

Interim 2018/19 influenza vaccine effectiveness: six European studies, October 2018 to January 2019

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Influenza A(H1N1)pdm09 and A(H3N2) viruses both circulated in Europe in October 2018–January 2019. Interim results from six studies indicate that 2018/19 influenza vaccine effectiveness (VE) estimates among all ages in primary care was 32–43% against influenza A; higher against A(H1N1)pdm09 and lower against A(H3N2). Among hospitalised older adults, VE estimates were 34–38% against influenza A and slightly lower against A(H1N1)pdm09. Influenza vaccination is of continued benefit during the ongoing 2018/19 influenza season.

Seasonal influenza vaccine is recommended in all European Union (EU) countries for older people and others at increased risk of severe influenza and its complications, including those with chronic diseases [1]. In the United Kingdom (UK), incremental introduction of a universal childhood influenza vaccination programme began in 2013/14 [2].

The World Health Organization (WHO) recommendations for trivalent influenza vaccine strains for the 2018/19 northern hemisphere influenza season included an A/Michigan/45/2015 (H1N1)pdm09-like virus, an A/Singapore/INF16H-16-0019/2016 (H3N2)-like virus and a B/Colorado/06/2017-like virus from the B/Victoria lineage [3].

The early 2018/19 influenza season in Europe was characterised by both influenza A virus subtypes circulating widely. There was co-circulation in some countries, with others reporting dominance of either A(H1N1)pdm09 or A(H3N2) viruses. The season started

late in most countries compared with previous seasons, with few influenza B viruses detected in the WHO European Region [4]. Since the 2008/09 season, the UK, Denmark, Spain, and several other EU countries conducting multicentre studies, have participated in I-MOVE (Influenza – Monitoring Vaccine Effectiveness in Europe), a network measuring influenza vaccine effectiveness each season.

We summarise interim 2018/19 season influenza vaccine effectiveness (VE) estimates from four single-country and two multi-country studies, including both outpatient and hospital settings, in order to help guide influenza prevention and control measures for the rest of the 2018/19 season.

Study setting

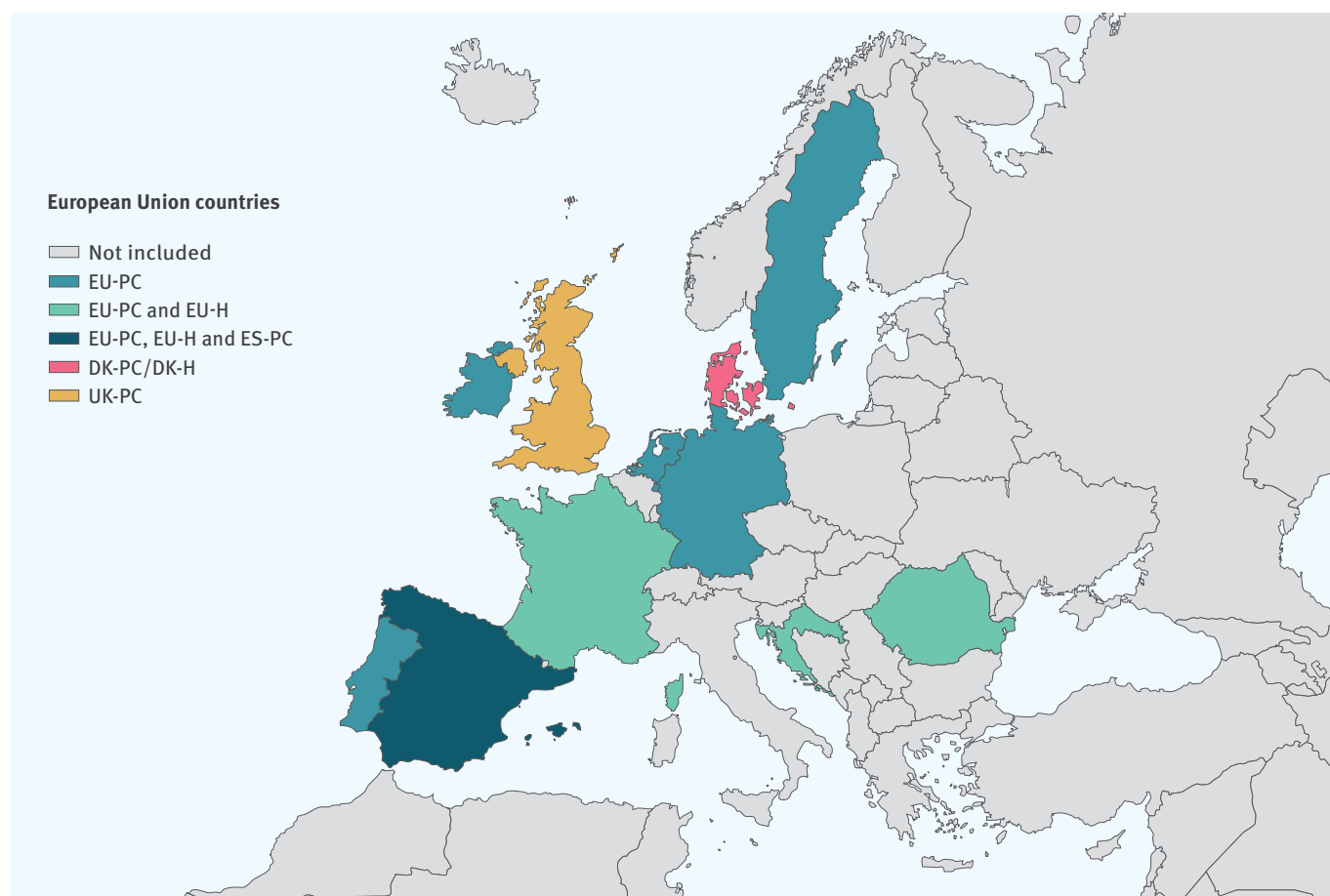
The primary care (PC) setting studies were conducted in Denmark (DK-PC), Spain (ES-PC), the UK (UK-PC) and via the European Union (EU) I-MOVE multi-country network (EU-PC). The hospital setting (H) studies were undertaken in Denmark (DK-H) and via the EU I-MOVE multi-country network (EU-H) (Figure 1).

Study design and estimation of vaccine effectiveness

The methods of these six studies are described in detail elsewhere [5–9]. All six studies used a test-negative case control design, with differences between studies in how data were collected and how patients were selected (Table 1) [10]. Briefly, individuals presenting to participating healthcare settings with symptoms of influenza-like illness (ILI) (primary care settings)

FIGURE 1

European Union countries contributing to the interim influenza vaccine effectiveness results, influenza season 2018/19 (n = 11)



DK-PC/DK-H: Denmark primary care and hospital studies; ES-PC: Spain primary care study; EU-H: European hospital-based multi-country I-MOVE study; EU-PC: European primary care-based multi-country I-MOVE study; I-MOVE: Influenza - monitoring of vaccine effectiveness in Europe; UK: United Kingdom; UK-PC: UK primary care study.

or severe acute respiratory infection (hospital settings) were swabbed. These samples were then tested by reverse transcription (RT)-PCR for influenza virus. Patients with positive results were classified as cases (by influenza virus (sub)type), and those with negative results as controls.

Patients were defined as vaccinated with the 2018/19 influenza vaccine if they were vaccinated at least 14 or 15 days (depending on the study) before symptom onset. Patients were excluded if they were vaccinated fewer than 14 or 15 days before symptom onset, or if the date of vaccination was unknown.

In eight EU-PC countries, DK-PC and DK-H, all or a random sample of influenza virus-positive specimens were selected for sequencing (haemagglutinin genome segment and/or whole genome). In ES-PC, in regions not included in EU-PC, an ad hoc sample of influenza viruses was sequenced. In UK-PC, all influenza viruses with sufficient genetic material (Ct value < 31) were sequenced, as well as all viruses derived from

vaccinated cases. Sequencing results in Denmark were combined for both studies (DK-PC and DK-H).

We computed VE by comparing the odds of vaccination between cases and controls ($VE = (1 - \text{odds ratio (OR)}) \times 100\%$). All studies used logistic regression to adjust their VE for measured confounding variables (Table 1). Study-specific VE was estimated overall and where possible, by age group and target population (as defined locally in the various studies and study sites) against influenza A overall, A(H1N1)pdm09 and A(H3N2). If the number of cases (or controls if lower) per parameter was less than 10, a sensitivity analysis was performed using Firth's method of penalised logistic regression to assess small sample bias [11,12]. Where exposed case numbers were zero, exact logistic regression was used.

Results

From 1 October 2018 to 31 January 2019, the total number of patients included in each study for the influenza A analysis in primary care settings was: DK-PC (11,910; 2,807 cases), ES-PC (1,204; 476 cases), UK-PC (936;

TABLE 1

Summary characteristics of the included influenza vaccine effectiveness studies, Europe, interim influenza season 2018/19 (n = 23,007)

	DK-PC	ES-PC	EU-PC	UK-PC	DK-H	EU-H
Study period	1 November 2018–31 January 2019	5 November 2018–18 January 2019	21 October 2018–23 January 2019	1 October 2018–18 January 2019	1 November 2018–31 January 2019	5 December 2018–18 January 2019
Setting	Primary care	Primary care	Primary care	Primary care	Hospital	Hospital
Location	Denmark	Spain: Sentinel networks in 16 of 19 regions	Croatia, France, Germany, Ireland, the Netherlands, Portugal, Romania, Spain (five regions) and Sweden	England, Scotland, Northern Ireland and Wales	Denmark	11 hospitals in: Croatia, France, Spain and Romania
Study design	TND	TND	TND	TND	TND	TND
Data source	Data linkage of Danish Microbiology Database, the Danish Vaccination Register and the Danish National Discharge Register	Sentinel physicians and laboratory ^a	Sentinel physicians and laboratory ^a	Sentinel physicians and laboratory	Data linkage of Danish Microbiology Database, the Danish Vaccination Register and the Danish National Discharge Register	Hospital charts, vaccine registers, interviews with GPs, laboratory
Age groups of study population	All ages	≥ 6 months	≥ 6 months	All ages	All ages	≥ 65 years
Case definition	Sudden onset of symptoms with fever, myalgia and respiratory symptoms	EU ILI	EU ILI	ILI: Patient presenting in primary care with an acute respiratory illness with physician diagnosed fever with onset in previous 7 days	SARI: Sudden onset of symptoms with fever, myalgia and respiratory symptoms among hospitalised patients	EU SARI
Selection of patients	At practitioner's judgement	Systematic	Systematic	At practitioner's judgement	At practitioner's judgement	Exhaustive
Vaccine types used nationally or in the study ^b	In the study among controls: 21% QIV, 79% TIV	The following vaccine types are available in Spain: TIV, adjuvanted TIV, QIV	In the study among controls: 44% QIV, 29% TIV, 23% unavailable, 3% adjuvanted TIV, 1% LAIV ₄	Healthy children 2–11 years of age: LAIV ₄ ; At risk children <18 years of age: QIV; Adults 18–64 years of age: QIV; Adults ≥65 years: mainly adjuvanted TIV with some differences across UK countries.	In the study among controls: 18% QIV, 82% TIV	In the study among controls: 53% TIV, 35% adjuvanted TIV, 6% QIV and 6% unknown
Variables of adjustment	Age group, sex, presence of chronic conditions, number of hospitalisations in previous year, calendar time as month (Nov-Jan)	For all ages: Age (RCS), onset date (RCS), sex, chronic conditions, region; For target groups: Age (RCS), onset date (RCS), sex, region	Age (modelled as RCS or age group depending on analysis), sex, presence of any chronic condition associated with influenza vaccination recommendation, onset date (RCS) and study site	Age group, sex, onset month, pilot area for child vaccination programme, surveillance scheme, risk group	Age group, sex, presence of chronic conditions, number of hospitalisations in previous year, calendar time as month (November–January)	Age, sex, presence/number of chronic conditions, onset date (modelled as RCS or categorical depending on analysis) and study site

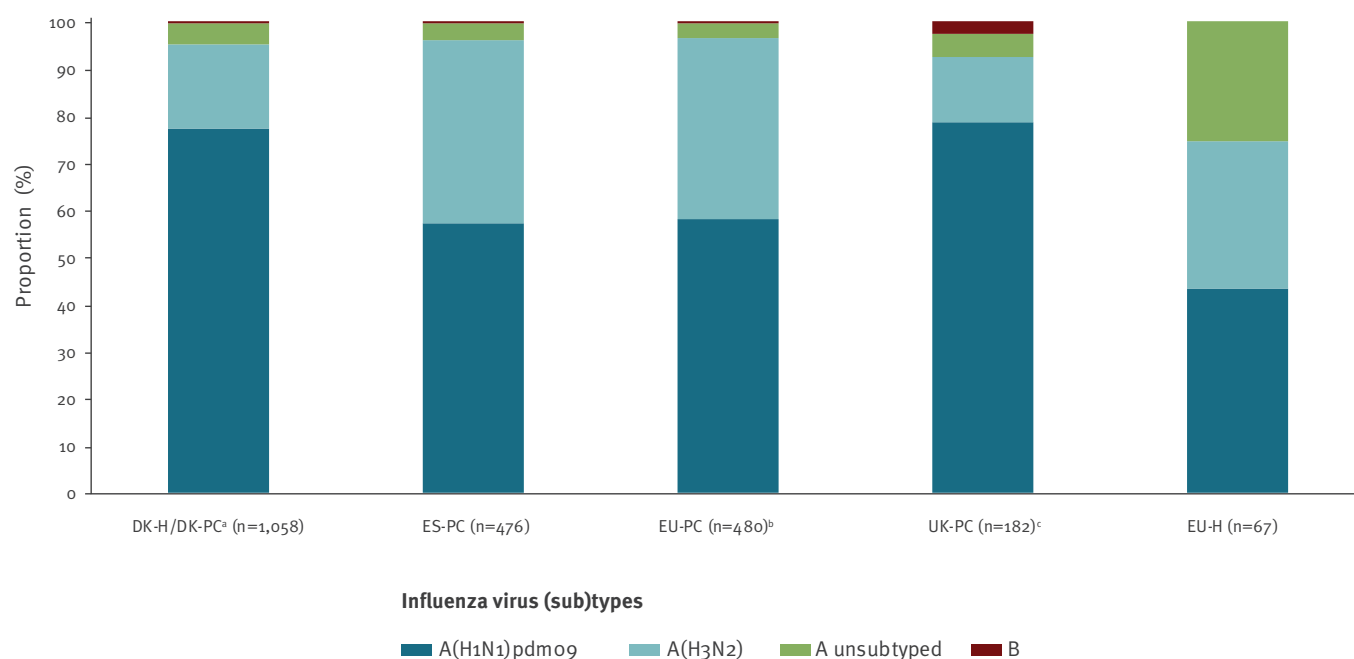
DK-H: Denmark hospital study; DK-PC: Denmark primary care study; ES-PC: Spain primary care study; EU: European Union; EU-H: European hospital multicentre I-MOVE study; EU-PC: European primary care multicentre I-MOVE study; GP: general practitioner; ILI: influenza-like illness; I-MOVE: Influenza - monitoring of vaccine effectiveness in Europe; LAIV₄: quadrivalent live attenuated influenza vaccine; LRI: lower respiratory infection; QIV: quadrivalent inactivated influenza vaccines; RCS: restricted cubic spline; SARI: severe acute respiratory infection; TND: test-negative design; UK: United Kingdom; UK-PC: UK primary care study.

^a122 of 805 physicians included in ES-PC were also included in EU-PC.

^bVaccines were egg-propagated, non-adjuvanted and administered intramuscularly unless otherwise specified.

FIGURE 2

Proportion of influenza virus (sub)types by study, 11 European countries, interim influenza season 2018/19 (n = 2,263)



DK-H: Denmark hospital study; DK-PC: Denmark primary care study; ES-PC: Spanish primary care study; UK: United Kingdom; UK-PC: UK primary care study; EU-H: European hospital multicentre I-MOVE study; EU-PC: European primary care multicentre I-MOVE study; I-MOVE: Influenza - monitoring of vaccine effectiveness in Europe.

^aBased on data obtained at the National Influenza Centre, Denmark (cannot be divided into hospital and primary care separately). A further 2,404 influenza A cases from other laboratories were included in the vaccine effectiveness analysis, representing all clinical microbiological laboratories in Denmark.

^b62 of influenza A(H1N1)pdm09 and 46 of A(H3N2) cases were also in ES-PC.

^cIncludes one A(H1N1)pdm09 and B co-infection.

177 cases), EU-PC (2,079; 478 cases). In the hospital settings numbers were: DK-H (6,520; 653 cases), EU-H (298; 67 cases).

In all studies combined, 99.5% (2,252/2,263) of cases were influenza A virus-positive. The proportion of influenza A viruses subtyped in the DK-H/DK-PC, ES-PC, EU-PC and UK-PC was $\geq 95\%$ and in the EU-H it was 75%. Of influenza viruses subtyped, 58–60% were influenza A(H1N1)pdm09 viruses in ES-PC, EU-PC and EU-H; while this proportion was $> 80\%$ in DK-PC/DK-H and UK-PC (Figure 2).

Influenza A overall

Primary care settings

In primary care settings among all ages, VE against laboratory-confirmed influenza A ranged between 32% (95% confidence interval (CI): -25 to 63) in ES-PC and 43% in UK-PC and in EU-PC (95% CI: 3 to 67 and 6 to 65, respectively). The VE against influenza A among patients aged 18–64 years ranged from 32% (95% CI:

-31 to 65) in the EU-PC to 55% (95% CI: 44 to 64) in the DK-PC study. In children aged 2–17 years in UK-PC, the VE of quadrivalent live attenuated influenza vaccines (LAIV4) was 80% (95% CI: -54 to 97) (Table 2). Among target groups for influenza vaccination, VE was 59% in both ES-PC and EU-PC (95% CI: -1 to 83 and 32 to 78, respectively).

Hospital settings

VE against laboratory-confirmed hospitalised influenza A among all ages in DK-H was 38% (95% CI: 24 to 49) and in patients aged 65 years and older, VE was 34% (95% CI: 16 to 48) in DK-H and 38% (95% CI: -12 to 66) in EU-H.

Influenza A(H1N1)pdm09

Primary care settings

In the primary care studies, VE against laboratory-confirmed influenza A(H1N1)pdm09 among all ages ranged from 45% (95% CI: -20 to 75) in ES-PC to 71% (95% CI: 38 to 86) in EU-PC.

TABLE 2

Adjusted seasonal vaccine effectiveness against laboratory-confirmed influenza A, A(H1N1)pdm09 and A(H3N2), by age group, target group for vaccination and study, 11 European countries, interim influenza season 2018/19

Influenza type/ subtype and study site	Setting	Study population	Cases			Controls			Adjusted VE	95% CI
			All	Vacc	%	All	Vacc	%		
Influenza A										
DK-PC	PC	All ages	2,807	342	12	9,103	1,925	21	38	29 to 46
		18–64 years	1,509	112	7	4,298	633	15	55	44 to 64
		≥65 years	398	218	55	2,115	1,183	56	4	-19 to 23
ES-PC	PC	All ages	476	32	7	728	57	8	32	-25 to 63
		Target group	85	19	22	145	42	29	59	-1 to 83
EU-PC	PC	All ages	478	35	7	1,601	160	10	43	6 to 65
		0–17 years	142	4	3	570	17	3	58	-111 to 92
		18–64 years	296	19	6	846	62	7	32	-31 to 65
		Target group ^a	123	25	20	412	124	30	59	32 to 78
UK-PC	PC	All ages	177	31	18	819	224	27	43	3 to 67
		2–17 years (LAIV ₄)	27	2	NC	119	25	21	80	-54 to 97
		2–17 years (LAIV ₄ or TIV)	28	3	NC	123	29	24	67	-80 to 94
		18–64 years	135	20	15	440	90	20	37	-20 to 67
DK-H	Hospital	All ages	653	187	29	5,867	2,321	40	38	24 to 49
		18–64 years	272	46	17	1,894	455	24	39	14 to 57
		≥65 years	297	138	46	3,174	1,827	58	34	16 to 48
EU-H	Hospital	≥65 years	67	30	45	231	144	62	38	-12 to 65
Influenza A(H1N1)pdm09										
DK-PC	PC	All ages	980	72	7	9,103	1,925	21	55	41 to 65
		18–64 years	573	32	6	4,298	633	15	66	51 to 77
		≥65 years	72	38	53	2,115	1,183	56	0	-61 to 38
ES-PC	PC	All ages	272	14	5	728	57	8	45	-20 to 75
		Target group ^a	49	8	NC	145	42	29	61	-22 to 88
EU-PC	PC	All ages	272	10	4	1,381	153	11	71	38 to 86
		18–64 years	178	5	3	736	59	8	75	27 to 91
UK-PC	PC	All ages	143	20	14	819	224	27	57	20 to 77
		2–17 years (LAIV) ^b	23	0	NC	123	29	24	87	4 to 100
		2–17 years (LAIV ₄ or TIV) ^b	23	0	NC	123	29	24	89	19 to 100
		18–64 years	111	16	14	440	90	20	39	-23 to 69
DK-H	Hospital	All ages	228	57	25	5,867	2,321	40	40	17 to 57
		18–64 years	110	17	15	1,894	455	24	49	13 to 70
		≥65 years	85	38	45	3,174	1,827	58	37	3 to 60
EU-H	Hospital	≥65 years	28	13	NC	177	112	63	29	-75 to 71
Influenza A(H3N2)										
DK-PC	PC	All ages	136	24	18	9103	1,925	21	24	-22 to 55
		18–64 years	78	6	8	4,298	633	15	48	-23 to 78
ES-PC	PC	All ages	186	17	9	728	57	8	-9	-147 to 52
EU-PC	PC	All ages	179	21	12	1,437	134	9	-3	-100 to 47
UK-PC	PC	All ages	25	9	NC	819	224	27	-39	-305 to 52
EU-H	Hospital	≥65 years	20	9	NC	198	127	64	47	-48 to 81

CI: confidence interval; DK-PC: Denmark primary care study; DK-H: Denmark hospital study; ES-PC: Spain primary care study; EU-H: European hospital multicentre I-MOVE study; EU-PC: European primary care multicentre I-MOVE study; I-MOVE: Influenza - monitoring of vaccine effectiveness in Europe; LAIV4: quadrivalent live attenuated influenza vaccine; NC: Not calculated (percentages not shown where denominators < 60); TIV: trivalent live attenuated vaccines; UK: United Kingdom; UK-PC: UK primary care study; Vacc: vaccinated; VE: vaccine effectiveness.

^aGroups targeted by seasonal influenza vaccination as defined locally in the studies and study sites.

^bWhile the modal estimate of VE is 100% due to no exposed cases, the point estimates given are from exact logistic regression in Stata with adjustment for month and age where the median estimate is used from the conditional likelihood distribution.

Study sites included in EU-H analysis for influenza A: Croatia, France, Romania and Spain. For analysis against influenza A(H1N1)pdm09: Romania and Spain only. For analysis against influenza A(H3N2): Romania and Spain only.

Study sites included in EU-PC analysis for influenza A: Croatia, France, Germany, Ireland, the Netherlands, Portugal, Romania, Spain and Sweden. For analysis against influenza A(H1N1)pdm09: France, Germany, Ireland, the Netherlands, Portugal, Romania, Spain and Sweden are included. For analysis against influenza A(H3N2): France, Germany, the Netherlands, Portugal, Romania, Spain and Sweden are included.

TABLE 3

Influenza viruses characterised by clade, amino acid substitutions and study site, 11 European countries, interim influenza season 2018/19 (n = 428)

	Clade	DK-H/DK-PC ^a		ES-PC ^b		EU-PC ^{c,d}		UK-PC ^d	
		n	%	n	%	n	%	n	%
Total influenza A(H1N1)		n = 820		n = 272		n = 272		n = 152	
Sequenced		83	100	78	100	79	100	25	NC
A/Michigan/45/2015	6B.1 / Substitutions not available	0	0	0	0	0	0	25	NC
A/Michigan/45/2015 ^e	6B.1 / None of the below	2	2	3	4	4	5	NA	NA
A/Michigan/45/2015 ^e	6B.1 / T120A	29	35	8	10	2	3	NA	NA
A/Michigan/45/2015 ^e	6B.1 / N129D	25	30	31	40	50	63	NA	NA
A/Michigan/45/2015 ^e	6B.1 / E235D	0	0	19	24	3	4	NA	NA
A/Michigan/45/2015 ^e	6B.1 / K302T	27	33	17	22	15	19	NA	NA
A/Michigan/45/2015 ^e	6B.1 / T120A + K302T	0	0	0	0	1	1	NA	NA
Total influenza A(H3N2)		n = 187		n = 186		n = 179		n = 34	
Sequenced		30	NC	79	100	52	NC	2	NC
A/Alsace/1746/2018 ^f	3C.2a1b	29	NC	31	39	34	NC	2	NC
A/Switzerland/8060/2017 ^f	3C.2a2	1	NC	0	0	1	NC	0	NC
A/Cote d'Ivoire/544/2016 ^f	3C.2a3	0	NC	4	5	7	NC	0	NC
A/England/538/2018 ^f	3C.3a	0	NC	44	56	10	NC	0	NC

DK-PC: Denmark primary care study; DK-H: Denmark hospital study; ES-PC: Spain primary care study; EU-PC: European primary care multicentre I-MOVE study; I-MOVE: Influenza - monitoring of vaccine effectiveness in Europe; NA: not available; NC: not calculated (percentages not shown where denominators < 60); UK: United Kingdom; UK-PC: UK primary care study.

^aDK-H and DK-PC are combined; sequence information is based on influenza-positive samples received for surveillance at the National Influenza Center Denmark from week 41/2018 and 03/2019.

^bSpecimens sequenced from Spain originate from the entire National Influenza Surveillance System in weeks 45/2018–03/2019.

^c18 specimens from ES were also included in EU-PC data (12 A/Alsace/1746/2018, 4 A/Cote d'Ivoire/544/2016, two A/Michigan/45/2015).

^dAt time of publishing, not all specimens from the study period were processed.

^eAll include additional substitutions S74R, S164T and I295V, and most also include S183P substitutions.

^fRepresentative strains for the clades.

In UK-PC, the VE of LAIV₄ among children aged 2–17 years was 87% (95% CI: 4 to 100). Among patients aged 18–64 years, VE was between 39% (95% CI: -23 to 69) and 75% (95% CI: 27 to 91) in UK-PC and EU-PC, respectively. VE among those aged 65 years and older was 0% (95% CI: -61 to 38) in the DK-PC study.

Hospital settings

In hospital-based studies among patients aged 65 years and older, VE was 29% (95% CI: -75 to 71) in EU-H and 37% (95% CI: 3 to 60) in the DK-H study (Table 2). VE among those aged 18–64 years was 49% (95% CI: 13 to 70; DK-H).

Virological results

All 265 A(H1N1)pdm09 viruses sequenced belonged to clade 6B.1 (A/Michigan/45/2015) (Table 3). Among 240 viruses (91%) with information on substitutions in the haemagglutinin gene, all harboured additional substitutions of S74R (except one of the 83 sequenced in DK-H/DK-PC), S164T and I295V, and most of them also included the substitution S183P. The proportion of other substitutions identified (T120A, N129D, E235D and K302T) differed by study (Table 3). None of these substitutions involve a change in potential glycosylation sites.

Influenza A(H3N2)

Primary care and hospital settings

In primary care studies, among all ages, VE against influenza A(H3N2) ranged from -39% (95% CI: -305 to 52) in UK-PC to 24% (95% CI: -22 to 55) in DK-PC. VE among patients aged 65 years and older hospitalised for influenza A(H3N2) was 47% (95% CI: -48 to 81) in EU-H (Table 2).

Virological results

Of 163 influenza A(H3N2) viruses sequenced, 59% (n = 96) belonged to genetic clade 3C.2a1b, 33% (n = 54) to 3C.3a, 7% (n = 11) to 3C.2a3 and 1% (n = 2) to 3C.2a2 (Table 3). Both A(H3N2) viruses sequenced in UK-PC, 29/30 A(H3N2) viruses sequenced in DK-H/DK-PC, 34/52 in EU-PC and 31/79 in ES-PC belonged to clade 3C.2a1b. Of 79 A(H3N2) viruses sequenced in ES-PC, 44 (56%) belonged to clade 3C.3a.

Sensitivity analyses

Sensitivity analyses for small sample size gave similar results (absolute difference range 1–9%).

Discussion

Interim results from six established influenza VE studies across Europe for the 2018/19 season indicate that VE against laboratory-confirmed influenza A ranged between 32% and 43% among all ages in primary care and hospital settings and was 59% in the target groups for vaccination.

Against influenza A(H1N1)pdm09, VE point estimates among all ages ranged from 40% to 71%, and were lower among older adults in DK-PC, DK-H and EU-H, ranging from 0% to 37%. Against influenza A(H3N2), the results of three of four primary care studies suggest that the vaccine was not effective among all ages combined. The VE point estimate against A(H3N2) was higher among older adults in EU-H and among 18–64-year-olds in DK-PC (47% and 48%, respectively). The low number of A(H3N2) cases in all studies resulted in less precise VE estimates against A(H3N2) than against A(H1N1)pdm09.

The influenza A(H1N1)pdm09 VE point estimates among all ages in EU-PC, among adults in DK-PC and EU-PC and among children in the UK-PC were similar to 2018/19 interim VE estimates in Canada [13]. For all ages combined, point estimates for this subtype for ES-PC and DK-H were similar to those recently reported from the United States (US) [14]. In UK-PC, the LAIV4 VE point estimate was high against influenza A(H1N1)pdm09, although sample size was very small. This suggests that the A(H1N1)pdm09 LAIV4 vaccine virus strain change from A/Bolivia/559/2013 to A/Slovenia/2903/2015 that took place after the 2016/17 season may have improved vaccine performance against circulating strains in 2018/19. Compared with 2017/18 interim season estimates in studies where influenza A(H1N1)pdm09 VE results were available, the 2018/19 adjusted VE against influenza A(H1N1)pdm09 was similar in the 18–64 years age group in DK-PC (66% vs 60%, respectively, noting that in 2017/18 the setting in Denmark was primary care and hospital combined) and among all ages in EU-PC (71% vs 68%, respectively). VE was lower among those aged 65 years and older in DK-PC, but similar in the DK-H study.

The genetic diversity observed in the ongoing 2018/19 season did not seem to affect the VE against influenza A(H1N1)pdm09 in most groups and studies. To date, all A(H1N1)pdm09 viruses characterised in Europe were antigenically similar to the vaccine virus [15]. The lower VE among those aged 65 and older in DK-PC may be explained by small sample size, but needs further investigation.

As observed in the 2017/18 season, the 2018/19 interim primary care results suggest that VE against medically attended laboratory-confirmed influenza A(H3N2) was low or non-existent although, due to small sample size, these interim 2018/19 results need to be confirmed by the end-of-season results. End-of-season clade-specific VE results may help us understand whether

regional differences in circulating clades of A(H3N2) viruses explain the difference in VE in DK-PC compared with all other primary care studies. Adaptation/alteration of the vaccine seed virus during propagation in eggs, impacting antigenicity, may have been an important explanation for low VE against influenza A(H3N2) in recent and current seasons [16].

The late start of the season resulted in small sample sizes and low precision of many VE estimates, which presents a limitation in this interim analysis. We thus conducted a sensitivity analysis to address potential small sample bias arising from this. Further limitations potentially present in all observational studies include residual confounding and bias.

Vaccination continues to be the most effective preventive measure against influenza and uptake of the 2018/19 influenza vaccines should still be promoted in countries with ongoing influenza virus circulation in line with national guidelines and recommendations. Our results further support the need for effective interventions against influenza A(H3N2) across all age groups. In the UK, the Joint Committee on Vaccination and Immunisation has recently advised the use of cell-grown influenza vaccine that will be licensed for the 2019/20 season for older children and adults in the UK [17]. In addition, given the observed non-effectiveness of the A(H3N2) component of the current vaccine in previous seasons, in settings with influenza A(H3N2) virus circulation, prophylactic and prompt therapeutic use of neuraminidase inhibitors is important to help prevent severe outcomes, irrespective of vaccination status [18].

The Global Influenza VE (GIVE) Collaboration reports on the effectiveness of influenza vaccine in previous and current influenza seasons. Interim VE results presented here were included in the February 2019 GIVE report to help inform the WHO vaccine strain selection committee meeting on 18–21 February 2019 in Beijing. For the 2019/20 northern hemisphere trivalent vaccine, this selection committee recommended to include an A/Brisbane/02/2018 (H1N1)pdm09-like virus and a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage) [19]. For the quadrivalent vaccine WHO recommended an additional B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage). The recommendation for the A(H3N2) component will be postponed until 21 March 2019, due to changes in the proportions of genetically and antigenically diverse A(H3N2), notably an increase in clade 3C.3a in several geographic regions.

End-of-season VE and antigenic studies will provide insight into age- and study-specific variation in VE estimates. In addition, monitoring effectiveness of the 2019 southern hemisphere influenza vaccine against influenza viruses and their genetic diversity will be important to prepare for the next influenza season in the northern hemisphere.

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Conflict of interest

None declared.

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References

1. European Centre for Disease Prevention and Control (ECDC). Seasonal influenza vaccination and antiviral use in EU/EEA Member States. Stockholm: ECDC. [Accessed 8 Feb 2019]. Available from: https://ecdc.europa.eu/sites/portal/files/documents/Seasonal-influenza-antiviral-use-EU-EEA-Member-States-December-2018_o.pdf
2. Department of Health/National Health Service (DoH/NHS). The flu immunisation programme 2013/14 – extension to children. London: DoH/NHS; 2013. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/225360/Children_s_flu_letter_20
3. World Health Organization (WHO). Recommended composition of influenza virus vaccines for use in the 2018-2019 northern hemisphere influenza season. Geneva: WHO; 2018. Available from: https://www.who.int/influenza/vaccines/virus/recommendations/201802_recommendation.pdf?ua=1
4. European Centre for Disease Prevention and Control (ECDC), World Health Organization Regional Office for Europe. (WHO/Europe). Flu News Europe. Summary week 3/2019 (14-20 January 2019). Stockholm: ECDC; 2019. Available from: <https://flunewseurope.org/Archives>
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6. European Union (EU). Generic protocol for the test negative design case control studies to measure pandemic and seasonal influenza vaccine effectiveness in the European Union and European Economic Area Member States. Brussels: EU; 2015. Available from: <https://drive.google.com/file/d/0Byv9pYYPpY4PM25qSXczQ3g4ToE/view>
7. Jiménez-Jorge S, de Mateo S, Delgado-Sanz C, Pozo F, Casas I, García-Cenoz M, et al. Spanish Influenza Sentinel Surveillance System. Estimating influenza vaccine effectiveness in Spain using sentinel surveillance data. *Euro Surveill*. 2015;20(28):21187. <https://doi.org/10.2807/1560-7917.ES2015.20.28.21187> PMID: 26212144
8. Pebody R, Warburton F, Ellis J, Andrews N, Potts A, Cottrell S, et al. Effectiveness of seasonal influenza vaccine for adults and children in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 end-of-season results. *Euro Surveill*. 2016;21(38):30348. <https://doi.org/10.2807/1560-7917.ES.2016.21.38.30348> PMID: 27684603
9. Emborg HD, Krause TG, Nielsen L, Thomsen MK, Christiansen CB, Skov MN, et al. Influenza vaccine effectiveness in adults 65 years and older, Denmark, 2015/16 - a rapid epidemiological and virological assessment. *Euro Surveill*. 2016;21(14):30189. <https://doi.org/10.2807/1560-7917.ES.2016.21.14.30189> PMID: 27101732
10. Fukushima W, Hirota Y. Basic principles of test-negative design in evaluating influenza vaccine effectiveness. *Vaccine*. 2017;35(36):4796-800.
11. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J Clin Epidemiol*. 1995;48(12):1503-10. [https://doi.org/10.1016/0895-4356\(95\)00048-8](https://doi.org/10.1016/0895-4356(95)00048-8) PMID: 8543964
12. Covenay J. FIRTHLOGIT: Stata module to calculate bias reduction in logistic regression. Boston College Department of Economics; 2015.
13. Skowronski DM, Leir S, Sabaiduc S, Murti M, Dickinson JA, Olsha R, et al. Interim estimates of 2018/19 vaccine effectiveness against influenza A(H1N1)pdm09, Canada, January 2019. *Euro Surveill*. 2019;24(4):1900055. <https://doi.org/10.2807/1560-7917.ES.2019.24.4.1900055> PMID: 30696523
14. Doyle JD, Chung JR, Kim SS, Gaglani M, Raiyani C, Zimmerman RK, et al. Interim Estimates of 2018-19 Seasonal Influenza Vaccine Effectiveness - United States, February 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68(6):135-9. <https://doi.org/10.15585/mmwr.mm6806a2> PMID: 30763298
15. European Centre for Disease Prevention and Control (ECDC), World Health Organization Regional Office for Europe. (WHO/Europe). Flu News Europe. Virus characteristics week 6/2019 (4-10 February 2019). Stockholm: ECDC; 2019. Available from: <https://flunewseurope.org/VirusCharacteristics>
16. Zost SJ, Parkhouse K, Gumina ME, Kim K, Diaz Perez S, Wilson PC, et al. Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains. *PNAS*. 2017;114(47):12578-12583.
17. Public Health England/Department of Health/National Health Service (PHE/DoH/NHS). Vaccines for 2019/20 seasonal flu vaccination programme. London: PHE/DoH/NHS; 2018. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/757784/Vaccines_for_2019_20_seasonal_flu_vaccination_programme.pdf
18. European Centre for Disease Prevention and Control (ECDC). Seasonal influenza vaccination and antiviral use in Europe. Overview of vaccination recommendations and coverage rates in the EU Member States for the 2013-14 and 2014-15 influenza seasons. VENICE technical report. Stockholm: ECDC; 2016. Available from: <http://venice.cineca.org/Seasonal-influenza-vaccination-antiviral-use-europe.pdf>
19. World Health Organization (WHO). Recommended composition of influenza virus vaccines for use in the 2019-2020 northern hemisphere influenza season. Geneva: WHO; 2019. Available from: https://www.who.int/influenza/vaccines/virus/recommendations/201902_recommendation.pdf?ua=1

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