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Vaccine effectiveness against laboratory-confirmed influenza in Europe – Results from the DRIVE network during season 2018/19

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ABSTRACT

The DRIVE project aims to establish a sustainable network to estimate brand-specific influenza vaccine effectiveness (IVE) annually. DRIVE is a public–private partnership launched in response to EMA guidance that requires effectiveness evaluation from manufacturers for all individual influenza vaccine brands every season. IVE studies are conducted by public partners in DRIVE. Private partners (vaccine manufacturers from the European Federation of Pharmaceutical Industries and Association (EFPIA)) provide written feedback moderated by an independent scientific committee.

Test-negative design (TND) case-control studies (4 in primary care and five in hospital) were conducted in six countries in Europe during the 2018/19 season. Site-specific confounder-adjusted vaccine effectiveness (VE) estimates for any vaccine exposure were calculated by age group (<18 years (y), 18-64y and 65 + y) and pooled by setting (primary care, hospital) through random effects *meta*-analysis. In addition, one population-based cohort study was conducted in Finland.

TND studies included 3339 cases and 6012 controls; seven vaccine brands were reported. For ages 65 + y, pooled VE against any influenza strain was estimated at 27% (95%CI 6–44) in hospital setting. Sample size was insufficient for meaningful IVE estimates in other age groups, in the primary care setting, or by vaccine brand.

The population-based cohort study included 274,077 vaccinated and 494,337 unvaccinated person-years, two vaccine brands were reported. Brand-specific IVE was estimated for Fluenz Tetra (36% [95% CI 24–45]) for ages 2-6y, Vaxigrip Tetra (54% [43–62]) for ages 6 months to 6y, and Vaxigrip Tetra (30% [25–35]) for ages 65 + y.

The results presented are from the second influenza season covered by the DRIVE network. While sample size from the pooled TND studies was still too low for precise (brand-specific) IVE estimates, the network has approximately doubled in size compared to the pilot season. Taking measures to increase sample size is an important focus of DRIVE for the coming years.

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1. Introduction

Development of Robust and Innovative Vaccine Effectiveness (DRIVE) is a new and developing network launched in July 2017 in response to the European Medicines Agency (EMA) guidance on influenza vaccines that came into effect in February 2017 [1]. EMA has requested that marketing authorization holders perform influenza vaccine effectiveness (IVE) evaluation at brand level every season, a task that demands international cooperation between public health institutions and vaccine manufacturers. DRIVE is funded by the Innovative Medicines Initiative (IMI), a public–private partnership between the European Union and the European pharmaceutical industry, and aims to establish, over a five-year period, a sustainable network to annually estimate the brand-specific IVE for all influenza vaccines used in the European Union [2].

The results presented here come from the second influenza season covered by the network. IVE studies in DRIVE are conducted by the public partners (such as public health institutes and universities) in the consortium. All scientific output on IVE studies undergo review by an Independent Scientific Committee. Private partners (vaccine manufacturers from the European Federation of Pharmaceutical Industries and Association (EFPIA)) provide written feedback moderated by an independent scientific committee. To guarantee scientific independence, private partners are not involved in data collection or analysis. The DRIVE study governance has been adapted from previous work [3] and is described in more detail elsewhere [4]. Data from several independently operating national or regional study sites, identified following an international selection and following core common protocols for different study designs, are analysed jointly to allow obtaining sufficient sample size and geographical coverage to capture as many influenza vaccine brands as possible. With time, DRIVE aims to obtain increasingly precise IVE results.

The 2018/19 influenza season in Europe was characterized by variable co-circulation of A(H1N1)pdm09 and A(H3N2) and little to no circulation of influenza B viruses [5]. Generally, A(H1N1)pdm09 was dominant at the start of the season and A(H3N2) at the end of the season[6]. There was a good match between the circulating and vaccine strains for A(H1N1)pdm09, however, the most recent A (H3N2) strains, belonging to clade 3C.3a, showed antigenic difference in comparisons to the strains included in the 2018/2019 vaccine [6]. Nine influenza vaccines from five manufacturers were licensed and used in Europe in the 2018/19 season: four conventional inactivated trivalent vaccines (TIV) (Influvac (Abbott), Vaxigrip (Sanofi Pasteur), Afluria and Agrippal (Seqirus)), one inactivated adjuvanted TIV (Fluad (Seqirus)), three inactivated quadrivalent vaccines (QIV) (Fluarix Tetra (GlaxoSmithKline), Influvac Tetra (Abbott), Vaxigrip Tetra (Sanofi Pasteur)) and one live attenuated QIV (Fluenz Tetra (AstraZeneca)). In addition, one inactivated TIV, 3Fluart (Fluart Innovative Vaccines), was only available in Hungary.

The scientific primary objective of DRIVE project is to calculate vaccine effectiveness (VE) for any influenza vaccine and brand-specific VE, against any influenza, by type and subtype/lineage. To this end, age- and setting-stratified pooled IVE estimates were calculated from test-negative design (TND) case-control studies conducted in six countries in Europe during the 2018/19 influenza season. In addition, age-stratified IVE estimates were calculated from one population-based cohort study in Finland.

2. Methods

2.1. Study design

The core protocols for TND studies and population-based database cohort studies are available from the DRIVE website [7,8].

2.1.1. TND studies

TND studies were conducted at four primary care sites (four networks) and at five hospital sites (three individual hospitals and two hospital networks) (Table 1). The primary care sites were coordinated in each respective country by the Medical University Vienna (MUV) in Austria, Interuniversity Research Center on Influenza and other Transmissible Infections (CIRI-IT) in Italy, the Italian National Institute of Health (ISS), and the Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) in England. The individual hospitals were Jorvi Hospital (part of the Helsinki University Hospital (HUS)) in Finland, Vall d'Hebron University Hospital (VHUH) in Spain and the National Institute for Infectious Diseases "Prof. Dr. Matei Balș" (NIID) in Romania. The hospital networks were the Italian Hospital Network (BIVE), tertiary care hospitals serving the Baria, Rome and Siena provinces and the Liguria and Lazio regions, and the hospitals from the Foundation for the Promotion of Health and Biomedical Research of the Valencia Region (FISABIO) in Spain.

The study population consisted of community-dwelling subjects $\geq$ 6 months of age, who presented either with influenza-like illness (ILI; ECDC case definition [9]) in the primary care setting or with severe acute respiratory infection (SARI; IMOVE + 2017/18 case definition [10]) in the hospital inpatient setting (except one site, see Table 1), and for whom a swab was taken for laboratory-confirmation of influenza < 8 days after symptom onset. Subjects with a contraindication for influenza vaccination and subjects with a prior positive influenza test in the same season were excluded. In addition, in hospital settings, subjects previously hospitalized < 48 h prior to symptom onset and subjects with symptom onset $\geq$ 48 h after hospital admission were excluded. At VHUH, controls were matched to cases (1:1) by epidemiological week (same or adjacent week) and age group. Further details on the inclusion of ILI/SARI subjects and the type of specimen taken are available elsewhere [11].

Laboratory confirmation for influenza was performed through molecular or antigen detection tests and influenza subtypes were available for the majority of sites (Table 1).

Covariate information was collected for all subjects, and vaccine brand and date of vaccination were collected for vaccinated subjects from medical records, vaccination registries, or vaccination cards, as appropriate.

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, 2019, whichever occurred first. The reason to define the end of the season with a specific date was practical rather than scientific.

2.1.2. Population-based cohort study

A population-based cohort study was conducted by the Finnish Institute for Health and Welfare among Finnish residents aged 6 months (m) to 6 years (y) and 65–100 years, by linking five national registers (Population Information System, National Vaccination Register, National Infectious Diseases Register, Register of Primary Health Care Visits, Care Register for Health Care) through personal identifiers. Cases were defined based on laboratory confirmation of influenza only, no clinical criteria were used. Further details are available in Table 1 and Baum et al. [12]. The study period for analysis was defined a priori from week 40/2018 to week 17/2019.

2.2. Statistical methods

Data collected at the study sites were transferred to the GDPR-compliant DRIVE Research Server by May 15, 2019, where they

Table 1
Study sites in the DRIVE network, by study design and setting, 2018/19.

Country	Site name	Source of study population	Case definition	Laboratory test	Influenza A subtypes available
TND - hospital					
Finland	Jorvi Hospital, Helsinki University Hospital (HUS)	1 hospital	SARI[b]	RT-PCR	Yes
Italy	Italian Hospital Network (BIVE)	5 hospitals	SARI[b]	RT-PCR	Yes
Romania	National Institute for Infectious Diseases "Prof. Dr. Matei Balș" (Institutul Național de Boli Infecțioase "Prof. Dr. Matei Balș" NIID)	1 hospital	SARI[b]	RT-PCR	Yes
Spain	Foundation for the Promotion of Health and Biomedical Research of the Valencia Region (Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunitat Valenciana FISABIO)	4 hospitals	ILI[c]	RT-PCR	Yes
Spain	Vall d'Hebron University Hospital (VHUH)	1 hospital	SARI[b]	<18y: antigen detection≥18y: RT-PCR	Yes
TND - primary care					
Austria	Medical University Vienna (MUV)	90 physicians	ILI[a]	RT-PCR	Yes
England	Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC)	44 physicians (6 practices)	ILI[a]	RT-PCR	No
Italy	Interuniversity Research Center on Influenza and other Transmissible Infections (Centro Interuniversitario di Ricerca sull'Influenza e sulle altre infezioni trasmissibili, CIRI-IT)	21 physicians	ILI[a]	RT-PCR	Yes
Italy	Italian National Institute of Health (Istituto Superiore di Sanità, ISS)	245 physicians	ILI[a]	RT-PCR	Yes
Population-based cohort - primary care and hospital					
Finland	Finnish Institute for Health and Welfare (Terveyden ja hyvinvoinnin laitos, THL)	Population Information System	Laboratory-confirmed influenza[d]	RT-PCR or antigen detection	No

a. ECDC case definition; b. IMOVE + 2017/18 case definition; c. < 5y: hospitalized for any acute reason with symptom onset in the 7 days prior to admission, ≥5y: modified ECDC case definition (without "sudden onset"); d. as registered in the National Infectious Diseases Register

were analyzed centrally by the P95 authors. Individual-level data were transferred for the TND studies and aggregated data (by age, sex, chronic condition, number of hospital visits in the previous 12 months, number of General Practitioner (GP) visits in the previous 12 months, vaccination in previous season, vaccination brand) for the population-based cohort study. Data were anonymized. Full details on the statistical methods are available from [13].

2.2.1. TND studies

For the TND studies, subjects with missing outcome, missing swab date, missing or unconfirmed vaccination status or date, and those recently vaccinated (≤14 days before ILI/SARI symptom onset) were excluded. The number of subjects retained for analysis is reported.

Site-specific age-stratified (<18y, 18-64y, 65 + y) crude and confounder-adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated using logistic regression. IVE was defined as 100 * (1 - OR). A pre-defined set of confounders was considered for each individual site, and consisted at minimum of sex, a smooth function of age and a smooth function of symptom onset date. Smoothing was achieved using penalized cubic splines [14]. Addition covariates included pregnancy, influenza vaccination in the previous season, and respectively number of primary care visits (0, 1–5, >5) or hospitalization (0, 1–2, >2) in the previous 12 months for primary care and hospital studies. Complete case analyses were performed. For some sites, some covariates were not collected (i.e. pregnancy at BIVE and ISS, vaccination status in the previous season at ISS, number of GP visits at MUV and CIRI-IT). When covariate information was missing for a substantial number (defined as > 10%) of the subjects (i.e. pregnancy at NIID, vaccination status in the previous season at HUS and BIVE, number of hospitalizations in the past year at BIVE) the covariate was not adjusted for and the subjects were retained in the analysis. This was done to prevent removing too many subjects from the analysis, which would have had a large impact on the sample size and consequently on the precision of the IVE estimates. The important confounders age, sex and date of symptom onset were always available.

Pooled IVE estimates by age and setting were obtained through random-effects *meta*-analysis of the site-specific estimates. A random-effects model was chosen to account for heterogeneity among site-specific estimates beyond the variation due to random error. To enable future incorporation of estimates from cohort studies as well as data from sites only sharing aggregated rather than individual-level data, a *meta*-analytic approach was chosen. Meta-analysis and individual-level data pooling have been shown to be essentially equivalent [15]. Estimates for primary care and hospital settings were not pooled to reduce clinical heterogeneity. Estimates obtained from the primary care setting should be interpreted as IVE against medically-attended virologically confirmed ILI due to influenza, estimates from the hospital setting as IVE against hospitalized virologically confirmed SARI due to influenza.

2.2.2. Population-based cohort study

Age-stratified (6 m-6y, 65 + y) crude and confounder-adjusted relative risks (RR) and 95%CI were estimated using Poisson regression. IVE was defined as 100 * (1 - RR). Confounders included sex, a penalized cubic splines of age and calendar week, presence of at least one chronic condition, number of primary care visits in the previous 12 months (0, 1–5, >5), number of hospitalizations in the previous 12 months (0, 1–2, >2) and influenza vaccination in the previous season. As it is an open cohort, person-years were used. No distinction could be made between cases from primary care and cases from hospital setting.

2.2.3. Quality control and transparency

The statistical analysis plan [13] underwent review by the Independent Scientific Committee and was registered at the ENCePP EU PAS Register (EUPAS29817). 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.

A quality control and assurance committee evaluated how quality was managed at the site-level.

2.3. Ethical approval

Each local study was approved by national, regional or institutional ethics committees, as appropriate [16]. In the case of ISS, the study was submitted to the ethics committee for information, but approval was not required as the study is nested in the National Influenza Surveillance Scheme. Similarly, for the Finnish population-based cohort study, an ethical evaluation was not mandatory, however an evaluation from an institutional ethical review group was requested.

2.4. Data sharing

Aggregated data from the DRIVE studies are available upon request from info@drive-eu.org.

3. Results

The main results are presented here. Additional results and further details are available in the DRIVE annual report [11].

3.1. Subject characteristics

3.1.1. TND studies

Subject characteristics are shown in Table 2. Across the nine sites, 3339 cases and 6012 controls were retained for analysis (4467 (88.3%) among 5061 subjects enrolled in the primary care setting and 4884 (67.8%) among 7207 subjects enrolled in the hospital setting). In the primary care setting, 9.4% of the subjects were 65 + y compared to 44.9% in the hospital setting. In addition, patients 65 + y in the hospital setting had at least one chronic condition (95.4%) more often than in the primary care setting (76.0%).

The proportion of A(H1N1)pdm09 vs. A(H3N2) among influenza A cases at primary care sites for which subtype was known was 69% vs. 31% (MUV), 40% vs. 60% (CIRI-IT), 51% vs. 49% (ISS). Among cases at hospital sites this was 65% vs. 35% (BIVE), 39% vs. 61% (HUS), 67% vs. 33% (NIID), 40% vs. 60% (FISABIO), and 56% vs. 44% (VHUH).

Overall, vaccine coverage among subjects < 18y old was 8% and 4% in the primary care and hospital setting, respectively. Corresponding vaccine coverages for the 18-64y old subjects were 11% and 18%, and for 65 + y old subjects were 62% and 58%. The largest difference in vaccine coverage between cases and controls was observed in the hospital setting for the age groups 18-64y (13.5% vs. 20.3%) and 65 + y (47.8% vs. 61.0%). An overview of vaccination coverage in the general population in the geographic areas of the sites is given in Supplementary Table 1.

Fig. 1 shows the age-specific brand distribution among vaccinated subjects at each site, for each age- and setting stratum. Seven brands were captured in the TND studies. The total number of vaccine brands in each age- and setting stratum varied from four to six. The most commonly reported brand was Fluarix Tetra (49.8% of those vaccinated) in the < 18y age group, Vaxigrip Tetra (38.7%) in the 18-64y age group, and Fluad (47.5%) in the 65 + y age group. The number of vaccinated subjects in most age- and setting-specific strata was low. The number of children vaccinated by brand (for which there was at least one vaccinated subject) ranged from 12 to 22 (median 16) and from 1 to 91 (14) in hospital and primary care setting, respectively, the number of adults vaccinated by brand ranged from 12 to 74 (21) and from 2 to 108 (5.5), and the number of elderly vaccinated by brand ranged from 35 to 608 (139) and from 1 to 115 (28.5).

3.1.2. Population-based cohort study

Overall, 168,020 person-years for children between 6 months and 6y old and 600,394 person-years for elderly 65 + y old were included. Subject characteristics are shown in Table 3. Among those 65 + y old and vaccinated, the proportion of person-years with at least one chronic disease and the number of primary care visits were higher compared to those non-vaccinated.

The proportion of follow-up time during which subjects were vaccinated was 22.5% among children and 39.4% among the elderly, respectively. Among vaccinated children, approximately two-thirds were vaccinated with Fluenz Tetra and one third with Vaxigrip Tetra. All vaccinated elderly received Vaxigrip Tetra.

3.2. IVE estimates

3.2.1. TND studies

Pooled VE estimates for any vaccine against any influenza viruses, influenza A, and influenza A subtypes are shown in Fig. 2. For the age group < 18y, pooled VE against any influenza viruses was estimated at 48% (95%CI 0–78) (primary care) and 38% (-65–81) (hospital). Corresponding estimates for the age group 18-64y were 45% (18–63) and 40% (2–63), and for the age group 65 + y 18% (-85, 71) and 27% (6–44). Crude estimates are presented in the Supplementary Fig. 1.

In a sensitivity analysis of the TND data, only subjects with respiratory specimens taken < 4 days of ILI or SARI onset were included. Results are in line with the main analysis. Sample size was too small to obtain meaningful brand-specific IVE estimates. Results are available in the DRIVE annual report [11].

3.2.2. Population-based cohort study

Brand-specific IVE estimates were obtained for the Finnish population-based cohort. VE for any influenza vaccine against any influenza in the age group 6 m-6y was 44% (95%CI 36–51). For the age group 6 m-6y, VE of Vaxigrip Tetra against any influenza was estimated at 54% (43–62) and for the age group 2-6y, VE of Fluenz Tetra was estimated at 36% (24–45). For the age group 65 + y, only one vaccine brand was available; VE of Vaxigrip Tetra against any influenza was estimated at 30% (25–35). Crude estimates are presented in Supplementary Table 2.

4. Discussion

In the 2018/19 season, the DRIVE network estimated IVE using data from nine TND study sites that included 400 primary care physicians (including pediatricians) and 12 hospitals in six countries, and one cohort study based on linked national registers in Finland. Overall, seven vaccine brands were reported. Compared to the 2017/2018 pilot year, the number of TND sites and subjects included has approximately doubled (from four to nine sites, and from ca. 5000 to ca. 9350 subjects). Data quality at site-level was improved, for example vaccine brand was missing for more than half of the subjects in the pilot year but was available for the majority of enrolled subjects. A dedicated web application was developed, the Electronic Study Support Application (ESSA), which allows data providers to upload a dataset using a secure mechanism and allows the user to perform various data quality checks.

Pooled VE estimates for any influenza vaccine from the DRIVE TND studies are in line with the 2018/19 interim estimates from individual sites from the European IVE Group [17]. For children in primary care, the European IVE Group estimated VE at 87% (95%CI 4 to 100) against A(H1N1)pdm09 compared to 77% (53–89) in our study. For adults in primary care, the VE estimates from the European IVE Group ranged from 32% (-31 to 65) to 55% (44 to 64) against influenza A compared to 43% (15 to 62) in our study.

Table 2
Characteristics of subjects retained for analysis across primary care and hospital sites, TND studies, 2018/19.

	<18y		18-64y		65 + y	
	Cases n(%)	Controls n(%)	Cases n(%)	Controls n(%)	Cases n(%)	Controls n(%)
Hospital	512 (100)	1083 (100)	371 (100)	724 (100)	559 (100)	1635 (100)
Vaccinated	16 (3.1)	53 (4.9)	50 (13.5)	147 (20.3)	267 (47.8)	997 (61.0)
Female	228 (44.5)	462 (42.7)	189 (50.9)	354 (48.9)	283 (50.6)	789 (48.3)
Pregnant						
Yes	1 (0.4)	0 (0.0)	16 (8.5)	8 (2.3)	n/a	n/a
No	57 (25.0)	114 (24.7)	133 (70.4)	268 (75.7)	n/a	n/a
Unknown	170 (74.6)	348 (75.3)	40 (21.2)	78 (22.0)	n/a	n/a
At least 1 chronic disease*	102 (19.9)	216 (19.9)	252 (67.9)	495 (68.4)	526 (94.1)	1567 (95.8)
Vaccinated in 2017/18						
Yes	11 (2.1)	36 (3.3)	47 (12.7)	139 (19.2)	279 (49.9)	990 (60.6)
No	481 (93.9)	950 (87.7)	303 (81.7)	559 (77.2)	262 (46.9)	599 (36.6)
Unknown	20 (3.9)	97 (9.0)	21 (5.7)	26 (3.6)	18 (3.2)	46 (2.8)
Number of hospitalizations in past year						
0	212 (41.4)	346 (31.9)	198 (53.4)	401 (55.4)	288 (51.5)	866 (53.0)
1–2	72 (14.1)	164 (15.1)	60 (16.2)	151 (20.9)	147 (26.3)	492 (30.1)
>2	26 (5.1)	33 (3.0)	37 (10.0)	63 (8.7)	37 (6.6)	141 (8.6)
Unknown	202 (39.5)	540 (49.9)	76 (20.5)	109 (15.1)	87 (15.6)	136 (8.3)
Site						
Finland - HUS	0 (0.0)	0 (0.0)	25 (6.7)	78 (10.8)	45 (8.1)	126 (7.7)
Italy - BIVE	241 (47.1)	579 (53.5)	104 (28.0)	174 (24.0)	143 (25.6)	357 (21.8)
Romania - NIID	213 (41.6)	305 (28.2)	144 (38.8)	212 (29.3)	71 (12.7)	82 (5.0)
Spain - FISABIO	23 (4.5)	164 (15.1)	35 (9.4)	199 (27.5)	165 (29.5)	934 (57.1)
Spain - VHUH	35 (6.8)	35 (3.2)	63 (17.0)	61 (8.4)	135 (24.2)	136 (8.3)
Primary care	939 (100)	1071 (100)	814 (100)	1222 (100)	144 (100)	277 (100)
Vaccinated	60 (6.4)	100 (9.3)	68 (8.4)	158 (12.9)	88 (61.1)	175 (63.2)
Female	434 (46.2)	475 (44.4)	416 (51.1)	605 (49.5)	86 (59.7)	136 (49.1)
Pregnant						
Yes	1 (0.2)	1 (0.2)	1 (0.2)	12 (2.0)	n/a	n/a
No	188 (43.3)	215 (45.3)	190 (45.7)	317 (52.4)	n/a	n/a
Unknown	245 (56.5)	259 (54.5)	225 (54.1)	276 (45.6)	n/a	n/a
At least 1 chronic disease*	58 (6.2)	64 (6.0)	184 (22.6)	302 (24.7)	106 (73.6)	214 (77.3)
Vaccinated in 2017/18						
Yes	19 (2.0)	41 (3.8)	26 (3.2)	70 (5.7)	34 (23.6)	95 (34.3)
No	336 (35.8)	465 (43.4)	340 (41.8)	578 (47.3)	36 (25.0)	78 (28.2)
Unknown	584 (62.2)	565 (52.8)	448 (55.0)	574 (47.0)	74 (51.4)	104 (37.5)
Number of primary care visits in past year						
0	63 (6.7)	64 (6.0)	131 (16.1)	148 (12.1)	4 (2.8)	8 (2.9)
1–5	467 (49.7)	430 (40.1)	304 (37.3)	433 (35.4)	56 (38.9)	66 (23.8)
>5	70 (7.5)	100 (9.3)	31 (3.8)	47 (3.8)	17 (11.8)	47 (17.0)
Unknown	339 (36.1)	477 (44.5)	348 (42.8)	594 (48.6)	67 (46.5)	156 (56.3)
Site						
Austria - MUV	159 (16.9)	273 (25.5)	198 (24.3)	224 (18.3)	17 (11.8)	16 (5.8)
England - RCGP	16 (1.7)	29 (2.7)	18 (2.2)	54 (4.4)	3 (2.1)	17 (6.1)
Italy - CIRI-IT	180 (19.2)	204 (19.0)	150 (18.4)	370 (30.3)	50 (34.7)	140 (50.5)
Italy - ISS	584 (62.2)	565 (52.8)	448 (55.0)	574 (47.0)	74 (51.4)	104 (37.5)

BIVE: Italian Hospital Network; CIRI-IT: Interuniversity Research Center on Influenza and other Transmissible Infections; FISABIO: Foundation for the Promotion of Health and Biomedical Research of the Valencia Region; HUS: Helsinki University Hospital; ISS: Italian National Institute of Health; 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

For elderly in hospital, they estimated VE at 34% (16 to 48) and 38% (-12 to 66) against influenza A compared to 27% (6 to 44) in our study [17]. In the 2018/19 season, A(H1N1)pdm09 and A(H3N2) co-circulated at different levels in Europe, consequently, the pooled VE estimates against any influenza and influenza A are influenced by the underlying strain circulation at the included sites.

Two brand-specific estimates from the Finnish population-based cohort were available for children and one for the elderly. The brand-specific point estimate for Fluenz Tetra from the Finnish population-based cohort study for children 2-6y (36% [95%CI 24 to 45]) is in line with the end-of-season Fluenz Tetra estimates for children 2-17y in the primary care setting in the UK (48.6% [-4.4 to 74.7%]) [18] and in the hospital setting in England (49.1% [25.9, 65.0]) [18], and the estimate for any vaccine in hospitalized children 2-9y in England (52.3% [29.4, 67.8]) [19].

Overall, CIs from the TND studies were wide and should be interpreted with caution. This is in part because the European influenza season was generally mild. Also, in many strata the overall vaccination coverage was low (range 1% to 75%), resulting in very low brand-specific vaccine coverage (and consequently low precision) especially for sites where multiple vaccine brands were used within the same population (see also Supplementary Table 1).

4.1. Limitations

At some sites, covariate information was missing for > 10% of the subjects or was not collected at all. This resulted in a large percentage of missing data for some subject characteristics (e.g. 36% to 56.3% for 'number of primary care visits in past year' in Table 2) and in confounder-adjustment using a small set of confounders for some sites. We do not expect this to have a large impact on

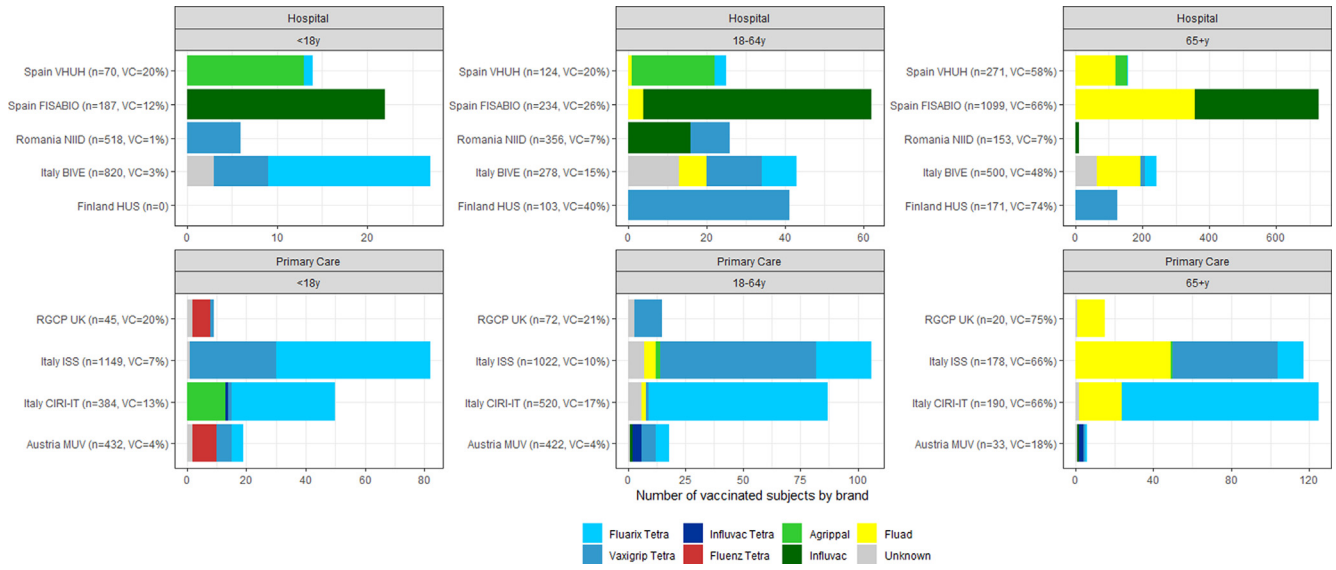

Fig. 1. Vaccine brand distribution among vaccinated subjects at each site, by age and setting. n: number of subjects; VC: % vaccine coverage all influenza brands. BIVE: Italian Hospital Network; CIRI-IT: Interuniversity Research Center on Influenza and other Transmissible Infections; FISABIO: Foundation for the Promotion of Health and Biomedical Research of the Valencia Region; HUS: Helsinki University Hospital; ISS: Italian National Institute of Health; MUV: Medical University Vienna; NIID: National Institute for Infectious Diseases "Prof. Dr. Matei Balş"; RCGP RSC: Royal College of General Practitioners Research and Surveillance Centre; VHUH: Vall d'Hebron University Hospital.

Table 3
Subject characteristics, population-based cohort study, 2018/19.

	6 m-6y		65 + y	
	Vaccinated	Non-vaccinated	Vaccinated	Non-vaccinated
	Person years	**Person years**	**Person years**	**Person years**
Total	37,780	130,240	236,297	364,097
Influenza cases	343 (0.9)	1491 (1.1)	1974 (0.8)	2571 (0.7)
Female	18,460 (48.9)	63,694 (48.9)	133,121 (56.3)	204,275 (56.1)
At least 1 chronic disease	3790 (10.0)	11,329 (8.7)	177,739 (75.2)	245,666 (67.5)
Number of primary care visits in past year				
0	13,609 (36.0)	49,723 (38.2)	71,764 (30.4)	156,856 (43.1)
1–5	22,509 (59.6)	74,560 (57.2)	133,063 (56.3)	173,780 (47.7)
>5	1662 (4.4)	5958 (4.6)	31,471 (13.3)	33,462 (9.2)
Number of hospitalizations in past year				
0	34,764 (92.0)	121,737 (93.5)	193,179 (81.8)	300,577 (82.6)
1–2	2797 (7.4)	8048 (6.2)	37,827 (16.0)	54,864 (15.1)
>2	219 (0.6)	455 (0.3)	5291 (2.2)	8656 (2.4)
Vaccinated in 2017/18	16,989 (45.0)	116,134 (89.2)	42,967 (18.2)	283,058 (77.7)

m: months; y: years

the IVE estimates. Lane et al. defined a parsimonious logistic regression model for TND studies [20] and this did not include any of the confounders that were excluded due to lack of data from the site-specific analyses (i.e. pregnancy, vaccination in previous season, number of primary care visits or hospitalizations in the past year).

Systematic inclusion and swabbing of ILI subjects is encouraged at all sites. If this does not happen systematically, IVE estimates are likely to be affected only if the decision to include or not include a patient with ILI is based on their influenza vaccination status.

4.2. Expanding the DRIVE network

It is known that sample size requirements for estimating brand-specific IVE are large [21,22]. Taking measures to increase sample size and precision, such as more and larger studies and selecting sites that include populations with higher vaccination coverage is, therefore, an important focus of DRIVE for the coming years. The DRIVE network, which included 4 TND sites in the influenza season 2017/18, has grown to 9 TND sites in the season 2018/19 and is expected to expand to 13 TND sites in the season 2019/20.

In addition, the use of real-world data from registers or other electronic healthcare databases will be explored as a potential sustainable solution [23]. The Finnish study based on linked national registers, including the National Vaccination Register [24], enabled the calculation of precise brand-specific estimates for the two vaccines available in Finland in 2018/19. However the results could not be stratified by healthcare setting, nor was subtype-specific data available as most laboratories reporting to the National Infectious Disease Register do not routinely perform such analyses on respiratory samples; therefore, these estimates could not be pooled with the estimates from the TND studies. One of the main limitations of register-based cohort studies is the potential presence of unmeasured confounding that could lead to differential outcome misclassification due to different influenza case detection rates among the vaccinated and unvaccinated; however major advantages are that data collection is almost fully automated and that the sample size is large [12].

Due to the *meta*-analytic approach chosen, DRIVE is also able to incorporate data from sites that only share aggregated data. To encourage data-sharing, aggregated data for this study are available upon request.

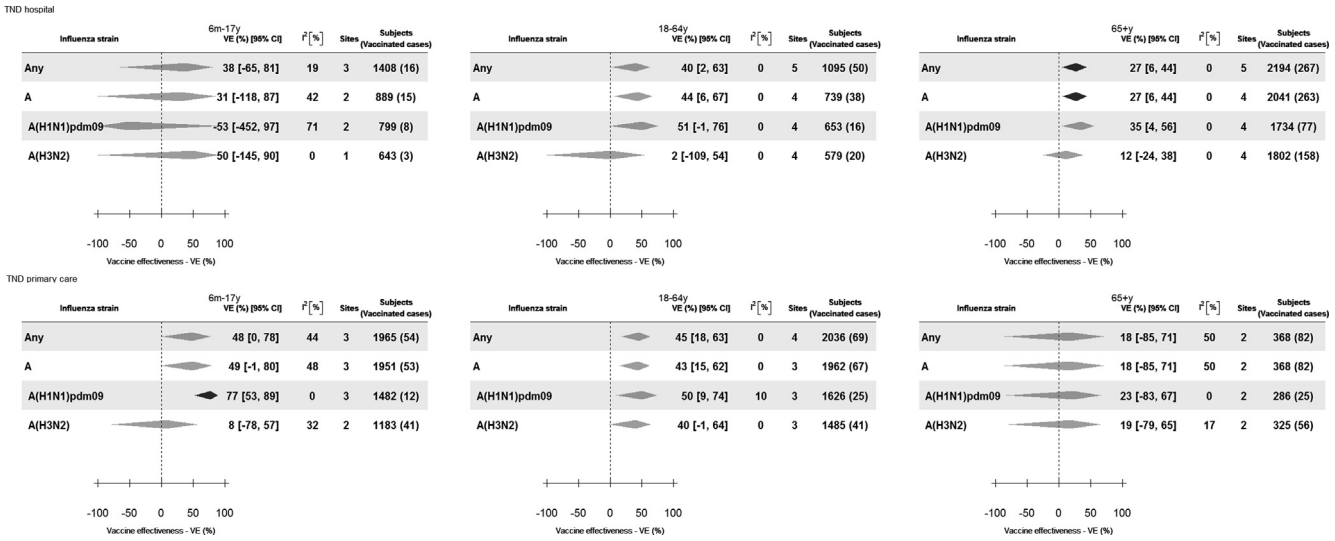

Fig. 2. Pooled confounder-adjusted influenza vaccine effectiveness against laboratory confirmed influenza from TND studies, overall and per type and subtype/lineage, by setting and age group, 2018/2019. Black diamonds indicate estimates with CI width < 40%. The I^2 statistic is to be interpreted as the proportion of total variation in the estimates of treatment effect that is due to heterogeneity between studies. Subjects and vaccinated cases refer to total numbers across sites for which IVE estimates could be calculated. BIVE: Italian Hospital Network; CIRI-IT: Interuniversity Research Center on Influenza and other Transmissible Infections; FISABIO: Foundation for the Promotion of Health and Biomedical Research of the Valencia Region; HUS: Helsinki University Hospital; ISS: Italian National Institute of Health; MUV: Medical University Vienna; NIID: National Institute for Infectious Diseases "Prof. Dr. Matei Balș"; RCGP RSC: Royal College of General Practitioners Research and Surveillance Centre; VHUH: Vall d'Hebron University Hospital.

The DRIVE consortium expects that increasingly more precise age- and setting-stratified IVE estimates will be obtained in future seasons as the network continues to expand. Over time, DRIVE aims to build a sustainable network for brand-specific IVE evaluation in the European Union.

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Role of the funding source

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Anke L. Stuurman, Kaatje Bollaerts, Maria Alexandridou, Jorne Biccler, Tom De Smedt, Nick De Smedt and Margarita Riera-Montes declare that P95 Epidemiology and Pharmacovigilance has held contracts for research work with GSK and Seqirus.

Javier Díez-Domingo declares to have received honoraria from Sanofi Pasteur for advisory boards.

Hanna Nohynek declares that her institution holds / has held a research contract with influenza vaccine manufactures GSK and Sanofi Pasteur on both non-influenza and influenza related research but she is not a recipient of these funds.

Caterina Rizzo declares to have received an unconditional funding from Seqirus for a cost-effectiveness analysis in 2019.

Topi Turunen declares to be the local subinvestigator in the FinFluHD study funded by the Finnish Institute for Health and Welfare and Sanofi Pasteur.

Anca Cristina Dragonescu declares that she is the principal investigator for the GIHSN project funded by Foundation for Influenza Epidemiology financed by Sanofi Pasteur.

Anuta Bilasco, Ovidiu Vlaicu and Dan Otelea have no conflict of interest to declare.

Adrian Streinu-Cercel declares that he is a member of the research team of the GIHSN project funded by Foundation for Influenza Epidemiology financed by Sanofi Pasteur, and a subinvestigator in influenza clinical trials by Shionogi and F. Hoffmann-La Roche.

Anca Streinu-Cercel declares that she is principal investigator for the I-MOVE + study funded through the European Union's HORIZON 2020 research and innovation programme, and a subinvestigator in influenza clinical trials by Shionogi and F. Hoffmann-La Roche.

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José Ángel Rodrigo-Pendás declares that he is a collaborator in two studies funded by GSK (Enhanced safety surveillance of GSK's quadrivalent seasonal influenza vaccines. EPI-FLU-056 VS EUR (2018–2019) & EPI-FLU- 056 VS EUR (2019–2020) and Safety and immunogenicity study of GSK Biologicals' Herpes Zoster subunit vaccine (HZ/su) GSK1437173A on a two-dose schedule in adults $\geq$ 50 years of age with a prior episode of Herpes Zoster (ZOSTER-062 (204939)). EudraCT number: 2016–000744-34) and a collaborator in a clinical trial funded by a government grant (Phase IV, open, low-level intervention, clinical trial to compare the immunogenicity in immunosuppressed patients of an adjuvanted anti-hepatitis B vaccine with an anti-hepatitis B vaccine with increased antigenic load (HEPB-VAC-01). EudraCT number: 2018–002368-18).

Paolo Bonanni declares that he has taken part as a co-author in different HTA evaluations of influenza vaccines in the Italian context for the elderly (co-financed by Seqirus) and for children (co-financed by Sanofi Pasteur) with no personal fees received. He has also taken part in advisory boards and formative events for Seqirus and Sanofi Pasteur with occasional payment of expenses and fees.

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Ulrike Baum declares that her employer (Finnish Institute for Health and Welfare) has been contracted for a clinical trial of influenza vaccines in the elderly funded by Sanofi Pasteur.

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Appendix A. Supplementary data

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