Research article

Vaccine effectiveness in preventing laboratory-confirmed influenza in primary care patients in a season of co-circulation of influenza A(H1N1)pdm09, B and drifted A(H3N2), I-MOVE Multicentre Case–Control Study, Europe 2014/15

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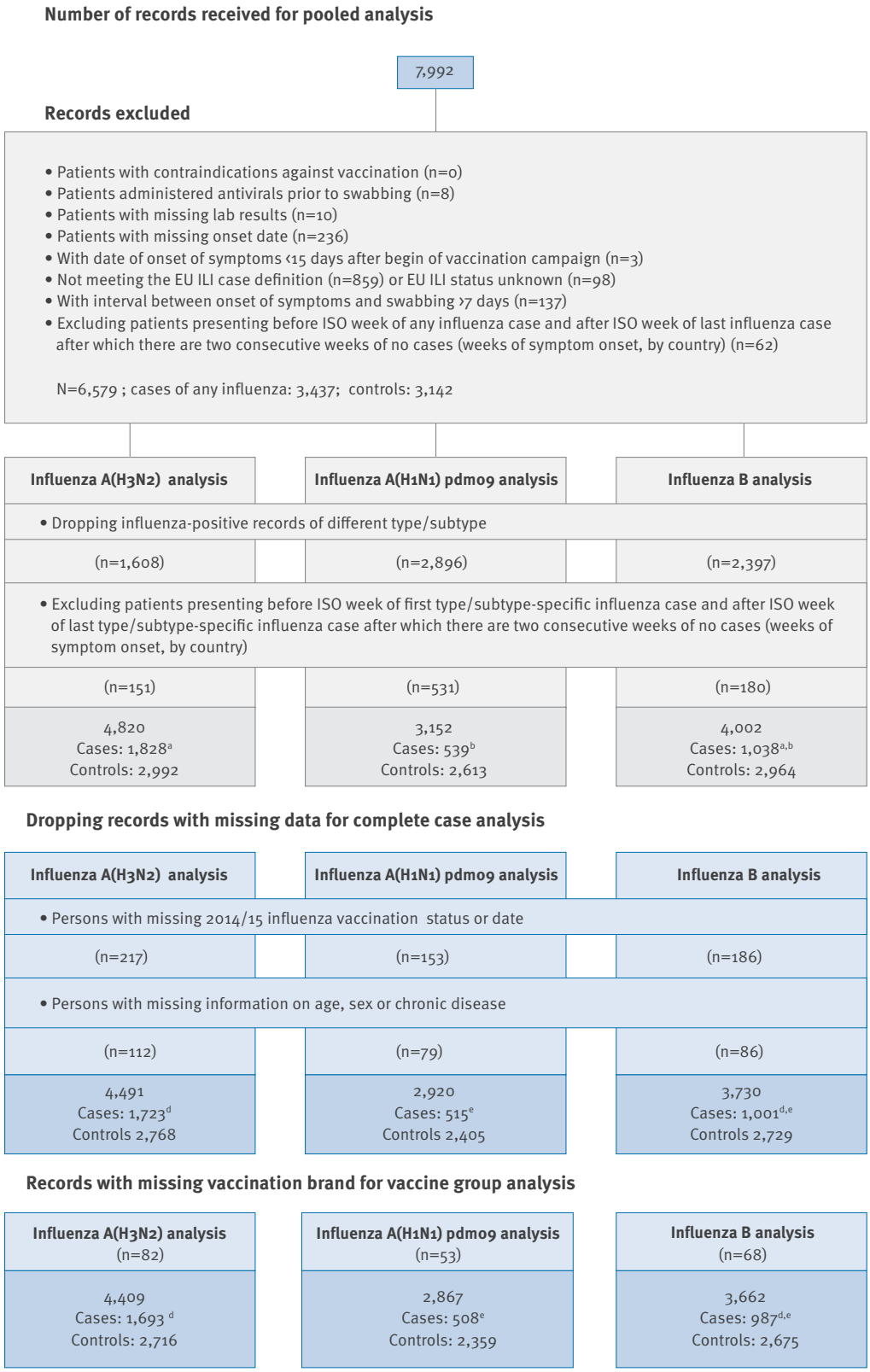
Influenza A(H3N2), A(H1N1)pdm09 and B viruses co-circulated in Europe in 2014/15. We undertook a multicentre case–control study in eight European countries to measure 2014/15 influenza vaccine effectiveness (VE) against medically-attended influenza-like illness (ILI) laboratory-confirmed as influenza. General practitioners swabbed all or a systematic sample of ILI patients. We compared the odds of vaccination of ILI influenza positive patients to negative patients. We calculated adjusted VE by influenza type/subtype, and age group. Among 6,579 ILI patients included, 1,828 were A(H3N2), 539 A(H1N1)pdm09 and 1,038 B. VE against A(H3N2) was 14.4% (95% confidence interval (CI): -6.3 to 31.0) overall, 20.7% (95%CI: -22.3 to 48.5), 10.9% (95%CI -30.8 to 39.3) and 15.8% (95% CI: -20.2 to 41.0) among those aged 0–14, 15–59 and ≥60 years, respectively. VE against A(H1N1) pdm09 was 54.2% (95%CI: 31.2 to 69.6) overall, 73.1% (95%CI: 39.6 to 88.1), 59.7% (95%CI: 10.9 to 81.8), and 22.4% (95%CI: -44.4 to 58.4) among those aged 0–14, 15–59 and ≥60 years respectively. VE against B was 48.0% (95%CI: 28.9 to 61.9) overall, 62.1% (95%CI: 14.9 to 83.1), 41.4% (95%CI: 6.2 to 63.4) and 50.4% (95%CI: 14.6 to 71.2) among those aged 0–14, 15–59 and ≥60 years respectively. VE against A(H1N1)pdm09 and B was moderate. The low VE against A(H3N2) is consistent with the reported mismatch between circulating and vaccine strains.

Introduction

In February 2014 each year, the World Health Organization (WHO) provides recommendations for the composition of the northern hemisphere vaccines, based on information from the WHO Global Influenza Surveillance and Response System. In 2014, the WHO vaccine strain selection committee recommended that the 2014/15 northern hemisphere influenza vaccine should include the same components as in 2013/14: an A/California/7/2009 (H1N1)pdm09-like

Figure 1

Flowchart of data exclusion for pooled analysis, I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015)



EU: European Union; ILI: influenza-like illness; I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe; ISO: International Organization for Standardization.

[a] Includes 15 influenza B + A(H3N2) co-infections.

[b] Includes 8 influenza B + A(H1N1)pdm09 co-infections.

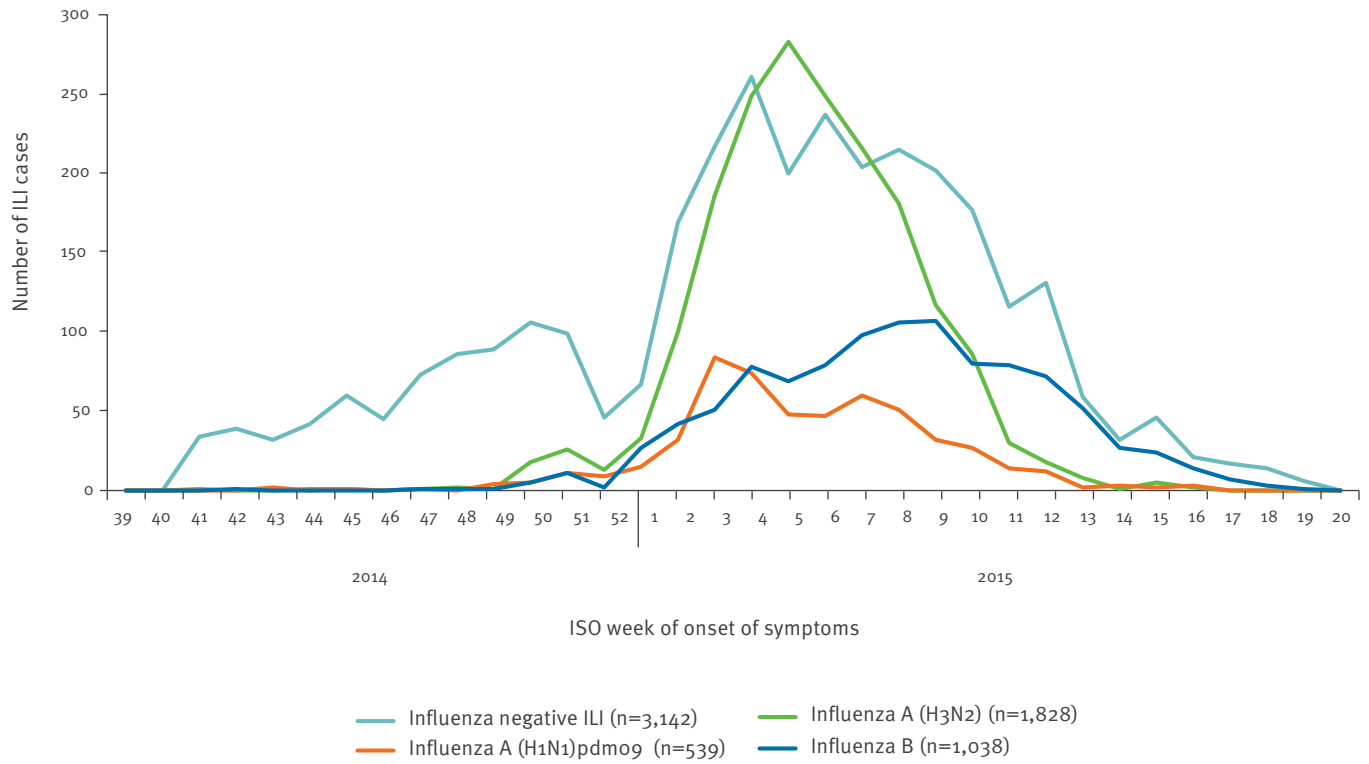
[c] Includes 3 influenza B + A(H3N2)pdm09, and 7 A(H1N1)pdm09 + A(H3N2) co-infections.

[d] Includes 14 influenza B + A(H3N2)pdm09 co-infections.

[e] Includes 7 influenza B + A(H1N1)pdm09 co-infections.

Figure 2

Number of influenza-like illness reports by case status and week of symptom onset, all influenza, target groups for vaccination, I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015) (n=6,524[a])



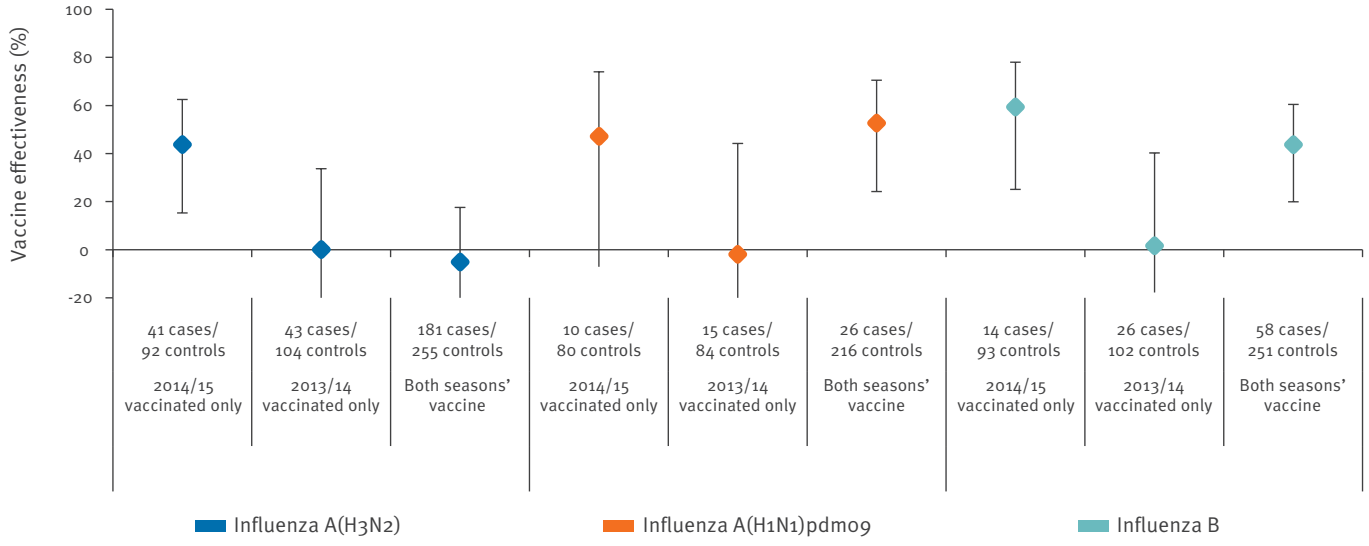
ILI: influenza-like illness; I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe, ISO: International Organization for Standardization.

[a] This includes 15 influenza B + A(H3N2) co-infections and eight influenza B + A(H1N1)pdm09 co-infections. Note that numbers of cases come from influenza type/subtype specific databases. Some cases are excluded due to their restriction criteria. Any influenza A non-typed cases are dropped from analysis.

The proportion vaccinated with the 2014/15 influenza vaccine was 13.2% among controls, 13.0% among A(H3N2) cases, 6.9% among A(H1N1) pdm09 cases and 7.4% among B cases (Table 2).

Figure 3

Pooled crude and adjusted seasonal vaccine effectiveness against laboratory confirmed influenza by influenza type/subtype, and by season of vaccination, I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015)



I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe.

virus, an A/Texas/50/2012 (H3N2)-like virus, and a B/Massachusetts/2/2012-like virus [1].

In September 2014, the WHO reported the emergence of two new influenza virus genetic clades for A(H3N2), clade 3C.2a and 3C.3a [1]. These clades had first circulated in Europe during the 2013/14 influenza season [2].

In December 2014, the United States (US) Centers for Disease Control and Prevention (CDC) issued a Health Alert reporting that 52% of the A(H3N2) viruses circulating were antigenically different from the A(H3N2) component of the northern hemisphere 2014/15 influenza vaccine. CDC recommended the use of antiviral medications where indicated for the treatment and prevention of influenza, as an adjunct to vaccination [3]. Concordant with the reports of the drifted A(H3N2) viruses, in January 2015, the US, Canada and the United Kingdom (UK) reported low influenza vaccine effectiveness (VE) against A(H3N2) [4-6]. Canadian results suggested that VE against influenza A(H3N2) among individuals who had been vaccinated in both 2013/14 and 2014/15 seasons was lower than among those who were only vaccinated in 2014/15 [5].

In Europe, the influenza season started later than in the US and Canada. Increased influenza activity in Europe was first reported in early January 2015, with a predominance of A(H3N2) but with influenza A(H1N1) pdm09 and B circulating as well [7].

For this seventh season of the Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) multicentre case–control study we aimed to measure the 2014/15 effectiveness of the seasonal influenza vaccine against the three co-circulating viruses by age group and by vaccine type. In addition, due to the potential implications for vaccination policy we explored the effect of previous vaccinations on the current season VE.

Methods

Eight study sites (Germany, Hungary, Ireland, Italy, Poland, Portugal, Romania and Spain) participated in the test-negative 2014/15 multicentre case–control study. The methods have been described previously [7-9] and are based on the European Centre for Disease Prevention and Control (ECDC) generic case–control study protocol [10].Briefly, participating general practitioners (GPs) interviewed and collected naso-pharyngeal specimens from all (seven study sites) or a systematic sample (in Germany) of patients consulting for influenza- like illness (ILI) aged 60 (Germany, Poland, and three regions in Spain) or 65 years old (Hungary, Ireland, Italy, Portugal, Romania and three regions in Spain) and older and from a systematic sample of ILI patients in the other age groups. In Hungary, only patients aged 18 years or over were eligible for inclusion in the study. GPs collected clinical and epidemiological information as previously described [8]. We included patients in the study who presented to the GPs more than 14 days after the start of the national vaccination campaigns and who met the European Union (EU) ILI case definition [11], were swabbed within seven days of symptom onset, and who had not received antivirals before swabbing.

Cases were ILI patients who were swabbed and tested positive for influenza virus using real-time reverse-transcription PCR (RT-PCR). Controls were ILI patients who tested negative for any influenza virus using RT-PCR. Cases and controls were not included in the influenza type/subtype-specific analyses if fewer than five type/subtype-specific cases were reported by study site. Influenza A cases of unknown subtype were excluded from the analysis.

For each study site and for each influenza type/subtype, the study period started on the week of onset of the first influenza case recruited and ended on the week of onset of the last influenza case after which there were at least two consecutive weeks with no further influenza positive cases.

We defined a patient as vaccinated if they had received minimum one dose of 2014/15 influenza vaccine at least 15 days before ILI symptom onset. We considered all other patients unvaccinated. GPs ascertained vaccination based on vaccination records or patient's self-report.

For each study site, we compared the odds of vaccination in cases and controls calculating the odd ratio (OR). We conducted a complete case analysis excluding patients with missing values for any of the variables in the model measuring adjusted VE. We carried out a one-stage model with study site as a fixed effect. We used Cochran's Q-test and the I^2 index to test the heterogeneity between study sites [12].

We used a logistic regression model to calculate VE including potential confounding factors: age (modelled as a restricted cubic spline with four knots or age group as a categorical variable depending on the analysis), sex, presence of at least one underlying chronic condition (including pregnancy and obesity where available) and date of symptom onset (modelled as a restricted cubic spline with four knots where sample size allowed).

To study the effect of 2013/14 vaccination on the 2014/15 VE, we conducted a stratified analysis using four categories: individuals unvaccinated in both seasons (reference category), vaccinated in 2013/14 only, vaccinated in 2014/15 only, and those vaccinated in both seasons.

We measured VE by age group (0–14, 15–59 and ≥60 years) and by type of vaccine (adjuvanted, egg-derived inactivated subunit, cell-derived inactivated subunit, egg-derived inactivated split virion). We excluded

Figure 4

Phylogenetic tree I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015)

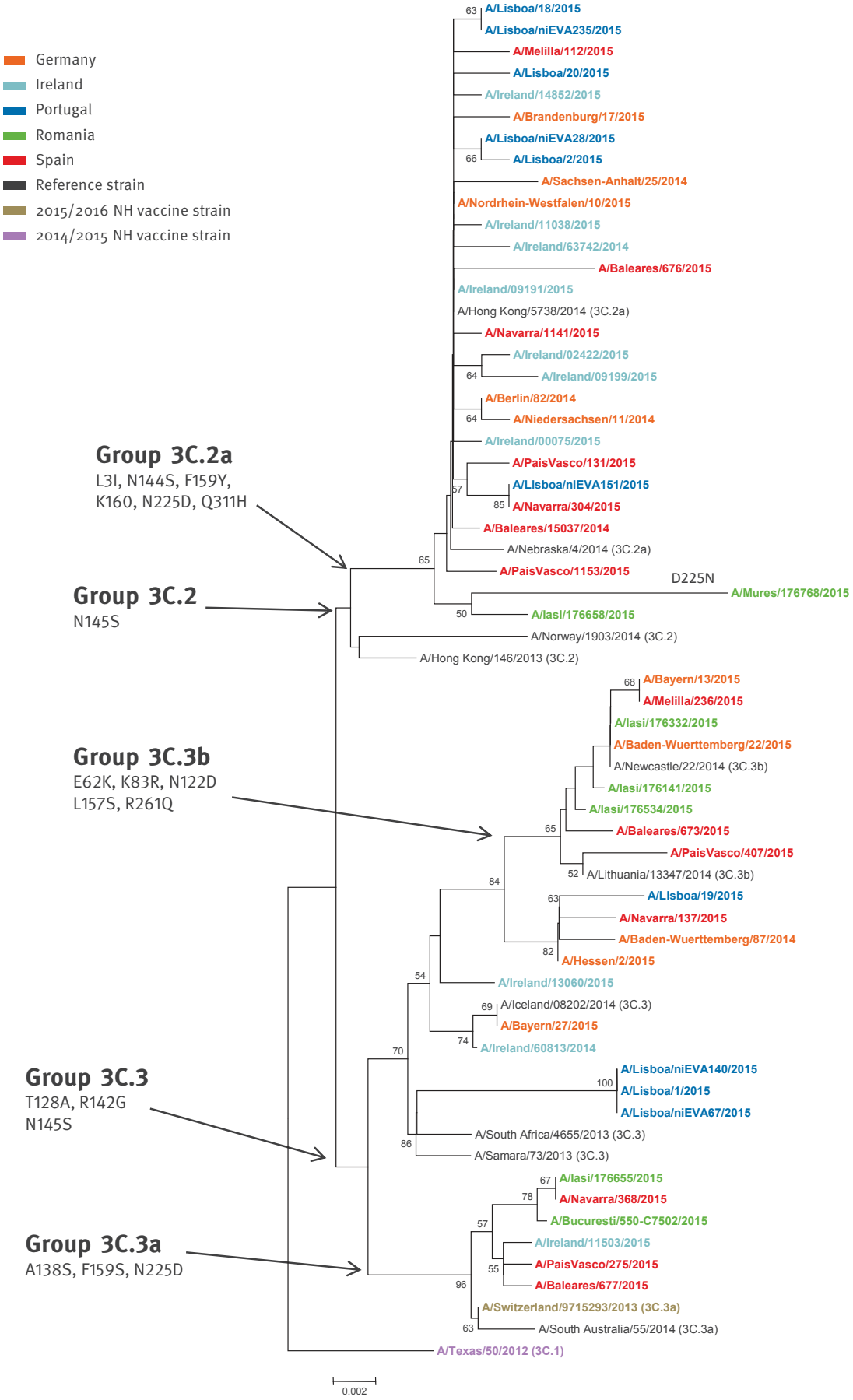


Table 1 a

Details of influenza haemagglutinin sequences obtained from GISAID used in the phylogenetic analysis, I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015)

Segment ID	Segment	Country	Collection date	Isolate name	Originating Laboratory	Submitting Laboratory	Authors
I-MOVE sequences							
EPI568197	HA	Germany	2 Feb 2015	A/Bayern/27/2015	NA	Robert Koch Institute	Wedde, M; Schweiger, S
EPI568195	HA		28 Jan 2015	A/Brandenburg/17/2015			
EPI566844	HA		19 Jan 2015	A/Bayern/13/2015			
EPI566843	HA		26 Jan 2015	A/Baden-Wuerttemberg/22/2015			
EPI566664	HA		9 Jan 2015	A/Nordrhein-Westfalen/10/2015			
EPI566662	HA		20 Jan 2015	A/Hessen/2/2015			
EPI566657	HA		22 Dec 2014	A/Sachsen-Anhalt/25/2014			
EPI562792	HA		22 Dec 2014	A/Baden-Wuerttemberg/87/2014			
EPI562791	HA		18 Dec 2014	A/Berlin/82/2014			
EPI562793	HA		24 Dec 2014	A/Niedersachsen/11/2014			
EPI599601	HA	Ireland	2 Mar 2015	A/Ireland/14852/2015	National Virus Reference Laboratory	National Virus Reference Laboratory	Dunford, L
EPI599599	HA		17 Feb 2015	A/Ireland/13060/2015			
EPI599597	HA		13 Feb 2015	A/Ireland/11503/2015			
EPI599594	HA		9 Feb 2015	A/Ireland/09191/2015			
EPI599593	HA		13 Jan 2015	A/Ireland/02422/2015			
EPI582398	HA		13 Feb 2015	A/Ireland/11038/2015			
EPI582390	HA		9 Feb 2015	A/Ireland/09199/2015			
EPI582379	HA		25 Nov 2014	A/Ireland/60813/2014			
EPI555113	HA		12 Dec 2014	A/Ireland/63742/2014			
EPI582380	HA		22 Dec 2014	A/Ireland/00075/2015			
EPI583766	HA	Portugal	3 Mar 2015	A/Lisboa/20/2015	Instituto Nacional de Saude	INSA National Institute of Health Portugal	Guiomar, R;Pechirra, P; Cristóvão, P; Costa, I
EPI583765	HA		20 Feb 2015	A/Lisboa/19/2015			
EPI583762	HA		16 Feb 2015	A/Lisboa/niEVA235/2015			
EPI583761	HA		6 Feb 20150	A/Lisboa/18/2015			
EPI583759	HA		22 Jan 2015	A/Lisboa/niEVA151/2015			
EPI583741	HA		29 Jan 2015	A/Lisboa/2/2015			
EPI583740	HA		27 Jan 2015	A/Lisboa/1/2015			
EPI565347	HA		16 Jan 2015	A/Lisboa/niEVA140/2015			
EPI558632	HA		2 Jan 2015	A/Lisboa/niEVA67/2015			
EPI558621	HA		30 Dec 2014	A/Lisboa/niEVA28/2015			
EPI599624	HA	Romania	11 Feb 2015	A/Bucuresti/550-C7502/2015	Cantacuzino Institute	Cantacuzino Institute	NA
EPI599678	HA		19 Jan 2015	A/Iasi/176332/2015			
EPI599698	HA		22 Jan 2015	A/Iasi/176534/2015			
EPI600298	HA		23 Jan 2015	A/Iasi/176655/2015			
EPI599769	HA		26 Jan 2015	A/Iasi/176658/2015			
EPI599770	HA		26 Jan 2015	A/Mures/176768/2015			
EPI599771	HA		13 Jan 2015	A/Iasi/176141/2015			
EPI566948	HA	Spain	3 Feb 2015	A/Baleares/676/2015	Servicio de Microbiología Hospital Universitario Son Espases	Instituto de Salud Carlos III	Pozo,F Calderon,A; Gonzalez -Esguevillas,M; Molinero,M; Casas,I
EPI616537	HA		10 Mar 2015	A/Navarra/1141/2015			
EPI616553	HA		10 Mar 2015	A/PaisVasco/1153/2015			
EPI559629	HA		17 Jan 2015	A/Melilla/236/2015			
EPI557585	HA		12 Jan 2015	A/Melilla/112/2015			
EPI616494	HA		3 Feb 2015	A/Baleares/677/2015			
EPI616493	HA		3 Feb 2015	A/Baleares/673/2015			
EPI557566	HA		13 Dec 2014	A/Baleares/15037/2014			
EPI566285	HA		21 Jan 2015	A/Navarra/368/2015	Servicio de Microbiología Complejo Hospitalario de Navarra		
EPI559633	HA		12 Jan 2015	A/Navarra/137/2015			
EPI567981	HA		23 Jan 2015	A/PaisVasco/407/2015			
EPI566296	HA		15 Jan 2015	A/PaisVasco/275/2015			
EPI566975	HA		12 Jan 2015	A/PaisVasco/131/2015			
EPI566282	HA		19 Jan 2015	A/Navarra/304/2015			

GISAID: Global Initiative on Sharing Avian Influenza Data.

Table 1 b

Details of influenza haemagglutinin sequences obtained from GISAID used in the phylogenetic analysis, I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015)

Segment ID	Segment	Country	Collection date	Isolate name	Originating Laboratory	Submitting Laboratory	Authors
I-MOVE sequences							
Reference sequences							
EPI398417	HA	United States	15 Apr 2012	A/Texas/50/2012	Texas Department of State Health Services-Laboratory Services	Centers for Disease Control and Prevention	NA
EPI460558	HA	Russian Federation	12 Mar 2013	A/Samara/73/2013	WHO National Influenza Centre Russian Federation	National Institute for Medical Research	
EPI696965	HA		29 Jan 2015	A/South Australia/55/2014 (14/226)	NA	National Institute for Biological Standards and Control (NIBSC)	Nicolson, C
EPI466802	HA	South Africa	25 Jun 2013	A/South Africa/4655/2013	Sandringham, National Institute for Communicable D	National Institute for Medical Research	NA
EPI536340	HA	Iceland	10 Jun 2014	A/Iceland/08202/2014	Landspitali - University Hospital		
EPI539598	HA	Lithuania	8 May 2014	A/Lithuania/13347/2014	Lithuanian AIDS Center Laboratory		
EPI541459	HA	Australia	16 Jun 2014	A/Newcastle/22/2014	WHO Collaborating Centre for Reference and Research on Influenza		
EPI426061	HA	Hong Kong (SAR)	11 Jan 2013	A/Hong Kong/146/2013	Government Virus Unit		
EPI539806	HA	Hong Kong (SAR)	30 Apr 2014	A/Hong Kong/5738/2014			
EPI539619	HA	United States	11 Mar 2014	A/Nebraska/4/2014	Centers for Disease Control and Prevention		
EPI530687	HA	Switzerland	6 Dec 20130	A/Switzerland/9715293/2013	Hopital Cantonal Universitaire de Geneve		

GISAID: Global Initiative on Sharing Avian Influenza Data.

study sites from the vaccine type analysis, where the given type of vaccine was not available.

We conducted four sensitivity analyses (i) restricting the study to patients swabbed less than 4 days after symptom onset, (ii) restricting to the population targeted for vaccination as defined in each country [23] (iii) excluding patients vaccinated < 15 days after symptom onset, (iv) calculating adjusted VE using a two-stage model using random effects.

The respective country's National Influenza Reference Laboratories tested swab specimens for influenza by real-time RT-PCR assays. In Spain, other laboratories participating in the National Influenza Sentinel Surveillance System tested specimens. In each study site, a non-random selection of positive specimens or isolated viruses from positive specimens were subsequently sent to the corresponding National Influenza Centre, where influenza diagnosis was confirmed and viruses characterised either by sequencing the HA1 coding portion of the haemagglutinin gene (genetic characterisation) or by haemagglutination inhibition (antigenic characterisation). The criteria to select the specimens for genetic and antigenic characterisation varied by study site.

For the I-MOVE pooled analysis, the Spanish and Portuguese National Influenza Centres analysed the nt and amino acid sequences of the HA1 coding portion of the haemagglutinin gene and used the neighbour-joining method and the Kimura 2-parameter nt substitution model for phylogenetic analysis. A phylogenetic tree was constructed with a bootstrap analysis of 500 replicates (values above 50 are shown) using MEGA software version 6 (Tamura, Stecher, Peterson, Filipski,

and Kumar 2013). HA sequences from reference strains used in the phylogenetic analysis were obtained from the EpiFlu database of the Global Initiative on Sharing Avian Influenza Data (GISAID) (Table 1).

Results

Within the I-MOVE multicentre case–control study, the start of country-specific study periods ranged from week 41, 2014 (Germany) to week 3, 2015 (Poland), and the end from week 13, 2015 (Portugal) to week 19, 2015 (Germany). Study period duration ranged from 14 (Poland) to 31 (Germany) weeks.

Among the 7,992 ILI patients recruited, 6,579 ILI patients met the eligibility criteria including 3,142 testing negative for all influenza viruses. For the influenza type/subtype-specific analysis datasets, we included 1,828 influenza A(H3N2), 1,038 influenza B, 539 influenza A(H1N1)pdm09 (Figure 1).

The median onset date was 1 February for A(H1N1) pdm09, 1 February for A(H3N2), and 20 February for B cases (Figure 2). Forty-one percent of A(H3N2) cases were recruited in Germany, 44% of A(H1N1)pdm09 in Italy and 30% of B cases in Spain.

The median age was higher in influenza B cases (39 years) compared with influenza A(H3N2) and A(H1N1) cases (28 and 30 years respectively) and controls (31 years).

The proportion of patients swabbed more than three days after ILI onset was 15.9% among controls, and 10.3%, 13.5% and 15.9% among A(H3N2), A(H1N1) pdm09 and B cases respectively.

The proportion of patients belonging to the target group for vaccination, or with at least one chronic condition or with at least one hospitalisation in the previous 12 months was similar between influenza A(H3N2), A(H1N1)pdm09, B cases and controls.

Nine percent of controls, and 11%, 5% and 6% of A(H3N2), A(H1N1)pdm09 and B cases had received both the 2013/14 and the 2014/15 vaccines.

Of the 735 vaccinated individuals, 620 (84%) had information on the vaccine type received; they were vaccinated with ten different brands. By vaccine type, 40% had received egg-derived inactivated subunit (used in all sites except in Hungary and Italy), 33% egg-derived inactivated split virion (used in all sites except in Ireland and Romania), 21% adjuvanted (used in Germany, Hungary, Italy and Spain) and 5% cell-derived inactivated subunit vaccines (used in Germany and Spain).

After excluding patients with missing information (n = 833; 7%), we included 4,491, 2,920 and 3,730 patients in the complete case analysis of VE against influenza A(H3N2), A(H1N1)pdm09 and B respectively (Figure 1).

The I^2 was < 50% ($p > 0.05$) when assessing crude type/subtype specific VE by study site and age group. Sample size among the 0–14 year-olds for the A(H1N1) pdm09 analysis was too small to carry out tests for heterogeneity. When assessing crude VE against A(H3N2) by study site among the target group for vaccination, the I^2 was 61.5% ($p = 0.016$).

Influenza A(H3N2)

The overall adjusted VE against influenza A(H3N2) was 14.4% (95% CI: -6.3 to 31.0) (Table 3).

Adjusted VE was 20.7% (95% CI: -22.3 to 48.5) among the 0–14 year olds, 10.9% (95% CI: -30.8 to 39.3) among the 15–59 year olds and 15.8% (95% CI: -20.2 to 41.0) among those ≥60 years. By vaccine type, the adjusted VE point estimates were lower for cell-derived inactivated subunit vaccines (-9.3%) compared with egg-derived inactivated subunit, egg-derived inactivated split virion, and adjuvanted vaccines (10.9%, 18.6% and 14.0% respectively) (Table 4).

The adjusted VE was 43.7% (95% CI: 15.3 to 62.5) among those vaccinated in 2014/15 only, 0.0% (95%CI: -50.7 to 33.7) among those vaccinated in 2013/14 only, and -5.2% (95%CI: -34.3 to 17.6) among those vaccinated in both seasons (Table 4, Figure 3).

The overall adjusted VE point estimate was similar to the adjusted VE among those swabbed less than 4 days of symptom onset (17.4%) and to the adjusted VE excluding individuals vaccinated less than 15 days after symptom onset (13.7%). The adjusted VE point estimate was higher when restricting the analysis to the target population (26.2%) (Table 2). The adjusted VE estimates using a two-stage random effects model were similar (within 6 % points) to the one-stage pooled analysis VE for all population and restricted to the target group for vaccination (Table 2). The two-stage VE point estimate in the ≥60 year- olds was 10% higher than the one-stage VE but three study sites were excluded from the two-stage analysis due to their limited sample size.

One hundred and fourteen (6%) of the 1,828 A(H3N2) viruses included in the analysis were genetically or antigenically characterised. Seventy-five viruses of the 114 (66%) were antigenically distinct from the vaccine virus A/Texas/50/2012: 58 belonged to clade 3C.2a, represented by A/HongKong/5738/2014, and 17 belonged to clade 3C.3a represented by A/Switzerland/9715293/2013 (Table 5).

Of the 114 characterised A(H3N2) viruses, 107 (94%) were sequenced. Compared with A/Texas/50/2012, 17 viruses had the T128A, R142G and N145S mutations that define the group 3.C represented by A/Samara/73/2013. Eight viruses had in addition the

Table 2

Details for influenza, A(H3N2), A(H1N1)pdm09 and influenza B cases and controls, I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015) (n=6,524[a])

Variables	Number of test-negative controls /total n(%) (n=3,142) [b]	Number of influenza A(H3N2) cases /total n(%) (n=1,828)[c]	Number of influenza A(H1N1) pdm09 /total n(%) (n=1,038)[d]	Number of influenza B cases /total n(%) (n=539) [c,d]
Median age (years)	31.0	28.0	30.0	39.0
Missing	5	1	1	0
Age groups				
0–4 years	620/3,137 (19.8)	212/1,827 (11.6)	136/538 (25.3)	62/1,038 (6)
5–14 years	459/3,137 (14.6)	451/1,827 (24.7)	85/538 (15.8)	219/1,038 (21.1)
15–59 years	1,539/3,137 (49.1)	885/1,827 (48.4)	256/538 (47.6)	619/1,038 (59.6)
≥60 years	519/3,137 (16.5)	279/1,827 (15.3)	61/538 (11.3)	138/1,038 (13.3)
Missing	5	1	1	0
Sex				
Female	1,610/3,132 (51.4)	945/1,825 (51.8)	283/539 (52.5)	556/1,037 (53.6)
Missing	10	3	0	1
Days between onset of symptoms and swabbing				
0	254/3,142 (8.1)	128/1,828 (7)	55/539 (10.2)	32/1,038 (3.1)
1	1,076/3,142 (34.2)	662/1,828 (36.2)	206/539 (38.2)	286/1,038 (27.6)
2	816/3,142 (26)	574/1,828 (31.4)	128/539 (23.7)	317/1,038 (30.5)
3	497/3,142 (15.8)	275/1,828 (15)	77/539 (14.3)	238/1,038 (22.9)
4–7	499/3,142 (15.9)	189/1,828 (10.3)	73/539 (13.5)	165/1,038 (15.9)
Seasonal vaccination, 2014/15e	392/2,978 (13.2)	228/1,759 (13.0)	36/522 (6.9)	75/1,010 (7.4)
Missing	164	69	17	28
Previous season influenza vaccination				
Not vaccinated or vaccinated<15 days before onset	2,432/2,918 (83.3)	1,461/1,733 (84.3)	464/515 (90.1)	901/1,001 (90)
Current season vaccination only	98/2,918 (3.4)	41/1,733 (2.4)	10/515 (1.9)	14/1,001 (1.4)
Previous season vaccination only	113/2,918 (3.9)	47/1,733 (2.7)	15/515 (2.9)	27/1,001 (2.7)
Current and previous season vaccination	275/2,918 (9.4)	1,84/1,733 (10.6)	26/515 (5.0)	59/1,001 (5.9)
Missing	224	95	24	37
2014/15 vaccine type				
Not vaccinated or vaccinated<15 days before onset	2,586/2,978 (82.3)	1,531/1,759 (83.8)	486/522 (90.2)	935/1,010 (90.1)
Egg-derived inactivated subunit	124/2,978 (3.9)	89/1,759 (4.9)	10/522 (1.9)	27/1,010 (2.6)
Egg-derived inactivated split virion	115/2,978 (3.7)	56/1,759 (3.1)	16/522 (3)	19/1,010 (1.8)
Adjuvanted	81/2,978 (2.6)	38/1,759 (2.1)	3/522 (0.6)	8/1,010 (0.8)
Cell- derived inactivated subunit	10/2,978 (0.3)	13/1,759 (0.7)	0/522 (0)	7/1,010 (0.7)
Unknown vaccine type	62/2,978 (2)	32/1,759 (1.8)	7/522 (1.3)	14/1,010 (1.3)
Missing vaccination status or date	164	69	17	28
At least one chronic condition	661/3,024 (21.9)	384/1,776 (21.6)	110/525 (21.0)	216/1,023 (21.1)
Missing	118	52	14	15
At least one hospitalisation in the previous 12 months for chronic conditions	56/3,100 (1.8)	25/1,806 (1.4)	7/534 (1.3)	23/1,033 (2.2)
Missing	42	22	5	5
Belongs to target group for vaccination	902/3,069 (29.4)	511/1,801 (28.4)	141/530 (26.6)	301/1,029 (29.3)
Missing	73	27	9	9
Study sites				
Germany	1,472/3,142 (46.8)	741/1,828 (40.5)	185/539 (34.3)	268/1,038 (25.8)
Ireland	109/3,142 (3.5)	102/1,828 (5.6)	11/539 (2)	57/1,038 (5.5)
Hungary	379/3,142 (12.1)	232/1,828 (12.7)	32/539 (5.9)	42/1,038 (4)
Portugal	102/3,142 (3.2)	45/1,828 (2.5)	0/539 (0)	98/1,038 (9.4)
Italy	594/3,142 (18.9)	229/1,828 (12.5)	237/539 (44)	123/1,038 (11.8)
Poland	77/3,142 (2.5)	18/1,828 (1)	21/539 (3.9)	70/1,038 (6.7)
Romania	76/3,142 (2.4)	80/1,828 (4.4)	43/539 (8)	73/1,038 (7)
Spain	333/3,142 (10.6)	381/1,828 (20.8)	10/539 (1.9)	307/1,038 (29.6)

I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe.

[a] This includes 15 influenza B+A(H3N2) co-infections and 8 influenza B+A(H1N1)pdm09 co-infections. Note that numbers of cases come from influenza type/subtype specific databases. Some cases are excluded due to their restriction criteria. Any influenza A non-typed cases are dropped from analysis.

[b] Controls from 'any influenza' analysis used.

[c] Includes 15 influenza B+A(H3N2) co-infections.

[d] Includes 8 influenza B+A(H1N1)pdm09 co-infections.

[e] Vaccination more than 14 days before onset of influenza like illness symptoms.

Table 3

Pooled crude and adjusted seasonal vaccine effectiveness against laboratory-confirmed influenza by influenza type/subtype, overall and by age groups, I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015)

Type/subtype	Analysis scenario		N[a,b]	Cases;vaccinated/Controls; vaccinated[a,b]	Crude VE[a,c]	95% CI	Adjusted VE	95% CI
A(H3N2)	1-stage pooled analysis[d]	All ages	4,491	1,723;225/2,768;365	-1.9	-22.2 to 15.1	14.4	-6.3 to 31.0
		0–14 years	1,505	607;54/898;64	-38.4	-103.5 to 5.9	20.7	-22.3 to 48.5
		15–59 years	2,245	846;57/1,399;91	-2.2	-45.3 to 28.1	10.9	-30.8 to 39.3
		≥60 years	741	270;114/471;210	7.3	-26.9 to 32.2	15.8	-20.2 to 41.0
		Target group for vaccination	1,287	483;155 / 804;276	10.9	-14.5 to 30.6	26.2	1.6 to 44.7
		Vaccinated <15 days excluded	4,475	1,718;225/2,757;365	-1.8	-22.2 to 15.1	13.7	-7.2 to 30.5
		Restricted delay onset and swabbing<4 days	3,869	1,543;196/2,326;280	-10.1	-34.4 to 9.8	17.4	-4.6 to 34.8
	2-stage pooled analysis	All ages	4,503	1,724;225/2,779;366	-0.6	-31.2 to 22.8	9.0	-28.2 to 35.4
		0–14[e] years	1,418	564;54/853;63	-42.2	-109.2 to 3.3	22.9	-20.7 to 50.8
		15–59[f] years	2,192	853;57/1,357;88	-6.6	-53.2 to 25.8	12.3	-31.6 to 41.5
		≥60[g] years	678	254;108/424;187	11.3	-24.9 to 37.1	25.5	-24.5 to 55.4
		Target group for vaccination[h]	1,240	473;153/767;274	6.4	-43.2 to 38.9	20.7	-32.5 to 52.5
A(H1N1)pdm09	1-stage pooled analysis[i]	All ages	2,920	515;36/2,405;314	53.7	33.1 to 68.0	54.2	31.2 to 69.6
		0–14 years	1,023	211;8/812;63	59.9	13.4 to 81.5	73.1	39.6 to 88.1
		15–59 years	1,436	245;8/1191;75	47.5	-13.1 to 75.6	59.7	10.9 to 81.8
		≥60 years	451	59;20/392;171	22.4	-44.4 to 58.4	22.4	-44.4 to 58.4
		Target group for vaccination	832	138;26/694;232	53.8	26.0 to 71.2	53.6	22.1 to 72.3
		Vaccinated<15 days excluded	2,914	515;36/2,399;314	53.9	33.3 to 68.1	54.5	31.6 to 69.7
		Restricted delay onset and swabbing<4 days	2,471	443;26/2,028;242	57.8	35.3 to 72.5	61.0	37.7 to 75.6
	2-stage pooled analysis	All ages[j]	2,650	494;34/2,156;285	53.6	20.6 to 72.9	53.5	27.8 to 70.1
		0–14[k] years	916	196;7/720;59	59.5	-79.6 to 90.9	71.6	20.5 to 89.9
		15–59[l] years	941	195;7/746;52	35.4	-51.3 to 72.4	51.8	-15.9 to 79.9
		≥60[m] years	290	41;18/249;120	15.8	-65.3 to 57.1	NA	NA
		Target group for vaccination[n]	536	105;22/431;160	53.8	22.3 to 72.5	58.4	10.7 to 80.6
Influenza B	1-stage pooled analysis	All ages	3,730	1,001;74 / 2,729;362	47.9	31.3 to 60.4	48.0	28.9 to 61.9
		0–14 years	1,143	269;11 / 874;62	37.8	-23.2 to 68.6	62.1	14.9 to 83.1
		15–59 years	1,986	602;29 / 1,384;94	29.6	-10.3 to 55.0	41.4	6.2 to 63.4
		≥60years	601	130;34 / 471;206	54.4	25.8 to 72.0	50.4	14.6 to 71.2
		Target group for vaccination	1,083	290;56 / 793;273	54.6	35.2 to 68.2	49.8	26.2 to 65.9
		Vaccinated <15 days excluded	3,719	998;74/2,721;362	47.8	31.3 to 60.4	47.8	28.6 to 61.8
		Restricted delay onset and swabbing <4 days	3,132	841;63/2,291;278	41.8	21.3 to 57.0	44.4	21.8 to 60.5
	2-stage pooled analysis	All ages	3,734	1,003;74/2,731;363	48.9	25.3 to 65.0	51.5	26.8 to 61.8
		0–14[p] years	1,057	230;12/827;61	29.5	-41.3 to 64.8	47.5	-15 to 76.0
		15–59 years	1,995	603;29/1,392;96	28.1	-17.1 to 55.9	43.2	5.2 to 66.0
		≥60[q] years	611	132;34/479;208	53.5	24.1 to 71.5	54.1	22.4 to 72.8
		Target group for vaccination[r]	1,057	293;56/764;266	54.9	27.2 to 72.0	56.0	26.2 to 73.8

CI: confidence interval; DE: Germany; ES: Spain; HU: Hungary; IE: Ireland; I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe; IT: Italy; PL: Poland; PT: Portugal; RO: Romania; VE: vaccine effectiveness.

[a] Based on the complete case analysis: records with missing age, sex, chronic condition, vaccination status are dropped.

[b] Totals may differ between one-stage and two-stage models, as adjustment at study site-level may vary to the one-stage pooled model adjustment, resulting in different missing data dropped depending on included covariates. In addition different numbers of study sites may be included in each analysis due to sample size issues.

[c] Crude VE adjusted by study site.

[d] Data adjusted for age (restricted cubic spline), onset date (restricted cubic spline), sex, chronic condition and study site. Exceptions are A(H3N2) all ages, where age groups (0–4, 5–14, 15–59 and ≥60 years) are used instead of restricted cubic splines.

[e] Study sites include DE, ES, IT. HU not included in the 0–14 year old analysis, as no patients included aged <18 years. Sample size too low for IE, PT and RO.

[f] Study sites include DE, ES, HU, IE, IT, PT, RO. Sample size too low for PL. Crude VE for RO used in adjusted estimate, due to low sample size.

[g] Study sites include DE, ES, HU, IT, RO. IE, PL and PT not included due to low sample size. Crude VE for RO used in adjusted estimate, due to low sample size.

[h] Study sites include DE, ES, IE, IT, PL, PT, RO. HU not included in the 0–14 year old analysis, as no patients included aged <18 years.

[i] Data adjusted for age (restricted cubic spline), onset date (restricted cubic spline), sex, chronic condition and study site. Exceptions the A(H1N1)pdm09 analysis among the elderly, where data are adjusted for age (restricted cubic spline), onset date (restricted cubic spline), and study site only.

[j] Study sites include DE, HU, IE, IT, RO, PL. ES and IE dropped from analysis due to small sample size.

[k] Study sites include DE, IT. ES, IE, PL, RO not included as sample size too low. HU not included in the 0–14 year old analysis, as no patients included aged<18 years.

[l] Study sites include DE, IT, RO. ES, HU, IE and PL not included as sample size too small. Crude VE for RO used in adjusted estimate, due to low sample size.

[m] Study sites include DE, IT. ES, HU, IE, PL and RO not included as sample size too small. Only crude VE available, due to low sample size.

[n] Study sites include DE, IT, RO. ES, HU, IE and PL not included as sample size too small. Crude VE for RO used in adjusted estimate, due to low sample size.

[o] Data adjusted for age (restricted cubic spline), onset date (restricted cubic spline), sex, chronic condition and study site. Exceptions the B analysis among the elderly, where data are adjusted for age (restricted cubic spline), onset date (restricted cubic spline), and study site only.

[p] Study sites include DE, ES, IT. IE, PL, PT and RO not included as sample size too low. HU not included in the 0–14 year old analysis, as no patients included aged<18 years.

[q] Study sites include DE, ES, HU, IE, IT, PL, PT, RO. Crude VE for DE, HU, IE, PL and RO due to low sample size.

[r] Study sites include DE, ES, HU, IE, IT, PL, PT, RO. Crude VE for HU, IE and RO due to low sample size.

mutations G5E and N31S. Twenty viruses belonged to the group 3C.3b represented by A/Newcastle/22/2014 and characterised by T128A, R142G, N145S, E62K, K83R, N122D, L157S and R261Q mutations. Seven of these presented an additional amino acid change Q197H at the antigenic site B (Figure 4).

Twelve viruses belonged to the group 3C.3a that harbours the T128A, R142G, A138S, N145S, F159S and N225D mutations. Nine of them had an extra mutation K276N at the antigenic site C. Fifty-eight viruses belonged to group 3C.2a and the only mutations identified were L3I, N144S, N145S, F159Y, K160T, N225D and Q311H - amino acid mutations that define the group.

Influenza A(H1N1)pdm09

The overall adjusted VE against influenza A(H1N1) pdm09 was 54.2% (95% CI: 31.2 to 69.6) (Table 3).The adjusted VE was 73.1% (95% CI: 39.6 to 88.1) among the 0–14 year olds, 59.7% (95% CI: 10.9 to 81.8) among the 15–59 year olds and 22.4% (95% CI: -44.4 to 58.4) among those ≥60 years of age.

By vaccine type, the adjusted VE point estimate was higher for the adjuvanted vaccine (79.8%) than for the egg-derived inactivated subunit and the inactivated split virion vaccines (53.0% and 51.5% respectively). We could not compute the VE for the cell-derived inactivated subunit due to small numbers (7 controls vaccinated and no cases vaccinated) (Table 4).

The adjusted VE point estimate was lower (-1.9%) among those vaccinated in 2013/14 only compared with those vaccinated in 2014/15 only (47.2%) and to those vaccinated in both seasons (52.7%) (Table 4).

The overall adjusted VE point estimate did not vary when restricting the analysis to the target group for vaccination (53.6%), when excluding those vaccinated<15 days (54.5%) before symptom onset and when using a two-stage pooled model (53.5%). It was 61.0% when restricted to those swabbed less than 4 days of symptom onset (Table 3).

Of the 539 A(H1N1)pdm09 viruses, 24 (4%) were genetically characterised and all belonged to the group 6B defined by the amino acid substitutions D97N, K163Q, S185T, S203T, A256T and K283E compared with A/California/07/2009.

Influenza B

The overall adjusted VE against influenza B was 48.0% (95% CI: 28.9 to 61.9). The adjusted VE was 62.1% (95% CI: 14.9 to 83.1) among the 0–14 year olds, 41.4% (95% CI: 6.2 to 63.4) among the 15–59 year olds and 50.4% (95% CI: 14.6 to 71.2) among those ≥60 years old (Table 3).

By vaccine type, the adjusted VE point estimates were lower for cell-derived inactivated subunit vaccines (16.0%) than for egg-derived subunit, split virion and adjuvanted vaccines (52.4%, 60.1%, 51.9% respectively) (Table 4).

The adjusted VE point estimate was lower among those vaccinated only in 2013/14 (1.7%) than among those vaccinated only in 2014/15 (59.4%) or among those vaccinated in both seasons (43.8%) (Table 4).

There was less than 9% absolute difference between the overall adjusted VE point estimates and the VE in all sensitivity analyses (Table 3). The two-stage VE point estimate in the 0–14 years old was 15% lower than the one-stage VE point estimate but five study sites were excluded from the two-stage analysis due to their limited sample size.

Among 746 cases for which the lineage was available, 740 (99.2%) were Yamagata and six Victoria.

One hundred and fifty-three (15%) of the 1,038 B viruses were characterised: 151 B Yamagata and two B Victoria viruses. Of the 151 B Yamagata lineage viruses genetically characterised, 148 (98%) belonged to B/Phuket/3073/2013, clade 3 and three to B/Massachusetts/02/2012. The two B Victoria viruses genetically characterised belonged to B/Brisbane/60/2008 (1A).

Discussion

The results of the I-MOVE multicentre case–control study suggest a low 2014/15 influenza VE against medically attended ILI due to A(H3N2) and a moderate VE against medically attended ILI due to A(H1N1)pdm09 or B.

The sample size of the I-MOVE multicentre case–control study for the 2014/15 season was one of the largest since 2008/09. We could estimate VE against the three circulating viruses. However, with the low influenza vaccination coverage in the participating sites, we still have limited statistical power for some subgroup analyses that provide important information for public health action like VE by previous vaccination or VE by type of vaccine. The current sample size is still too small to measure VE by vaccine product.

Measuring VE by study sites was not among the objectives of our multicentre study. In addition, as in previous seasons, study sites, sample size pending, are publishing their own results. However, even if not statistically significant, VE may differ between study sites. Differences in site-specific adjusted VE may be explained, among other factors, by variability due to the limited number of samples, unknown residual confounding, or different vaccines used. In future seasons we are confident that, with more resources, sample sizes should increase allowing for better adjustment and stratification including by vaccine brand.

Integrating virological and epidemiological information is essential to interpret VE estimates [5]. For the

Table 4

Pooled crude and adjusted seasonal vaccine effectiveness against laboratory- confirmed influenza by influenza type/subtype, by vaccine type and by influenza vaccination status in 2013/14, I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015)

Influenza type/subtype		Vaccine type	N	Cases/controls	Crude VE[a,b]	95% CI	Adjusted VE[c]	95% CI
A(H3N2)	By vaccine type	Unvaccinated	3,901	1,498/2,403	Ref	NA	Ref	NA
		Egg-derived inactivated subunit	205	88/117	-5.7	-41.7 to 21.2	10.9	-24.3 to –36.1
		Egg-derived inactivated split virion	164	56/108	-0.4	-41.2 to 28.6	18.6	-17.4 to 43.5
		Adjuvanted	116	38/78	11.8	-32.7 to 41.4	14.0	-34.1 to 44.9
		Cell-Derived inactivated subunit	23	13/10	-15.3	-167.0 to 50.2	-9.3	-159.1 to 53.9
		Unknown	82	30/52	-12.0	-77.1 to 29.2	21.3	-29.7 to 52.3
	By previous vaccination	Unvaccinated in both seasons	3,697	1,434/2,263	Ref	NA	Ref	NA
		Vaccinated in 2014/15 only	133	41/92	29.8	-2.7 to 52.0	43.7	15.3 to 62.5
		Vaccinated in 2013/14 only	147	43/104	28.2	-3.4 to 50.2	0.0	-50.7 to 33.7
		Vaccinated in both seasons	436	181/255	-16.4	-43.1 to 5.3	-5.2	-34.3 to 17.6
A(H1N1)pdm09	By vaccine type	Unvaccinated	2,570	479/2,091	Ref	NA	Ref	NA
		Egg-derived inactivated subunit	113	10/103	47.1	-4.5 to 73.2	53.0	4.1 to 76.9
		Egg-derived inactivated split virion	104	16/88	47.5	8.1 to 70.0	51.5	13.4 to 72.8
		Adjuvanted	73	3/70	84.4	49.3.to.95.2	79.8	31.0.to.94.1
		Cell-derived inactivated subunit	7	0/7	NA	NA	NA	NA
		Unknown	53	7/46	24.8	-70.7 to 66.8	35.3	-48.5 to 71.8
	By previous vaccination	Unvaccinated in both seasons	2,438	459/1,979	Ref	NA	Ref	NA
		Vaccinated in 2014/15 only	90	10/80	46.6	-5.8 to 73.0	47.2	-7.1 to 74.0
		Vaccinated in 2013/14 only	99	15/84	11.8	-56.8 to 50.4	-1.9	-86.2 to 44.2
		Vaccinated in both seasons	242	26/216	53.8	28.9 to 69.9	52.7	24.2 to 70.5
B	By vaccine type	Unvaccinated	3,294	927/2,367	Ref	NA	Ref	NA
		Egg-derived inactivated subunit	146	27/119	49.3	20.7 to 67.6	52.4	22.9 to 70.6
		Egg-derived Inactivated split virion	119	18/101	59.5	30.8 to 76.3	60.1	30.1 to 77.3
		Adjuvanted	86	8/78	51.3	-4.1 to 77.2	51.9	-6.2 to 78.2
		Cell-derived Inactivated subunit	17	7/10	22.5	-108.0 to 71.1	16.0	-129.9 to 69.3
		Unknown	68	14/54	25.0	-40.7 to 60.0	27.3	-40.2 to 62.3
	By previous vaccination	Unvaccinated in both seasons	3,127	894/2,233	Ref	NA	Ref	NA
		Vaccinated in 2014/15 only	107	14/93	61.1	29.8 to 78.4	59.4	25.1 to –78.0
		Vaccinated in 2013/14 only	128	26/102	20.3	-26.6 to 49.8	1.7	-61.8 to 40.3
		Vaccinated in both seasons	309	58/251	43.3	22.5 to 58.6	43.8	20.0 to 60.5

CI: confidence interval; Ref: reference; I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe; NA: not applicable; VE: vaccine effectiveness.

[a] Based on the complete case analysis: records with missing age, sex, chronic condition, vaccination status are dropped).

[b] Crude VE adjusted by study site.

[c] Data adjusted for age (restricted cubic spline or age group), onset date (restricted cubic spline), sex, chronic condition and study site.

Note: Egg-derived inactivated subunit vaccines used in DE, IE, PO, PT, RO, ES.

Egg-derived inactivated Split virion vaccines used in DE, HU, IT, PO, PT, ES.

Adjuvanted vaccines used in DE, HU, IT, ES.

Cell-derived inactivated subunit vaccines used in Germany, ES.

Table 5

Influenza A(H3N2), A(H1N1)pdm09, B Yamagata, B Victoria viruses characterised by clade and study site, I-MOVE multicentre case–control study, Europe, influenza season 2014/15 (week 41/2014-week 19/2015) (n=291)

Characterised viruses	Clade	Germany N	Hungary N	Ireland N	Portugal N	Romania N	Spain N	Total (%)
A(H3N2) (n=114)								
A/HongKong/5738/2014	3C.2a	12	NA	11	14	2	19	58 (51)
A/Switzerland/9715293/2013	3C.3a	NA	NA	1	NA	11	5	17 (15)
A/Samara/73/2013	3C.3	5	NA	3	4	3	4	19 (17)
A/Newcastle/22/2014	3C.3b	5	2	1	NA	3	9	20 (17)
Total A(H3N2)	NA	22	2	16	18	19	37	114 (100)
A(H1N1)pdm09 (n=24)								
A/SouthAfrica/3626/2013	6B	12	NA	5	2	5	NA	24 (100)
B Yamagata (n=151)								
B/Phuket/3073/2013	Clade 3	31	NA	5	56	28	28	148 (98)
B/Massachusetts/02/2012	Clade 2	NA	NA	NA	1	2	NA	3 (2)
Total B Yamagata	NA	31	NA	5	57	30	28	151 (100)
B Victoria (n=2)								
B/Brisbane/60/2008	NA	NA	NA	2	NA	NA	NA	2 (100)

NA: not applicable.

last two seasons, the I-MOVE multicentre case–control teams have made an effort to include genetic and antigenic results from a sample of the cases included in the study. However, the proportion of strains genetically and antigenically characterised (8.5%) is still low, and varied by site. Two study sites (Italy, Poland) could not provide results and some sites with a low number of cases characterised a higher proportion of viruses than sites with high number of cases. For instance, 11 of the 17 clade 3C.3a viruses characterised were from Romania, a site that contributed to only 4.4% of the A(H3N2) cases. In addition, the viruses characterised were selected according to virological surveillance objectives (e.g. selection of viruses from more severe cases, from vaccinated cases, etc.). Due to the non-random selection and the different proportion of viruses characterised we cannot exclude that the viruses characterised may not be representative of the viruses from cases included in the study. For the 2015/16 season, the I-MOVE multicentre case–control study will pilot a selection procedure aiming to provide a representative sample of viruses characterised. If resources are available, the number of viruses characterised should increase.

The VE against influenza A(H3N2) was low overall, by age group and among the target group for vaccination. Four different genetic clades of A(H3N2) viruses (3C.2a, 3C.3a, 3C.3 and 3C.3b) circulated in the eight countries participating in I-MOVE. The low VE are in concordance with the high proportion (66%) of 3C.2a and 3C.3a drifted viruses identified among those genetically characterised. Additional mutations were detected in the 3C.3 and 3C.3b influenza A(H3N2) viruses characterised but those are considered antigenically similar to the vaccine virus [13]. This season, estimates are similar to the VE against A(H3N2) we observed in 2011/12 and 2013/14 [8,9]. They are lower than the final 2014/15 VE against A(H3N2) reported in the UK even if the proportion of drifted virus among those genetically characterised are higher in UK than in our study [14]. VE against A(H3N2) was below 20% for all vaccine types with a lower point estimate for the cell-derived subunit vaccine. The effectiveness was lower in those vaccinated in both 2013/14 and 2014/15 than in those vaccinated only in the 2014/15 season. These observations are in line with the results of the 2014/15 early A(H3N2) VE estimates in Canada [5] and with those observed in previous studies [15-17]. They are congruent with the hypothesis that prior immunisation may decrease the effectiveness of the vaccine and that this negative interference is more important when the antigenic distance is small between successive vaccine components but large between vaccine and circulating strain [18]. These conditions were present in 2014/15 with an unchanged A(H3N2) vaccine component compared with the 2013/14 vaccine and with a mismatch between the vaccine and a high proportion of circulating strains. However, those results may be due to chance, or to bias. We need a much larger sample size to have higher precision in the estimates and to study the effect of prior vaccinations by age group. In our study, individuals vaccinated in both seasons are older than those vaccinated only in one season (median age 63 years and 50 years respectively). Unmeasured differences between individuals vaccinated in two consecutive seasons and those vaccinated only in one season may have affected the results. Previous vaccination was documented through GP records or patient self-reports and may be subject to error. Since neither the ILI patient nor the GPs knew if the patient was an influenza case we are confident that differential recall

did not bias the results. If the results were not due to bias or to chance, concurrent immunological studies will be essential to better understand the biological mechanism behind, and the role of natural vs vaccine-acquired immunity.

The VE estimates against influenza A(H1N1)pdm09 are similar to our results in previous seasons [7-9]. The laboratory results indicate that the strains isolated from study participants were similar to the A(H1N1) pdm09 component of the 2014/15 influenza vaccine. As in 2013/14, we observed a lower VE among the elderly and higher among those aged 0–14 years old, however sample sizes were small in the age group analyses. The VE point estimates of the adjuvanted vaccines were higher but the small sample size in the analysis does not allow a comparison of effectiveness between vaccine types.

The VE against influenza B ranged from 41% to 62% in the overall population and was 56% in the target group for vaccination. Our estimates are similar to those reported by the UK [14]. Nearly all viruses (99%) for which lineage was available were B/Yamagata and 98% of those characterised belonged to clade 3 that is antigenically similar to the vaccine virus. VE was similar by vaccine type with lower point estimate for cell-derived inactivated subunit vaccines but the sample size is too low to interpret this observed difference. The results suggested no effect of the 2013/14 vaccine and a slightly lower VE among those vaccinated in both seasons.

This is the third season we provide VE by vaccine type. A high proportion of vaccinated study participants (84%) had vaccine product documented. Even with one of the largest sample size since 2008/09, the numbers are still too low to measure adjusted VE by vaccine type and age group. The European Medicines Agency (EMA) requests that vaccine producers provide product-specific vaccine effectiveness [19]. Taking into account the high number of vaccine products and the low vaccination coverage in countries participating in the study [20] the sample size to measure VE by vaccine product with high precision has to be much larger and substantial additional resources are needed. In a survey among I-MOVE partners to assess the feasibility of conducting product-specific VE in Europe (data not shown) most experts considered that in terms of resources allocation, providing precise estimates early in the season, by age group, by previous vaccination were of higher priority than measuring VE by product.

In summary, the 2014/15 results suggest a moderate effectiveness against influenza A(H1N1)pdm09 and B. The low effectiveness of the influenza vaccines against A(H3N2) observed again this season underlines the need to improve the A(H3N2) component of the vaccine especially among the target group for vaccination. This would be even more important if the observed negative effect of previous vaccination was confirmed. Since A(H3N2) virus is generally associated with more severe disease in the elderly and high-risk groups [21,22] and the vaccine is less effective against this influenza subtype, in seasons of A(H3N2) circulation early antiviral treatment should be recommended in these groups [3,6].

The effect of previous vaccinations is one of the questions that I-MOVE and other influenza VE teams in the US, Canada and Australia started to raise some years ago [17,24-27]. This is an important issue that may impact vaccination policy in Europe. They need to be addressed through international collaboration, a multidisciplinary approach and with long-term scientific independent studies. The I-MOVE multicentre case–control study should continue to increase the sample size and to strengthen the virological component of the study to contribute to answer these questions.

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Conflict of interest

None declared.

Authors' contributions

All authors provided contribution to the research article and approved the final version.

Marta Valenciano, coordinated the I-MOVE multicentre case control study network, supervised the statistical analysis and interpretation of the results, led the writing of the research article.

Esther Kissling was responsible for the data management of the multicentre study, undertook the statistical analysis on which the research article is based, contributed to the writing of the research article

Marta Valenciano, Esther Kissling and Alain Moren were involved in the original methodological design

Annicka Reuss, Caterina Rizzo, Alin Gherasim, Judit Krisztina Horváth, Lisa Domegan, Daniela Pitigoi, Ausenda Machado, Iwona Anna Paradowska-Stankiewicz, Antonino Bella, Amparo Larrauri, Annamária Ferenczi, Joan O´Donell, Mihaela Lazar, Ausenda Machado, Monika Roberta Korczyńska, coordinated the corresponding national component of the I-MOVE study, contributed to the conception, design, acquisition and interpretation of the data.

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