & University of Oxford	450
Hospital		
France	Innovative Clinical Research Network in Vaccinology (I-REIVAC)	5
Iceland	Directorate of–Health - Embætti landlæknis (EL HOSP). Landspitali University Hospital.	1*
Italy	Italian Hospital Network coordinated by Centro Interuniversitario di Ricerca sull'Influenza e le altre infezioni trasmissibili Italy (CIRI-BIVE)	5
Romania	National Institute for Infectious Disease "Prof. Dr. Matei Balș" (NIID), Bucharest	1
Spain	Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana (FISABIO)	4
Spain	Hospital Universitario Germans Trias i Pujol (GTPUH), Badalona	1
Spain	Hospital Universitario La Paz (LPUH), Madrid	1
Spain	Hospital Universitario de Salamanca (SUH), Salamanca	1
Spain	Hospital Universitari Vall d'Hebron (HUVH), Barcelona and Hospital Universitari de Girona Doctor Josep Trueta (HUJT), Girona	2
Register-based cohort		
Finland	The Finnish Institute for Health and Welfare (THL)	All

*All samples sent to national reference laboratory.

4.2 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).

4.2.1 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 I-MOVE+ 2017/18 case definition as a hospitalised 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 8.3 (WebANNEX - SAP).

During the previous season, 2020/21, the COVID-19 pandemic situation and the lack of influenza circulation prioritised COVID-19 testing over influenza. Therefore, several sites did not test all the admitted SARI or ILI patients for influenza. In contrast, in the present season, 2021/22, all the participating sites reported that all subjects presenting SARI or ILI symptoms were tested for influenza. In addition, at most sites, all ILI and SARI subjects were also tested for SARS-CoV-2. This has been done either simultaneously, by using the same swab in a multiplex PCR (e.g. Spain FISABIO), by testing consecutively for COVID-19 and influenza using the same swab (e.g. France I-REIVAC, Italy CIRI-BIVE), or by testing first for COVID-19 with an initial swab, and later on testing for influenza with a different swab (e.g. Romania NIID or Spain GTPUH) (SAP–table 8 - WebANNEX - SAP).

Subjects aged < 6 months at the time of symptom onset presenting with ILI or SARI were excluded. Other exclusion criteria were a contraindication for influenza vaccine, a prior positive influenza test in the 2021/22 season, living in a communal establishment (e.g., a long-term care facility), and unwillingness to participate or to give consent, if applicable. In addition, SARI patients who were previously hospitalised < 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 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 11.2 (WebANNEX - SAP).

The start of the study period for IVE analyses for the DRIVE studies is defined as the first week of two consecutive weeks when influenza viruses were detected at the study-site level (based on the data 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 2022, whichever occurred first. Because of the time required to prepare the Icelandic data for submission, the cut-off data for the Icelandic studies was set at April 17th, 2022. For Italy ISS, the data cut-off at the sitelevel was done on May 11th. The dates of the first and last swab and the study period for each site are shown in Table 2.

In the 2021/22 season, two distinct influenza peaks were observed, a smaller one in December 2021/January 2022 and a larger one in March/April 2022 (see section 5.2). Three observations with respect to the study period for analysis were observed:

1) The first "peak" did not lead to enough cases to trigger the "study start" definition but only the second peak did (e.g. Italy CIRI-BIVE)
2) The first peak did trigger the study start definition and the occasional influenza cases observed between the first/second peak made sure the "study-end" definition did not get triggered before the second peak occurred (e.g. France I-REIVAC)
3) There was a very minor first peak, which triggered the study start definition with no cases until the second wave started. In this case only the second wave was considered (Romania NIID).

Table 2. Dates of first and last swab, by site, TND studies, 2021/22

Site	Date of first swab	Date of last swab	Start study period for analysis	End study period for analysis
Primary care				
Austria MUV	28/10/2021	29/04/2022	03/01/2022	27/04/2022
Iceland EL GP	03/10/2021	15/04/2022	28/02/2022	15/04/2022
Italy ISS				30/04/2022
	18/10/2021	11/05/2022	07/02/2022	
UK RCGP RSC	01/09/2021	19/03/2022	n/a	n/a
Hospital				
France I-REIVAC	28/10/2021	29/04/2022	28/10/2021	28/04/2022
Iceland EL HOSP	04/10/2021	17/04/2022	24/01/2022	17/04/2022
Italy CIRI-BIVE	28/10/2021	03/05/2022	21/02/2022	17/04/2022
Romania NIID	30/10/2021	28/04/2022	23/02/2022	24/04/2022
Spain FISABIO	01/11/2021	03/05/2022	26/10/2021	28/04/2022
Spain GTPUH	09/12/2021	29/04/2022	14/12/2021	24/04/2022
Spain HUVH-HUJT	30/10/2021	28/04/2022	15/11/2021	25/04/2022
Spain LPUH	24/11/2021	28/04/2022	07/03/2022	26/04/2022

Site	Date of first swab	Date of last swab	Start study period for analysis	End study period for analysis
Spain SUH	18/11/2021	17/04/2022	21/02/2022	13/04/2022

n/a: not applicable, the study period could not be defined because of the absence of influenza cases

4.2.2 Register-based cohort study

The register-based cohort was conducted in Finland among children (6m - 6y) and older adults (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 Population Information System, National Vaccination Register, Register of Primary Health Care Visits and the Care Register for Health Care. Both primary care and hospital settings are covered. Hospitalisation 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 may receive part of its data delayed. Therefore, results are presented for 'mixed' and 'hospital' settings. Subjects with presumably incomplete vaccination records in 2021/22 and 2020/21 were excluded[1]; as were FinFluHD trial participants. The study period was defined a priori from October 4th 2021 to April 30th, 2022.

4.3 Statistical methods

The statistical methods are briefly described below. Further details are available from the SAP sections 15 and 16 (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.

4.3.1 Test-negative design studies

For the TND studies, individual-level data were transferred from the study sites to the GDPR-compliant DRIVE Research Server. Site-specific crude and confounder-adjusted IVE and 95% CI 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 participants. Confounder-adjusted IVE estimates were derived from logistic regression models. Estimates were adjusted for age, sex and calendar time (i.e. date of symptom onset). A complete case analysis was performed.

[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(17):30520.

Site-specific VE estimates from the different TND studies are pooled by using a random-effects meta-analysis. This is the main analysis in this study. Further details are given in SAP section 16 (WebANNEX - SAP). Due to the unknown impact – at the time of protocol–writing - of COVID-19 measures on the circulation of influenza in 2021/22, the protocol and SAP specified that strata-specific VE analyses would only be conducted in 2021/22 if minimum thresholds regarding the number of influenza cases in age- and setting-specific strata were met (Table 3; see also SAP section 15.2 (WebANNEX - SAP). A Supplementary Table 1 with the corresponding observed numbers in the 2021/22 season is presented in the WebANNEX.

Table 3. Vaccination coverage among control subjects and control:case ratio observed in the DRIVE data from the 2019/2020 season and the number of influenza cases required to perform the analyses in the 2021/22 season. The required numbers were obtained assuming a power of 50% and an IVE of 60%, additional information can be found in the SAP.

	Primary care			**Hospital setting**		
	6m-17yr	**18-64yr**	**≥65yr**	**6m-17yr**	**18-64yr**	**≥65yr**
Observed coverage among the controls 2019/20	13%	10%	61%	5%	23%	56%
Control:case ratio	0.8	1.7	4.3	1.1	2.2	4.5
Number of influenza cases required for performing the analysis	155	102	24	155	45	18

Several sensitivity analyses were performed: 1) models were additionally adjusted for the presence of at least one chronic condition; 2) models were additionally adjusted for COVID-19 vaccination; 3) analyses were stratified by SARS-CoV-2 status at the time of ILI/SARI presentation; 4) the time between ILI/SARI onset and the swab was reduced to a maximum of 3 days; 5) outlying/influential studies were included; 7) data from Iceland EL GP and Iceland EL HOSP were excluded; 8) the analysis will be conducted using Firth corrected estimation procedure. The planned sensitivity analysis including UK RCGPRSC-OX, where data on symptom onset was systematically unavailable, was not performed because of the absence of influenza cases in the UK RCGPRSC-OX dataset.

4.3.2 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% CI 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.

A sensitivity analysis additionally adjusting for presence of at least one chronic condition, number of GP visits, number of hospitalisations, and vaccination in the previous was performed.

4.4 Quality control

Procedures for quality control are described in the SAP section 20 (WebANNEX - SAP). The findings and conclusions of the Quality Control and Audit Committee (QCAC) will be made available in a separate report.

4.5 Ethics

Each local study was approved by national, regional or institutional ethics committees, as appropriate. The 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 for 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, except for THL (Finland), ISS (Italy) 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. For ISS, submission to the ethics committee was done for information only.

In several study sites, namely, 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.

4.6 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 Iceland EL GP and EL HOSP:

  - As described in the SAP, samples were taken and sent for analysis of respiratory viruses if there were signs of respiratory infection (upper or lower), and the decision to take a sample was based on clinician assessment. Date of symptom onset was available for most subjects; however, the actual symptoms were frequently not described or inconsistently so. Therefore no restriction in terms of ILI/SARI symptoms could be applied.
- For Italy ISS:
  - The following obligatory covariates were not collected by ISS: contraindication for influenza vaccination, institutionalisation. Furthermore, the following preferred covariate was not collected: chronic condition.
- For CIRI-IT (no impact on the study as resolved during the site's quality control procedure):
  - 25 patients were subsequently excluded from the study (prior to sharing the dataset with DRIVE) because they did not meet the inclusion criteria (eg. enrolment date after 7 days of onset, not meeting SARI definition, lives in a long-term care facility)
- For Spain SUH (no impact on the study as resolved during the site's quality control procedure):
  - One patient was excluded from the study (prior to sharing the dataset with DRIVE) because the respiratory specimen had been taken ≥ 8 days after ILI onset.
- For Iceland EL GP and EL HOSP, Italy ISS, Spain HUVH-HUJT and Spain SUH
  - No data on SARS-CoV-2 status at the time of admission has been submitted.

The following deviations from the SAP took place:

- Subjects for whom the ILI/SARI episode was not the first from recurrent episodes within the study period were not discarded, as this goes against the idea of a TND study based on incidence sampling (see SAP section 16.2.1) with the exception that subjects with a prior influenza-related ILI/SARI episode were excluded.
- Romania NIID: included in the primary analysis (instead of sensitivity analysis only), as screening for influenza was not restricted to patients with COVID-19
- Iceland: added sensitivity analysis excluding EL GP and EL HOSP in a sensitivity analysis because of inability to apply ILI/SARI case definitions
- THL analysis: in the children group, the age spline was five-dimensional instead of ten-dimensional as there were too few unique age values for the ten-dimensional spline
- THL analysis: added sensitivity analysis adjusting for all available covariates (age, sex, onset date, numbers of GP visits, numbers of hospitalisations, presence of chronic conditions)

5 Results

5.1 Influenza vaccines in Europe, 2021/22

5.1.1 Vaccine recommendations

National or regional vaccine recommendations by target group and recommendations for the use of specific vaccine types are summarised in the WebANNEX (Vaccine Recommendations). For season 2021-22, the national recommendations have been extended to essential public service workers in Spain (e.g., police, firefighters) and workers exposed to swine and avian influenza viruses in France. In 2020/21, due to the COVID-19 pandemic, persons aged 50-64y in England and 60-65y in Italy were newly eligible for a free influenza vaccination; this expanded offer was continued in 2021/22.

5.1.2 Vaccine indications

Thirteen influenza vaccines were licensed and marketed in the EU/European Economic Area (EEA)/UK for the season 2021/22. Afluria Tetra, Efluelda, Fluad Tetra and Supemtek are newly available in the EU/EEA/UK. Details on vaccine characteristics, the approved age indication and, for each age group, the sites that reported the vaccine brand in the 2021/22 studies are listed in Table 4, 8 of the 12 licensed and marketed vaccines were reported in the DRIVE dataset.

Table 4. Vaccine characteristics and age indications by vaccine brand, 2021/22

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	Sites in which the vaccine brand was observed in the DRIVE dataset, by age group		
							6m – 17y	18 - 64y	≥ 65y	
Vaccines licensed and marketed in Europe										
Afluria Tetra	Seqirus	4	Inactivated	Non-adjuvanted	Egg	Standard	≥18y	n/a	-	-
Chiroflu	Seqirus	3	Inactivated	Non-adjuvanted	Egg	Standard	≥6m	-	-	-
Efluelda	Sanofi	4	Inactivated	Non-adjuvanted	Egg	High	≥60y	n/a	MUV	CIRI-BIVE, GTPUH, HUVH-HUJT, I-REIVAC, MUV
Fluad	Seqirus	3	Inactivated	Adjuvanted	Egg	Standard	≥65y	n/a	n/a	FISABIO, ISS, LPUH, SUH
Fluad Tetra	Seqirus	4	Inactivated	Adjuvanted	Egg	Standard	≥65y	n/a	n/a	CIRI-BIVE, GTPUH, HUVH-HUJT, MUV, SUH
Fluarix Tetra	GSK	4	Inactivated	Non-adjuvanted	Egg	Standard	≥6m	ISS, MUV	ISS, MUV	CIRI-BIVE, ISS, MUV
Flucelvax Tetra	Seqirus	4	Inactivated	Non-adjuvanted	Cell (mammalian)	Standard	≥2y	-	CIRI-BIVE, FISABIO, MUV	CIRI-BIVE, FISABIO, MUV
Fluenz Tetra	AstraZeneca	4	Live	Non-adjuvanted	Egg	Standard	2-17y	THL, ISS, MUV	n/a	n/a
Influvac	Abbott	3	Inactivated	Non-adjuvanted	Egg	Standard	≥6m	-	-	-

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	Sites in which the vaccine brand was observed in the DRIVE dataset, by age group		
								6m – 17y	18 - 64y	≥ 65y
Influvac Tetra	Abbott	4	Inactivated	Non-adjuvanted	Egg	Standard	≥6m	FISABIO, MUV	FISABIO, GTPUH, HUVH-HUJT, I-REIVAC, MUV, NIID	EL HOSP, FISABIO, GTPUH, HUVH-HUJT, I-REIVAC, MUV
Supemtek	Sanofi	4	Recombinant	Non-adjuvanted	Cell (insect)	Standard	≥18y	n/a	-	-
Vaxigrip Tetra	Sanofi	4	Inactivated	Non-adjuvanted	Egg	Standard	≥6m	EL GP, EL HOSP, ISS, MUV, NIID, THL	CIRI-BIVE, EL GP, EL HOSP, HUVH-HUJT, I-REIVAC, ISS, LPUH, MUV, NIID, SUH	CIRI-BIVE, EL GP, EL HOSP, HUVH-HUJT, I-REIVAC, ISS, MUV, THL

-: 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

5.1.3 Composition of influenza vaccines

The strains contained in the 2021/22 Northern hemisphere vaccines are described below [7]:

Egg-based vaccines:

- an A/Victoria/2570/2019 (H1N1)pdm09-like virus;
- an A/Cambodia/e0826360/2020 (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).

Cell- or recombinant based vaccines:

- an A/Wisconsin/588/2019 (H1N1)pdm09-like virus;
- an A/Cambodia/e0826360/2020 (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).

5.2 Influenza epidemiology in Europe, 2021/22

The non-pharmaceutical measures in place to contain SARS-CoV-2 infection, such as the use of face masks, physical distancing and the frequent use of hand sanitizers, had a great impact on the influenza circulation worldwide, especially in the beginning of the 2021/22 influenza season.

5.2.1 Influenza epidemiology in Europe and vaccine match

In contrast to the 2020/21 season, co-circulation of influenza and SARS-CoV-2 has been observed in several European countries during the 2021/22 season. In most of the participating countries, the influenza season initially overlapped with the SARS-CoV-2 Omicron wave (starting in November 2021 and finishing in February 2022) and presented two peaks of higher activity: the first one in December 2021-January 2022, and an unusual late peak in March-April 2022. Strikingly, the influenza activity has continued much longer than normal and has also occurred during March, April and even May 2022 in several European countries (Table 5). Globally, the second wave of influenza activity (March-April 2022) has been larger than the December-January wave [8].

Table 5. Start and end of the influenza season, by country

Country	Start of influenza season	End of influenza season
Austria	8 Nov 2021	May 2022
Finland	4 Oct 2021	16 May 2022
France	13 Dec 2021	8 May 2022
Iceland	4 Oct 2021	16 May 2022
Italy	15 Nov 2021	29 Apr 2022
Romania	Nov 2021	May 2022
Spain	4 Oct 2021	16 May 2022
United Kingdom	4 Oct 2021	16 May 2022

As of week 13/2022 of the 90,644 influenza detections across the WHO European Region reported to TESSy, The European Surveillance System, 98% were type A viruses and 2% were type B viruses. Although a 115-fold increase in detections has been observed compared to 2020-2021 season, these were substantially lower than before the COVID-19 pandemic; namely a 44% reduction compared to 2019-2020 season, on account of non-pharmaceutical interventions to combat SARS-CoV-2 infections still in place. Subtype A(H3N2) has been dominating over A(H1N1)pdm09 (93% vs 7%). All but one among 32 detected B viruses were B/Victoria lineage [9].

As mentioned before, influenza activity peaked in week 52/2021, when it reached 19% positivity; it declined thereafter until week 4/2022, when it increased for a second time to reach a plateau phase between weeks 10 and 15/2022 (25-30% positivity), before declining once again (Figure 1).

The descent of the SARS-CoV-2 circulation in March, accompanied by the lifting of most of the COVID-19 interventions and restrictions in Europe could explain the late surge of influenza between March and April 2022.

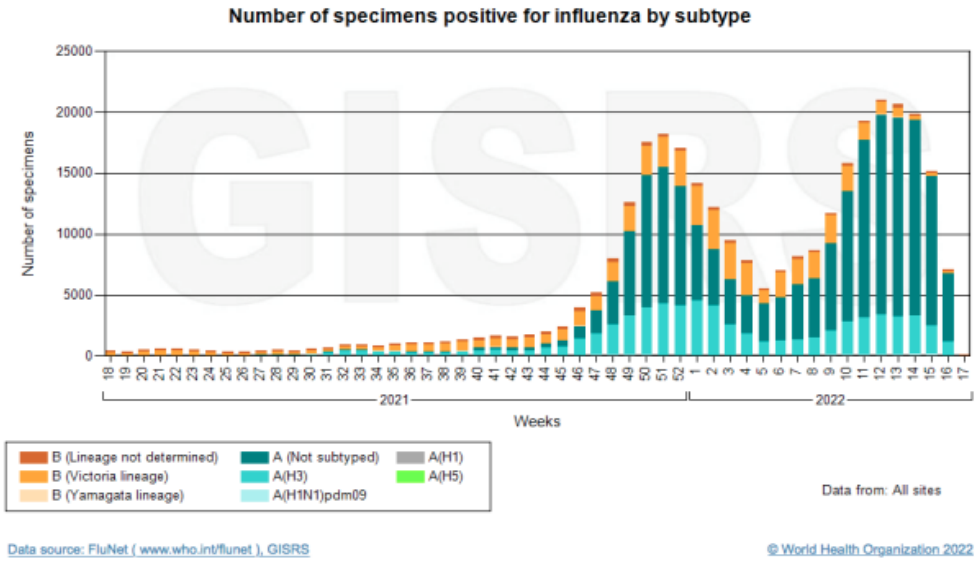


Figure 1. Circulation of influenza viruses in Europe (2021-2022). Source: FluNet [10]

The COVID-19 pandemic has also led to a reduction in influenza virus diversity. The major changes in virus diversity that have occurred since the start of the pandemic include (ref InFluNews, issue April 2022):

• No detections of three of eight A(H3N2) subclades since April 2020 (A3, A1b/135K, and A1b/197R)

• No detections of two B/Victoria clades (V1A.1 and V1A.2)

• No confirmed detections of the B/Yamagata lineage between March 2020 to February 2022, as reported by the WHO, suggesting that B/Yamagata may have been eliminated.

Within the influenza A viruses, the vast majority of the circulating influenza A viruses detected in Europe were A(H3N2) viruses. Different A(H3N2) clades have been detected worldwide; however, in Europe, three A(H3N2) subclades circulated. The predominant was subclade 3C.2a1b.2a.2, close to the Darwin prototype strain, with a hemagglutinin (HA) that has several substitutions relative to the 2021-2022 H3N2 vaccine strain. This lineage was indeed antigenically different from the Cambodia lineage (3C.2a1b.2a.1) included in the 2021-2022 vaccine.

Therefore, a mismatch between the circulating A(H3N2) influenza strain and the strain included in this season's vaccine composition has been observed. The observed difference could have resulted in a reduction of vaccine effectiveness. The older 3C.2a1b.1a lineage was not detected during the 2021/22 season (Supplementary Figure 1). The A(H3N2) subclade 3C.2a1b.2a.2 has been proposed as the H3N2 vaccine strain included in the composition of the 2022 southern hemisphere and the 2022-2023 northern hemisphere influenza vaccines.

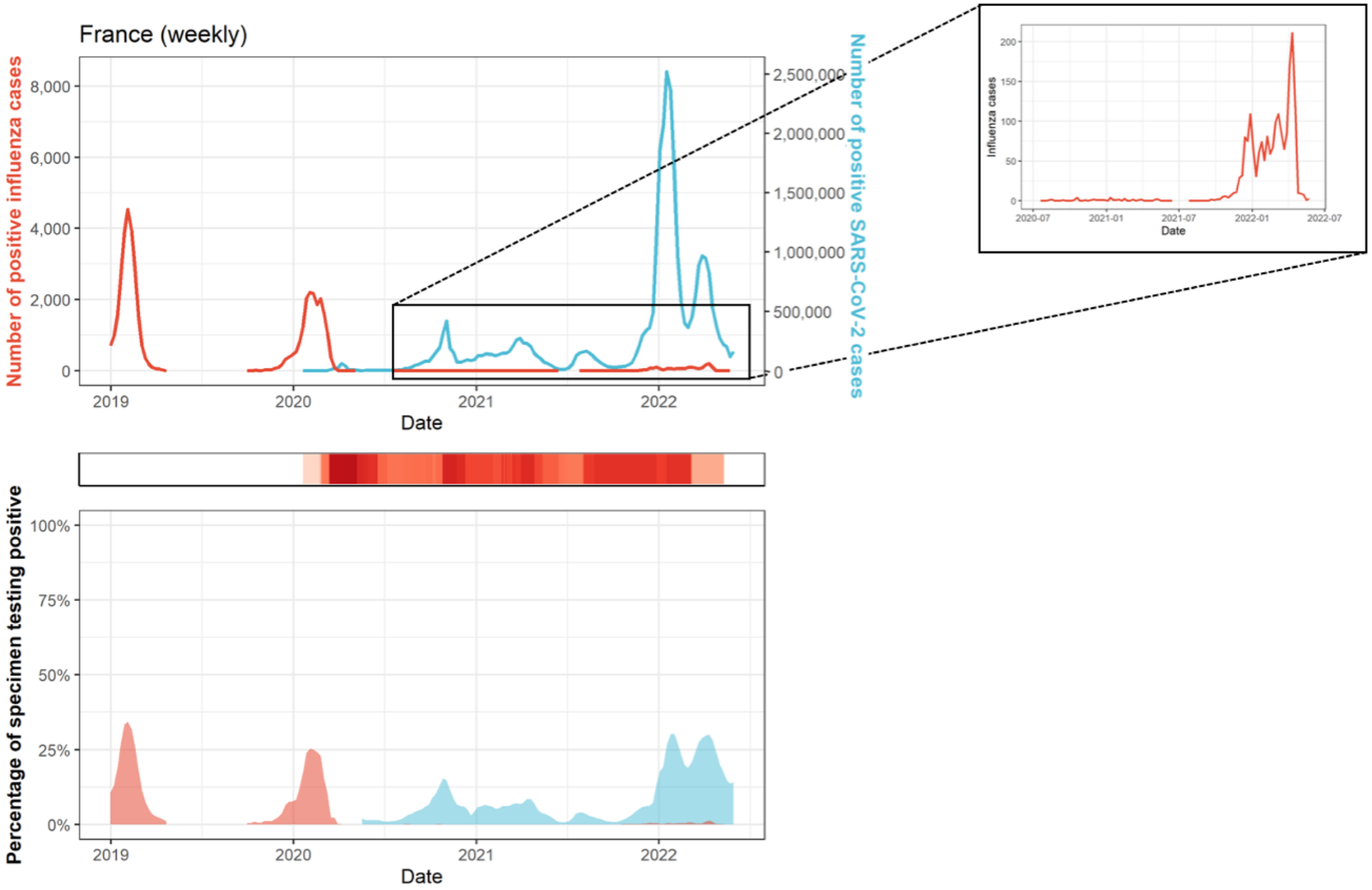
The A(H1N1)pdm09 virus circulation was limited in 2021-2022 in Europe, where two different lineages circulated (Supplementary Figure 2), with antigenic differences. The majority of the viruses were similar to the A/Guangdong/Maonan/SWL1536/2019 strain (clade 6B.1A.5a.1), the A/Victoria/2570/2019 viruses included in the 2021-2022 vaccine (clade 6B.1A.5a.2) were detected in a limited number of cases.

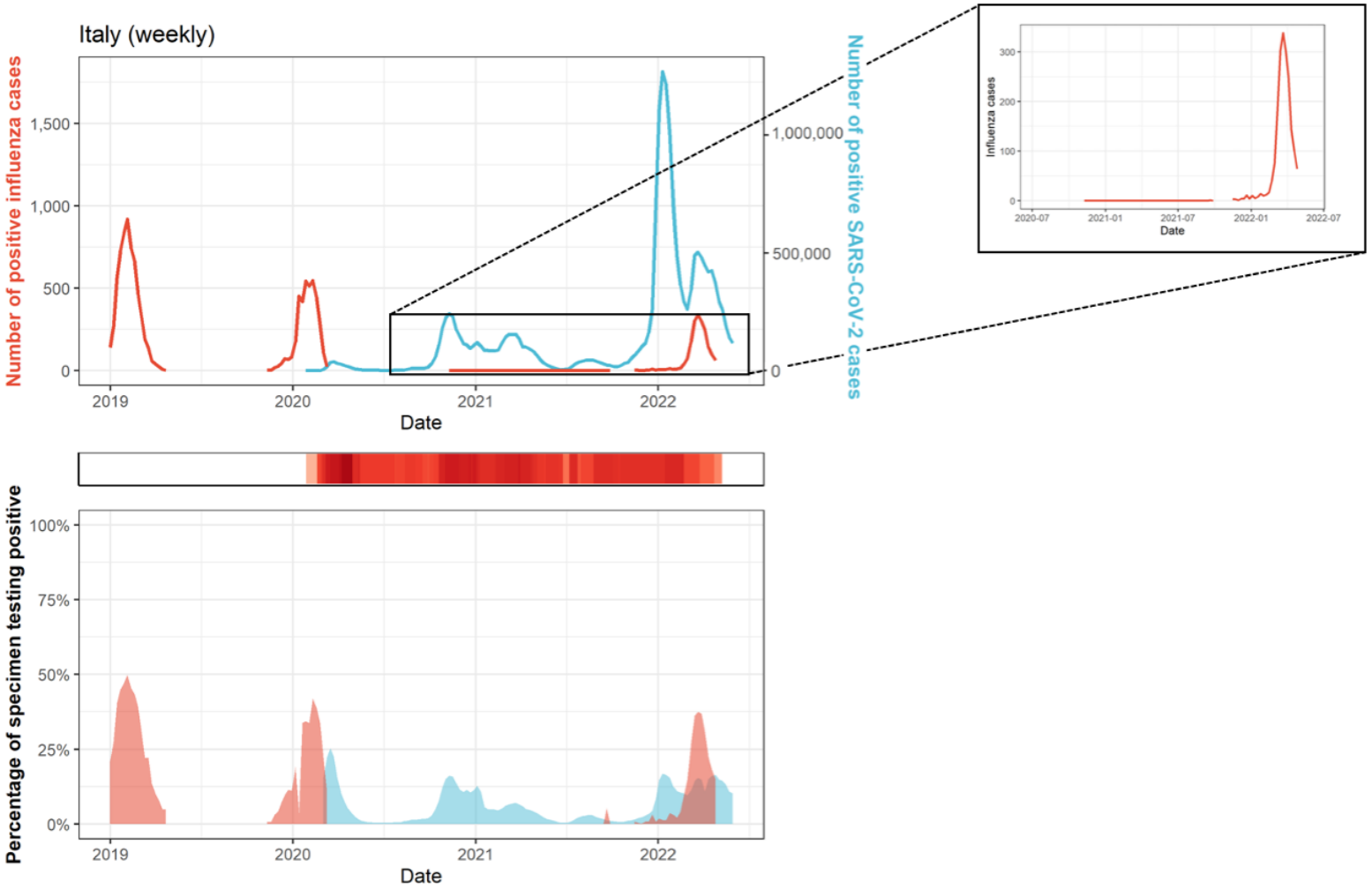
5.2.2 Influenza epidemiology by site

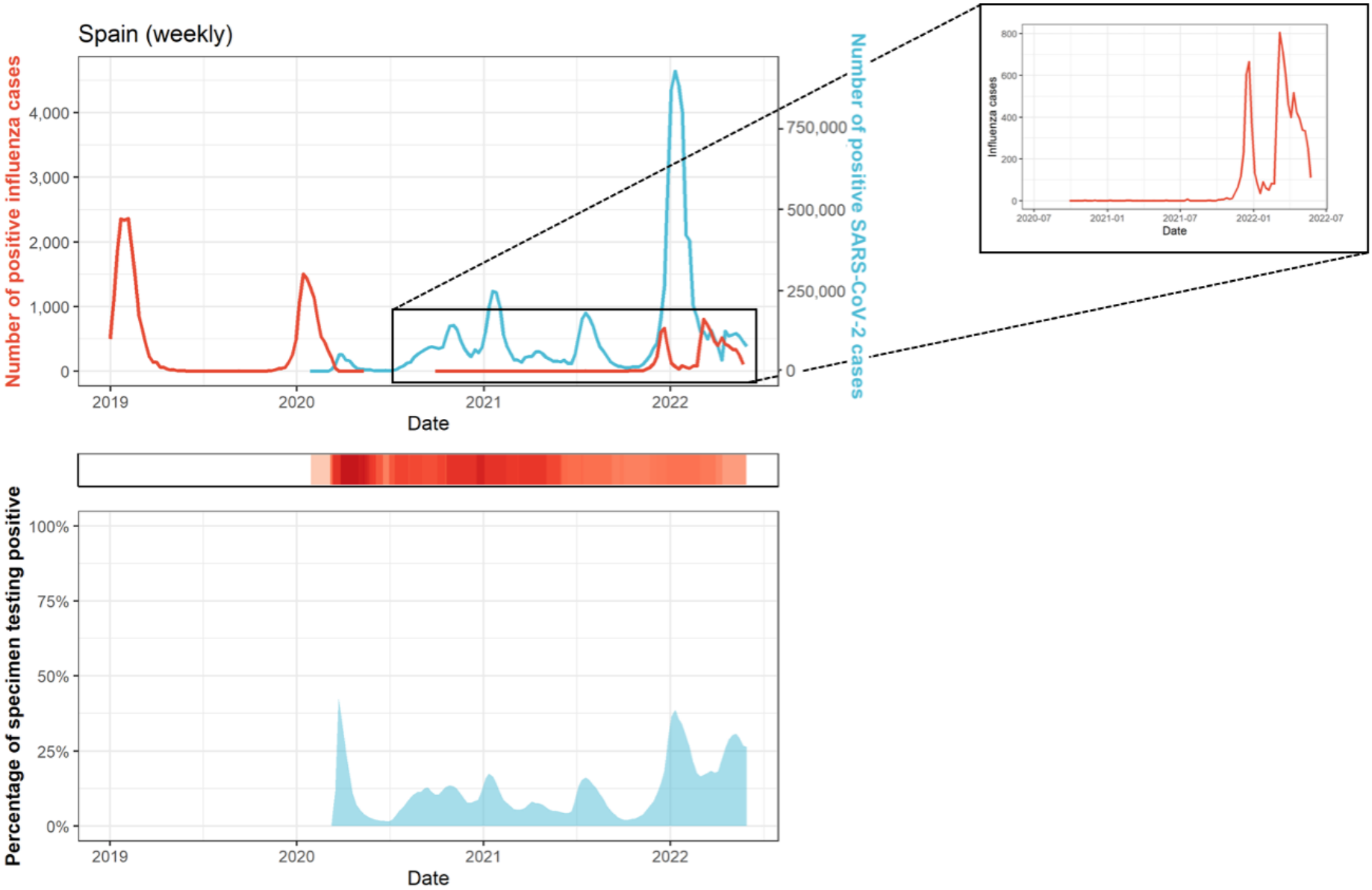
In total, 1046 influenza cases were reported in the DRIVE dataset in the TND studies and 331 in the register-based cohort study.

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

Examples of influenza and SARS-CoV-2 circulation in several European countries represented in DRIVE (Figure 2)


France (weekly)
Number of positive influenza cases
8,000
6,000
4,000
2,000
0
2,500,000
2,000,000
1,500,000
1,000,000
500,000
0
Number of positive SARS-CoV-2 cases
2019
2020
2021
2022
Date
Influenza cases
200
150
100
50
0
2020-07
2021-01
2021-07
2022-01
2022-07
Date
Percentage of specimen testing positive
100%
75%
50%
25%
0%
2019
2020
2021
2022
Date


Italy (weekly)
Number of positive influenza cases
1,500
1,000
500
0
2019
2020
2021
2022
Date
1,000,000
500,000
0
Number of positive SARS-CoV-2 cases
Influenza cases
300
200
100
0
2020-07
2021-01
2021-07
2022-01
2022-07
Date
Percentage of specimen testing positive
100%
75%
50%
25%
0%
2019
2020
2021
2022
Date


Spain (weekly)
Number of positive influenza cases
4,000
3,000
2,000
1,000
0
2019
2020
2021
2022
Date
750,000
500,000
250,000
0
Number of positive SARS-CoV-2 cases
Influenza cases
800
600
400
200
0
2020-07
2021-01
2021-07
2022-01
2022-07
Date
Percentage of specimen testing positive
100%
75%
50%
25%
0%
2019
2020
2021
2022
Date

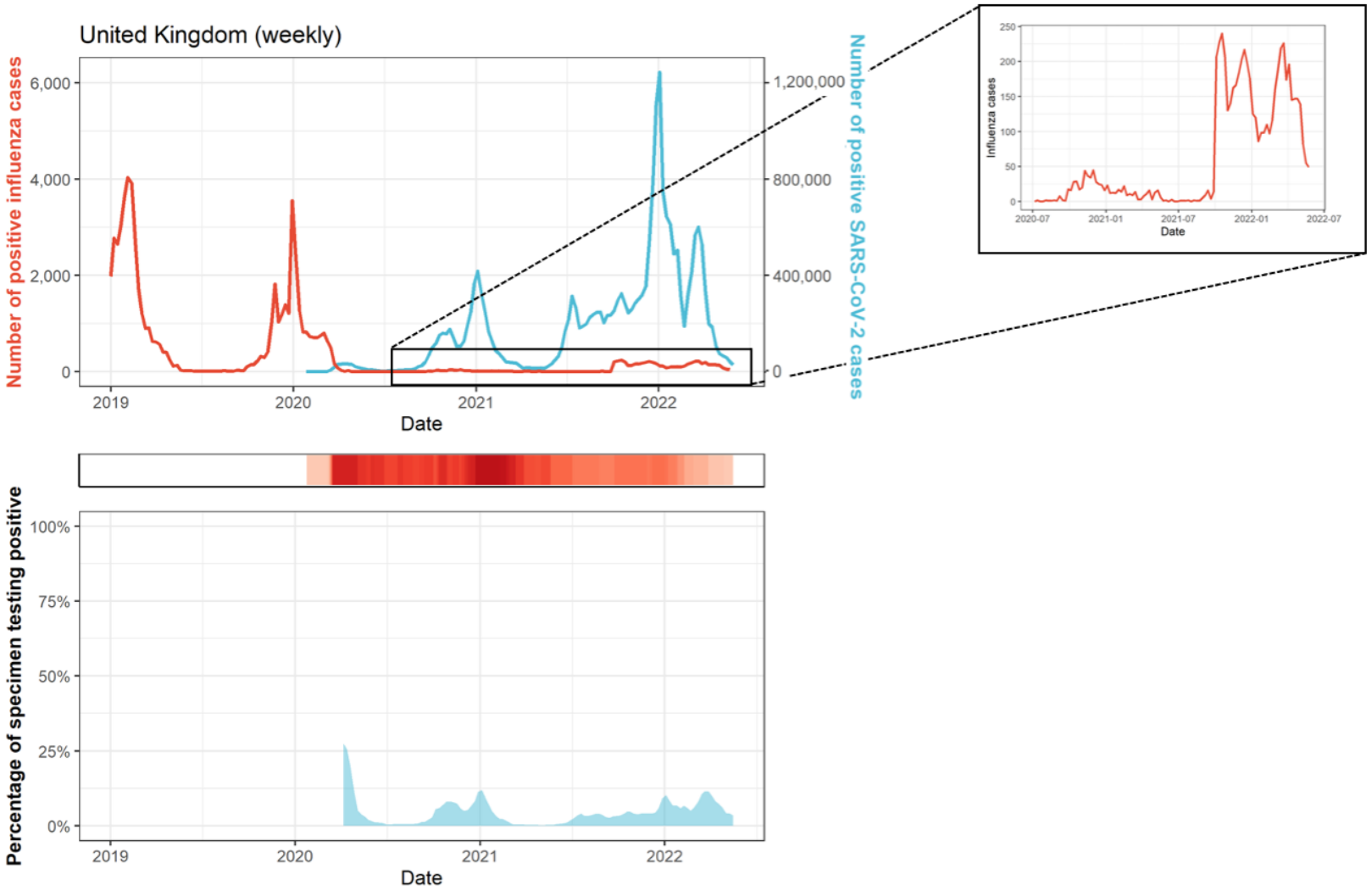


Figure 2. Influenza and SARS-CoV-2 circulation in France, Italy, Spain and the United Kingdom. Note 1: Spain and United Kingdom do not have a positivity rate for influenza because the denominator was deemed unreliable. Note 2: No influenza data for Italy has been uploaded onto FluNet since week 17, 2022. Red: number of positive influenza cases. Blue: number of positive SARS-CoV-2 cases. Source: FluCov EpiBulletin May 2022 [8]

Table 6. Influenza epidemiology and influenza cases in the DRIVE dataset, 2021/22

			Influenza type/subtype					
	Number of tested samples for influenza*	**All influenza cases (% of total tested samples)**	**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	2427	171 (7)	170 (99)	6 (4)	162 (96)	1 (1)	NA	NA
Finland								
THL	NA	331 (NA)	308 (93)	NA	NA	23 (7)	NA	NA
France								
I-REIVAC	306	42 (14)	42 (100)	8 (53)	7 (47)	0 (0)	0 (0)	0 (0)
Iceland								
EL GP	296	96 (32)	96 (100)	0 (0)	95 (100)	0 (0)	0 (0)	0 (0)
EL HOSP	1203	309 (26)	309 (100)	2 (1)	307 (99)	0 (0)	0 (0)	0 (0)
Italy								
CIRI-BIVE	317	15 (5)	15 (100)	0 (0)	15 (100)	0 (0)	0 (0)	0 (0)
ISS	534	144 (27)	144 (100)	1 (1)	142 (99)	0 (0)	0 (0)	0 (0)
Romania								
NIID	141	77 (55)	77 (100)	3 (4)	72 (96)	0 (0)	0 (0)	0 (0)
Spain								
FISABIO	645	57 (9)	57 (100)	0 (0)	55 (100)	0 (0)	0 (0)	0 (0)
GTPUH	71	34 (48)	34 (100)	0 (0)	8 (100)	0 (0)	0 (0)	0 (0)
HUVH-HUJT	279	44 (16)	44 (100)	1 (3)	36 (97)	0 (0)	0 (0)	0 (0)

			Influenza type/subtype					
	Number of tested samples for influenza*	**All influenza cases (% of total tested samples)**	**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)**
LPUH	40	10 (25)	10 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SUH	58	40 (69)	40 (100)	0 (0)	39 (100)	0 (0)	0 (0)	0 (0)
UK								
RCGP RSC	21	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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

5.2.3 COVID-19 in Europe

As of May 12, 2022, 213,041,317 COVID-19 cases have been reported in Europe since the start of the pandemic, with France (28,967,440), Germany (25,347,256), United Kingdom (22,127,666), Russia (18,227,666) and Italy (16,798,998) being the five countries reporting most cases [11]. As of week 2022-18, 138,837,0839 cases and 1,092, 498 deaths have been reported in the EU.

At the European level, from April until the end of June 2021, a decline in the number of COVID-19 contagions was observed, concomitantly with the increasing COVID-19 vaccination coverage in the region. COVID-19 incidence started increasing again following the easing of lockdown measures to contain the spread of SARS-CoV-2 in the summer, with the circulation of the SARS-CoV-2 Delta variant. However, the increase became much steeper at the end of 2021 and in January 2022, following the emergence of the Omicron variant and subvariants and the relaxation of non-pharmaceutical interventions (Figure 3). Incidence peaked in Europe at the end of January 2022, to decline thereafter at the beginning of March, when it increased again to reach the second annual peak in the first week of April, as a result of the emergence of the Omicron BA.2 variant, ~~l,~~ which, however, was significantly lower. This second peak, directly related to the circulation of the BA.2 Omicron variant, was not observed in some countries (i.e.: Portugal and Spain). Early May, a new Omicron variant (BA.5) has been circulating significantly in Portugal.

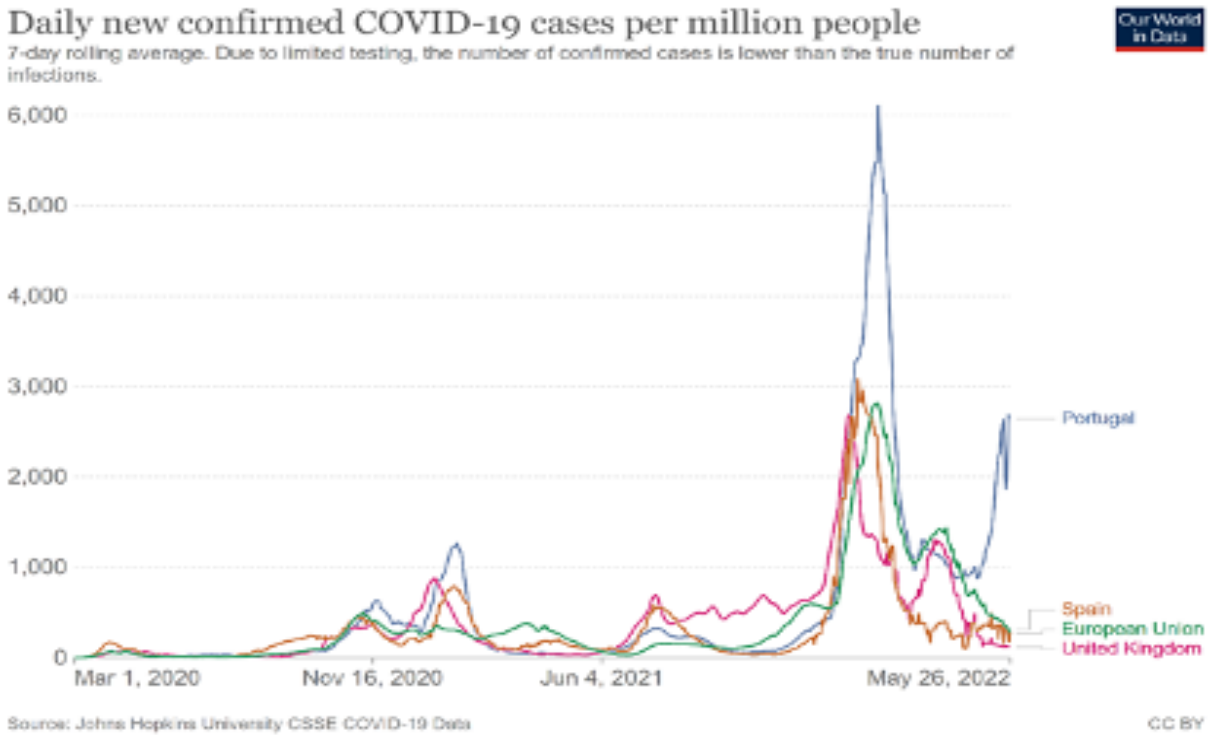


Figure 3. COVID-19 epidemiology in the European Union overall and by country: Spain, Portugal (no peak in April-May 2022) the United Kingdom. (2020-2022). Data from 2020 to 2022. Source: Our world in Data [12]

Thus, in terms of COVID-19 epidemiology, the 2021/22 influenza season was marked by the irruption in Europe of the SARS-CoV-2 Omicron variant wave from late November 2021 to February 2022, followed by a rapid descent of the SARS-CoV-2 circulation in the latter part of the influenza season (February to April 2022).

COVID-19 epidemiology by site is available in the local study reports (WebAnnex). More information is available on the ECDC website.

The COVID-19 vaccination campaign started in December 2020. It first targeted the most vulnerable population groups such as elderly people, the residents of long-term care facilities, patients with chronic diseases that were at higher risk of complications in case of SARS-CoV-2 infection, as well as the health care personnel. As the vaccine roll-out proceeded, the campaign was expanded to cover progressively younger age groups and finally also children with at least 5 years of age at the end of 2021. During autumn 2021, the administration of booster doses started with the elderly and patients with chronic diseases and was soon extended to the adult population. As of May 16, 2022, 73.6% of the total EU residents have been fully vaccinated (I.e., received all doses prescribed by the initial vaccination protocol) and 52.2% have received the booster dose [12].

5.3 Descriptive analysis

For the TND studies, 411cases and 2805 controls were retained in the primary care setting and 628 cases and 2450 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 342,078 vaccinated and 494,544 unvaccinated person-years were received and included in the analysis (Table 8).

Table 7. Number of cases and controls retained for analysis per study setting and age categories, TND studies, 2021/22

TND	**6m-17y**		**18-64y**		**≥ 65y**	
Setting	**Cases (%PV)**	**Controls (%PV)**	**Cases (%PV)**	**Controls (%PV)**	**Cases (%PV)**	**Controls (%PV)**
PC	189 (11)	1106 (16)	181 (18)	1448 (13)	41 (41)	251 (33)
Hosp	211 (4)	589 (6)	206 (14)	677 (22)	211 (65)	1184 (56)

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, 2021/22

Register-based cohort Setting	6m-6y				≥65y			
	Vac py (% of total py)	Unvac py (% of total py)	Vac cases	Unvac cases	Vac py (% of total py)	Unvac py (% of total py)	Vac cases	Unvac cases
Mixed	37508 (22)	132315 (78)	29	93	304570 (46)	362229 (54)	118	91
Hospital	37508 (22)	132315 (78)	8	17	304570 (46)	362229 (54)	51	41

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

5.3.1 Test-negative design studies

For the combined data of the primary care TND studies, 189 cases and 1106 controls were included in the primary analysis for children 6m-17y, 181 vs. 1448 for adults 18-64y, and 41 vs. 251 for those aged ≥65y. For the combined data of the hospital TND studies, 211 cases and 589 controls were included in the primary analysis for children 6m-17y, 206 vs. 677 for adults 18-64y, and 211 vs. 1184 for those aged ≥65y (Table 7). The attrition diagrams by setting are shown in Figure 4 and Figure 5. Attrition diagrams by site are available in the Data Quality Reports in the WebANNEX. 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.

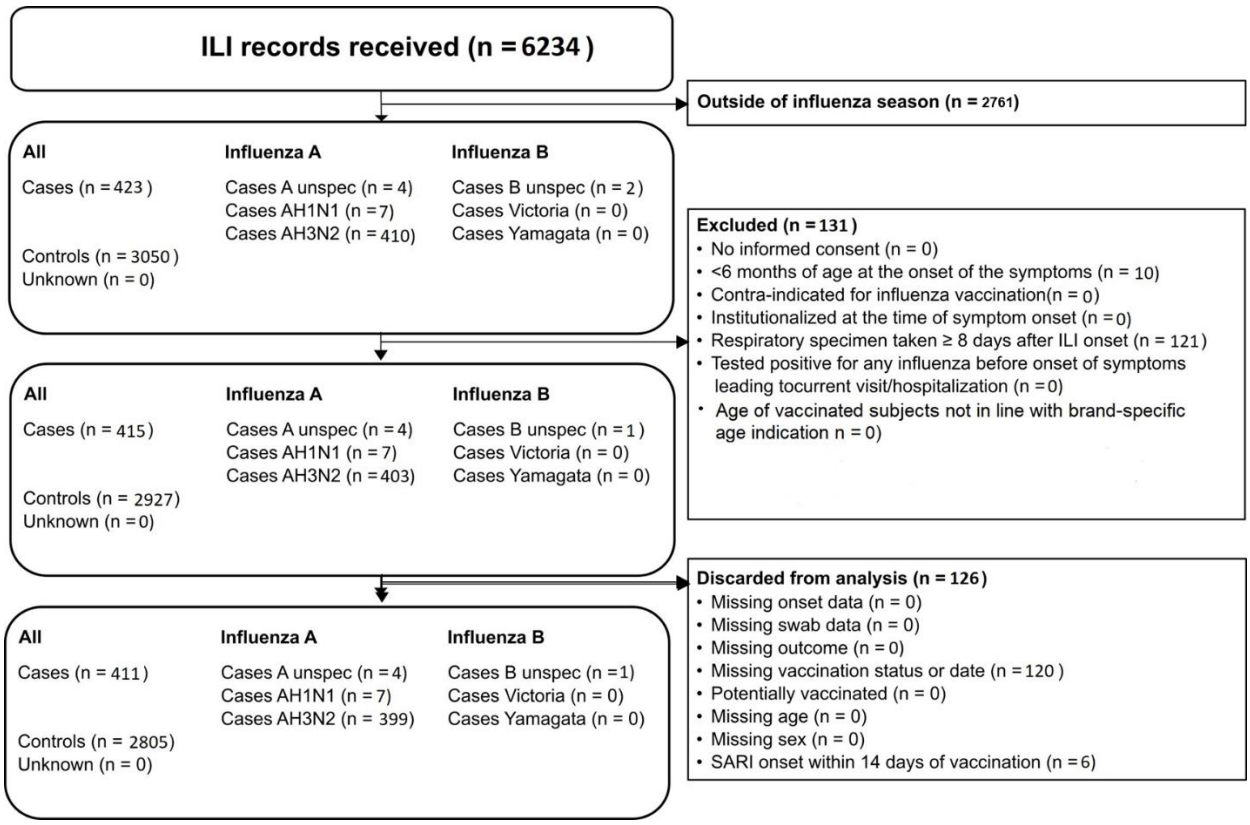


Figure 4. Attrition diagram primary care TND studies, pooled analysis, 2021/22.

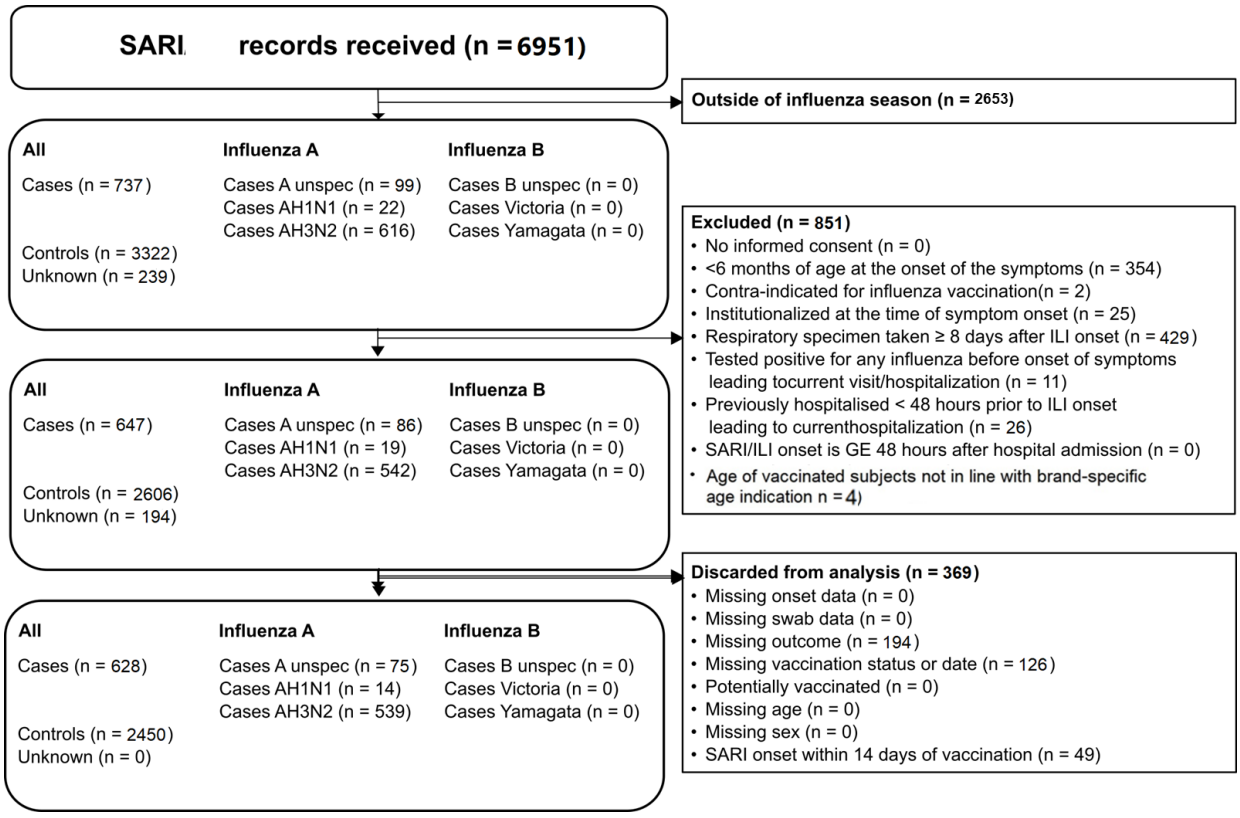


Figure 5. Attrition diagram hospital TND studies, pooled analysis, 2021/22

Table 9. Number of cases and controls by exposure status, primary care TND studies, 2021/22.*

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	1295	189	1106	20 (11)	169 (89)	174 (16)	932 (84)
	18-64y	1629	181	1448	32 (18)	149 (82)	187 (13)	1261 (87)
	≥65y	292	41	251	17 (41)	24 (59)	84 (33)	167 (67)
Vaccine brand analyses								
Fluad								
	≥65y	201	25	176	1 (4)	24 (96)	9 (5)	167 (95)
FluadTetra								
	≥65y	204	24	180	0 (0)	24 (100)	13 (7)	167 (93)
FluarixTetra								
	6m-17y	1127	171	956	2 (1)	169 (99)	24 (3)	932 (97)
	18-64y	1414	150	1264	1 (1)	149 (99)	3 (0)	1261 (100)
	≥65y	197	26	171	2 (8)	24 (92)	4 (2)	167 (98)
FluenzTetra								
	6m-17y	1210	180	1030	11 (6)	169 (94)	98 (10)	932 (90)
FlucelvaxTetra								
	2y-17y	1101	169	932	0 (0)	169 (100)	0 (0)	932 (100)
	18-64y	1416	149	1267	0 (0)	149 (100)	6 (0)	1261 (100)
	≥65y	197	24	173	0 (0)	24 (100)	6 (3)	167 (97)
Efluelda								
	60-64y	1412	149	1263	0 (0)	149 (100)	2 (0)	1261 (100)
	≥65y	192	24	168	0 (0)	24 (100)	1 (1)	167 (99)
InfluvacTetra								
	6m-17y	1105	170	935	1 (1)	169 (99)	3 (0)	932 (100)
	18-64y	1461	152	1309	3 (2)	149 (98)	48 (4)	1261 (96)
	≥65y	207	26	181	2 (8)	24 (92)	14 (8)	167 (92)
VaxigripTetra								
	6m-17y	1154	174	980	5 (3)	169 (97)	48 (5)	932 (95)
	18-64y	1564	177	1387	28 (16)	149 (84)	126 (9)	1261 (91)
	≥65y	237	35	202	11 (31)	24 (69)	35 (17)	167 (83)

*Only age groups for which the vaccine is licensed are shown

Table 10. Number of cases and controls by exposure status, hospital TND studies, 2021/22

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	800	211	589	8 (4)	203 (96)	38 (6)	551 (94)
	18-64y	883	206	677	29 (14)	177 (86)	150 (22)	527 (78)
	≥65y	1395	211	1184	138 (65)	73 (35)	666 (56)	518 (44)
Vaccine brand analyses								
Efluelda								
	60-64y	704	177	527	0 (0)	177 (100)	0 (0)	527 (100)
	≥65y	610	75	535	2 (3)	73 (97)	17 (3)	518 (97)
Fluad								
	≥65y	832	120	712	47 (39)	73 (61)	194 (27)	518 (73)
FluadTetra								
	≥65y	784	92	692	19 (21)	73 (79)	174 (25)	518 (75)
FluarixTetra								
	6m-17y	754	203	551	0 (0)	203 (100)	0 (0)	551 (100)
	18-64y	704	177	527	0 (0)	177 (100)	0 (0)	527 (100)
	≥65y	598	74	524	1 (1)	73 (99)	6 (1)	518 (99)
FlucelvaxTetra								
	2y-17y	754	203	551	0 (0)	203 (100)	0 (0)	551 (100)
	18-64y	731	178	553	1 (1)	177 (99)	26 (5)	527 (95)
	≥65y	607	73	534	0 (0)	73 (100)	16 (3)	518 (97)
InfluvacTetra								
	6m-17y	767	205	562	2 (1)	203 (99)	11 (2)	551 (98)
	18-64y	725	183	542	6 (3)	177 (97)	15 (3)	527 (97)
	≥65y	642	90	552	17 (19)	73 (81)	34 (6)	518 (94)
VaxigripTetra								
	6m-17y	787	209	578	6 (3)	203 (97)	27 (5)	551 (95)
	18-64y	833	199	634	22 (11)	177 (89)	107 (17)	527 (83)
	≥65y	851	123	728	50 (41)	73 (59)	210 (29)	518 (71)

*Only age groups for which the vaccine brand is licensed are shown

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 6. The percentage of subjects that tested positive for influenza over time is shown in Figure 7. An increase of cases starting in week 8 2022 is observed. Site-specific figures are shown in the WebANNEX.

The number of vaccinated subjects among enrolled subjects and the distribution of vaccine brands are shown in Figure 8. The highest proportion of vaccinated subjects was observed in the ≥65y age group (33% in primary care setting and 56% in hospital setting) compared to the 18-64y age group (13% and 22%) and 6m-17y (16% and 6%). The most frequently reported vaccine brands 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.

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 TND studies used an unmatched design for data collection.

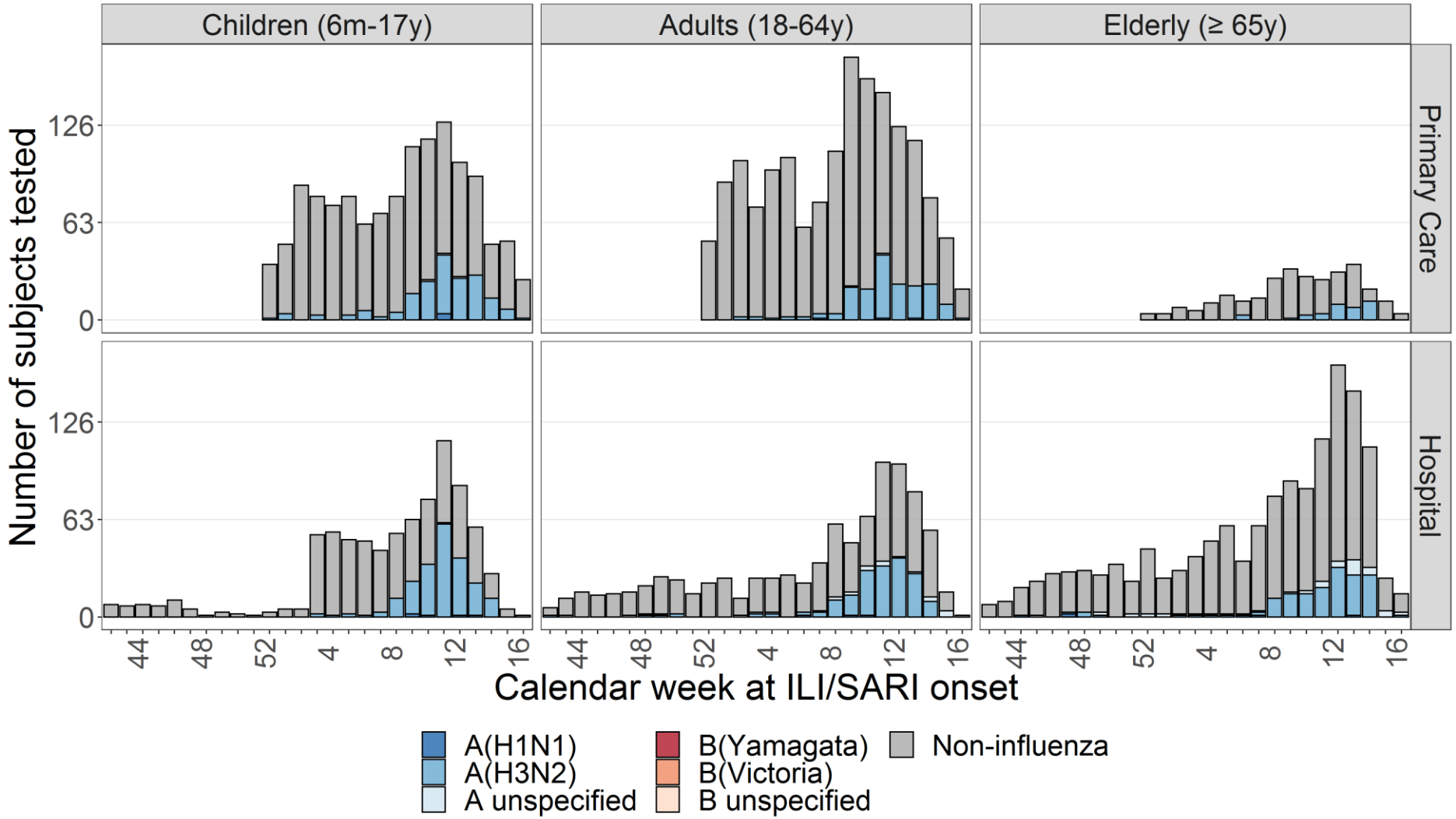


Figure 6. Distribution of ILI/SARI cases over time; TND studies, 2021/22

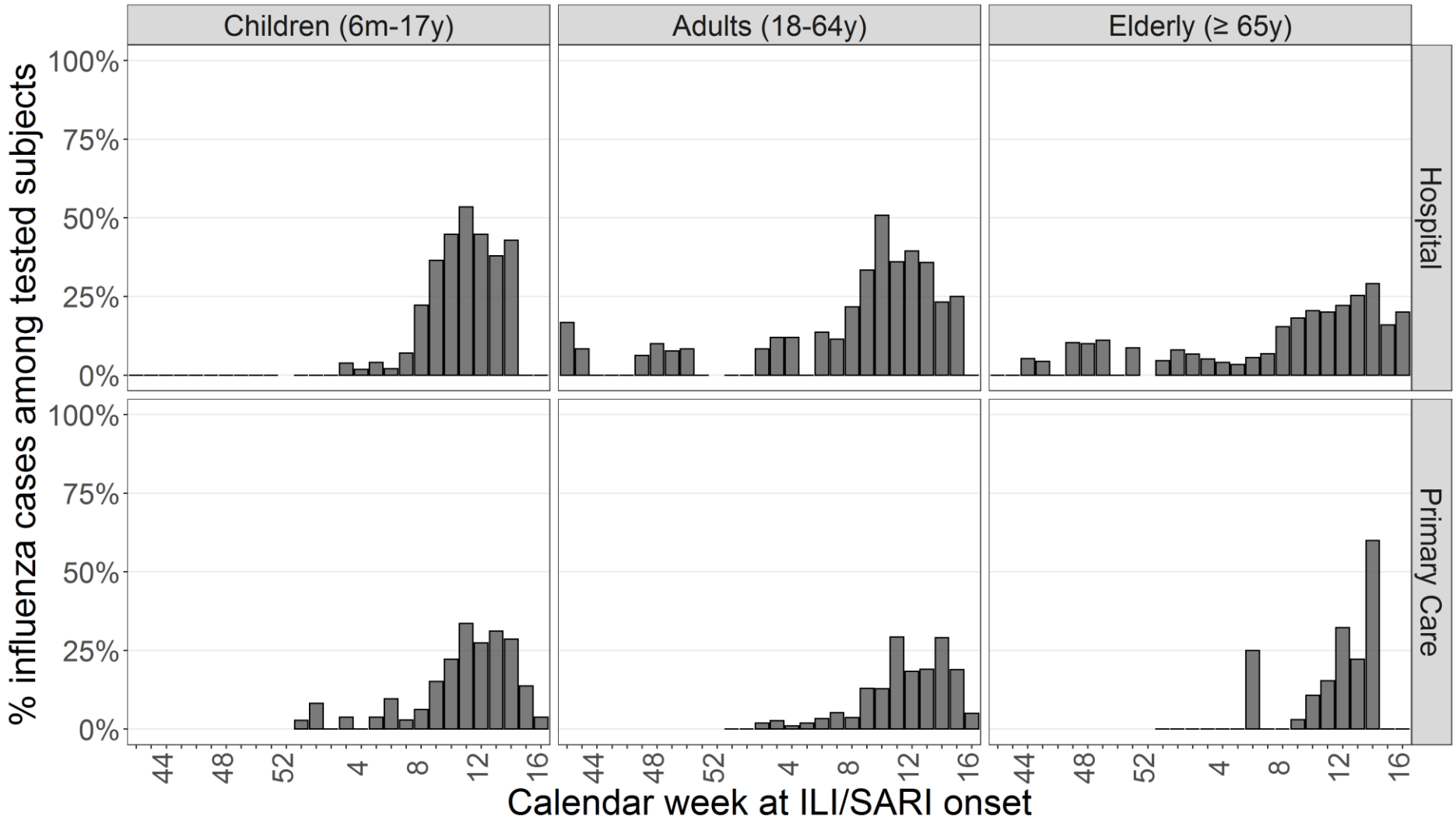
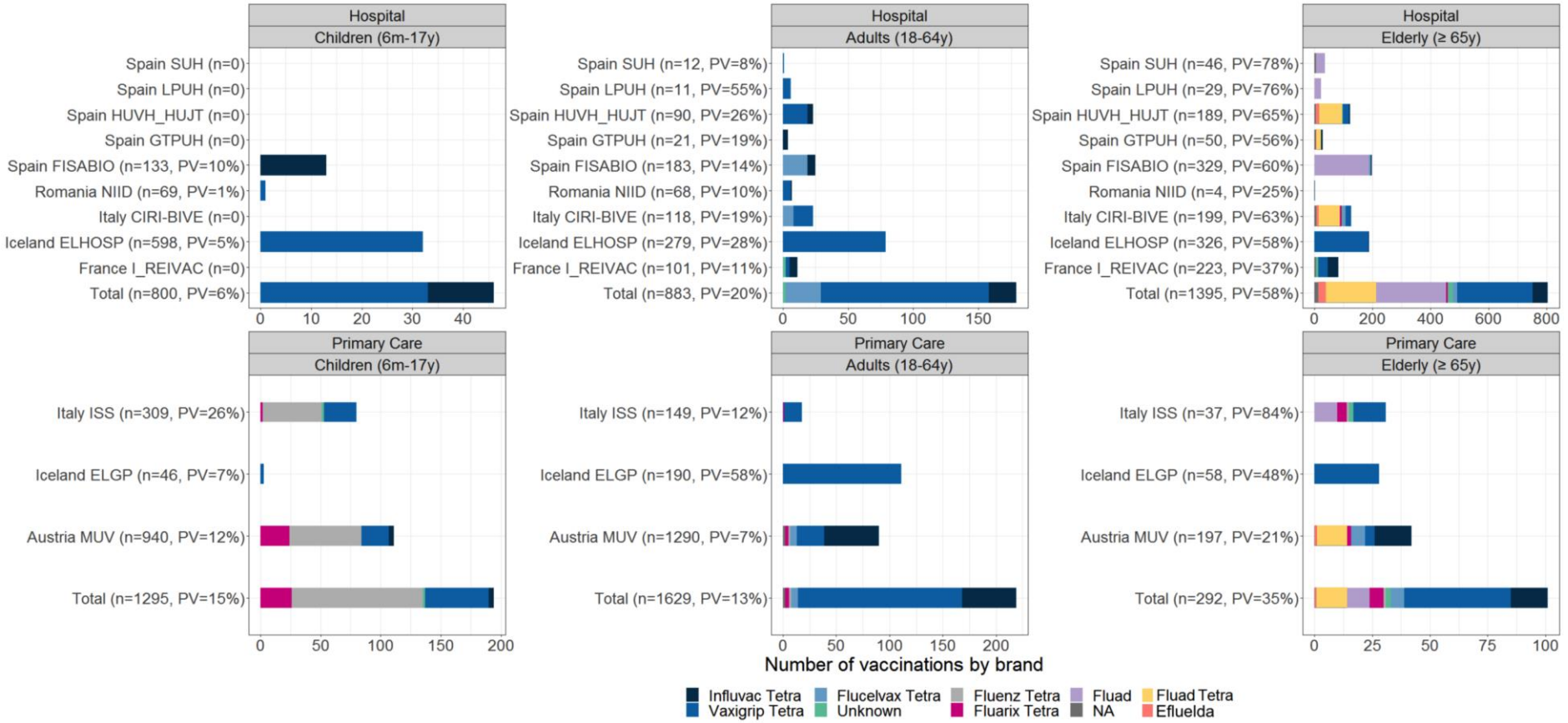


Figure 7. Distribution of percentage of influenza cases among tested ILI/SARI subjects over time, TND studies, 2021/22



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

Figure 8. Number of vaccinated subjects among enrolled subjects and distribution of vaccine brands; TND studies, 2021/22

The percentage of cases and controls with a positive SARS-CoV-2 test (among those tested for SARS-CoV-2) is shown in Table 10**Error! Reference source not found.**. The proportion of subjects with SARS-CoV-2 was highest among adults 18-64y (39% in primary care and 20% in hospital) and those aged ≥65y (46% and 19%, respectively). A total of 29 co-infections of influenza and SARS-CoV-2 were identified during the study period. COVID-19 vaccination status is shown in Table 12.

Table 11. Number and percentage of subjects with a confirmed SARS-CoV-2 infection at the time of study swab by influenza case/control and influenza vaccination status, TND studies, 2021/22

		Influenza cases			Controls			Total
Age group	**SARS-CoV-2 test result**	**All, n (% of cases)**	**Vacc., n (% of vacc cases)**	**Unvac., n (% of unvacc cases)**	**All, n (% of cases**	**Vacc., n (% of vacc controls)**	**Unvac., n (% of unvacc controls)**	**n (% of total)**
Primary care								
6m-17y	Pos.	1 (0.5)	0 (0.0)	1 (0.6)	352 (31.8)	23 (13.2)	329 (35.3)	353 (27.3)
	Neg.	77 (40.7)	7 (35.0)	70 (41.4)	510 (46.1)	81 (46.6)	429 (46.0)	587 (45.3)
	Mis.	111 (58.7)	13 (65.0)	98 (58.0)	244 (22.1)	70 (40.2)	174 (18.7)	355 (27.4)
18-64y	Pos.	2 (1.1)	0 (0.0)	2 (1.3)	635 (43.9)	34 (18.2)	601 (47.7)	637 (39.1)
	Neg.	87 (48.1)	6 (18.8)	81 (54.4)	566 (39.1)	50 (26.7)	516 (40.9)	653 (40.1)
	Mis.	92 (50.8)	26 (81.2)	66 (44.3)	247 (17.1)	103 (55.1)	144 (11.4)	339 (20.8)
≥65y	Pos.	1 (2.4)	0 (0.0)	1 (4.2)	132 (52.6)	30 (35.7)	102 (61.1)	133 (45.5)
	Neg.	3 (7.3)	2 (11.8)	1 (4.2)	61 (24.3)	10 (11.9)	51 (30.5)	64 (21.9)
	Mis.	37 (90.2)	15 (88.2)	22 (91.7)	58 (23.1)	44 (52.4)	14 (8.4)	95 (32.5)
Hospital								
6m-17y	Pos.	3 (1.4)	0 (0.0)	3 (1.5)	23 (3.9)	0 (0.0)	23 (4.2)	26 (3.2)
	Neg.	43 (20.4)	2 (25.0)	41 (20.2)	133 (22.6)	12 (31.6)	121 (22.0)	176 (22.0)
	Mis.	165 (78.2)	6 (75.0)	159 (78.3)	433 (73.5)	26 (68.4)	407 (73.9)	598 (74.8)
18-64y	Pos.	15 (7.3)	0 (0.0)	15 (8.5)	159 (23.5)	26 (17.3)	133 (25.2)	174 (19.7)
	Neg.	86 (41.7)	8 (27.6)	78 (44.1)	242 (35.7)	42 (28.0)	200 (38.0)	328 (37.1)
	Mis.	105 (51.0)	21 (72.4)	84 (47.5)	276 (40.8)	82 (54.7)	194 (36.8)	381 (43.1)
≥65y	Pos.	7 (3.3)	5 (3.6)	2 (2.7)	262 (22.1)	118 (17.7)	144 (27.8)	269 (19.3)
	Neg.	81 (38.4)	50 (36.2)	31 (42.5)	483 (40.8)	284 (42.6)	199 (38.4)	564 (40.4)
	Mis.	123 (58.3)	83 (60.1)	40 (54.8)	439 (37.1)	264 (39.6)	175 (33.8)	562 (40.3)

Mis.: missing; Neg.: negative; Pos.: positive; Vacc.: vaccinated with influenza vaccine; unvacc.: not vaccinated with influenza vaccine

Table 12. Number and percentage of subjects by COVID-19 vaccination status by influenza case/control and influenza vaccination status, TND studies, 2021/22*

		Influenza cases			Controls			Total
Age group	**COVID-19 vaccination status**	**All, n (% of cases)**	**Vacc., n (% of vacc cases)**	**Unvac., n (% of unvacc cases)**	**All, n (% of cases)**	**Vacc., n (% of vacc controls)**	**Unvac., n (% of unvacc controls)**	**n (% of total)**
Primary care								
6m-17y	Booster	6 (3.2)	0 (0.0)	6 (3.6)	13 (1.2)	1 (0.6)	12 (1.3)	19 (1.5)
	Fully vaccinated	5 (2.6)	0 (0.0)	5 (3.0)	98 (8.9)	9 (5.2)	89 (9.5)	103 (8.0)
	Partially vaccinated	11 (5.8)	2 (10.0)	9 (5.3)	69 (6.2)	17 (9.8)	52 (5.6)	80 (6.2)
	Not vaccinated	36 (19.0)	3 (15.0)	33 (19.5)	540 (48.8)	62 (35.6)	478 (51.3)	576 (44.5)
	Unknown	131 (69.3)	15 (75.0)	116 (68.6)	386 (34.9)	85 (48.9)	301 (32.3)	517 (39.9)
18-64y	Booster	25 (13.8)	2 (6.2)	23 (15.4)	382 (26.4)	41 (21.9)	341 (27.0)	407 (25.0)
	Fully vaccinated	11 (6.1)	0 (0.0)	11 (7.4)	178 (12.3)	4 (2.1)	174 (13.8)	189 (11.6)
	Partially vaccinated	29 (16.0)	2 (6.2)	27 (18.1)	311 (21.5)	29 (15.5)	282 (22.4)	340 (20.9)
	Not vaccinated	16 (8.8)	2 (6.2)	14 (9.4)	247 (17.1)	1 (0.5)	246 (19.5)	263 (16.1)
	Unknown	100 (55.2)	26 (81.2)	74 (49.7)	330 (22.8)	112 (59.9)	218 (17.3)	430 (26.4)
≥ 65y	Booster	1 (2.4)	1 (5.9)	0 (0.0)	109 (43.4)	24 (28.6)	85 (50.9)	110 (37.7)
	Fully vaccinated	1 (2.4)	0 (0.0)	1 (4.2)	10 (4.0)	1 (1.2)	9 (5.4)	11 (3.8)
	Partially vaccinated	2 (4.9)	1 (5.9)	1 (4.2)	44 (17.5)	12 (14.3)	32 (19.2)	46 (15.8)
	Not vaccinated	0 (0.0)	0 (0.0)	0 (0.0)	24 (9.6)	0 (0.0)	24 (14.4)	24 (8.2)
	Unknown	37 (90.2)	15 (88.2)	22 (91.7)	64 (25.5)	47 (56.0)	17 (10.2)	101 (34.6)
Hospital								
6m-17y	Fully vaccinated	8 (3.8)	1 (12.5)	7 (3.4)	3 (0.5)	0 (0.0)	3 (0.5)	11 (1.4)
	Partially vaccinated	1 (0.5)	0 (0.0)	1 (0.5)	6 (1.0)	1 (2.6)	5 (0.9)	7 (0.9)
	Not vaccinated	37 (17.5)	1 (12.5)	36 (17.7)	147 (25.0)	11 (28.9)	136 (24.7)	184 (23.0)
	Unknown	165 (78.2)	6 (75.0)	159 (78.3)	433 (73.5)	26 (68.4)	407 (73.9)	598 (74.8)
18-64y	Booster	30 (14.6)	6 (20.7)	24 (13.6)	112 (16.5)	35 (23.3)	77 (14.6)	142 (16.1)
	Fully vaccinated	32 (15.5)	2 (6.9)	30 (16.9)	163 (24.1)	20 (13.3)	143 (27.1)	195 (22.1)
	Partially vaccinated	25 (12.1)	1 (3.4)	24 (13.6)	40 (5.9)	5 (3.3)	35 (6.6)	65 (7.4)

	Not vaccinated	28 (13.6)	0 (0.0)	28 (15.8)	78 (11.5)	1 (0.7)	77 (14.6)	106 (12.0)
	Unknown	91 (44.2)	20 (69.0)	71 (40.1)	284 (41.9)	89 (59.3)	195 (37.0)	375 (42.5)
≥ 65y	Booster	40 (19.0)	27 (19.6)	13 (17.8)	283 (23.9)	195 (29.3)	88 (17.0)	323 (23.2)
	Fully vaccinated	27 (12.8)	16 (11.6)	11 (15.1)	234 (19.8)	80 (12.0)	154 (29.7)	261 (18.7)
	Partially vaccinated	38 (18.0)	28 (20.3)	10 (13.7)	57 (4.8)	35 (5.3)	22 (4.2)	95 (6.8)
	Not vaccinated	6 (2.8)	1 (0.7)	5 (6.8)	71 (6.0)	6 (0.9)	65 (12.5)	77 (5.5)
	Unknown	100 (47.4)	66 (47.8)	34 (46.6)	539 (45.5)	350 (52.6)	189 (36.5)	639 (45.8)

*indicate how one~~1~~ dose of Janssen is considered in a footnote. Vacc.: vaccinated with influenza vaccine; unvacc.: not vaccinated with influenza vaccine

5.3.2 Register-based cohort study, Finland

The Finland THL register-based cohort includes children 6m-6y (169,823 person-years) and older adults 65-100y (666,799 person-years). Tabular and graphical summaries of the data are provided in Table 13 and Figure 9. Very little influenza virus circulation was observed (Figure 9, top left). The vaccine brands used were Fluenz Tetra and Vaxigrip Tetra in children, and Vaxigrip Tetra in adults ≥65y (Figure 9, bottom left). Key covariates are shown (Figure 9, bottom right).

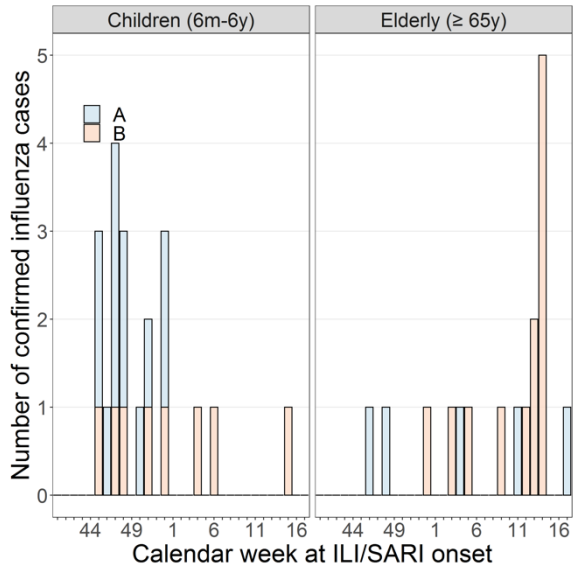
Population characteristics for each exposure, and for influenza in the hospital setting, are provided on the WebANNEX.

Table 13. Number of influenza infections and person-years by vaccination status and exposure, Finland THL register-based cohort study, 2021/22

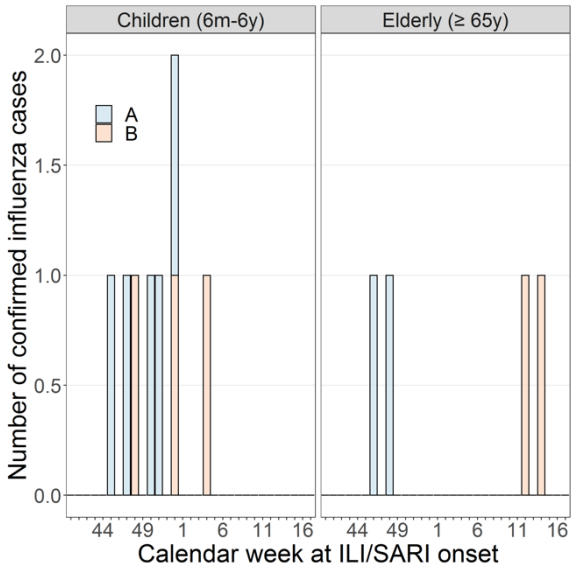
Analysis	**Age group**	**Vaccinated**			**Unvaccinated**		
		Number of influenza infections	**Number of hospitalised influenza infections***	**Person-years**	**Number of influenza infections**	**Number of hospitalised influenza infections***	**Person-years**
Any vaccine							
	6m-6y	29	8	37508	93	17	132315
	≥65y	118	51	304570	91	41	362229
Vaxigrip Tetra							
	6m-6y	6	1	8747	93	17	132315
	≥65y	118	51	300590	91	41	362229

Analysis	Age group	Vaccinated			Unvaccinated		
		Number of influenza infections	Number of hospitalised influenza infections*	Person-years	Number of influenza infections	Number of hospitalised influenza infections*	Person-years
Fluenz Tetra							
	2y-6y	22	7	28508	79	16	109650

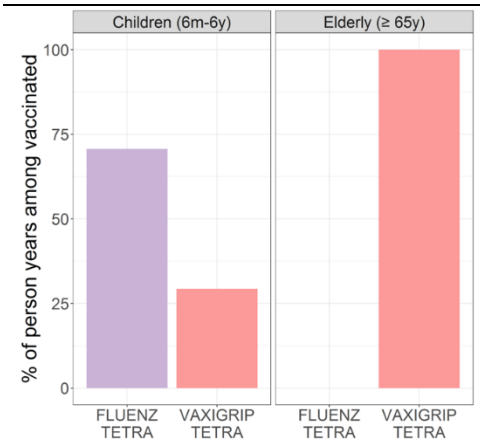
*infections timely associated with a hospitalisation



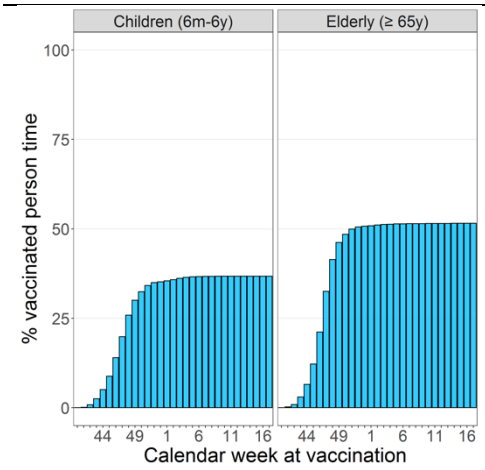
Number of influenza cases by type, mixed setting, by week



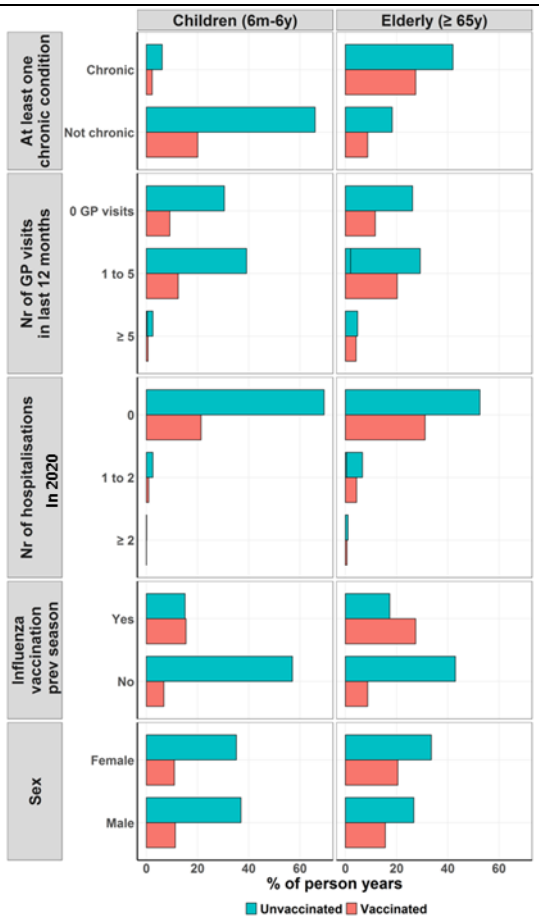
Number of influenza cases by type, hospital setting, by week



Distribution of vaccine brands



Percentage of vaccinated person time, by week



Distribution of covariates among exposed and unexposed

Figure 9. Data visualisations, Finland THL register-based cohort study, 2021/22

5.4 Primary objective: overall IVE and IVE by brand

5.4.1 Test-negative design studies

5.4.1.1 Main analysis

For all strata, the thresholds described in Table 3 were met. For the exposure 'any influenza', the age groups for which the site-specific VE estimates could be obtained are shown in Table 14. Site-specific VE estimates could be obtained for at least one stratum per site, except for UK RCGP RSC.

Table 14. Overview of age groups for which site-specific VE analyses could be obtained

	Site-specific VE analysis performed		
Site	**6m-17y**	**18-64y**	**≥65y**
Primary care			
Austria MUV			
Iceland EL GP			
Italy ISS			
UK RCGP RSC			
Hospital			
France I-REIVAC			
Iceland EL HOSP			
Italy CIRI-BIVE			
Romania NIID			
Spain FISABIO			
Spain GTPUH			
Spain HUVH-HUJT			
Spain LPUH			
Spain SUH			

Legend	Yes	No	Not applicable as site did not plan recruitment in this age group

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

The pooled confounder-adjusted IVE estimates for every exposure of interest (any vaccine, by brand) stratified by age group and health care setting are provided in Figure 10 to Figure 18. Wide CI (with a confidence interval width > 40%) are coloured light grey to emphasise that estimates with wide CI 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.

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.

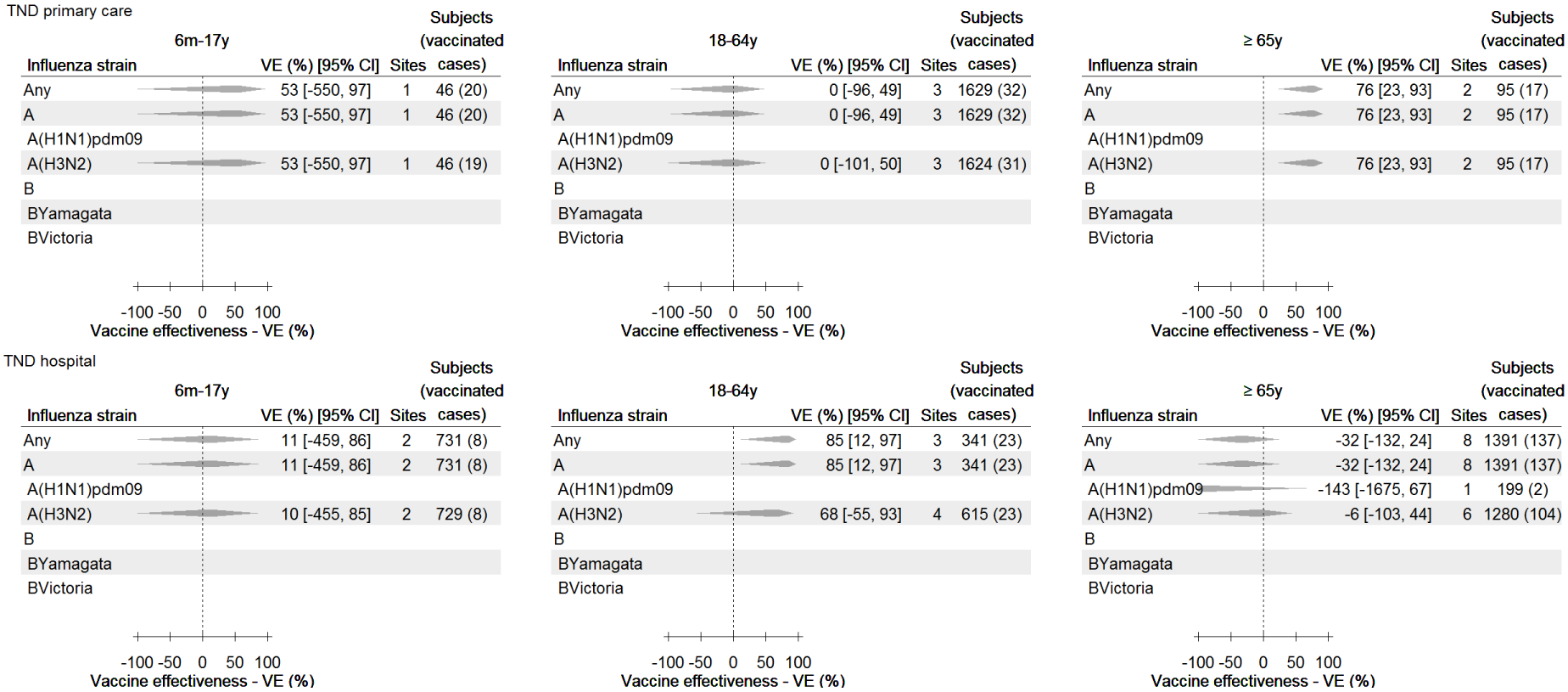


Figure 10. Any influenza vaccine: pooled confounder-adjusted (age, sex and date of symptom onset) influenza vaccine effectiveness against laboratory-confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2021/22

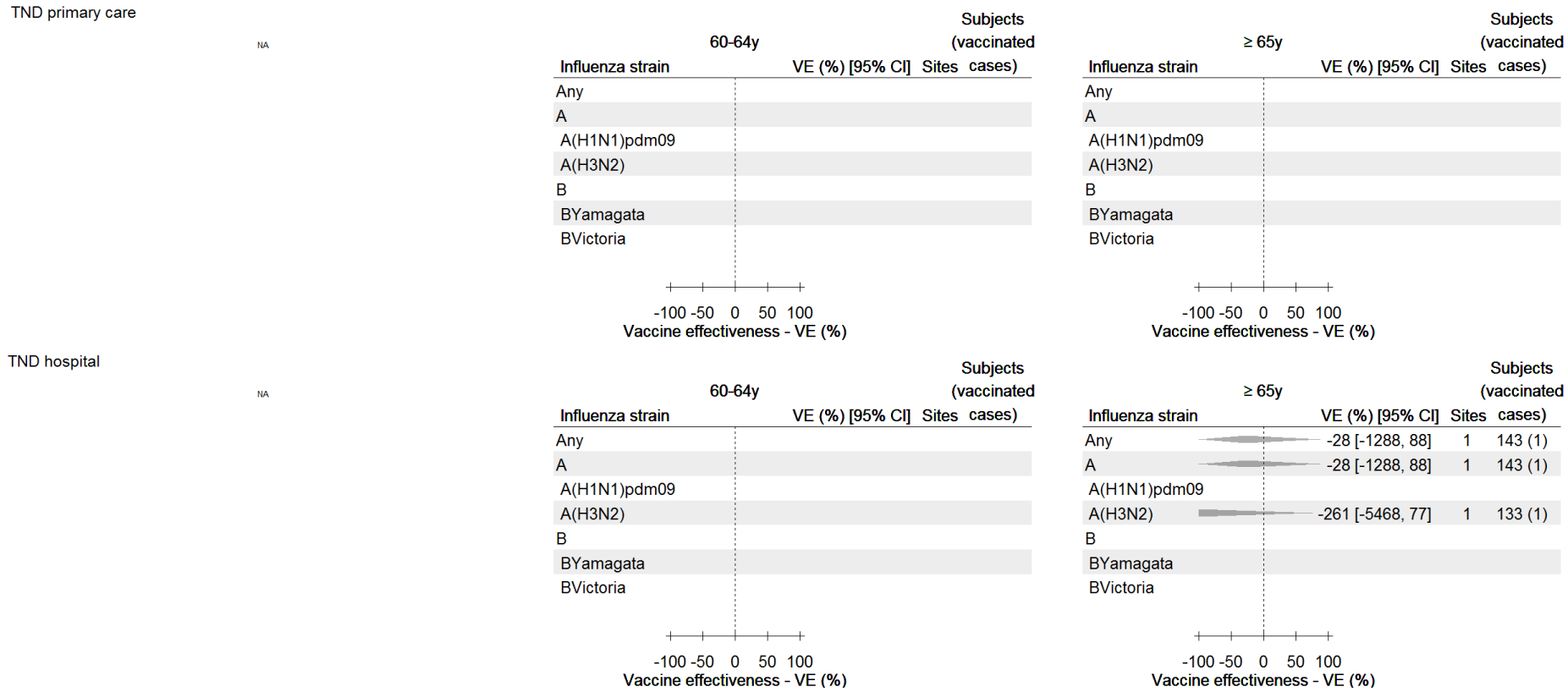
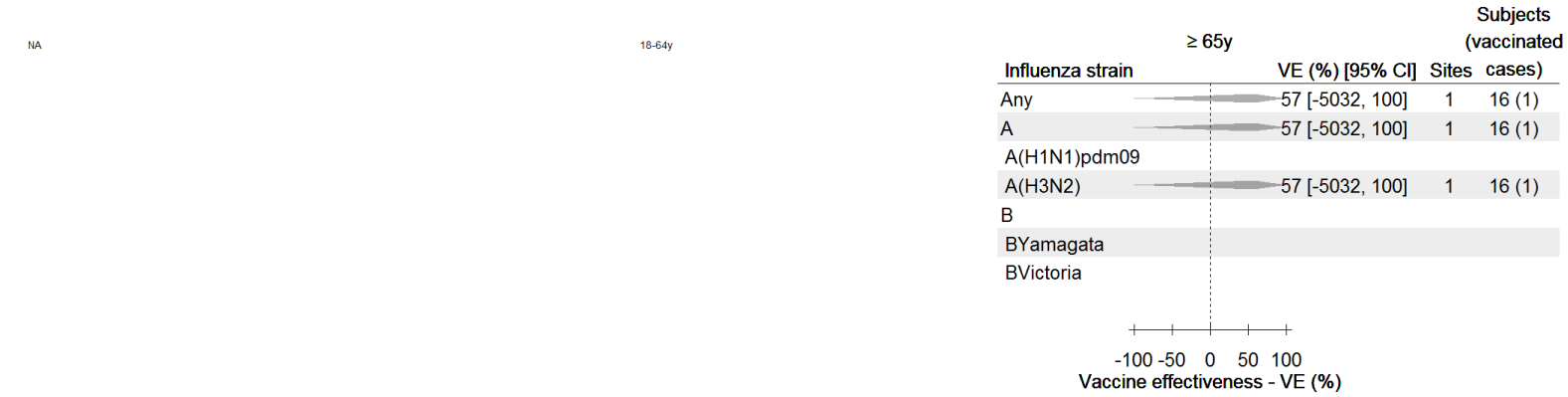


Figure 11. EFLUELDA (SANOFI): pooled confounder-adjusted (age, sex and date of symptom onset) influenza vaccine effectiveness against laboratory-confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2021/22

TND primary care



TND hospital

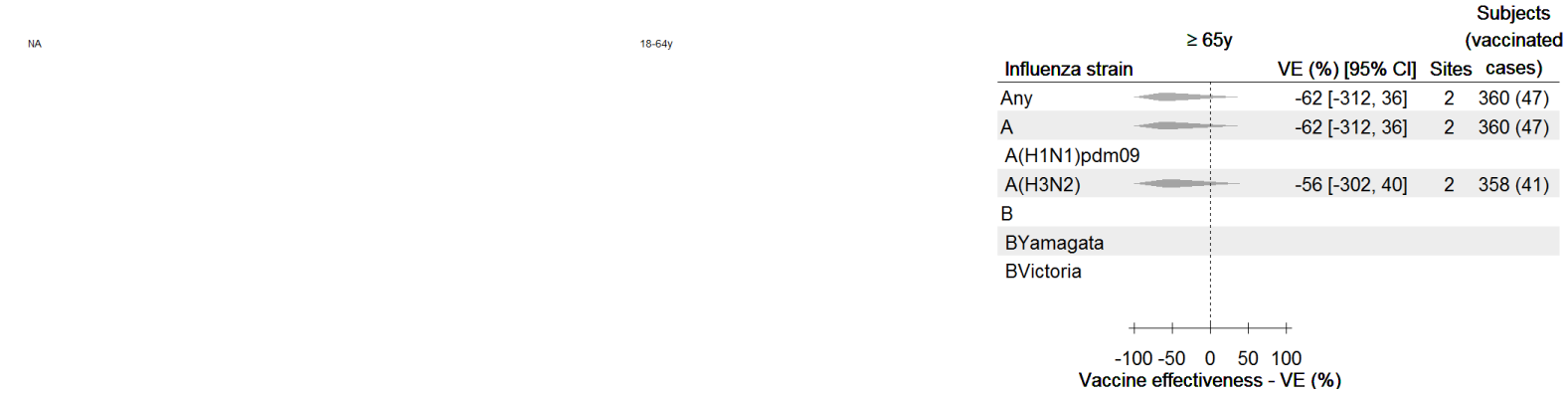


Figure 12. FLUAD (SEQIRUS): pooled confounder-adjusted (age, sex and date of symptom onset) influenza vaccine effectiveness against laboratory-confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2021/22

Figure 13. FLUAD TETRA (SEQIRUS): pooled confounder-adjusted (age, sex and date of symptom onset) influenza vaccine effectiveness against laboratory-confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2021/22

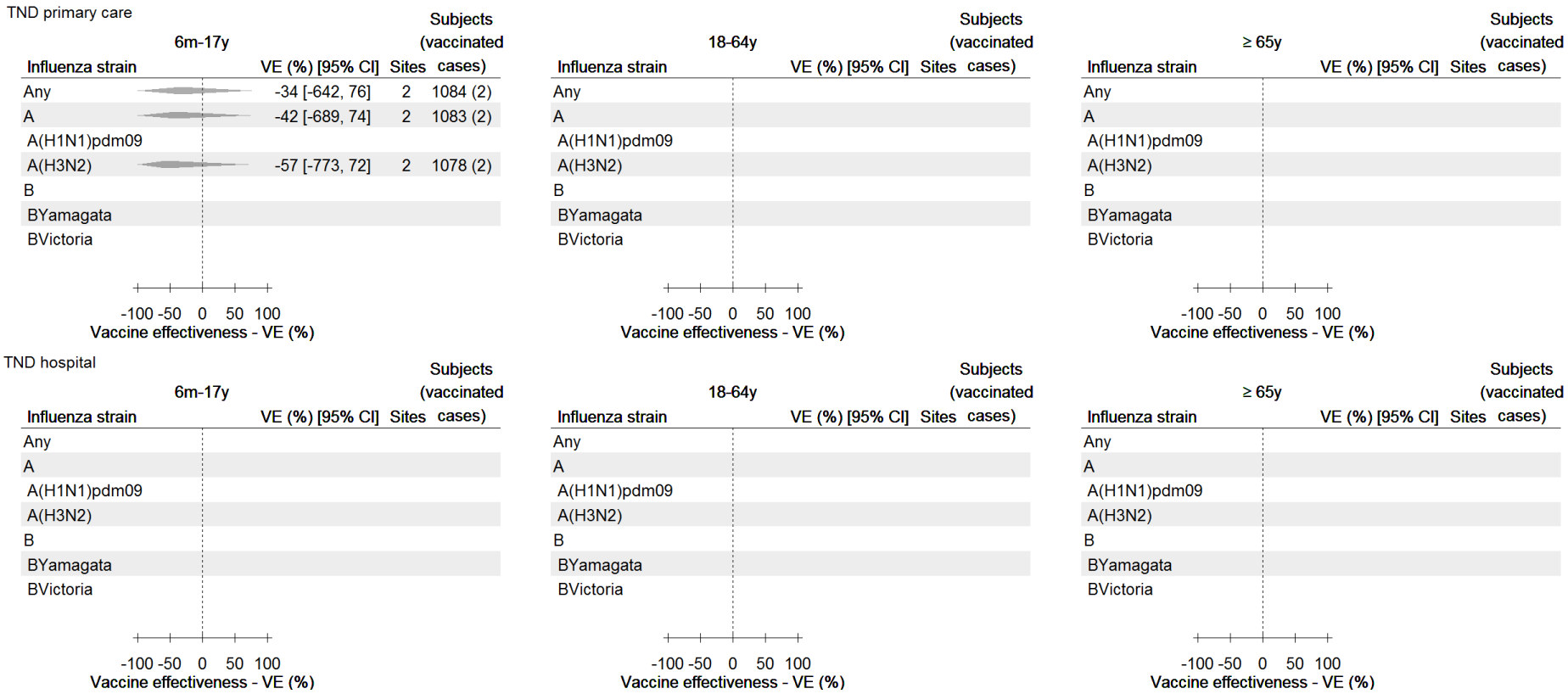


Figure 14. FLUARIX TETRA (GSK): pooled confounder-adjusted (age, sex and date of symptom onset) influenza vaccine effectiveness against laboratory-confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2021/22

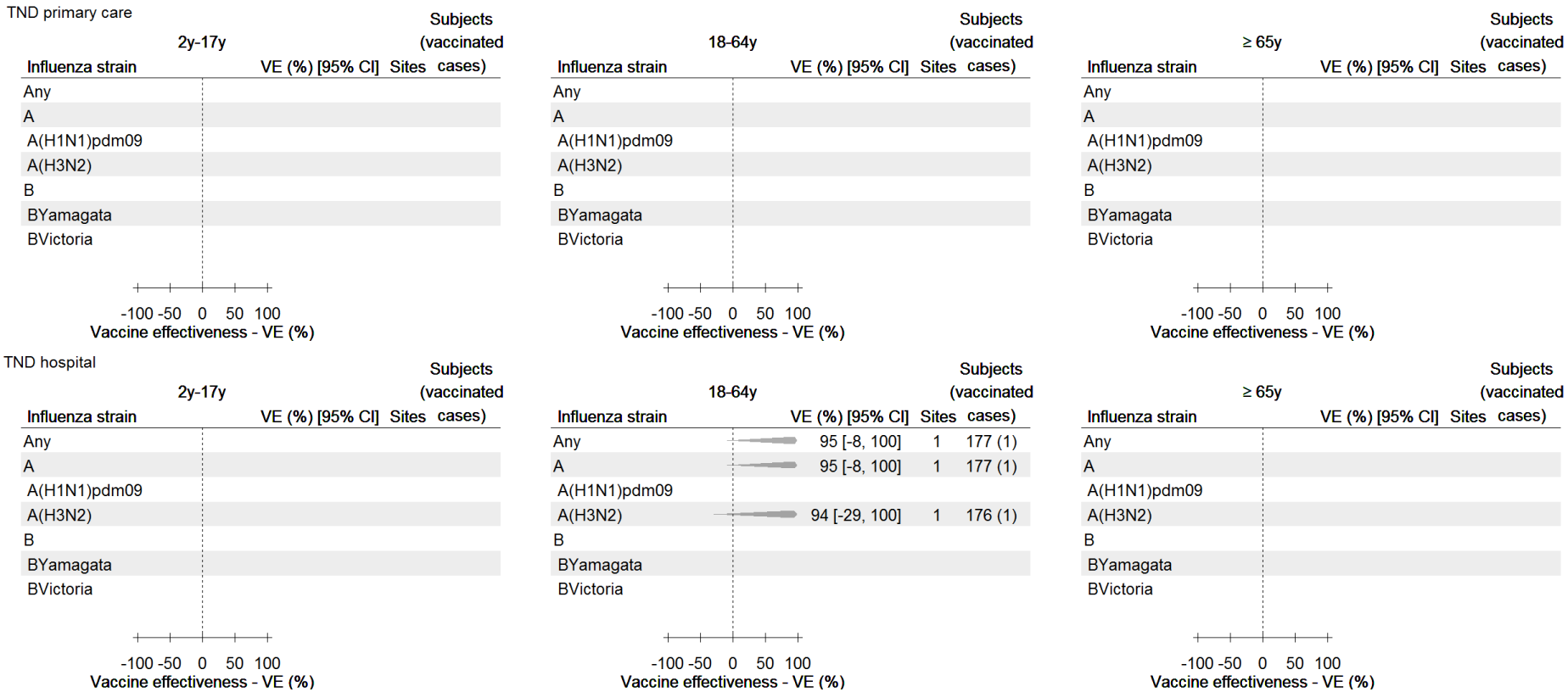


Figure 15. FLUCELVAX TETRA (SEQIRUS): pooled confounder-adjusted (age, sex and date of symptom onset) influenza vaccine effectiveness against laboratory-confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2021/22

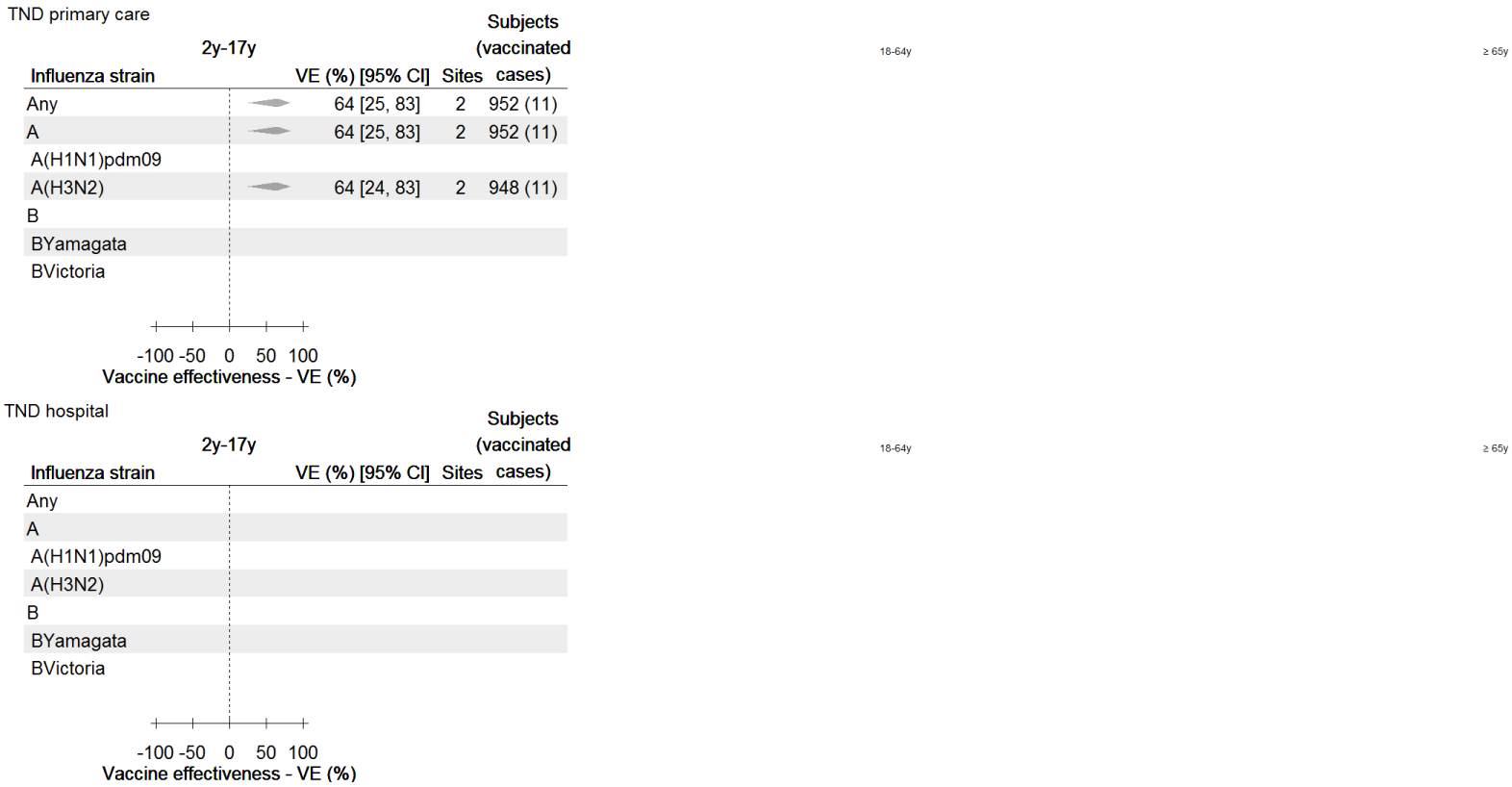


Figure 16. FLUENZ TETRA (ASTRAZENECA): pooled confounder-adjusted (age, sex and date of symptom onset) influenza vaccine effectiveness against laboratory-confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2021/22

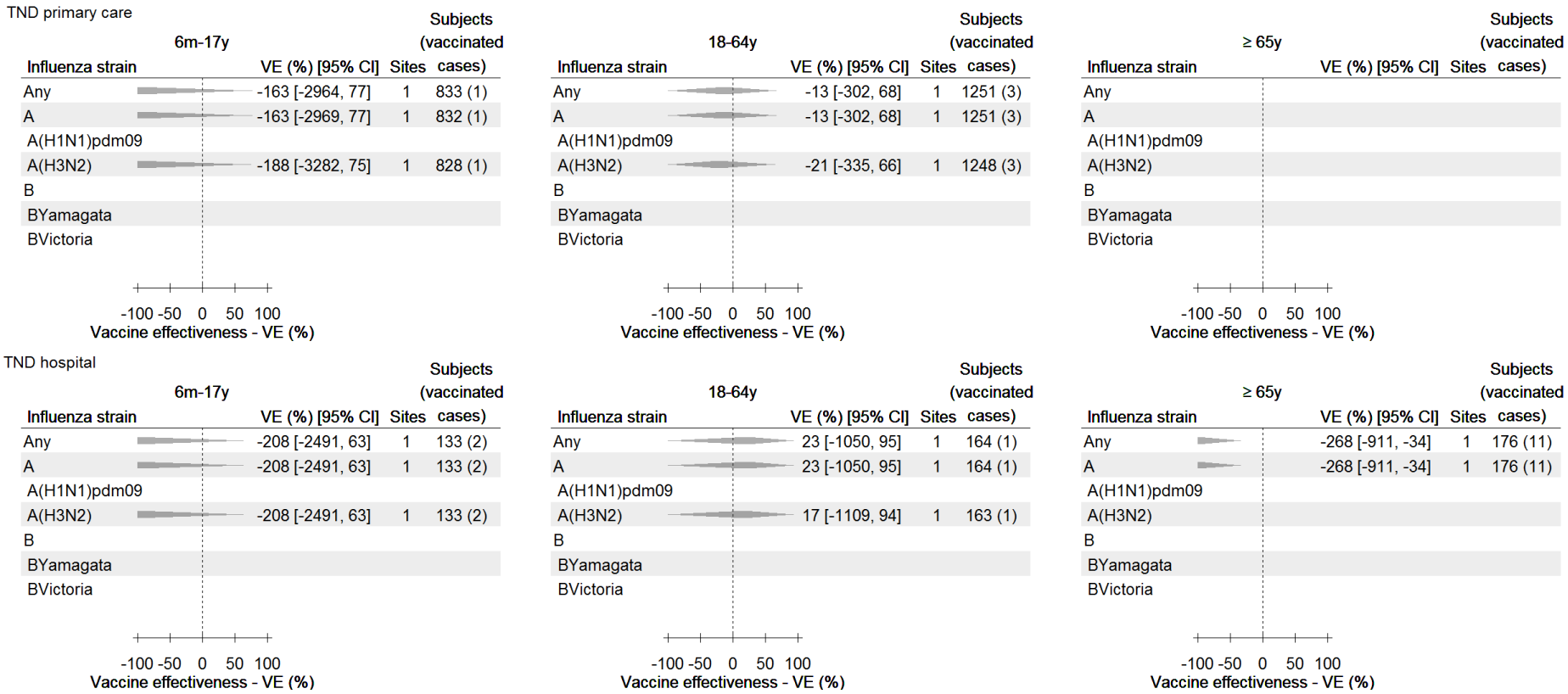


Figure 17. INFLUVAC TETRA (ABBOTT): pooled confounder-adjusted (age, sex and date of symptom onset) influenza vaccine effectiveness against laboratory-confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2021/22

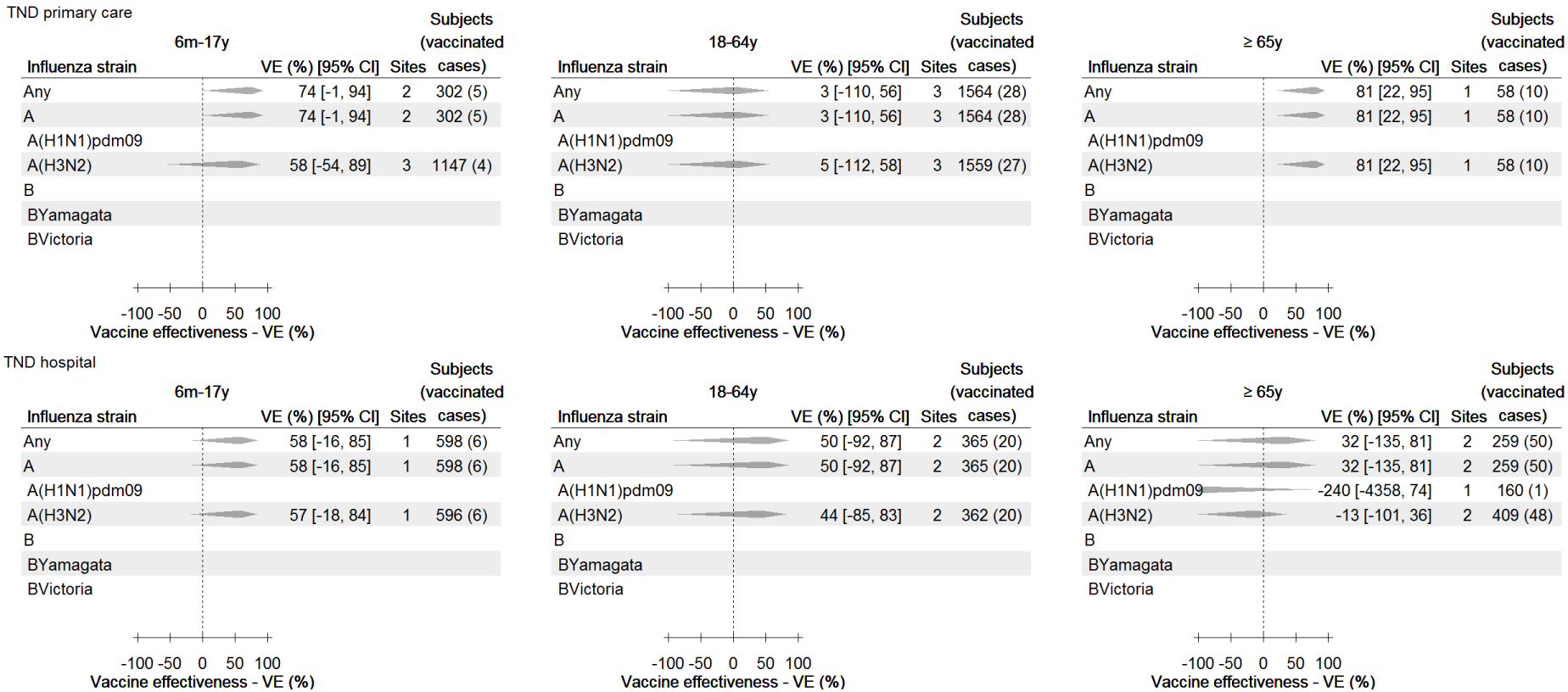


Figure 18. VAXIGRIP TETRA (SANOFI): pooled confounder-adjusted (age, sex and date of symptom onset) influenza vaccine effectiveness against laboratory-confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2021/22

5.4.1.2 Sensitivity analyses

Sensitivity analysis: additionally adjusting for 1) the presence of at least one chronic condition and 2) for COVID-19 vaccination

Adjusting for the presence of at least one chronic condition or for COVID-19 vaccination vastly decreased the number of vaccinated subjects in the analysis (exposure: any influenza vaccine) as estimates from several sites were considered outliers/influential or were no longer considered outliers/influential. Therefore the impact of additional covariate adjustment could not be well assessed.

Sensitivity analysis: stratification by SARS-CoV-2 status

Due to the low number of co-infections (n=29) across all age groups/settings), the threshold for VE analyses was not met and no sensitivity analysis stratified by SARS-CoV-2 status was conducted.

Sensitivity analysis: excluding subjects with time between ILI/SARI onset and swab ≥ 4 days

Restricting the time between ILI/SARI onset and the swab led to decreases in the point estimate of any vaccine against any influenza by 5 to 71 percentage points among children and adults in the primary care setting, and did not affect the estimates obtained among older adults. In the hospital setting, the restriction led to increases in the point estimate by 30 to 55 percentage points among children and older adults. Conversely, VE against any influenza decreased from 85% (95%CI 12 to 97) to 79% (95%CI -121 to 98) among adults.

Sensitivity analysis: inclusion of outlying/influential studies

The VE estimates for older adults from the primary care site Austria MUV (-502% [95%CI -4873 to 27] for any influenza, influenza A and influenza A(H3N2)) were excluded as they were outlying/influential. Including this estimate decreases the pooled VE from 76% (95%CI 23 to 93) to 32 (95%CI -6008 to 99).

Sensitivity analysis: exclusion of the site Iceland EL GP and Iceland EL HOSP

In the primary care setting, excluding EL GP from the pooled analysis did not impact the VE point estimate of any vaccine against any influenza among children and adults. Among older adults in the primary care setting, two sites changed (because of the outlier/influential criterion) and, therefore, it is difficult to compare the results. In the hospital setting, the point estimate for children dropped by more than 200 percentage points and the width of the CI increased 5-fold when EL HOSP was excluded. Among adults in the hospital setting, excluding EL HOSP did not change the pooled VE (85% [95%CI 12 to 97)] , and decreased by 10 percentage points the estimate among older adults.

Sensitivity analysis: site-specific estimates obtained using estimation method with Firth correction

In three of the six age/setting strata, the VE against any influenza was 4 to 11 percentage points lower than in the primary analysis, and in the remaining three sites the estimates were 26 to 40% higher.

5.4.2 Register-based cohort study

5.4.2.1 Main analysis

IVE estimates against influenza in any setting are shown in Table 15, and estimates against influenza in the hospital setting in Table 16. VE against any laboratory-confirmed influenza in children was estimated at 23% (95%CI -17 to 50). The VE estimate for influenza A was 38% (95%CI 1 to 62). The point estimate for influenza B and the upper limit of the 95%CI were below 0% but the number of cases was small, i.e., less than ten in each exposure group. In the brand-specific analysis, the VE for Vaxigrip Tetra given to children aged 6m-6y was 37% (-50 to 73) and the VE for Fluenz Tetra given to children aged 2y-6y was 25% (-21 to 53). VE against any laboratory-confirmed influenza in older adults was estimated at 16% (95%CI -11% to 36%). The type-specific estimates were 14% (95%CI -14% to 35%) for laboratory-confirmed influenza A and 61% (95%CI -108% to 93%) for laboratory-confirmed influenza B. The brand-specific VE estimates for Vaxigrip Tetra were nearly identical to the overall VE estimates. VE against inpatient influenza in older adults was estimated at 17% (95%CI -26 to 45) and thus similar to the estimates originating from the mixed setting. Estimates for any virus subtype/lineage included in the vaccine are not available for this dataset.

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, mixed setting, 2021/22

	Any influenza VE (95%CI)	**A VE (95%CI)**	**B VE (95%CI)**
Mixed setting			
6m-6y			
Any vaccine	23.3 (-17.1,49.7)	38.4 (1.1,61.6)	-240.4 (-911,-14.6)
Vaxigrip Tetra	36.9 (-50.1,73.4)	53.9 (-30.3,83.7)	-134.3 (-1133,55.5)
Fluenz Tetra (2-6y)	24.9 (-21.2,53.4)	39.6 (-2.9,64.5)	-322 (-1467.9,-13.6)
≥65y			
Any vaccine	16.1 (-10.7,36.4)	13.8 (-14.2,34.9)	61.5 (-107.8,92.9)
Vaxigrip Tetra	15.2 (-11.9,35.7)	12.9 (-15.4,34.3)	61.1 (-109.7,92.8)

Table 16. Confounder-adjusted influenza vaccine effectiveness of any vaccine and by vaccine brand against any influenza, Finland THL register-based cohort, hospital setting, 2021/22

	Any influenza VE (95%CI)
Hospital setting	
6m-6y	
Any vaccine	-13.8 (-169.1,51.9)
Vaxigrip Tetra	50.7 (-304.4,94)
Fluenz Tetra (2-6y)	-42.3 (-265.3,44.6)
≥65y	
Any vaccine	17.1 (-25.9,45.4)
Vaxigrip Tetra	16.3 (-27.2,44.9)

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

5.4.2.2 Sensitivity analysis: additional covariate adjustment

In the sensitivity analysis, the models were additionally adjusted for the presence of at least one chronic condition, as well as vaccination history and health care utilisation in the past. Additional covariate adjustment for factors influencing the vaccine uptake and the risk of influenza increased the VE estimates by up to 20%-points; for example, from 16% (95%CI -11% to 36%) to 32% (95%CI 5% to 52%) for any laboratory-confirmed influenza in older adults. The full results of the sensitivity analysis are presented in the WebANNEX.

5.5 Secondary objective: influenza vaccine effectiveness by type

Vaccine-type specific IVE estimates from the TND studies were calculated only for QIVe (Figure 19), the only vaccine type for which a minimum of two brands were available.

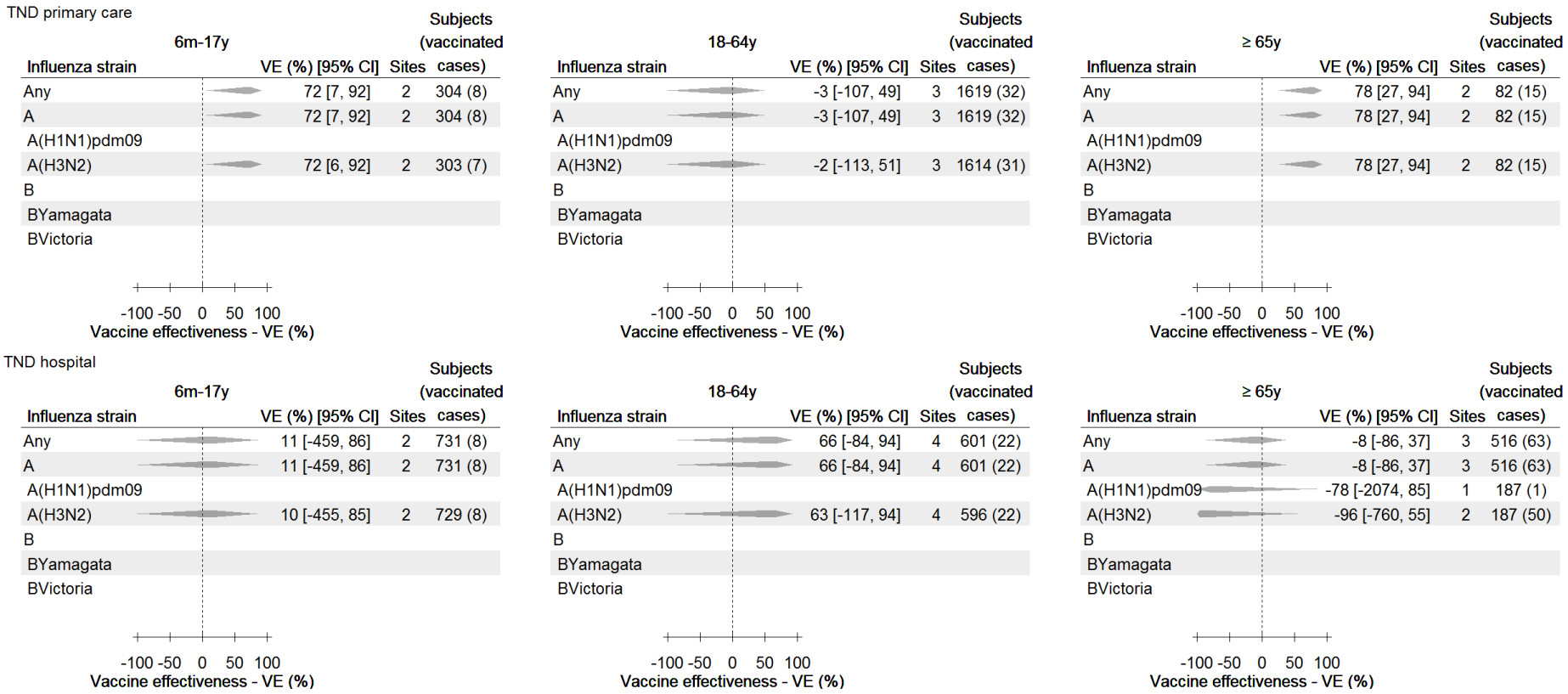


Figure 19. QIVe: pooled confounder-adjusted (age, sex and date of symptom onset) influenza vaccine effectiveness against laboratory-confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2021/22

6 Discussion

DRIVE's final season

DRIVE is a 5-year project funded under the IMI. The project kicked off in 2017 and is run by a consortium composed of 16 public and private partners, who joined efforts to establish a sustainable study platform based on a sufficiently sized network to provide robust, high-quality, brand-specific effectiveness estimates for all influenza vaccines used in the EU each season. In DRIVE, data from several independently operating national or regional study sites is analysed jointly to increase geographical coverage and sample size for brand-specific IVE estimates and account for various vaccination recommendations and uptakes.

The DRIVE study platform has progressively grown since its first pilot season (2017/18), and in its final 2021/22 season, included 21 hospitals and more than 1000 general practices in eight European countries, as well as one nationwide register-based cohort, in Finland. The 2021/22 was characterised by a late influenza epidemic peak surging in many European countries in March-April 2022, coinciding with the lift of many public health restrictions aimed at preventing transmission of SARS-CoV-2. Influenza circulation was significantly higher than in 2021/22, when it was nearly absent, although the total circulation was still lower than in pre-COVID-19 influenza seasons. Despite this, several IVE estimates were obtained from the DRIVE network.

Twelve influenza vaccine brands were marketed in the EU/EEA/UK in the 2020/21 season. The DRIVE dataset has captured 8 of these 12 brands. The most frequently (Vaxigrip Tetra in all age groups) and second most frequently (Fluenz Tetra in children, Influvac Tetra in adults, Fluad in older adults) observed vaccine brands per age group are the same as in 2020/21. The brands that were not identified were Afluria Tetra (Seqirus), Chiroflu (Seqirus), Influvac (Abbott) and Supemtek (Sanofi). Afluria Tetra was only distributed in Germany, a country not included in DRIVE, and Supemtek was only available in the UK, where only a very limited number of subjects was enrolled. Chiroflu and Influvac are both trivalent vaccines, which are being phased out.

Results from TND studies

VE estimates for eight vaccine brands were available from the TND studies. The number of brand-specific estimates was largest among older adults in the hospital setting (5 brands), followed by children in the primary care setting (4 brands), adults 18-64y in the hospital setting (3 brands) and two brands each for the other age/setting strata. The majority of estimates had very wide CI; however, several significant VE estimates were found. These estimates are among older adults in the primary care setting, with VE for any vaccine against any influenza of 76% (95%CI 23 to 93), and VE for Vaxigrip Tetra against any influenza of 81% (95%CI 22 to 95); and among children in the primary care setting with VE for Fluenz Tetra against any influenza of 64% (95%CI 25 to 83). In the hospital setting, the IVE estimate for any vaccine against any influenza among adults was 82% (95%CI 12 to 97).

In the 2021/22 season, the test-negative control population differs from influenza seasons pre-COVID-19 pandemic because a significant number of controls had COVID-19 and the control:case ratio was much higher than in pre-COVID-19 seasons, particularly among children and adults 18-64y in the primary care setting. The percentage of controls known to be infected with SARS-CoV-2 ranged from 31.8% (children) to 52.6% (older adults) in the primary care setting and was 23.5% and 22.1% in adults and older adults, respectively, in the hospital setting. However, information on SARS-CoV-2 status was missing for approximately 20% of controls in the primary care setting and roughly 40% among adults and older adults in the hospital setting, driven by the absence of information on this variable by a number of large sites. Only for children in the hospital setting the percentage of controls known to be infected with SARS-CoV-2 was low (3.9%, status unknown 73.5%). In addition, health care seeking behaviour has changed during the pandemic, through different periods in the pandemic, and the changes are likely not uniform across countries. Therefore it is not clear how this affects the TND.

Due to the high number of (vaccinated) subjects for which covariate information (presence of at least one chronic condition, COVID-19 vaccination status) was unavailable, no solid assessment of the impact of additional adjustment for these variables could be made. From an exploratory analysis of the 2018/19 and 2019/20 data, we learned that additionally adjusting for the presence of at least one chronic condition did not have an important impact on VE estimates [13]. However, as in all observational studies, residual confounding may be present. From an exploratory analysis of the 2018/19 and 2019/20 data, we learned that additionally adjusting for the presence of at least one chronic condition did not have an important impact on VE estimates [13].

In Iceland, swabs are taken from subjects presenting with respiratory tract infection and are tested for influenza at the national virology laboratory. Medical records were subsequently consulted centrally to extract data relevant to the DRIVE TND studies. However, recording of symptoms in the medical records was inconsistently available/absent and consequently, it could not be verified whether the subjects tested for influenza fulfilled the ILI/SARI case definition. As only patients with respiratory tract infection are eligible for swabbing and the date of symptom onset is available in the medical records, we have assumed that these subjects do fulfil the ILI/SARI case definition. Recognising that this is an assumption that cannot be checked, we have conducted an additional sensitivity analysis excluding the data from Iceland. The values from the Icelandic sites often fall within the range of point estimates from the other sites, and for three age/setting strata, the change in the point estimate when excluding Icelandic data is minor.

Data from UK RCGP RSC OX were not included in any analyses due to the absence of influenza cases. The total number of included subjects was 21. This low number of subjects despite the high number of GPs (450) from which data was extracted can be explained by the fact that none of those GPs participated in the UK Health Security Agency (formerly Public Health England) influenza surveillance programme, and therefore none of them systematically performed testing for influenza.

Results from the register-based cohort study

As the influenza season was still ongoing in Finland when the register-based cohort study was ended, the presented 2021/22 VE estimates are preliminary; however, the study period could not be extended beyond April

30 due to the end of the DRIVE project on June 30. Due to the small number of influenza cases, VE in children could not be estimated precisely; the estimate was 23.3 (95%CI -17.1 to 49.7). In addition, estimates were available for Vaxigrip Tetra and Fluenz Tetra. Age and medical groups eligible for the two vaccines differ and there may be differential health-seeking behaviour associated with preference towards one of the two brands. VE in older adults was less than 50% and the lower bound of the 95% CI was below 0%. As estimates were imprecise, it is unclear whether VE against influenza B was better than VE against influenza A, which clearly dominated the season. Interestingly, the two different settings, hospital setting and mixed primary care and hospital setting, yielded similar results, although VE against severe disease is suspected to be higher than VE against infection. This might be a sign that the severity of detected infections in older adults does not differ much and that, especially during the pandemic, hospitalisation was driven by other factors, such as comorbidities or isolation measures, rather than the severity of the disease. The sensitivity analyses showed that covariate adjustment can have a relevant impact on the VE estimates of the register-based cohort study. As the additional covariates presence of at least one chronic condition, vaccination history and health care utilisation in the past are considered as the main potential confounders, we considered their inclusion in the model essential in an observational cohort study of influenza VE. However, acknowledge that residual confounding may pre present, due to measurement errors in the confounders and other unmeasured confounders.

Findings from other IVE studies in 2021/22

Several other studies with (preliminary) VE data on the 2021/22 season were identified, from Denmark, France, Sweden, the United States and the European I-MOVE network. VE against all-age outpatient influenza was estimated at 50% (95% CI 14 to 71) for any influenza and 31% (95%CI -29 to 64) for A(H3N2) in France [14]. Data from the United States show no reduction in risk of all-age outpatient respiratory illness caused by influenza A (VE of 14% [95%CI -17 to 37]) or influenza A(H3N2) (VE 16% [95%CI -16 to 39]) [15].

In children aged 2-6y in Denmark, VE was estimated at 64.2 (95%CI 50.5 to 74.1) against non-hospitalised influenza A and 62.7 (95%CI 10.9 to 84.4) against hospitalised influenza A; 92% of vaccinated children received LAIV[16]. These estimates are in line with the estimate for this vaccine against influenza A from the DRIVE TND primary care studies (VE 64% [95%CI 25 to 83]). The point estimate for LAIV against any influenza in any setting among children 2-6y from the Finnish register-based cohort study was lower (39.6% (95%CI -2.9 to 64.5).

Estimates from I-MOVE based on data from seven primary care study sites between October 2021 and March 2022 show a VE of 41% (95%CI 15 to 59) against influenza-like illness due to influenza A and 37% (95%CI 3 to 59%) against influenza A(H3N2) among adults aged 18-64y [14]. No evidence of protection was observed in the DRIVE primary care TND studies in the same age group (VE of -1% [95%CI -96 to 49] for influenza A and 0% [-101 to 50] for influenza A(H3N2)).

VE against laboratory-confirmed influenza was estimated at 47% for adults ≥65y in Sweden (inpatient and outpatient) [14]. In the DRIVE TND studies, VE in this age group was estimated at 76% (95%CI 23 to 93) in the primary care setting and -32 (95%CI 132 to 24) in the hospital setting.

DRIVE's platform and study conduct have been fine-tuned since the first pilot season (2017/18) and the site network has progressively grown through its annual Call for tenders and on-boarding of several National Public Health Institutes as Associate Partners. DRIVE's study evolution since 2017/18 to 2021/22 is summarised in Table 17. The DRIVE study yielded its best results in the 2019/20 season, in which brand-specific IVE estimates for eight of the 11 vaccines available in the European market were produced, just before the COVID-19 pandemic interfered with the project.

The minimal influenza virus circulation, partly due to the non-pharmaceutical interventions and lockdowns implemented to combat the COVID-19 pandemic, together with the shift of attention and resources from influenza to COVID-19 which resulted in no new study sites this season, has largely impacted the 2020/21 and 2021/22 seasons, preventing DRIVE from generating robust brand-specific IVE estimates. Furthermore, DRIVE has reached a plateau in the network expansion due to the abovementioned situation generated by the COVID-19 pandemic, the PPP hesitancy among certain institutions in Europe and the existence of competing initiatives for IVE monitoring in Europe.

Table 17. Evolution of the DRIVE study from 2017/18 to 2021/22

Flu season	**2017/18**	**2018/19**	**2019/20**	**2020/21**	**2021/22**
Features	High flu circulation	Moderate flu circulation	Moderate flu circulation – capped due to COVID-19	No flu circulation – COVID-19 pandemic	Very low flu circulation – Omicron wave and late peak flu
Study network	5 sites 4 countries +950 GP 4 hospitals	10 sites 7 countries 377 GP 12 hospitals	14 sites 8 countries 388 GP 19 hospitals	14 sites 8 countries +500 GP 25 hospitals	13 sites 8 countries +1000 GP 21 hospitals
Number of subjects	5475 (TND) 288.655 p-y cohort	9351 (TND) 768.414 py cohort	9077 (TND) 511.854 py cohort	7025 (TND) 857.095 py cohort	6294(TND) 836.622 py cohort
Number of LCI	2844 (TND) 13.300 (cohort)	3339 (TND) 6379 (cohort)	> 3500 (TND) > 2400 (cohort)	4 (TND) 25 (cohort)	1039 (TND) 331 (cohort)
BS IVE estimates	Yes, 4/11 but pilot season	Yes, 7/10 flu vaccine brands	Yes, 8/11 flu vaccine brands	No	Yes, 8/12 flu vaccine brands

Key achievements during the DRIVE project include that:

- DRIVE has developed an agile, efficient, and cost-effective study platform: independent study sites following generic protocols using both a TND or a register-based cohort, built on national or regional surveillance systems.
- DRIVE has built a central IT infrastructure for efficient and GDPR-compliant data collection and pooled analysis.
- The study implementation has been improved thanks to the high-quality standards supported in DRIVE (role of the WP7 and QCAC).
- Recurring sites acquired expertise and capacity in VE studies with DRIVE and we have built an excellent communication and relationship.
- In five seasons (2017 to 2022), DRIVE included more than 35.000 patients, collecting approximately 60 variables and encompassing 13 different influenza vaccines. DRIVE consortium partners consider that this extremely valuable database should be leveraged and further utilised for various reasons, notably a strong interest in Research and Development activities for new generation of influenza vaccines and a contribution to the worldwide efforts to enhance a global surveillance network for respiratory viruses and associated diseases and monitor related vaccines performance. For this reason, DRIVE developed an open data research framework that will allow the secondary use of the data generated by the project since the 2018/19 season.
- 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 (https://covidrive.eu/). COVIDRIVE has been established by several of the DRIVE consortium partners and is currently conducting COVID-19 vaccine effectiveness studies leveraging the infrastructure and study sites network built in DRIVE.

7 Conclusions

- DRIVE has conducted its last IVE study in the 2021/22 season, after five seasons since its first pilot study in 2017/18.
- The low influenza virus circulation observed during the 2021/22 season, partly due to the non-pharmaceutical interventions and lockdowns implemented to combat the COVID-19 pandemic, together with the shift of attention and resources from influenza to COVID-19, which resulted in no new study sites this season, has largely impacted this season DRIVE's study, preventing it from generating robust brand-specific IVE estimates.
- DRIVE has created a solid study network composed of 21 hospitals, more than 1000 GP and a nationwide register from eight European countries despite the challenges raised by the COVID-19 pandemic, PPP hesitancy and the shift of attention to COVID-19.
- Despite the COVID-19 pandemic and the low influenza circulation in the 2021/22 season, the DRIVE network was able to produce brand-specific IVE estimates for eight of the 12 marketed influenza vaccines in Europe. This by itself, is a success. However, study power was insufficient for properly interpreting the estimates.

- Because of the challenges experienced in DRIVE and the ongoing evolution of the current European environment anticipated in the post-DRIVE setting, a deferral on generating brand-specific seasonal IVE for the influenza season 2022-23 was proposed to the EMA in May 2022.
- The lessons learnt from the DRIVE studies have been cardinal to the development of COVIDRIVE, a PPP conducting COVID-19 vaccine effectiveness studies since September 2021.

8 Funding

The DRIVE project has received funding from the IMI 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.

9 Study team

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

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11 ANNEXES

The WebAnnex is accessible at: https://apps.p-95.com/drivewebapp/. The results of all the analyses are available there. The results will be password protected until the report is made publicly available. In addition, the following documents are accessible:

Data processing (number of records retained during the data processing)
Vaccine recommendations
Local Study Reports 2021/22
Statistical Analysis Plan 2021/22 including Study teams 2021/22
All R scripts related to the workflow (excluding site-specific cleaning scripts)

WebAnnex hierarchy

1. 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

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

2. TND pooled analyses

Main analysis: Descriptive

Type: Any Vaccine

Type: Influenza over time (Figure 6)

Type: Influenza positivity over time (Figure 7

Figure 7)

Type: Vaccination distribution (Figure 8)

Type: Histogram of covariates SETTING/AGE

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 exposure 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 lineage)*

Type: Epidemiology data (Table 6)

Type: Table SARS-CoV-2 at study entry (**Error! Reference source not found.**Table 11**Error! Reference source not found.**)

Type: Table COVID-19 vaccination status (Table 12)

Type: COVID-19 vaccination detail availability

Type: Exposure-specific

Descriptive table by outcome exposure combination SETTING AGE EXPOSURE

Exposure

Descriptive table by strain SETTING AGE EXPOSURE

Exposure

Exploratory analyses

Type: Addition interaction effect COVID-19 vax and influenza vax

Type: Removing COVID-19 vaccination from model

Descriptive table of symptoms among influenza and covid-19 cases

3. Register-based cohort

Analysis: Descriptive

Number of vaccinated and unvaccinated person-years and influenza cases SETTING (Figure 9)

Histogram of covariates THLCohort SETTING (Figure 9)

Histogram of Cumulative number of vaccinations over time SETTING (Figure 9)

Histogram of infections over time THLCohort SETTING (Figure 9)

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 2021/2022

DRIVE

Development of Robust and Innovative Vaccine Effectiveness

QCAC – Quality Control & Audit Committee

QCAC members	Philippe Enfrin, EFPIA Partner, Sanofi Galina Gueneva-Colon, EFPIA Partner, GSK Claire Pope, EFPIA Partner, Seqirus	
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Delivery date	July 2022	
Description of Work	**Version**	**Date**
	2.0	04 July 2022

Document History

Version	Date	Description
V1.0	27 June 22	First version for QCAC / SC endorsement
V2.0	04 July 22	Final version

Summary

This is a summary of the DRIVE Quality Control and Audit Committee (QCAC) activities covering the 2021/2022 season which were focused on the conduct of an audit to assess the activities handled by P95 on behalf of the DRIVE consortium.

In prior seasons, the QCAC conducted reviews of the Site Quality Management Questionnaires developed by WP3 and designed to perform evaluations of study site's quality and feasibility. As the large majority of the study site network in 2021/2022 was the same as previous seasons and there were no concerns from previous assessments, no Questionnaire reviews were conducted for 2021/2022.

The proposal to conduct an audit was endorsed by the DRIVE steering committee (SC) in alignment with the auditee (P95) one of the DRIVE partners, a consulting business company based in Belgium and specialized in epidemiology and pharmacovigilance. P95 is in charge of Data Management and Biostatistics and is also accountable for the IT infrastructure used for data transfer and data storage for DRIVE supported studies.

The two-day audit was conducted by an independent third party on the 16th and 17th March 2022. The scope of the audit was to focus on specific components related to the P95 contribution for the DRIVE project: to evaluate whether ethics, regulatory and quality requirements were fulfilled and to ensure that the data and reported results were trustworthy, robust and accurate. The scope of the evaluation was focused on the following components:

- Data management including but not limited to an assessment of the data management plan, verification of processes and tools to ensure data integrity, data transfer, data Quality Control (QC), data storage, data privacy, data archiving, data retrieval and data decommissioning.

- Statistical analysis including but not limited to Statistical Analysis Plan, validation of statistical programs, mock report and tables, conduct of analysis, QC of analysis, documentation and archiving.

- IT infrastructure linked to data collection/data process including data security but not limited to the Electronic Study Support Application characteristics, data privacy, secured data transfer and storage, audit trail review, "Disaster Recovery Plan" to ensure remote access to the file/system and ensure business continuity, documentation and archiving.

A draft audit report was issued on 19th April 2022. The key observations were related to validation of computerized systems and deficiencies in good documentation practices for ALCOAC (Accurate, Legible, Contemporaneous, Original, Attributable and Complete) principles. The P95 response to address these and other observations including the proposed corrective and preventive actions were endorsed by the QCAC and SC. They were accepted by the auditors before release of the final audit report.

The audit has not raised significant issues regarding data quality and integrity and the analysis of the results. It served to enhance the P95 quality management systems and deliverables for DRIVE and the actions taken/lessons learned will be relevant for future Public/Private initiatives.