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Brand-specific influenza vaccine effectiveness estimates during 2019/20 season in Europe – Results from the DRIVE EU study platform

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ABSTRACT

DRIVE (Development of Robust and Innovative Vaccine Effectiveness) is an IMI funded public–private platform that aims to annually estimate brand-specific influenza vaccine effectiveness (IVE), for public health and regulatory purposes. IVE analyses and reporting are conducted by public partners in the consortium.

In 2019/20, four primary care-based test-negative design (TND) studies (Austria, England, Italy (n = 2)), eight hospital-based TND studies (Finland, France, Italy, Romania, Spain (n = 4)), and one population-based cohort study (Finland) were conducted. The COVID-19 pandemic affected influenza surveillance in all participating study sites, therefore the study period was truncated on February 29, 2020. Age-stratified (6 m-17y, 18-64y, ≥65y), confounder-adjusted, site-specific adjusted IVE estimates were calculated and pooled through *meta*-analysis. Parsimonious confounder-adjustment was performed, adjusting the estimates for age, sex and calendar time.

TND studies included 3531 cases (351 vaccinated) and 5546 controls (1415 vaccinated) of all ages. IVE estimates were available for 8/11 brands marketed in Europe in 2019.

Most children and adults < 64y were captured in primary care setting and the most frequently observed vaccine brand was Vaxigrip Tetra. The estimate against any influenza for Vaxigrip Tetra in primary care setting was 61% (95%CI 38–77) in children and 32% (95%CI −13–59) in adults up to 64y. Most adults ≥ 65y were captured in hospital setting and the most frequently observed brand was Fluad, with an estimate of 52% (95%CI 27–68).

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The population-based cohort covered 511,854 person-years and two vaccine brands. In children aged 2-6y, the IVE against any influenza was 68% (95%CI 58–75) for Fluenz Tetra and 71% (56–80) for Vaxigrip Tetra. In adults ≥ 65y, IVE against any influenza was 29% (20–36) for Vaxigrip Tetra.

DRIVE is a growing platform. Public health institutes with surveillance data and hospitals in countries with high influenza vaccine coverage are encouraged to join DRIVE.

1. Introduction

The Development of Robust and Innovative Vaccine Effectiveness (DRIVE) consortium was formed in 2017 and aims to establish within five years a sustainable network to estimate brand-specific influenza vaccine effectiveness (IVE) for influenza vaccines used in the European Union [1]. The IVE studies conducted through DRIVE are expected to increase the understanding of IVE, to fulfil the requirements of the European Medicines Agency, and to lead to enhanced monitoring of influenza vaccine performance by public health institutes [2].

European public health institutes can join DRIVE as associate partners of the IMI consortium agreement, and other sites can apply to join through the annual call for tenders [3]. The IVE studies are conducted by the public partners in the consortium. To guarantee scientific independence, private partners (vaccine manufacturers) are not involved in data collection and analysis. They can and do provide written feedback on the study documents, such as the protocol, statistical analysis plan and results report; their feedback is moderated by an Independent Scientific Committee before being taken into account by the public partners in the consortium [4].

The study conducted in the 2019/20 season builds upon the framework established in the previous two seasons [5,6]. Major improvements include expansion of the DRIVE network by three hospital sites in two countries, simplification of confounder-adjustment resulting in less data loss, and easier access to the full set of results through the WebAnnex.

In 2019/20, eleven influenza vaccines were marketed in Europe [7]. Two new vaccines were marketed, a cell-based quadrivalent vaccine Flucelvax Tetra (Seqirus), for ages 9 and above, and a high-dose vaccine (TIV-HD) (Sanofi Pasteur). Overall, six trivalent vaccines were available, including four conventional trivalent vaccines (TIV) (Afluria and Aggripal (Seqirus), Influvac (Abbott) and Vaxigrip (Sanofi Pasteur), one adjuvanted vaccine (aTIV) (Fluad (Seqirus)), and one TIV-HD (Sanofi Pasteur); five quadrivalent vaccines, including one live attenuated vaccine (LAIV) (Fluenz Tetra (AstraZeneca)); and four inactivated vaccines, of which three were egg-based (QIVe) (Fluarix Tetra (GlaxoSmithKline), Influvac Tetra (Abbott), Vaxigrip Tetra (Sanofi Pasteur)) and one was cell-based (QIVc) (Flucelvax Tetra (Seqirus)).

The 2019/20 influenza season in Europe started relatively early and peaked in week 5/2020 [8]. Both influenza A and B types co-circulated in Europe, with patterns of dominant influenza type and dominant A subtypes varying among the countries [8]. Antigenic changes in both A strains and in the B/Victoria over the season may have impacted vaccine effectiveness in the 2019/20 season, and led to a switch in the vaccine strains recommended for the 2020/21 season [7,9,10]. As of February/March 2020, influenza surveillance and circulation in Europe were affected by the COVID-19 pandemic and public health response. Local surveillance activities were adapted (e.g., inclusion of influenza cases stopped, or inclusion of influenza cases in DRIVE was conditional to SARS-CoV-2 negative test results), regional or national lockdowns and other measures aiming at reducing SARS-CoV-2 transmission were implemented, and healthcare seeking behavior changed. For these reasons, the DRIVE study period for the main analysis was truncated at the end of February.

Here we summarize IVE estimates for any vaccine and brand-specific estimates, against virologically-confirmed influenza from the 2019/20 season, based on four TND studies in the primary care setting, eight TND studies in the hospital setting, and one population-based cohort, from a total of seven countries in Europe.

2. Methods

2.1. Study design

The studies were based on the DRIVE generic protocols for TND and population-based cohort studies [11,12]. Four primary care-based TND studies were conducted through GP networks in Austria, Italy (two networks), and in the UK. Eight hospital-based TND studies were conducted at five individual hospitals in Finland, Romania and Spain (3 hospitals); and three hospital networks in France, Italy and Spain. One population-based cohort study was conducted by the Finnish Institute for Health and Welfare (THL) among Finnish residents aged 6 months to 6 years and 65 to 100 years. No universal influenza vaccine recommendation is in place in Finland for the age group 7-64y. Also, many of the influenza vaccinations of the working age adults are given within occupational health services, the data from which is not automatically transferred to the National Vaccine Register. Consequently, influenza vaccine exposure is not reliably captured in the vaccine registry. Primary care and hospital cases could not be differentiated. The reason for this is that the influenza diagnosis in the National Infectious Disease Registry is based on data received directly from laboratories, and this data does not automatically contain the origin of the sample.

Definitions for influenza-like illness (ILI), severe acute respiratory infection (SARI) and laboratory-confirmed influenza, along with other study site characteristics, are described in Table 1. Influenza laboratory confirmation for samples was undertaken through molecular tests at the majority of sites, including point of care RT-PCR assays at one site, or otherwise through antigen detection tests. Influenza subtypes were available for all but two sites. The study population's inclusion and exclusion criteria have been previously described [5]. Either all or a systematic selection of patients (e.g., the first 3 ILI patients every week) meeting the ILI/SARI were swabbed or asked to participate in the study. At two TND sites, controls were matched to cases (1:1), based on age and epidemiological week (VHUH) and additionally on gender (GTPUH). For each subject, data on age, sex, date of symptom onset, date of swab, date of vaccination and vaccine brand were collected. Additional covariates (presence of chronic condition, number of healthcare visits or hospitalizations in the past year, pregnancy, influenza vaccination in the previous season) were collected when possible. For studies in the primary care setting, vaccination status, vaccine brand and vaccination data were retrieved from the GP records. For studies in the hospital setting, the way this information was retrieved varied across sites, and included vaccine cards or vaccine registers (FISABIO, HUS), GP or pharmacy records, or patient interview

followed by confirmation through GP/pharmacy records for subjects reporting to be vaccinated [13].

For the TND studies, the start of the season was defined as the first of two consecutive weeks during which influenza viruses were detected at the study site level; the end as the week prior to the first of two consecutive weeks during which no influenza viruses were detected at study site level, or April 30, 2020, whichever occurred first. For the cohort study, the study period for analysis was defined a priori from week 40/2019 to April 30, 2020. For both study designs, the final study period was truncated on February 29, 2020 due to the COVID-19 pandemic. A sensitivity analysis was conducted with all data available until April 30, 2020.

The studies were not designed to detect relative IVE of different brands.

2.2. Statistical methods

The statistical methods have been described in detail previously [5]. Briefly, site-specific TND IVE estimates were calculated using logistic regression and pooled through random-effects *meta*-analysis. All TND estimates were stratified by age (6 m-17y, 18-64y, ≥65y) and setting; estimates were obtained for any influenza, by influenza type and by subtype/lineage. Pooled IVE estimates from primary care represent IVE against medically-attended virologically confirmed ILI due to influenza, and estimates from the hospital setting represent IVE against hospitalized virologically confirmed SARI due to influenza. Estimates for the population-based cohort were calculated using Poisson regression and were stratified by age (6 m-6y, ≥65y). Estimates from the population-based cohort study were not pooled with the estimates from the TND studies. For the 2019/20 season, site-specific estimates were adjusted for age, sex and calendar time (defined as date of symptom onset in TND studies).

As recommended by Lane et al [14], and supported by a post-hoc analysis of the 2018/19 DRIVE data (data not shown), the main analysis was based on a parsimonious model in which age, calendar time, and sex were adjusted for and a sensitivity analysis in which all available potential confounders (age, sex, onset date, presence of at least one chronic condition, pregnancy, number of primary care visits or hospitalizations in the previous year, and influenza vaccination in the previous season) were adjusted for was conducted.

To gain insight in potential unmeasured confounding of the IVE estimates for any vaccine against any influenza by age and setting, E-values for the IVE estimates and for the limit of the CI closest to 0 were calculated post-hoc [15]. VanderWeele and Ding defined E-values as "the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with (...)the treatment [vaccination] and [/or] outcome, conditional on the measured covariates, to fully explain away a specific treatment–outcome association" [15,16]. Under the rare disease assumption (<15% in the general population), we can interpret the OR as being approximately equal to the relative risk ratio, and therefore use methodology developed for the relative risk ratio [15].

2.3. Quality control

The statistical analysis plan underwent review by the vaccine manufacturers and the Independent Scientific Committee and was registered at the ENCePP EU PAS Register (EUPAS35685) [13]. 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 centrally produced. A quality control and assurance committee evaluated the quality of the study conduct, data reporting and the pooled analysis from an operational, process and compliance perspective.

2.4. Ethical considerations

Each local study was approved by national, regional or institutional ethics committees, as appropriate [13].

2.5. Data sharing

To improve accessibility and support the open data strategy, all study results are available in an interactive WebAnnex, accessible at https://apps.p-95.com/drivewebapp/?season=1920. Aggregated data from the DRIVE studies are available upon request from info@drive-eu.org

3. Results

3.1. Influenza epidemiology

Influenza A(H1N1)pm09, A(H3N2) and B/Victoria co-circulated in Europe. The number of influenza A cases exceeded the number of influenza B cases at all TND sites (range 52.8% to 95.8%), except at the Italy CIRI GP site (42.9%). The highest proportion of influenza A compared to influenza B cases was found at Finland HUS (95.8%). Among influenza A cases with a known subtype, the most frequently identified subtype was A(H1N1)pdm09 at the sites in Finland, France and Spain (range 71.7% to 91.3%), and A(H3N2) at the sites in Austria, Italy and Romania (range 56.9% to 62.6%).

3.2. Subject and exposure characteristics

1 TND studies

Overall, 3,531 cases and 5,546 controls of all ages were included in the main analysis of the TND studies (Table 2). The proportion of controls vaccinated ranged from 5.1% in children in the hospital setting to 61.3% among adults ≥ 65y in the primary care setting. Adults ≥ 65y had the highest proportion of subjects with at least one chronic disease, with ≥ 5 GP visits in the past year and ≥ 2 hospitalizations in the past year. Subject characteristics by vaccine brand are available in the WebAnnex.

Eight of the eleven vaccines marketed in Europe in 2019/20 were captured in the DRIVE network: Agrippal, Fluad, Fluarix Tetra, Flucelvax Tetra, Fluenz Tetra, Influvac, Influvac Tetra, Vaxigrip and Vaxigrip Tetra. No data was captured on Afluria, Vaxigrip and TIV-HD. In the 2019/20 TND studies, quadrivalent influenza vaccine (QIV) brands were captured in the pooled DRIVE datasets for most age groups in both settings, whereas more gaps in data availability were observed for TIV, reflective of the gradual phase out of TIV. Age-specific brand distribution among vaccinated subjects by site is shown in Fig. 1. The most commonly reported brands among vaccinated subjects by age were Vaxigrip Tetra in children (58.1%) and in adults up to 64y (39.9%), and Fluad in adults ≥ 65y (47.7%). The majority of reported vaccine types among vaccinated subjects were quadrivalent egg-based (82.6%) in children and in adults up to 64y (71.4%), and adjuvanted trivalent vaccine (47.7%) and quadrivalent egg-based vaccine (38.8%) in adults ≥ 65y. Across all age groups, only 4.6% of the vaccines were conventional trivalent vaccines.

2 Population-based cohort study

In total, 101 thousand person-years for children 6 m-6y and 411 thousand person-years for adults ≥ 65y were included in the Finnish population-based cohort study, and respectively 1,027 and 1,400 influenza cases were identified. Subject characteristics are shown in Table 3.

Table 1
Characteristics of studies in DRIVE 2019/20.

Country	Site	Nr of GPs or hospitals	Age	Eligibility criterion for testing	Virological test	Control matching
TND: PC setting						
Austria	MUV	96	>6*m*	ILI [a]	RT-PCR	No
Italy	CIRI-IT	35	>6*m*	ILI [a]	RT-PCR	No
Italy	ISS	245	>6*m*	ILI [a]	RT-PCR	No
UK	RCGP RSC	12	>6*m*	ILI [a]	Point of care test (RT-PCR; subtype/ lineage not available)	No
TND: Hospital						
Finland	HUS	1	>18y	SARI [b]	RT-PCR	No
France	INSERM	5	>18y	SARI [b]	RT-PCR	No
Italy	CIRI-IT BIVE	5	>6*m*	SARI [b]	RT-PCR	No
Romania	NIID	1	>6*m*	SARI [b]	RT-PCR	No
Spain	FISABIO	4	>6*m*	<5y: hospitalized for any acute reason with symptom onset in the 7 days prior to admission, ≥5y: SARI[b] (without criterion 'deterioration of general condition')	RT-PCR	No
Spain	GTPUH	1	>6*m*	SARI [b]	<18y: antigen detection; ≥18y: RT-PCR	No
Spain	LPUH	1	>14y	SARI [b]	RT-PCR	1:1 (age, week)
Spain	VHUH	1	>6*m*	SARI [b]	<18y: antigen detection; ≥18y: RT-PCR	1:1 (age, sex, week)
Population-based cohort: mixed setting						
Finland	THL	n/a	6 m-6y; 65-100y	Laboratory-confirmed influenza (National Disease Register)	Any (subtype/lineage not available)	n/a

CIRI-BIVE: Italian Hospital Network; CIRI-IT GP: Interuniversity Research Center on Influenza and other Transmissible Infections; FISABIO: Foundation for the Promotion of Health and Biomedical Research of the Valencia Region; GTPUH: Germans Trias i Pujol University Hospital; HUS: Helsinki University Hospital; INSERM: French National Institute of Health and Medical Research; ISS: Italian National Institute of Health; LPUH: La Paz University Hospital; m: months; MUV: Medical University Vienna; n/a: not applicable; NIID: National Institute for Infectious Diseases "Prof. Dr. Matei Balş"; RCGP RSC: Royal College of General Practitioners Research and Surveillance Centre; SD: standard deviation; VHUH: Vall d'Hebron University Hospital; y: years.

[a] An individual presenting with sudden onset of symptoms; AND at least one of the following systemic symptoms: fever/feverishness, malaise, headache, myalgia; AND at least one of the following respiratory symptoms: cough, sore throat, shortness of breath (ECDC case definition).

[b] A hospitalised person with a suspicion of infection, with at least one of the following systemic symptoms or signs: fever/feverishness, malaise, headache, myalgia, deterioration of general condition (asthenia or loss of weight or anorexia or confusion or dizziness); AND at least one of the following respiratory symptoms: cough, sore throat, shortness of breath, at admission or within 48 h after admission (IMOVE + 2017/18 case definition).

Table 2
Subject characteristics, TND studies, 2019/20.

	6 m-17y		18-64y		≥65y	
	Cases n (%)	Controls n (%)	Cases n (%)	Controls n (%)	Cases n (%)	Controls n (%)
Primary care	1332	1038	838	1403	65	282
Vaccinated	77 (5.8)	133 (12.8)	52 (6.2)	135 (9.6)	36 (55.4)	173 (61.3)
Female	646 (48.5)	494 (47.6)	399 (47.6)	773 (55.1)	37 (56.9)	155 (55.0)
Site						
CIRI_GP	397 (29.8)	301 (29.0)	106 (12.6)	415 (29.6)	10 (15.4)	136 (48.2)
ISS	502 (37.7)	436 (42.0)	330 (39.4)	532 (37.9)	30 (46.2)	89 (31.6)
MUV	398 (29.9)	239 (23.0)	360 (43.0)	313 (22.3)	21 (32.3)	26 (9.2)
RCGP RSC	35 (2.6)	62 (6.0)	42 (5.0)	143 (10.2)	4 (6.2)	31 (11.0)
Hospital	661	730	331	724	304	1369
Vaccinated	22 (3.3)	37 (5.1)	50 (15.1)	169 (23.3)	114 (37.5)	768 (56.1)
Female	295 (44.6)	326 (44.7)	176 (53.2)	371 (51.2)	147 (48.4)	618 (45.1)
Site						
CIRI-BIVE	311 (47.0)	459 (62.9)	73 (22.1)	221 (30.5)	89 (29.3)	495 (36.2)
FISABIO	3 (0.5)	16 (2.2)	20 (6.0)	137 (18.9)	37 (12.2)	449 (32.8)
GTPUH	12 (1.8)	13 (1.8)	32 (9.7)	36 (5.0)	41 (13.5)	48 (3.5)
HUS	n/a	n/a	15 (4.5)	41 (5.7)	9 (3.0)	60 (4.4)
INSERM	n/a	n/a	37 (11.2)	97 (13.4)	44 (14.5)	202 (14.8)
LPUH	n/a	n/a	11 (3.3)	4 (0.6)	11 (3.6)	10 (0.7)
NIID	296 (44.8)	203 (27.8)	84 (25.4)	137 (18.9)	25 (8.2)	53 (3.9)
VHUH	39 (5.9)	39 (5.3)	59 (17.8)	51 (7.0)	48 (15.8)	52 (3.8)

CIRI-BIVE: Italian Hospital Network; CIRI-IT GP: Interuniversity Research Center on Influenza and other Transmissible Infections; FISABIO: Foundation for the Promotion of Health and Biomedical Research of the Valencia Region; GTPUH: Germans Trias i Pujol University Hospital; HUS: Helsinki University Hospital; INSERM: French National Institute of Health and Medical Research; ISS: Italian National Institute of Health; LPUH: La Paz University Hospital; m: months; MUV: Medical University Vienna; n/a: not applicable; NIID: National Institute for Infectious Diseases "Prof. Dr. Matei Balş"; RCGP RSC: Royal College of General Practitioners Research and Surveillance Centre; SD: standard deviation; VHUH: Vall d'Hebron University Hospital; y: years.

*cardiovascular disease, lung disease, diabetes, immunodeficiency or organ transplant, chronic liver disease, cancer, anemia, renal disease, dementia, stroke, rheumatologic disease, obesity.

Two vaccine brands were reported. Among vaccinated children, roughly three quarters received Fluenz Tetra and one quarter received Vaxigrip Tetra. All vaccinated adults ≥ 65y received Vaxigrip Tetra.

3.3. Brand-specific IVE estimates for the 2019/2020 season

1 TND studies

Brand-specific vaccine effectiveness estimates against any influenza are shown in Table 4. All estimates obtained in the DRIVE study, including IVE by type and subtype/lineage, are available on the WebAnnex. Multiple estimates had a confidence interval containing only positive values; and none of the estimates had a confidence interval below 0.

Most children and adults < 64y were captured in the primary care setting and the most frequently observed vaccine brand was Vaxigrip Tetra. The estimate against any influenza for Vaxigrip Tetra was 61% (95%CI 38–77) in children. This estimate was obtained by pooling three site-specific estimates (Austria MUV in Austria, and CIRI-IT GP and ISS in Italy), and included data from 2,198 subjects, of whom 50 were vaccinated cases. The corresponding estimate in adults up to 64y was 32% (95%CI −13–59) (based on two sites – Austria MUV and Italy ISS – and 1509 subjects of whom 29 were vaccinated). Most adults ≥ 65y were captured in the hospital setting and the most frequently observed vaccine was Fluad. The estimate against any influenza for Fluad was 52% (95%CI 27–68) (based on five sites – CIRI BIVE in Italy and all sites in Spain – 1047 subjects of whom 63 were vaccinated). In the sensitivity analysis adjusting for all available potential confounders, the IVE estimates described above were 2% to 5% higher (absolute values). Overall for all strata, the estimates were not consistently higher or lower than those of the main analysis. Additionally, confidence intervals tended to be wider (WebAnnex).

The brand-specific IVEs described above could be explained away by an unmeasured confounder that was associated with the vaccination and/or the outcome by a risk ratio of at least 4.6, above and beyond the measured confounders, for children and 2.3 for adults < 64y (Vaxigrip Tetra, primary care), and at least 3.5 for adults ≥ 65y (Fluad, hospital). E-values for all brand-specific VE estimates against any influenza are shown in Supplementary Table 1.

The sensitivity analysis with the extended time period included 9,616 subjects (reflecting an increase of 6% compared to the main analysis), of which 3,628 were cases (3% more than the main analysis). Overall the estimates were comparable to the estimates in the main analysis. All point estimates against any influenza fell within corresponding CIs of the main analysis (WebAnnex).

2 Population-based cohort study

The Finnish cohort study provided brand-specific IVE estimates against any influenza for Fluenz Tetra in children 2-6y, 68% (95%CI 58–75), and Vaxigrip Tetra in children 6 m-6y, 71% (95%CI 56–80), and adults ≥ 65y, 29% (95%CI 20–36) (Table 5).

In the sensitivity analysis in which the estimates were adjusted for all available potential confounders, the estimates were slightly lower in children and higher in older adults (WebAnnex).

3.4. IVE estimates for any vaccine for the 2019/2020 season

1 Test Negative Design studies

IVE estimates for any vaccine are presented in Fig. 2. Precise estimates of IVE were obtained against any influenza in children in the primary care setting, 64% (95%CI 44–80), and against influenza A in adults ≥ 65y in the hospital setting, 53% (95%CI 35–67). In the sensitivity analysis adjusting for all available potential confounders, the IVE estimates were 5% and 1% higher, respectively (absolute values).

The E-values for the IVE for any vaccine against any influenza by age and setting are shown in Table 6. The observed IVE of 63% among children in primary care could be explained away by an unmeasured confounder that was associated with the vaccination and/or the outcome by a risk ratio of at least 5-fold each, above and beyond the measured confounders. Similarly, the corresponding value to explain away the observed IVE of 36% among adults ≥ 65y in the hospital setting is 2.5. For all six IVE point-estimates, the E-value is ≥ 2.0.

In the sensitivity analysis with the extended time period, the most precise estimates were among children in primary care setting against any influenza, 63% (95%CI 45–78), and among adults ≥ 65y in the hospital setting against influenza A, 54% (95% CI 33–70), and against A(H1N1)pdm09, 54% (95%CI 32–70).

2 Population-based cohort study

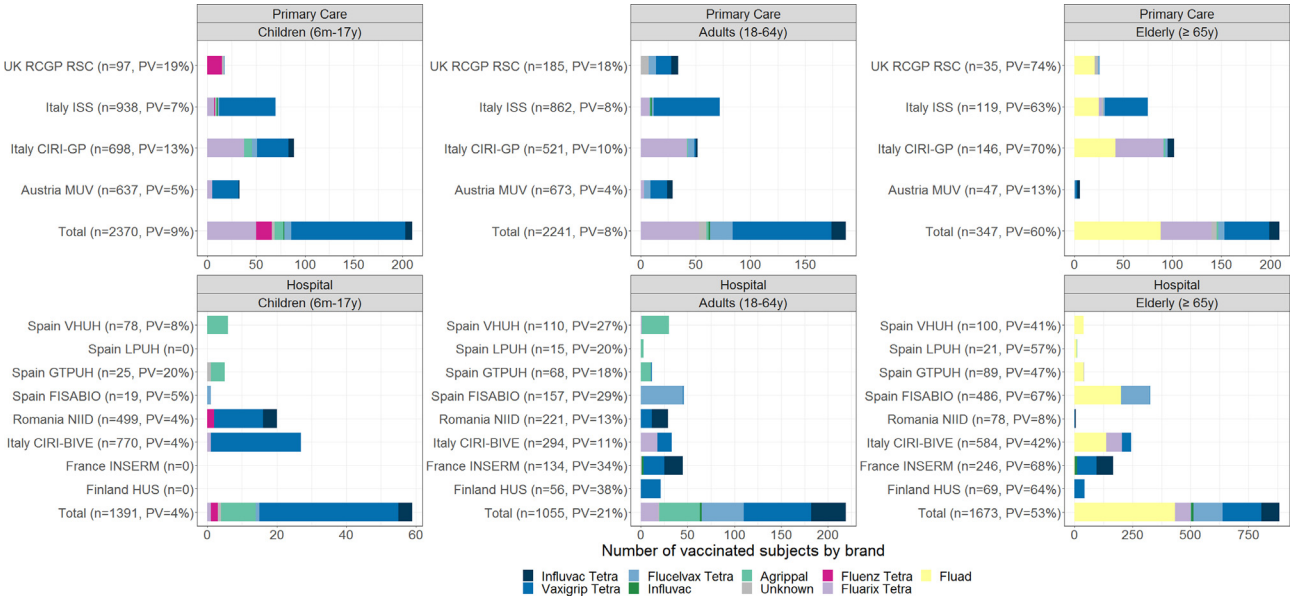

Fig. 1. Number of vaccinated subjects among enrolled subjects and distribution of vaccine brands; TND studies, 2019/20.

Table 3
Study characteristics, population-based cohort study, 2019/20.

Characteristic	6 m-6y				≥65y			
	Vaccinated Number of influenza infections	Person years (%)	Unvaccinated Number of influenza infections	Person years (%)	Vaccinated Number of influenza infections	Person years (%)	Unvaccinated Number of influenza infections	Person years (%)
Total	110	16,375	917	84,567	467	110,497	933	300,414
Female	42	8043 (10%)	409	41,224 (49%)	247	62,683 (21%)	518	167,943 (56%)
Vaccine brand								
Any*	110	16,375 (100%)	–	–	467	110,497 (100%)	–	–
Vaxigrip Tetra	25	4044 (25%)	–	–	451	108,124 (98%)	–	–
Fluenz Tetra	64	10,276 (63%)	–	–	–	–	–	–

*Vaxigrip Tetra and Fluenz Tetra.

IVE estimates for any vaccine from the Finnish population-based cohort are presented in Table 5. IVE against influenza A was higher in children < 6y than in adults ≥ 65y.

4. Discussion

In the 2019/20 season, which represented the third season of DRIVE, the network expanded by three TND hospital sites and included one additional country. In total, the DRIVE network encompassed twelve TND study sites, representing 388 primary care physicians and pediatricians and 19 hospitals, and one population-based cohort. Data from 9077 subjects, of which 3531 were cases, were analyzed in the TND studies, and 511,854 person-years were included in the population-based cohort.

Effectiveness estimates were obtained for eight of the eleven influenza vaccine brands marketed in Europe. This included estimates for all quadrivalent vaccines for all approved age indications, whereas no estimates were available for three of the six trivalent vaccines. This difference reflects the current transition to quadrivalent influenza vaccines in Europe. TIV-HD was not captured in the 2019/20 season, as this was only marketed in the UK where, unlike other influenza vaccines, it was not reimbursed in 2019/20 and will not be in 2020/21 either [17]. In light of this transition and the arrival of new vaccine types (such as cell-based and high dose influenza vaccines) and a more differentiated vaccine landscape, a strong network is key to capture an increasing number of brands and their actual protection.

For the first time, precise brand-specific estimates, below the internal threshold of CI width < 40% established in DRIVE, were obtained from the pooled TND studies in DRIVE (Fluarix Tetra and Vaxigrip Tetra), in addition to those from the population-based cohort study (Fluenz Tetra and Vaxigrip Tetra). This threshold is admittedly arbitrary, however it is used as a tool to help identify the most precise estimates among the numerous estimates (by age/setting/influenza virus/exposure) obtained in DRIVE. All these estimates showed a protective effect. One characteristic of the DRIVE network is that estimates from individual TND sites are pooled to increase precision. Currently, DRIVE is the only European network reporting brand-specific IVE estimates. Public Health England has calculated type-specific IVE estimates for vaccines aTIV, LAIV, QIVc and QIVe in primary care. The PHE estimates are 16.2% (-58.7–55.7) for aTIV in those aged ≥ 65y; 45.4% (12.6–65.9) for LAIV in children 2-17y; 63.9% (26.9–82.2) and 31.7% (-81.5–74.3) for QIVc in adults 18-64y and adults aged ≥ 65y, respectively, and 38.9% (-4.5–64.3) for QIVe in adults 18-64y [18]. The point estimates differ from those in DRIVE, where the point estimates for aTIV (–23%), QIVc and QIVe in adults up to 64y (35% and 21%) are lower. The corresponding TND point estimate for LAIV in DRIVE is based solely on data from England but is much higher (81%) than the one obtained by PHE. The confidence intervals of these estimates are wide and overlap with the confidence intervals of the respective DRIVE TND primary care estimates.

DRIVE point estimates for any vaccine against any influenza among children in primary care (64% from the TND studies and 66% in mixed setting from the population-based cohort study) overlap with the 2019/20 interim estimate from the EU I-MOVE multi-country network (until January 29, 2020), 64% (95% CI 16–85) [19]. For hospitalized patients ≥ 65y, the IVE estimate against influenza A from the DRIVE TND studies was 53%, which is comparable to the 62% (95%CI 41–76) reported by the EU I-MOVE multi-country network. However, the corresponding estimate from the Finnish population-based cohort study, 26% (18–34), was lower.

The point estimate for Vaxigrip Tetra against any influenza in children was similar between the primary care TND studies (61%)

Table 4
Pooled confounder-adjusted brand-specific vaccine effectiveness estimates against any influenza by age and setting from TND studies, 2019/20.

	IVE % (95%CI) against any influenza								
Age	Agrippal	Fluad	Fluarix Tetra	Flucelvax Tetra	Fluenz Tetra	Influvac	Influvac Tetra	Vaxigrip Tetra	Any vaccine
Primary care									
6 m-17y*	60 (-96; 92)	n/a	81 (58; 92)	72 (-100; 96)	81 (-6; 97)	x	53 (-182; 92)	61 (38; 77)	64 (44; 80)
18-64y	x	n/a	29 (-54; 68)	35 (-141; 83)	n/a	x	−95 (-879; 80)	32 (-13; 59)	30 (-3; 53)
≥65y	x	−23 (-317; 64)	−267 (-4638; 72)	x	n/a	x	−197 (-3626, 76)	55 (-35; 85)	−34 (-316; 74)
Hospital									
6 m-17y*	−1 (-402; 96)	n/a	x	x	51 (-767; 97)	x	61 (-229; 95)	28 (-73; 73)	33 (-26; 66)
18-64y	68 (22; 88)	n/a	6 (-251; 75)	59 (-53; 89)	n/a	x	−25 (-188; 48)	−19 (-142; 56)	29 (-8; 71)
≥65y	x	52 (27; 68)	67 (8; 88)	43 (-40; 76)	n/a	32 (-355; 90)	24 (-150; 87)	48 (-20; 87)	36 (7; 71)

*≥9y for Flucelvax Tetra; ≥2y for Fluenz Tetra; ≥3y for Influvac Tetra.
X: no estimate available; IVE: influenza vaccine effectiveness; n/a: not applicable because vaccine not licensed for age group.

Table 5
Confounder-adjusted pooled influenza vaccine effectiveness, Finnish population-based cohort 2019/20.

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

*2-6y for Fluenz Tetra.

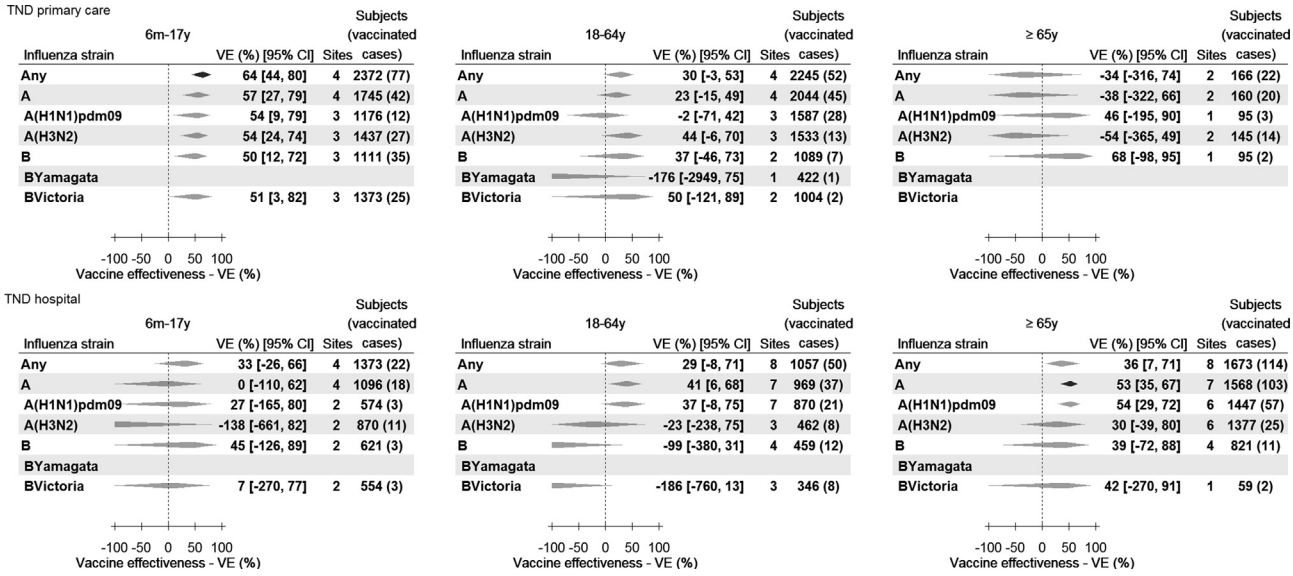

Fig. 2. Pooled confounder-adjusted (age, sex and calendar time) influenza vaccine effectiveness for any influenza vaccine against laboratory confirmed influenza, overall and per type and subtype/lineage, by setting and age group, TND studies, 2019/20. Estimates with a confidence interval<40% are marked with a dark diamond.

Table 6
E-values for VE estimates for any influenza vaccine against any influenza, by setting and age-group, TND studies, 2019/20.

Age group	VE	E-value for VE	Lower 95%CI limit of VE	E-value for lower limit
Primary care				
6 m-17y	64.3	5.0	44.3	3.0
18-64y	30.2	2.2	−2.5	1
≥ 65y	−33.9	2.0	−315.9	
Hospital				
6 m-17y	33.4	2.4	−26.2	1
18-64y	29.0	2.2	−7.5	1
≥ 65y	36.2	2.5	6.8	1.4

and the population-based cohort study (71%). However, the Vaxigrip Tetra point estimates from the TND studies (48% (-20–87) in hospital, 55% (-35–85) in primary care) were higher than the population-based cohort study (29% (20–36)), although TND confidence intervals are wide. One possible reason may be the presence of more healthcare seeking bias in the older age group.

Precise-brand-specific estimates were obtained despite the start of the COVID-19 pandemic during the current influenza season which shortened its observation period. This achievement reflects the robustness of the DRIVE study network. The pandemic and the subsequent lockdown measures interfered with and capped an already mild influenza circulation and impacted data collection within DRIVE study sites. Therefore, the study period for the main analysis was truncated at February 29, 2020, which was two months earlier than originally expected. Other influenza studies in the United States took a similar approach [20]. Consequently, fewer ILI and SARI subjects were included than expected. In the sensitivity analysis that included data up to April 30th, two additional precise brand-specific IVE estimates were obtained.

As compared to previous DRIVE studies, improvements were made to the methods and the reporting. First, the list of confounders considered was simplified. Using a simplified approach to adjust for confounding by defining a minimum set of key confounder variables avoided discarding data due to missing values, permitted participation of sites who have limited data on confounders, and avoided potential over-adjustment. Consequently, all TND study sites were able to collect data on the minimum confounder set in the main analysis, reducing heterogeneity. When comparing estimates to those from the fully adjusted sensitivity analysis, there was no consistent effect in a particular direction. The fully adjusted estimates had a larger standard error, which can be explained by the smaller sample size and possibly multicollinearity. Second, results of all site-specific, pooled, and population-based analyses are available in a WebAnnex, which increased the transparency and accessibility of the project outcomes.

4.1. Strengths

An important strength of the DRIVE network, compared to other European study platforms conducting IVE studies, is that information on the specific influenza vaccine brands used is available, allowing the estimation of brand-specific IVE estimates. Moreover, estimates from individual TND sites are pooled, which increases the precision of the IVE estimates and enables DRIVE to capture data on the majority of influenza vaccine brands marketed in Europe.

Although brand-specific IVE estimates were obtained from the TND studies, narrower confidence interval estimates were obtained from the THL population-based cohort. Clinical heterogeneity in the estimates was reduced by stratifying by age and, in the TND studies, by setting.

4.2. Limitations

Several limitations exist. Most of the CI in the TND studies are wide. Multiple factors affect the precision of the estimates, such as sample size, vaccine coverage and the influenza attack rate, but also the true IVE, test sensitivity and specificity, statistical methods, and the heterogeneity of site-specific IVE estimates. Limitation to sample size are in part due to the multiple stratifications required to reduce clinical heterogeneity; in an effort to improve this in future seasons, DRIVE has limited the next call-for-tenders to sites serving older age groups in hospital setting (see next steps). The sample size of the studies is not sufficient to detect relative IVE. A meaningful comparison between brands would require them to be used at the same site (or at least country) and in the same risk group and only few such situations were observed.

There were several differences in study conduct between the studies. The case definition at FISABIO varied slightly from the other SARI case definitions, for historical reasons as FISABIO provides data to DRIVE as part of their existing respiratory infections surveillance network in Valencia, with an already established SARI definition [21,22]. The different case definitions for children do no impact the pooled IVE estimates as no site-specific IVE could be calculate for children at FISABIO. For adults, the difference in case definition would have led to the exclusion of patients presenting with deterioration of general condition but no other systemic symptoms, the impact of this is expected to be minor as at other sites < 1% of SARI cases presented with no other systemic symptoms. Antigen detection was used to test for influenza in the pediatric population at two Spanish sites, as per their routine clinical practice, and this method is less sensitive than RT-PCR and may result in underestimation of the IVE [23]. However, the impact is likely limited as these two sites contributed<8% of children in hospital setting in the pooled analysis.

Residual confounding may be present. When the precise IVE estimates in the main analysis were adjusted for additional potential confounders in the sensitivity analysis, the shift in point estimates was small. However, the additional confounders mainly accounted for a possible association between vaccination and disease severity, but not necessarily for vaccination and influenza virus exposure (e.g. due to profession) or vaccination and pre-existing immunity [14]. The post-hoc analysis on unmeasured confounding showed that for all TND analyses on the VE of any vaccine against any influenza, showed that unmeasured confounders associated with vaccination and/or ILI or SARI by a risk ratio of at least 2.0–2.5 could explain away the observed association for most stratifications, whereas the estimate for ILI in children in primary care setting seems more robust (E = 5.0). Further research on confounding in the DRIVE TND studies is planned.

Due to the observational nature of the studies, selection bias cannot be ruled out. In TND studies, the relationship between influenza vaccine and testing positive for influenza among those who are tested is studied; thereby reducing confounding due to healthcare-seeking behavior but introducing selection bias and reducing generalizability to the general population [24–26]. It has been shown that selection bias due to differences in healthcare seeking behavior between influenza and non-influenza ILI/SARI is unlikely to be meaningful, at least in the primary care setting [27]. Finally, other limitations exist such as the non-collapsability of the odds ratio [26]. Possible origins of bias specifically in the population-based Finnish study have been previously described [28,29].

4.3. Next steps

The DRIVE network expands through the participation of additional public health institutes and through the annual call for tenders. The call for tenders for the 2020/21 influenza season focused on the adult and older adult populations in the hospital setting, to increase the efficiency and feasibility of the network. A relatively high vaccine coverage is observed among older adults, reflecting influenza vaccine recommendations in Europe, and in this age group vaccination can have the most direct impact on morbidity and mortality. The hospital setting was chosen as the proportion of older patients is higher than in primary care. By enhancing the homogeneity across sites, the number of site-specific estimates that can be pooled in the selected strata will be increased, which is expected to result in a larger sample size and (depending on the attack rate and brand-specific vaccine coverage) more precise IVE estimates. The trade-offs are that the coverage of some vaccine brands is low in the older age groups, that the data will not be representative for the licensed age indication of all

influenza vaccines and may not encompass exposure to all vaccine brands available in EU, and that the IVE estimated in the hospital setting is likely to reflect protection against more severe illness. However, it is important to note that national and regional public health institutes in Europe are encouraged to join DRIVE, regardless of the age groups or settings covered as DRIVE will still produce primary care brand-specific IVE estimates using surveillance data from public health institutes.

In addition, the DRIVE network aims to develop a transparent open data model to promote research collaboration between sites, which could support advanced knowledge in the field of IVE studies along with the study platform expansion.

Work is ongoing to assess the feasibility and sustainability of DRIVE beyond its 5 years under IMI funding (ending July 2022). The feasibility of developing a VE platform leveraging the knowledge and infrastructure developed in DRIVE has been applied in COVIDRIVE, a spin-off of DRIVE to assess brand-specific COVID-19 VE. COVIDRIVE has been built by several DRIVE partners and will be launched in May 2021, with a larger network of sites and new vaccine companies as partners. In the long term, we envision both initiatives merging in a universal VE platform for vaccine preventable respiratory infectious diseases.

COVID-19 is likely to have a significant impact on future DRIVE studies, both in terms of epidemiology and data collection at DRIVE study sites. Influenza and SARS-CoV-2 are expected to co-circulate and non-pharmaceutical interventions such as social distancing measures to prevent SARS-CoV-2 transmission, which has a higher reproduction number (R0 = 2–3.5) than influenza (R0 = 1.28), are likely to also prevent transmission of other respiratory viruses, including influenza [30]. The DRIVE generic protocol for TND studies has been adapted to encompass several COVID-19 components regarding the operational aspects of data collection and analysis, to estimate COVID-19 impact on IVE and to compare clinical and laboratory features of COVID-19 and influenza cases at the time of hospital admission. Healthcare seeking behaviour, triage strategies and testing pathways have been adapted in many European countries. The COVID-19 and influenza testing strategy at the sites must be understood (e.g. influenza testing conditional to a negative SARS-CoV-2 test, parallel testing, etc.). A good understanding of all the COVID-19 adaptations that DRIVE sites will implement will be important to accurately describe the study population and interpret the IVE estimates.

5. Conclusions

In 2019/20, overall VE for any vaccine estimated in the TND studies was 64% (44; 80) among children in primary care and 36% (7–71) adults $\geq$ 65y in the hospital setting, with similar findings from the Finnish population-based cohort study.

Eight out of eleven brands licensed and marketed in Europe in the 2019/2020 season were captured in the DRIVE data. The captured brands reflected the transition from conventional TIV to QIV over the past season, indicating that DRIVE network is representative of the wide variety of influenza vaccines present in Europe. The DRIVE network expanded from five to eight TND hospital sites, in addition to the existing TND primary care sites and the Finnish population-based cohort. The first relatively precise (CI width of < 40%) brand-specific IVE estimates were obtained from the TND studies, despite challenges faced in the context of the COVID-19 pandemic in the final part of the influenza season.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

[Anke L. Stuurman, Kaatje Bollaerts, Jorne Biccler, Tom De Smedt, and Margarita Riera-Montes declare that P95 Epidemiology and Pharmacovigilance has held contracts for research work with GSK and Seqirus. Odile Launay and Florence Galtier declare that they are principal investigator for clinical trials sponsored by Janssen, GSK, Pfizer, Sanofi Pasteur and MSD. Phillips Vanhems declares to have received grants and fees from Pfizer, Sanofi, Anios, MSD and Astellas. Hanna Nohynek and Ulrike Baum declare that THL holds / has held a research contract with influenza vaccine manufactures GSK and Sanofi Pasteur on both non-influenza and influenza related research but the authors are not recipients of these fund. Anca Cristina Drăgănescu, Oana Săndulescu, Victor Daniel Miron, Simona Paraschiv, Marius Surleac, Dragoș Florea, Ovidiu Vlaicu, Anuta Bilașco, Dan Oțelea, Monica Luminița Luminos, Daniela Pițigoi, and Adrian Streinu-Cercel declare being part of the GIHSN project research team that was co-funded by Foundation for Influenza Epidemiology. Oana Săndulescu, Anca Streinu-Cercel, and Adrian Streinu-Cercel declare being (sub)investigators in influenza clinical trials by Shionogi and F. Hoffmann-La Roche.].

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.05.059 and https://apps.p-95.com/drivewebapp/?season=1920.

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