DRIVE IVE Results Report 2021/22: 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.

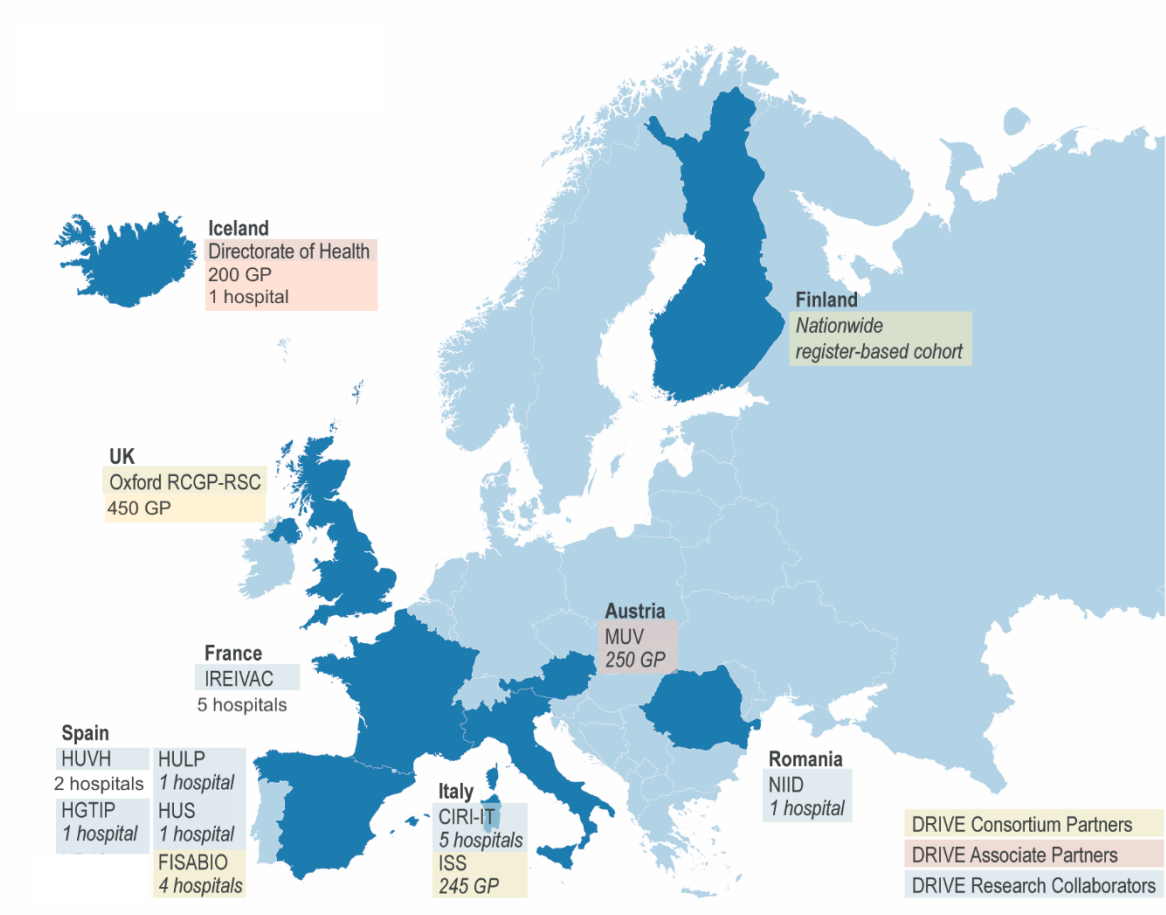

Figure E1. DRIVE Study network for season 2021-22. The DRIVE network is composed of (1) 12 independent study sites across seven European countries that conduct test-negative design (TND) prospective studies (which include a total of 21

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 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

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
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

Vaccine brand	Manufacturer	Sites in which the vaccine brand was observed in the DRIVE dataset		
		6m - 17y	18 - 64y	≥ 65y
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 against any influenza among adults was 82% (95%CI 12 to 97).

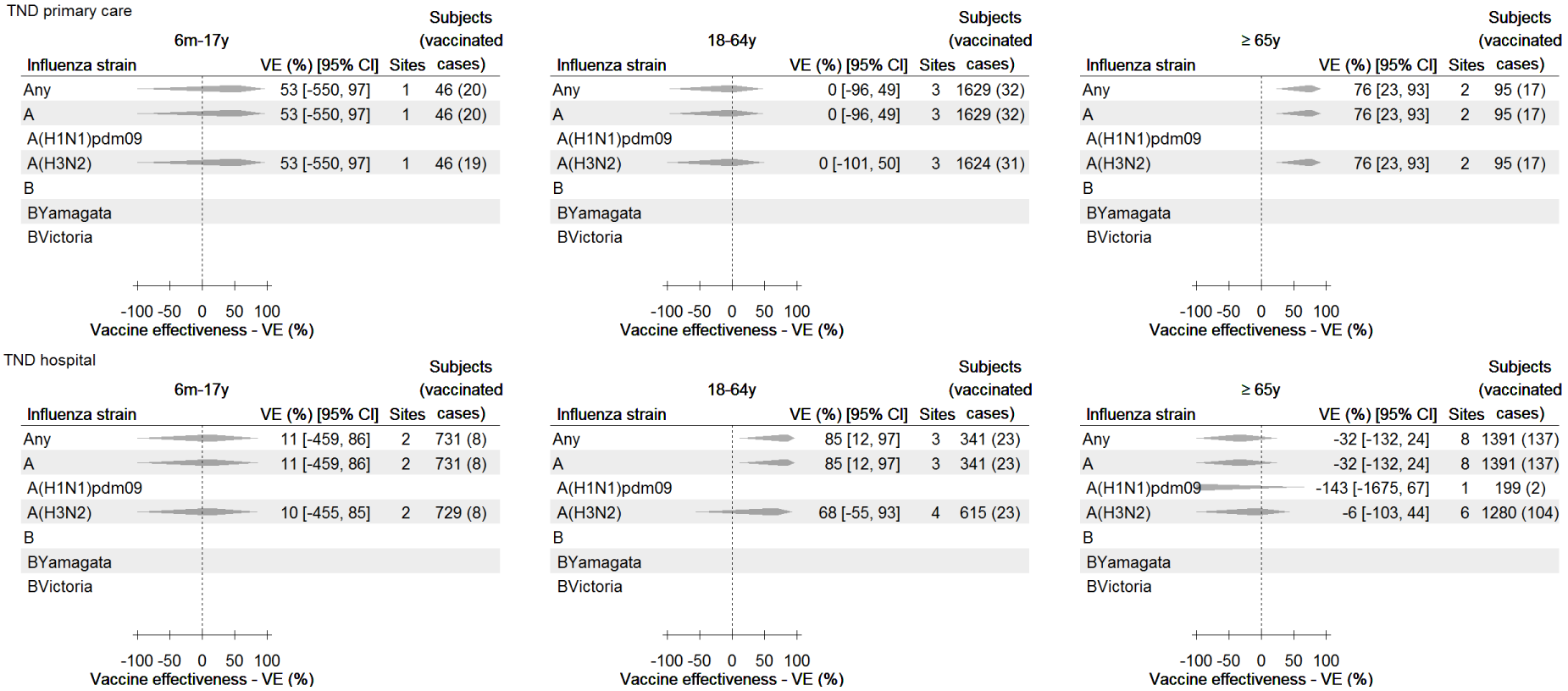

Figure E2. *Any influenza vaccine: pooled confounder-adjusted (age, sex and date of symptom onset) influenza vaccine effectiveness against laboratory-confirmed influenza, overall and per type and subtype/lineage, by setting and age group, 2021/22*

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.