# Influenza vaccine effectiveness estimates in Europe in a season with three influenza type/subtypes circulating: the I-MOVE multicentre case–control study, influenza season 2012/13

**E Kissling (e.kissling@epiconcept.fr)[1,2], M Valenciano[1,2], U Buchholz[3], A Larrauri[4], J M Cohen[5], B Nunes[6], J Rogalska[7,8], D Pitigoi[9,10], I Paradowska-Stankiewicz[11], A Reuss[3], S Jiménez-Jorge[4], I Daviaud[5], R Guiomar[6], J O'Donnell[7], G Necula[9], M Głuchowska[11], A Moren[1]**

1. EpiConcept, Paris, France
2. These authors contributed equally to this work as first author
3. Robert Koch-Institute, Berlin, Germany
4. National Centre for Epidemiology, Instituto de Salud Carlos III, Madrid, Spain
5. GROG/Open Rome, Paris, France
6. Instituto Nacional de Saude Dr Ricardo Jorge, Lisbon, Portugal
7. Health Protection Surveillance Centre, Dublin, Ireland
8. European Programme for Intervention Epidemiology Training (EPIET), European
9. Cantacuzino Institute, National Institute of Research – Development for Microbiology
10. Universitatea de Medicina si Farmacie Carol Davila, Bucharest, Romania
11. National Institute for Public Health, Warsaw, Poland

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**In the fifth season of Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE), we undertook a multicentre case–control study (MCCS) in seven European Union (EU) Member States to measure 2012/13 influenza vaccine effectiveness against medically attended influenza-like illness (ILI) laboratory confirmed as influenza. The season was characterised by substantial co-circulation of influenza B, A(H1N1)pdm09 and A(H3N2) viruses. Practitioners systematically selected ILI patients to swab ≤7 days of symptom onset. We compared influenza-positive by type/subtype to influenza-negative patients among those who met the EU ILI case definition. We conducted a complete case analysis using logistic regression with study as fixed effect and calculated adjusted vaccine effectiveness (AVE), controlling for potential confounders (age, sex, symptom onset week and presence of chronic conditions). We calculated AVE by type/subtype. Study sites sent 7,954 ILI/acute respiratory infection records for analysis. After applying exclusion criteria, we included 4,627 ILI patients in the analysis of VE against influenza B (1,937 cases), 3,516 for A(H1N1)pdm09 (1,068 cases) and 3,340 for influenza A(H3N2) (730 cases). AVE was 49.3% (95% confidence interval (CI): 32.4 to 62.0) against influenza B, 50.4% (95% CI: 28.4 to 65.6) against A(H1N1)pdm09 and 42.2% (95% CI: 14.9 to 60.7) against A(H3N2). Our results suggest an overall low to moderate AVE against influenza B, A(H1N1)pdm09 and A(H3N2), between 42 and 50%. In this season with many co-circulating viruses, the high sample size enabled stratified AVE by type/subtype. The low estimates indicate seasonal influenza vaccines should be improved to achieve acceptable protection levels.**

## Introduction

The 2012/13 influenza season in Europe was characterised by an extended season where the three influenza viruses A(H1N1)pdm09, A(H3N2), B/Yamagata lineage all contributed substantially to morbidity although marked geographical differences were noted [1]. Currently, the best preventive method against influenza is receipt of the influenza vaccine. The composition of the 2012/13 northern hemisphere influenza vaccine included A/California/7/2009 (H1N1)pdm09, A/Victoria/361/2011 (H3N2) and B/Wisconsin/1/2010-like (Yamagata lineage) viruses. The A(H3N2) and influenza B components were changed from those of the 2011/12 influenza season [2].

Influenza vaccine effectiveness (VE) studies are essential to monitor how the vaccine performs in the target populations. If VE estimates are available early in the season they can lead to additional preventive measures if they are low, such as stronger recommendations for antiviral treatment for those at risk of severe disease.

Since 2008/09, using a European multicentre case–control study, a component of the Influenza Monitoring Vaccine Effectiveness (I-MOVE) network, we have estimated the effectiveness of the seasonal and pandemic influenza vaccine to prevent medically attended influenza-like illness (ILI) laboratory confirmed as

influenza [3-6]. In February 2013, early influenza VE estimates from the multicentre case–control study for the 2012/13 influenza season by type/subtype were included among the VE estimates provided to the World Health Organization (WHO) for the vaccine strain selection meeting for the 2013/14 influenza vaccine: 78.2% (95% confidence interval (CI): 18.0 to 94.2) against influenza B, 62.1% (95% CI: -22.9 to 88.3) against A(H1) pdm09, 41.9 (95% CI: −67.1 to 79.8) against A(H3N2) [7]. Estimates were also sent to other major bodies supporting public health decision-making: The European Centre for Disease Prevention and Control and the European Medicines Agency. In this article we present the 2012/13 end of season pooled VE estimates, from study sites in seven European Union (EU) Member States. The objective of the fifth I-MOVE multicentre case–control study was to provide pooled adjusted influenza VE estimates by influenza type/subtype and age group for the overall population and for the target group for vaccination.

## Methods

The seven study sites undertaking case–control studies included in the 2012/13 analysis were based in France, Germany, Ireland, Poland, Portugal, Romania and Spain. All study sites used the test-negative design; detailed methods on the I-MOVE multicentre case–control study are described elsewhere [4-6]. In summary, participating practitioners interviewed and carried out nasopharyngeal swabbing of all or of a systematic sample of patients presenting with influenza-like illness (ILI) or acute respiratory infection (ARI); in France practitioners sampled ARI patients exclusively and in Germany in case of no patients consulting for ILI, practitioners sampled those consulting for ARI.

Practitioners from all study sites collected information on date of symptom onset and date of swabbing, 2012/13 seasonal influenza vaccination status, date and brand, 2011/12 seasonal influenza vaccination status, ILI symptoms, sex, presence of a chronic condition (including obesity, except Germany and Poland), number of hospitalisations for chronic conditions in the previous 12 months and pregnancy. Six study sites collected information on number of practitioner visits in the previous 12 months (not collected in Germany), five collected information on receipt of antivirals (not collected in Spain and France) and five on smoking status (not collected in Germany and France). To identify individuals belonging to the target group for vaccination, four study sites included a specific question and three used variables such as age, chronic conditions, and pregnancy to enable their identification.

We included patients in the study if they met the EU ILI case definition (sudden onset of symptoms and at least one of the following four systemic symptoms: fever or feverishness, malaise, headache, myalgia; and at least one of the following three respiratory symptoms: cough, sore throat, shortness of breath), if they were swabbed ≤7 days of symptom onset, had no contraindications to influenza vaccination and did not receive antivirals prior to swabbing [8].

We defined the study period as at least 15 days after the beginning of the 2012/13 country-specific seasonal influenza vaccination campaigns and excluded controls that had symptom onset before the week of onset of the first influenza type/subtype case depending on the outcome used. We also dropped ILI patients presenting after the week of onset of the last influenza type/subtype case depending on outcome used, after which there were at least two consecutive weeks with no further influenza positive cases of this type/subtype.

Swabs were tested for influenza at the respective country's National Influenza Reference Laboratory. In France and Spain, tests were also conducted in other laboratories participating in the National Influenza Sentinel Surveillance System. All the laboratories contributing to the National Influenza Sentinel Surveillance Systems are certified. At all study sites a subset of isolates were genetically and/or antigenically characterised. Details of laboratory viral detection, typing, subtyping and variant analysis performed in each country are described elsewhere [9].

Among study participants fulfilling the inclusion criteria, we defined a case as a patient who tested positive for influenza virus by reverse-transcription polymerase chain reaction (RT-PCR) or culture. We classified patients with swabs testing negative for influenza virus as controls.

We classified cases and controls as vaccinated if they had received at least one dose of 2012/13 seasonal influenza vaccine at least 15 days before ILI symptom onset. All other patients were classified as unvaccinated.

Study sites sent their anonymised data to EpiConcept, where we pooled them and carried out a complete case analysis (where records with missing values were dropped). Using a one-stage method with study site as fixed effect in the model, we estimated the pooled influenza VE as 1 minus the odds ratio (OR) of being vaccinated in cases versus controls multiplied by 100.

To test for heterogeneity by influenza type/subtype between study sites, we used Cochran's Q-test and the $I^2$ index [10]. In study sites with sample sizes large enough we used adjusted ORs and their standard error, otherwise we used the crude ORs. In study sites with no vaccinated cases, we reclassified one unvaccinated case as vaccinated chosen at random, in order to calculate the OR and standard error.

We used a logistic regression model to calculate VE including potential confounding factors: age (modelled as a restricted cubic spline with 4 knots [11]), sex, presence of at least one chronic condition (including

**Table 1**

Study details for the I-MOVE multicentre case–control study to measure 2012/13 influenza vaccine effectiveness, study sites in seven European Union Member States, ISO week 43 in 2012–ISO week 18 in 2013

| Study site | Week/year of start of influenza season[a] | Week/ year of peak of influenza season[a] | Number of practitioners recruiting at least one ILI patient[b] | Number of ILI patients[b] included in study | Inclusion period for the final analysis (ISO weeks/year)[c] | Number of included ILI patients positive for influenza and with known vaccination status[d] | | Number of included ILI patients negative for any influenza and with known vaccination status[d] | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Total | Vaccinated | Total | Vaccinated |
| France | 51/2012 | 5/2013 | 318 | 1,613 | 51/2012–15/2013 | 950 | 33 | 619 | 33 |
| Germany | 50/2012 | 8/2013 | 137 | 2,875 | 43/2012–18/2013 | 1,407 | 95 | 1,305 | 123 |
| Ireland | 50/2012 | 1/2013 | 21 | 264 | 48/2012–16/2013 | 167 | 10 | 96 | 10 |
| Poland | 47/2012 | 3/2013 | 4 | 54 | 49/2012–4/2013 | 24 | 0 | 30 | 0 |
| Portugal | 3/2013 | 10/2013 | 44 | 335 | 51/2012–15/2013 | 152 | 8 | 183 | 37 |
| Romania | 3/2013 | 8/2013 | 69 | 196 | 2/2013–17/2013 | 130 | 1 | 66 | 7 |
| Spain | 3/2013 | 8/2013 | 194 | 1,297 | 50/2012–16/2013 | 823 | 40 | 473 | 45 |
| Total | – | – | 787 | 6,634 | 43/2012–18/2013 | 3,653 | 187 | 2,772 | 255 |

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

The study sites for the 2012/13 influenza vaccine effectiveness analysis were respectively located in the seven following European Union Member States: France, Germany, Ireland, Poland, Portugal, Romania and Spain.

[a] According to the thresholds used to define the start of the influenza season in each of the countries.

[b] ILI patients meeting the European Union case definition, swabbed ≤7days after onset of symptoms within the study period.

[c] From 15 days after the start of the vaccination campaign to week 18, 2013. We excluded controls with onset of symptoms in the weeks before the week of the first influenza case and after the week of the influenza case after which there were two or more consecutive weeks with no further cases in the study site.

[d] ILI patients included in the study, after excluding those with missing information on vaccination status or date of vaccination.

pregnancy and obesity where available) and week of symptom onset.

We calculated VE against influenza type/subtype and carried out stratified analyses by age group (0–14 years, 15–59 years and ≥60 years). We categorised vaccines according to vaccine group: inactivated subunit egg-based, inactivated subunit cell-based, inactivated split virion egg-based and inactivated adjuvanted (squalene MF59) and calculated VE by influenza vaccine group, by age group and for the target group for vaccination.

In a sensitivity analysis we restricted to those swabbed within three days of symptom onset also and we also calculated VE adjusted by current smoking status and number of general practitioner (GP) visits in the previous 12 months (0–1 visits, 2–4 visits and ≥5 visits) among the five study sites collecting this information. We calculated VE with those vaccinated within 14 days of symptom onset excluded, instead of coded as unvaccinated. We also carried out a multiple imputation using chained equations to assess if there was any bias in dropping records with missing data. We used missing at random assumptions and independently analysed 20 copies of the data using 30 cycles of regression. The variables included in the model to create the imputation database were the respective outcomes and the predictors: vaccination status for the 2012/13 season, age group, sex, presence of chronic conditions and associated hospitalisations in the previous 12 months, 2011/12 seasonal vaccination status, belonging to a target group for vaccination, delay between onset and swabbing, onset month and study site.

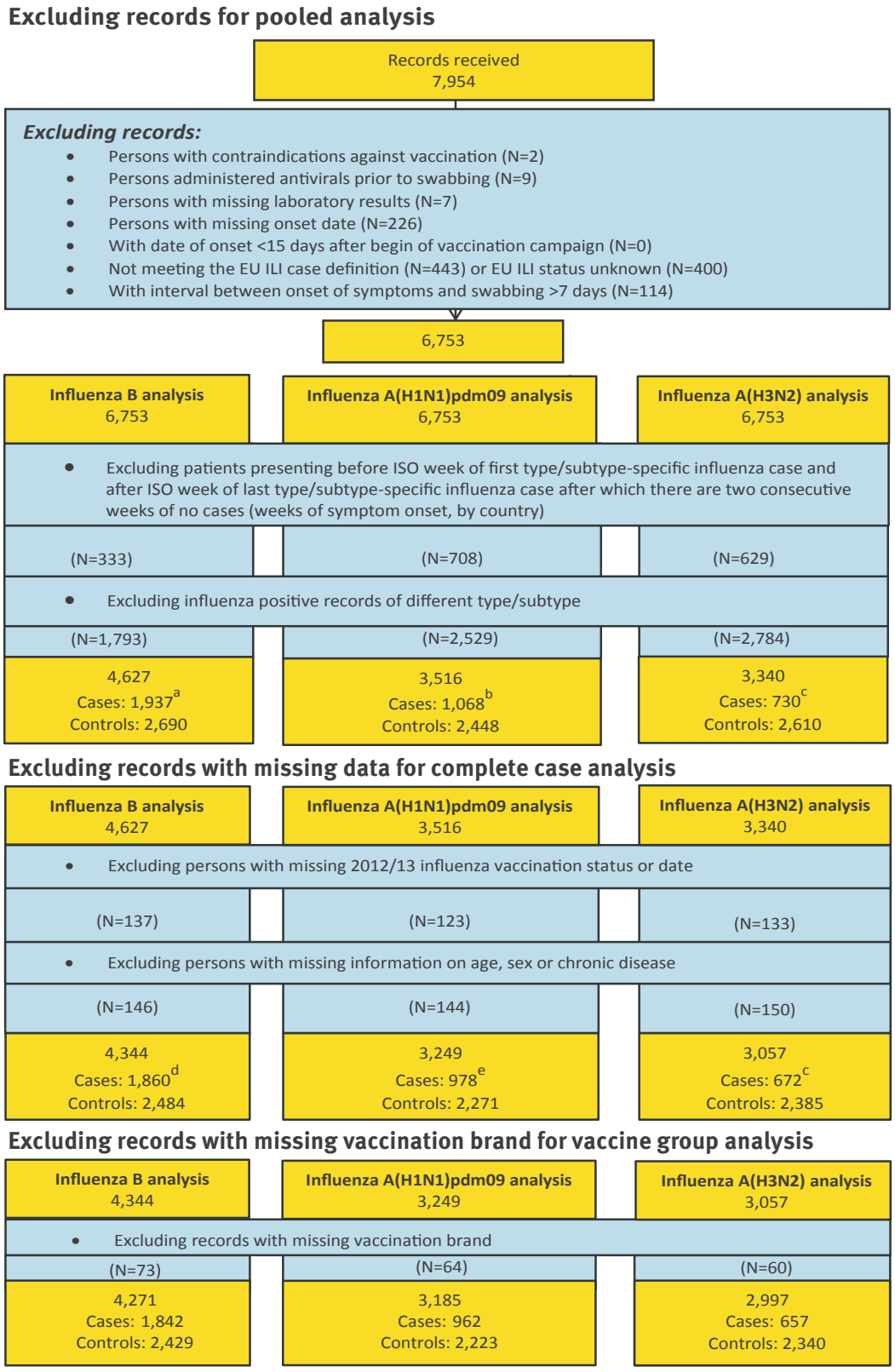
## Results

The influenza season in the seven countries where the seven respective study sites were located in started and peaked at different times, as defined by national thresholds (Table 1). The season started earliest in Poland (week 47, 2012) and latest in Portugal, Romania and Spain (week 3, 2013). The peak of the influenza season varied from week 1, 2013 in Ireland to week 10, 2013 in Portugal.

Study sites sent a total of 7,954 records of ILI/ARI patients for analysis (Figure 1). After applying exclusion criteria, we included 4,627 ILI patients in the analysis of VE against influenza B (1,937 cases), 3,516 in the analysis of VE against influenza A(H1N1)pdm09 (1,068 cases) and 3,340 in the analysis of VE against influenza A(H3N2) (730 cases). The maximum weekly

**Figure 1**

Flowchart of data exclusion, I-MOVE multicentre case–control study to measure 2012/13 influenza vaccine effectiveness, study sites in seven European Union Member States, influenza season 2012/13




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

[a] Includes 6 influenza B+A(H1N1)pdm09 and 3 influenza B+A(H3N2) co-infections.
[b] Includes 6 influenza B+A(H1N1)pdm09 and 7 A(H1N1)pdm09+A(H3N2) co-infections.
[c] Includes 3 influenza B+A(H3N2)pdm09 and 7 A(H1N1)pdm09+A(H3N2) co-infections.
[d] Includes 5 influenza B+A(H1N1)pdm09 and 3 influenza B+A(H3N2) co-infections.
[e] Includes 5 influenza B+A(H1N1)pdm09 and 7 A(H1N1)pdm09+A(H3N2) co-infections.

number of cases recruited by type/subtype occurred at different times in the study (Figure 2).

After excluding patients with missing information on 2012/13 seasonal vaccination status or date, age, sex or presence of chronic condition, we included 4,344, 3,249 and 3,057 individuals for the complete case analysis of VE against influenza B, influenza A(H1N1)pdm09 and A(H3N2) respectively.

The median age was 15 years for influenza B cases (interquartile range (IQR): 7–43 years), 31 years for A(H1N1)pdm09 cases (IQR: 10–46 years) and 20 years for A(H3N2) cases (IQR: 5–46 years). Controls had a median age of 22 years (IQR: 4–45 years).

Among controls, 18% had at least one chronic condition, compared to 15%, 15% and 13% of influenza B, A(H1N1)pdm09 and A(H3N2) cases respectively. The proportion vaccinated with the 2012/13 influenza vaccine was 9% among controls, 5% among influenza B cases, 5% among A(H1N1)pdm09 cases and 7% among A(H3N2) cases (Table 2).

Among controls, 22% belonged to the target group for vaccination compared to 19%, 20%, and 20% of influenza A(H1N1)pdm09, influenza A(H3N2) and influenza B cases respectively (Table 2).

Overall 90% of controls were swabbed within three days of symptom onset compared to 91%, 90% and 86% of influenza A(H1N1)pdm09, influenza A(H3N2) and influenza B, cases respectively.

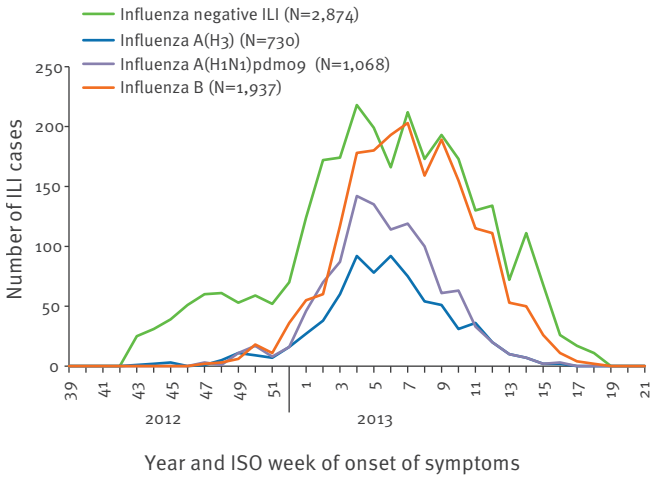
Among 331 vaccinated participants with known type of vaccine, 64% (213/331) had received split virion vaccine (note: one participant was co-infected with influenza A(H3N2) and influenza B). The proportion receiving split virion vaccine by country was: 0% (0/8) in Romania, 56% (87/156) in Germany, 71% (30/42) in France, 73% (62/85) in Spain, 76% (19/25) in Portugal and 100% (15/15) in Ireland. Ireland, however, was omitted from the vaccine type analysis as only one vaccine type was available. Four study participants in Spain and two in Germany had received an adjuvanted vaccine and one participant in Germany received a cell-mediated subunit vaccine. All others, including all eight vaccinated participants from Romania received an egg-derived subunit vaccine.

The Q test and $I^2$ index testing for heterogeneity of VE between study sites suggested no heterogeneity for influenza A(H1N1)pdm09 (p=0.849, $I^2$=0%), low heterogeneity for influenza B, (p=0.249, $I^2$=24.7%) and low to moderate heterogeneity for influenza A(H3N2) (p=0.168, $I^2$=37.9%).

Influenza VE adjusted by onset week, presence of chronic conditions age and sex was 49.3% (95% CI: 32.4 to 62.0) against influenza B, 50.4% (95% CI: 28.4 to 65.6) against influenza A(H1N1)pdm09 and 42.2% (95% CI: 14.9 to 60.7) against influenza A(H3N2) (Table 3).

**Figure 2**

Number of ILI cases included in the pooled analysis by influenza type/subtype and week of symptom onset, I-MOVE multicentre case–control study to measure 2012/13 influenza vaccine effectiveness, influenza season 2012/13 (n=6,609)




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

The seven European Union Member State study sites were respectively located in France, Germany, Ireland, Poland, Portugal, Romania and Spain.

Among those aged 0 to 14 years, the adjusted VE was 22.3% (95% CI: -37.0 to 55.9) against influenza B, 36.5% (95% CI: -44.1 to 72.0) against influenza A(H1N1)pdm09 and 36.1% (95% CI: -41.1 to 71.0) against influenza A(H3N2). Among those aged 15 to 59 years, the adjusted VE was 63.6% (95% CI: 42.1 to 77.1) against influenza B, 55.6% (95% CI: 28.3 to 72.5) against influenza A(H1N1)pdm09 and 43.6% (95% CI: -3.8 to 69.4) against influenza A(H3N2).The sample size did not enable measuring adjusted VE among those aged 60 years and above. The crude VE in this age group was 44.0% (95% CI: 8.9 to 65.5) against influenza B, 59.1% (95% CI: 14.3 to 80.5) against influenza A(H1N1)pdm09 and 37.3% (95% CI: -13.0 to 65.3) against influenza A(H3N2).

Due to small numbers, VE for the inactivated subunit cell-based vaccine and the adjuvanted vaccine were not estimated. The adjusted VE for the inactivated subunit vaccine group was 47.8% (95% CI: 12.0 to 69.0) against influenza B, 68.8% (95% CI: 32.3 to 85.6) against influenza A(H1N1)pdm09 and 63.1% (95% CI: 20.1 to 82.9) against influenza A(H3N2). The adjusted VE for the inactivated split virion vaccine group was 52.5% (95% CI: 29.5 to 68.0) against influenza B, 48.9% (95% CI:

## Table 2

Details for influenza B (n=1,937), A(H3N2) (n=730), A(H1N1)pdm09 (n=1,068) cases and controls (n=2,874) included in the 2012/13 season trivalent influenza vaccine effectiveness analysis, I-MOVE multicentre case–control study in seven European Union study sites, ISO week 43 in 2012–ISO week 18 in 2013, influenza season 2012/13

| Variables | Number of test-negative controls[a]/ total (%) | Number of influenza B cases[b,c]/total (%) | Number of influenza A(H1N1)pdm09 cases[b,d]/total (%) | Number of influenza A(H3N2) cases[c,d]/total (%) |
|---|---|---|---|---|
| Age groups in years | | | | |
| 0–4 | 739/2,871 (26) | 290/1,937 (15) | 162/1,068 (15) | 169/729 (23) |
| 5–14 | 474/2,871 (17) | 650/1,937 (34) | 160/1,068 (15) | 154/729 (21) |
| 15–64 | 1,396/2,871 (49) | 860/1,937 (44) | 693/1,068 (65) | 328/729 (45) |
| ≥60 | 262/2,871 (9) | 137/1,937 (7) | 53/1,068 (5) | 78/729 (11) |
| Sex–Female | 1,458/2,854 (51) | 965/1,933 (50) | 562/1,059 (53) | 355/727 (49) |
| Days between onset of symptoms and swabbing | | | | |
| 0 | 220/2,874 (8) | 73/1,937 (4) | 61/1,068 (6) | 58/730 (8) |
| 1 | 1,214/2,874 (42) | 652/1,937 (34) | 448/1,068 (42) | 306/730 (42) |
| 2 | 714/2,874 (25) | 626/1,937 (32) | 308/1,068 (29) | 201/730 (28) |
| 3 | 429/2,874 (15) | 324/1,937 (17) | 155/1,068 (15) | 93/730 (13) |
| 4–7 | 297/2,874 (10) | 262/1,937 (14) | 96/1,068 (9) | 72/730 (10) |
| Seasonal vaccination, 2012/13[e] | 255/2,772 (9) | 94/1,898 (5) | 48/1,031 (5) | 47/699 (7) |
| 2012/13 influenza vaccine group | | | | |
| Inactivated subunit egg-based | 68/2,713 (3) | 25/1,879 (1) | 9/1,013 (1) | 9/683 (1) |
| Inactivated split virion egg-based | 123/2,713 (5) | 48/1,879 (3) | 21/1,013 (2) | 22/683 (3) |
| Inactivated subunit cell-based | 1/2,713 (0) | 0/1,879 (0) | 0/1,013 (0) | 0/683 (0) |
| Inactivated adjuvanted (squalene MF59) | 4/2,713 (0) | 2/1,879 (0) | 0/1,013 (0) | 0/683 (0) |
| At least one chronic condition | 495/2,733 (18) | 278/1,896 (15) | 154/1,014 (15) | 91/690 (13) |
| At least one hospitalisation in the previous 12 months for chronic condition | 29/2,519 (1) | 18/1,816 (1) | 9/947 (1) | 5/632 (1) |
| Belongs to target group for vaccination | 624/2,801 (22) | 376/1,916 (20) | 199/1,045 (19) | 140/707 (20) |
| Study sites | | | | |
| France | 643/2,874 (22) | 534/1,937 (28) | 234/1,068 (22) | 179/730 (25) |
| Germany | 1,383/2,874 (48) | 519/1,937 (27) | 508/1,068 (48) | 471/730 (65) |
| Ireland | 96/2,874 (3) | 119/1,937 (6) | 17/1,068 (2) | 29/730 (4) |
| Poland | 30/2,874 (1) | 1/1,937 (0) | 22/1,068 (2) | 0/730 (0) |
| Portugal | 183/2,874 (6) | 66/1,937 (3) | 80/1,068 (7) | 6/730 (1) |
| Romania | 66/2,874 (2) | 74/1,937 (4) | 52/1,068 (5) | 2/730 (0) |
| Spain | 473/2,874 (16) | 624/1,937 (32) | 155/1,068 (15) | 43/730 (6) |

I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe; ISO: International Organization for Standardization.

Denominators of the fractions vary in each category of variables when the information in question is not known for all cases and/or controls. 36 influenza A cases that were not subtypable are not included in the Table.

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

[b] Six influenza cases positive for both influenza B and for influenza A(H1N1)pdm09 were included in the analysis.

[c] Three influenza cases positive for both influenza A(H3N2) and for influenza B were included in the analysis.

[d] Seven influenza cases positive for both influenza A(H3N2) and for influenza A(H1N1)pdm09 were included in the analysis.

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

## Table 3a

Pooled crude and adjusted seasonal vaccine effectiveness against laboratory-confirmed influenza by influenza type/subtype, overall and among target groups for vaccination, I-MOVE multicentre case–control study in seven European Union study sites to measure 2012/13 influenza vaccine effectiveness, ISO week 43 in 2012–ISO week 18 in 2013, influenza season 2012/13

| Analysis scenarios, population included | Influenza B VE (95%CI) | Influenza A(H1N1)pdm09 VE (95%CI) | Influenza A(H3N2) VE (95%CI) |
|---|---|---|---|
| Primary analysis | | | |
| All age groups[a] | | | |
| N (cases/vaccinated; controls/vaccinated) | 4,344 (1,860/92; 2,484/236) | 3,196 (978/44; 2,218/214) | 3,012 (672/46; 2,340/212) |
| Crude (study site as fixed effect) | 46.5 (30.9 to 58.6) | 56.1 (38.6 to 68.7) | 22.5 (-8.6 to 44.7) |
| Adj. for onset week | 50.2 (35.4 to 61.6) | 57.5 (40.2 to 69.8) | 29.1 (-0.5 to 50.0) |
| Adj. for sex | 46.6 (31.0 to 58.7) | 56.2 (38.7 to 68.7) | 22.4 (-8.7 to 44.6) |
| Adj. for chronic condition | 43.2 (25.9 to 56.5) | 54.0 (34.9 to 67.5) | 17.4 (-17.2 to 41.8) |
| Adj. for age | 45.7 (28.3 to 59.0) | 50.3 (28.9 to 65.2) | 38.6 (11.1 to 57.5) |
| Adj. for onset week, age | 50.1 (33.8 to 62.5) | 51.9 (30.9 to 66.6) | 45.7 (20.5 to 63.0) |
| Adj. for onset week, sex | 50.3 (35.5 to 61.7) | 57.6 (40.4 to 69.9) | 29.0 (-0.6 to 49.9) |
| Adj. for onset week, chronic condition, age, sex | 49.3 (32.4 to 62.0) | 50.4 (28.4 to 65.6) | 42.2 (14.9 to 60.7) |
| 0–14 year-olds[b] | | | |
| N (cases/vaccinated; controls/vaccinated) | 1,969 (905/26; 1,064/40) | 1,210 (292/8; 918/35) | 1,252 (296/9; 956/34) |
| Crude | 8.0 (-54.4 to 45.2) | 30.9 (-52.0 to 68.6) | 28.0 (-53.2 to 66.2) |
| Adj. for onset week, chronic condition, age, sex | 22.3 (-37.0 to 55.9) | 36.5 (-44.1 to 72.0) | 36.1 (-41.1 to 71.0) |
| 15–59 year-olds[c] | | | |
| N (cases/vaccinated; controls/vaccinated) | 1,994 (824/28; 1,170/95) | 1,709 (636/25; 1,073/85) | 1357 (303/15; 1,054/85) |
| Crude | 55.6 (30.8 to 71.6) | 52.9 (25.5 to 70.3) | 41.0 (-4.6 to 66.8) |
| Adj. for onset week, chronic condition, age, sex | 63.6 (42.1 to 77.1) | 55.6 (28.3 to 72.5) | 43.6 (-3.8 to 69.4) |
| ≥60 year-olds | | | |
| N (cases/vaccinated; controls/vaccinated) | 362 (131/38; 231/100) | 266 (50/11; 216/94) | 277 (73/22; 204/89) |
| Crude | 44.0 (8.9 to 65.5) | 59.1 (14.3 to 80.5) | 37.3 (-13.0 to 65.3) |
| Adj. for onset week, chronic condition, age, sex | Too few cases | Too few cases | Too few cases |
| Analysis by vaccine group[d] | | | |
| N (cases/vaccinated subunit/vaccinated split virion; controls/vaccinated subunit/vaccinated split virion) | 4,058 (1,724/24/44; 2,334/61/106) | 3,038 (945/8/20; 2,093/55/99) | 2,830 (630/9/20; 2,200/54/99) |
| Crude subunit<br>Crude split virion | 41.0 (3.7 to 63.9)<br>48.6 (25.7 to 64.4) | 72.0 (40.7 to 86.8)<br>55.0 (26.6 to 72.4) | 47.0 (-8.9 to 74.2)<br>19.0 (-33.5 to 50.9) |
| Fully adjusted[e] subunit<br>Fully adjusted[e] split virion | 47.8 (12.0 to 69.0)<br>52.5 (29.5 to 68.0) | 68.8 (32.3 to 85.6)<br>48.9 (13.7 to 69.8) | 63.1 (20.1 to 82.9)<br>41.7 (-1.3 to 66.5) |

Adj: adjusted; CI: confidence interval; GP: general practitioner; I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe; ISO: International Organization for Standardization; obs: observations; VE: vaccine effectiveness.

[a] Week 46 dropped (45 obs) for influenza A(H3N2); week 48 dropped (53 obs) for influenza A(H1N1).

[b] Weeks 48 and 13 dropped (27 obs) for influenza A(H1N1); weeks 46, 47 and weeks 14–16 and Romania dropped (119 obs) for influenza A(H3N2).

[c] Week 47 dropped (19 obs) for influenza B; weeks 48 and 15 dropped (37 obs) for influenza A(H1N1); weeks 43–46 dropped (52 obs) for influenza A(H3N2).

[d] Ireland excluded as only one vaccine group available (split virion). Records with adjuvanted or inactivated subunit cell-based vaccine group excluded due to very low sample sizes (8 and 1 respectively). Unknown or missing vaccine group excluded from analysis.

[e] Adjusted for onset week, chronic condition, age and sex.

[f] Weeks 18 and 47 dropped for influenza B (14 obs). Weeks 47,48 and 50 dropped for A(H1N1) (36 obs). October dropped for A(H3N2) – adjusted by onset month, not week, due to small sample size (3 obs dropped).

[g] Week 48 dropped for influenza A(H1N1) (47 obs). Week 46 dropped for influenza A(H3N2) (40 obs).

[h] Week 48 dropped for influenza A(H1N1) (53 obs). Week 46 dropped for A(H3N2) (45 obs).

[i] Numbers of vaccinated and unvaccinated are approximate, due to the nature of the imputed database. Week 46 dropped for influenza A(H3N2) (52 obs). Adjusted for age group (10 year age bands), sex, presence of chronic condition and week of symptom onset.

## Table 3b

Pooled crude and adjusted seasonal vaccine effectiveness against laboratory-confirmed influenza by influenza type/subtype, overall and among target groups for vaccination, I-MOVE multicentre case–control study in seven European Union study sites to measure 2012/13 influenza vaccine effectiveness, ISO week 43 2012–ISO week 18 2013, influenza season 2012/13

| Analysis scenarios, population included | Influenza B VE (95%CI) | Influenza A(H1N1)pdm09 VE (95%CI) | Influenza A(H3N2) VE (95%CI) |
|---|---|---|---|
| Sensitivity analysis | | | |
| Restricted to target group for vaccination[f] | | | |
| N (cases/vaccinated; controls/vaccinated) | 875 (356/69; 519/155) | 648 (184/29; 464/142) | 593 (126/29; 467/139) |
| Crude | 40.7 (17.2 to 57.6) | 55.8 (30.4 to 71.9) | 23.2 (-22.9 to 52.0) |
| Adj. for onset week, chronic condition, age, sex | 43.4 (17.9 to 61.0) | 35.7 (-6.0 to 61.0) | 39.0 (-3.4 to 63.9) |
| Restricted to those with delay onset and swabbing <4 days[g] | | | |
| N (cases/vaccinated; controls/vaccinated) | 3,855 (1,609/79; 2,246/196) | 2,912 (894/40; 2,018/178) | 2,721 (609/39; 2,112/174) |
| Crude | 40.3 (21.1 to 54.8) | 51.9 (31.3 to 66.3) | 20.1 (-15.3 to 44.6) |
| Adj. for onset week, chronic condition, age, sex | 45.1 (24.9 to 59.8) | 47.8 (23.2 to 64.6) | 40.3 (9.1 to 60.8) |
| Those vaccinated <15 days excluded[h] | | | |
| N (cases/vaccinated; controls/vaccinated) | 4,336 (1,858/92; 2,478/236) | 3,190 (978/44; 2,212/214) | 3,002 (670/46; 2,332/212) |
| Crude | 46.6 (31.0 to 58.7) | 56.3 (38.8 to 68.8) | 22.6 (-8.5 to 44.8) |
| Adj. for onset week, chronic condition, age, sex | 49.6 (32.8 to 62.2) | 50.7 (28.9 to 65.9) | 42.3 (15.0 to 60.8) |
| Adjusting by GP visits and smoking (Ireland, Poland, Portugal, Romania and Spain) | | | |
| N (cases/vaccinated; controls/vaccinated) | 1,678 (875/39; 803/97) | 1,105 (319/15; 786/93) | 684 (79/5; 605/73) |
| Crude | 62.5 (44.3 to 74.7) | 63.5 (35.5 to 79.4) | 47.3 (-37.4 to 79.8) |
| Adj. for onset week, chronic condition, age, sex | 62.4 (41.0 to 76.1) | 48.7 (3.3 to 72.8) | Too few cases |
| Adj. for onset week, chronic condition, age, sex, smoking | 62.3 (40.7 to 76.0) | 48.7 (3.2 to 72.8) | Too few cases |
| Adj. for onset week, chronic condition, age, sex, GP visits | 60.0 (37.0 to 74.6) | 46.0 (-2.0 to 71.4) | Too few cases |
| Adj. for onset week, chronic condition, age, sex, smoking, GP visits | 59.9 (36.8 to 74.6) | 45.9 (-2.1 to 71.4) | Too few cases |
| Imputed analysis[i] | | | |
| N (cases/vaccinated; controls/vaccinated) | 4,993 (2,016/101; 2,977/282) | 3,842 (1,138/54; 2,704/258) | 3,652 (793/55; 2,859/262) |
| Crude | 46.2 (31.4 to 57.8) | 53.4 (36.7 to 65.7) | 24.7 (-4.9 to 45.9) |
| Fully adjusted[e] | 48.9 (33.0 to 61.1) | 48.1 (27.3 to 63.0) | 48.2 (23.8 to 64.8) |

Adj: adjusted; CI: confidence interval; GP: general practitioner; I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe; ISO: International Organization for Standardization; obs: observations; VE: vaccine effectiveness.

[a] Week 46 dropped (45 obs) for influenza A(H3N2); week 48 dropped (53 obs) for influenza A(H1N1).

[b] Weeks 48 and 13 dropped (27 obs) for influenza A(H1N1); weeks46, 47 and weeks 14–16 and Romania dropped (119 obs) for influenza A(H3N2).

[c] Week 47 dropped (19 obs) for influenza B; weeks 48 and 15 dropped (37 obs) for influenza A(H1N1); weeks 43–46 dropped (52 obs) for influenza A(H3N2).

[d] Ireland excluded as only one vaccine group available (split virion). Records with adjuvanted or inactivated subunit cell-based vaccine group excluded due to very low sample sizes (8 and 1 respectively). Unknown or missing vaccine group excluded from analysis.

[e] Adjusted for onset week, chronic condition, age and sex.

[f] Weeks 18 and 47 dropped for influenza B (14 obs). Weeks 47,48 and 50 dropped for A(H1N1) (36 obs). October dropped for A(H3N2) – adjusted by onset month, not week, due to small sample size (3 obs dropped).

[g] Week 48 dropped for influenza A(H1N1) (47 obs). Week 46 dropped for influenza A(H3N2) (40 obs).

[h] Week 48 dropped for influenza A(H1N1) (53 obs). Week 46 dropped for A(H3N2) (45 obs).

[i] Numbers of vaccinated and unvaccinated are approximate, due to the nature of the imputed database. Week 46 dropped for influenza A(H3N2) (52 obs). Adjusted for age group (10 year age bands), sex, presence of chronic condition and week of symptom onset.

13.7 to 69.8) against influenza A(H1N1)pdm09 and 41.7% (95% CI: -1.3 to 66.5) against influenza A(H3N2).

The adjusted VE for the inactivated subunit vaccine group was 28.9% (95% CI: -60.6 to 68.5), 68.5% (95% CI: 32.6 to 85.3) and 64.6% (95% CI: 21.6 to 84.0) for the 0 to 14 year-olds, 15 to 59 year-olds and those aged 60 and older respectively (Figure 3). The adjusted VE for the inactivated split virion vaccine group was 12.2% (95% CI: -85.6 to 58.5), 63.7% (95% CI: 39.7 to 78.2) and 54.1% (95% CI: 16.8 to 74.7) for the 0 to 14 year-olds, 15 to 59 year-olds and those aged 60 and older respectively.

## Discussion

In the 2012/13 influenza season, all the I-MOVE multicentre case–control VE adjusted point estimates were below 70%. The design of the case–control study, which involved a multicentre approach, enabled to obtain a sample size large enough to calculate adjusted VE with reasonable precision by age group and type/subtype in this season with significant proportions of influenza B and both influenza A subtypes circulating in Europe.

Adjusted VE estimates against influenza type/subtype for all ages were lowest for influenza A(H3N2) and highest for A(H1N1)pdm09.

The obtained VE estimates by age group suggested differences in terms of age. Indeed, VE estimates were slightly higher among 15 to 59 year-olds while VE point estimates among children aged 0 to 14 years were low, with the lowest VE against influenza B. Two doses of vaccine are often recommended for children up to a certain age, usually before nine years of age, however information on number of doses received was not collected, so the results need to be interpreted with caution. Among the elderly, there were too few cases included in the study to estimate adjusted VE, despite GPs from five study sites including all elderly consulting for ILI in the study. The crude estimates however, suggest low VE against influenza B and influenza A(H3N2). Low VE among the elderly was also seen this season in Denmark (in mainly a hospital setting) and against A(H3N2) in the United States in the early adjusted VE estimates [12,13]. Influenza A(H1N1)pdm09 was less common than A(H3N2) and influenza B among the elderly in this study.

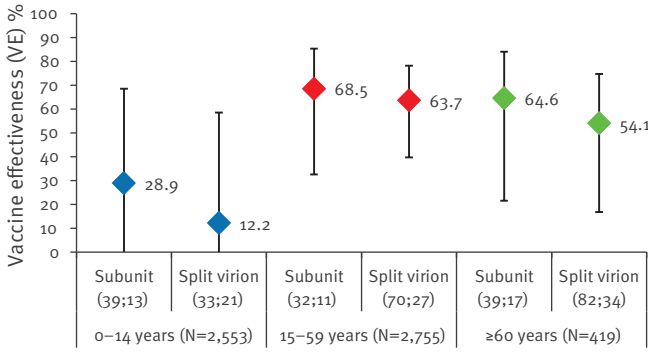
In four study sites, sampling schemes were different for elderly and other age groups. Therefore in analyses where it is not possible to stratify type/subtype-specific estimates further by age group, incorporating, in the future, a sampling fraction by age group and site may correct for any oversampling of a given age group by study site. This could render the comparison of results between countries and pooled estimates more accurate.

The analysis of VE by vaccine group suggested some differences between inactivated subunit and split virion vaccine types for VE against influenza A(H1N1)pdm09 and influenza A(H3N2), although no differences were statistically significant. Some of the vaccines targeted specific age groups, e.g. only the elderly, or only children. So the observed differences in VE may be due to differences in ages of persons using these vaccines. Again, an analysis by influenza type/subtype, age group and vaccine group was not possible due to low sample sizes. However an age-specific analysis of VE by vaccine group against any influenza showed smaller differences in adjusted VE of subunit and split virion vaccines among the different age groups.

Data completeness was good, with only between six and 10% of observations dropped for the type/subtype-specific complete case analyses. The multiple imputation sensitivity analysis showed very similar VE estimates to the complete case analysis for influenza B and influenza A(H1N1)pdm09), suggesting no bias was introduced by missing values for these viruses. The imputed analysis suggested a slightly higher VE for influenza A(H3N2), indicating there may be a small bias in the missing data for A(H3N2). There is a higher proportion of children aged under five years among influenza A(H3N2) cases in this study and there is a higher proportion of missing values in the age group 0 to 4 years. However practitioners are blinded to the outcome in this study design, so there should be no reason for differential incompleteness of data for cases and controls.

**Figure 3**

Pooled adjusted seasonal vaccine effectiveness by vaccine group against any laboratory-confirmed influenza by age group, I-MOVE multicentre case–control study in seven European Union study sites, ISO week 43 in 2012–ISO week 18 in 2013, influenza season 2012/13




I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe; ISO: International Organization for Standardization.

Below the X axis, the two numbers in parentheses for each vaccine type indicate the following: the first number represents all vaccinated with the vaccine group, while the second number represents the cases vaccinated: (N vaccinated; cases vaccinated).

The seven European Union study sites were respectively located in France, Germany, Ireland, Poland, Portugal, Romania and Spain.

Study sites collected potentially important information on positive and negative confounders [14]. Overall the magnitude of confounding was small for VE estimates against influenza B and A(H1N1)pdm09 (‹3% and ‹6% absolute difference between crude and adjusted VE estimates for all ages respectively). Confounding was much greater for VE against influenza A(H3N2), with around 20% absolute difference, mainly due to the age adjustment. Information on smoking and practitioner visits in the previous 12 months was not collected by two study sites, however the sensitivity analysis restricted to the five study sites collecting these variables, suggests no major change in VE following inclusion (‹3% absolute difference).

Influenza type/subtype VE estimates varied by study site (data not shown). An analysis of heterogeneity using the $I^2$ and Cochrane's Q test showed no, low or moderate heterogeneity between study sites depending on type/subtype, none of which was statistically significant. A possible reason for heterogeneity may be different age distributions by study site among circulating influenza type/subtypes. However an analysis of heterogeneity by age group and type/subtype together was not possible due to the small sample size. Ideally we need a large sample size by study site to carry out detailed study site-specific analyses; this will also enable a two-stage pooled analysis [15]. Other reasons for heterogeneity may include use of different vaccine brands and different healthcare seeking behaviour by study site.

Adjusted VE estimates among the target groups for vaccination were similar compared to the overall population for influenza B and A(H3N2), however lower for influenza A(H1N1)pdm09, although confidence intervals overlap. Influenza A(H1N1)pdm09 cases belonging to the target group for vaccination had a higher proportion of younger people with chronic conditions than other influenza type/subtypes. This suggests that the vaccine may not protect as well against influenza A(H1N1)pdm09 among those who are vulnerable to complications.

The inclusion weeks for the 2012/13 study ranged from week 43 2012 to week 18 2013, making this a very extended study period compared to previous I-MOVE multicentre case–control studies [3-6]. The ratio of controls to cases varied along the season, with a higher ratio of controls to cases at the very beginning of the study. An analysis restricted to peak weeks (weeks 1–12, 2013) showed very similar type/subtype-specific VE, suggesting that this season, there was no bias introduced by including periods with a high ratio of controls to cases (data not shown).

In the 2011/12 influenza season, the I-MOVE study looked at waning of vaccine-induced protection later in the season. In 2012/13, no vaccine-related waning of protection against A(H1N1) was evident, although sample sizes were low. Sample sizes for A(H3N2) were also too low to draw conclusions. For influenza B, there may have been some suggestion of waning of protection with more days between vaccination and onset of symptoms, however sample sizes are also too low to draw conclusions (data not shown).

While the test-negative design is commonly used in vaccine effectiveness studies, it remains a study design that needs to be validated [16-19]. Assumptions behind this study design and other biases associated with the test negative study design (e.g. representativeness of the test negative controls with regards the vaccine coverage of the source population of cases, role of other ARI virus infections among the control group, etc.) have been described elsewhere [20-24]. Larger sample sizes are needed to perform robust validation analyses to determine if controls properly reflect the vaccine coverage of the source population for cases in general and over time.

The predominant influenza B lineage circulating in the 2012/13 influenza season in Europe was the B/Yamagata lineage, which was also the vaccine virus lineage [1]. Among the 1,860 influenza B cases included in the study, 694 (37.3%) specimens were ascribed to a lineage; 630 of these (90.7%) were influenza B/Yamagata lineage (data not shown). Because of limited information on influenza B lineage in the study, we were unable to estimate VE by lineage, which would be important in the context of the introduction of the quadrivalent vaccines. Throughout the 2012/13 season in Europe, B/Yamagata-lineage viruses from an antigenically distinguishable genetic clade from the vaccine virus clade have increasingly been detected [1]. These are from clade 2 represented by B/Massachusetts/2/2012, which is a recommended vaccine component for the 2013/14 influenza vaccine [25]. While this may explain some of the lower VE estimates for influenza B in our study, we do not have virological data on an individual level to test this hypothesis.

The I-MOVE multicentre case–control study provided adjusted type/subtype-specific VE estimate early in this season, as did other studies [7,12,13,26-29]. The information was shared with WHO in time for the 2013/14 influenza vaccine composition meeting in February 2013. Early adjusted VE estimates for influenza B were higher than the final season adjusted estimates (78.2% vs. 49.3%), as well as for influenza A(H1N1)pdm09 (62.1% vs. 50.4%). Estimates for influenza A(H3N2) remained similar (41.9% vs. 42.2%). Differences between early and overall estimates may be due to different proportions of cases occurring by age group over time; however this cannot be verified as sample sizes were too small to provide early type/subtype estimates stratified by age. This strongly suggests that effort should be made worldwide to increase the sample size for precise and stratified early and overall estimates each season.

In conclusion, our estimates suggest that the 2012/13 influenza vaccine has low to moderate effectiveness in preventing medically attended laboratory-confirmed influenza, with varying effectiveness in different age groups. In a season with the co-circulation three influenza types and subtypes, the large sample size achieved by the multicentre case–control study was necessary to provide the important age-specific estimates. However an even greater sample size is needed to provide robust results among the elderly and to provide age group-specific estimates by type/subtype and vaccine type. While the vaccine remains the best method of protection against influenza, the low estimates emphasise the need for an improved influenza vaccine. Influenza VE studies worldwide need to continue with sample sizes large enough to enable precise stratified estimates in order to better understand the mechanisms for varying VE by season and age groups.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## Conflict of interest

EpiConcept analyses pooled data of a hospital-network multicentre case-control (HNMCC) study measuring influenza VE. The HNMCC analysis was co-funded in 2012/13 by Sanofi Pasteur, SPMSD, GlaxoSmithKline, EpiConcept and study sites.

## Authors' contributions

EpiConcept: Marta Valenciano coordinated the I-MOVE multicentre case control study network. Marta Valenciano and Esther Kissling led the writing of the research article. Esther Kissling undertook the statistical analysis on which the research article is based. All authors provided contribution to the research article and approved the final version. Alain Moren, Marta Valenciano, Esther Kissling were involved in the original methodological design. In general: Alain Moren, Marta Valenciano, Esther Kissling, Amparo Larrauri, Silvia Jiménez- Jorge, Joan O'Donnell, Emilia Lupulescu, Daniela Pitigoi, George Necula, Baltazar Nunes, Raquel Giuomar, Annicka Reuss, Udo Buchholz, Jean Marie Cohen and Isabelle Daviaud have all had a role in modification of this design over the years. All authors read, contributed and approved the manuscript final version. Germany: Annicka Reuss and Udo Buchholz were responsible for validation of data and interpretation of results. Spain: Amparo Larrauri and Silvia Jiménez-Jorge were responsible for the study design and coordination of the Spanish study and the national database. France: Jean Marie Cohen and Isabelle Daviaud were responsible for the study design in French study site, participated in the coordination of the French study and management of the French database. Portugal: Baltazar Nunes and Raquel Guiomar were responsible for the study design in Portugal study site. Ireland: Justyna Rogalska was involved in the collection and collation of the data. Joan O'Donnell was involved in the original methodology and final review of the paper. She was also coordinating the project in Ireland. Romania: Daniela Pitigoi and George Necula coordinated the Romanian study. Daniela Pitigoi was responsible for the study design in Romania study site. Daniela Pitigoi and George Necula collected data. Daniela Pitigoi enrolled patients. Poland: Iwona Paradowska-Stankiewicz and Malgorzata Głuchowska were responsible for the study design and coordination in the Polish study site.

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