2015/16 I-MOVE/I-MOVE+ multicentre case-control study in Europe: Moderate vaccine effectiveness estimates against influenza A(H1N1)pdm09 and low estimates against lineage-mismatched influenza B among children

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2015/16 I-MOVE/I-MOVE+ multicentre case-control study in Europe: Moderate vaccine effectiveness estimates against influenza A(H1N1)pdm09 and low estimates against lineage-mismatched influenza B among children

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**1 | INTRODUCTION**

In February 2015, WHO recommended that the 2015/16 Northern Hemisphere trivalent influenza vaccine should include the same influenza A(H1N1)pdm09 strain as the 2014/15 season vaccine (the same component for the trivalent vaccine since the 2010/11 season), but different influenza A(H3N2) and B components, namely a virus from the 3C.3a A(H3N2) genetic group and the genetic group 3 of the B/Yamagata lineage. The recommended strains were as follows: an influenza A/California/7/2009 (H1N1)pdm09-like virus, an influenza A/Switzerland/9715293/2013 (H3N2)-like virus and an influenza B/Phuket/3073/2013-like Yamagata lineage virus.

An interim analysis for the 2015/16 season published in early February 2016 from the European I-MOVE/I-MOVE+ multicentre case-control study showed a predominance of A(H1N1)pdm09 and B/Victoria, which was antigenically distinct from the B/Yamagata component in the trivalent influenza vaccine.

**Background:** During the 2015/16 influenza season in Europe, the cocirculating influenza viruses were A(H1N1)pdm09 and B/Victoria, which was antigenically distinct from the B/Yamagata component in the trivalent influenza vaccine.

**Methods:** We used the test-negative design in a multicentre case-control study in twelve European countries to measure 2015/16 influenza vaccine effectiveness (VE) against medically attended influenza-like illness (ILI) laboratory-confirmed as influenza. General practitioners swabbed a systematic sample of consulting ILI patients and a random sample of influenza-positive swabs was sequenced. We calculated adjusted VE against influenza A(H1N1)pdm09, A(H1N1)pdm09 genetic group 6B.1 and influenza B overall and by age group.

**Results:** We included 11,430 ILI patients, of which 2,272 were influenza A(H1N1)pdm09 and 2,901 were influenza B cases. Overall VE against influenza A(H1N1)pdm09 was 32.9% (95% CI: 15.5-46.7). Among those aged 0-14, 15-64 and ≥65 years, VE against A(H1N1)pdm09 was 31.9% (95% CI: 32.3 to 65.0), 41.4% (95% CI: 20.5-56.7) and 13.2% (95% CI: 38.0 to 45.3), respectively. Overall VE against influenza A(H1N1)pdm09 genetic group 6B.1 was 32.8% (95% CI: 4.1 to 56.7). Among those aged 0-14, 15-64 and ≥65 years, VE against influenza B was 47.6% (95% CI: 27.3% (95% CI: 46.6 to 49.4) and 9.3% (95% CI: 44.1 to 42.9), respectively.

**Conclusions:** Vaccine effectiveness (VE) against influenza A(H1N1)pdm09 and its genetic group 6B.1 was moderate in children and adults, and low among individuals ≥65 years. Vaccine effectiveness (VE) against influenza B was low and heterogeneous among age groups. More information on effects of previous vaccination and previous infection is needed to understand the VE results against influenza B in the context of a mismatched vaccine.

**Keywords:** case-control study, influenza, influenza vaccine, multicentre study, vaccine effectiveness

In this eighth season of the I-MOVE/I-MOVE+ multicentre case-control study, we aimed to measure end-of-season 2015/16 vaccine effectiveness against influenza A(H1N1)pdm09 and influenza B, by age group, vaccine type, by prior (2014/15) vaccination status and by time since vaccination and for the total population and the target group for vaccination.

Nine of twelve study sites also participated in a pilot laboratory project where they randomly selected specimens for sequencing of at least the gene segment coding for the haemagglutinin, in order to compute a representative VE estimate against the influenza A(H1N1) pdm09 6B.1 genetic group.

**2 | METHODS**

Twelve European study sites located in Croatia, France, Germany, Hungary, Ireland, Italy, Poland, Portugal, Romania, Spain, Sweden and the Netherlands participated in the test-negative 2015/16 multicentre case-control study. The methods have been described previously.

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and are based on the ECDC generic case-control study protocol and the I-MOVE+ protocol.1,6

Participating practitioners interviewed and collected nasopharyngeal or combined naso- and oropharyngeal specimens from a systematic sample of consenting patients seeking medical attention for influenza-like illness (ILI). In Hungary, only patients aged 18 years and older and in Croatia only patients aged 65 years and older were eligible. Practitioners collected in a standardised report form information including symptoms, date of onset and swabbing, 2015/16 seasonal vaccination status, date of influenza vaccination and vaccine product, prior (2014/15) seasonal vaccination status, sex, age and presence of chronic medical conditions in the past 12 months.

Seven study sites included a question on belonging to the target group for vaccination. In France, Germany, Poland, Portugal and Sweden, the target group was defined from patients’ information on age, chronic conditions and pregnancy. Additionally, in Portugal, being a health professional or carer and a cohabitant or carer of a patient at risk aged less than 6 months and in Poland, belonging to an occupational risk group (eg, healthcare worker), defined the target group.

In the pooled analysis, we included patients meeting the European Union ILI case definition,7 swabbed within 7 days of symptom onset, and who had not received antivirals in the 14 days prior to swabbing.

A case of confirmed influenza was an ILI patient who was swabbed and tested positive for influenza virus using real-time reverse-transcription polymerase chain reaction (RT-PCR). Controls were ILI patients who tested negative for any influenza virus using RT-PCR.

We defined a person as vaccinated if he or she had received at least one dose of a 2015/16 seasonal influenza vaccine more than 14 days before ILI symptom onset. Those vaccinated less than 15 days before ILI onset were excluded. All other patients were classified as unvaccinated.

For each study site, we included ILI patients presenting more than 14 days after the start of national or regional influenza vaccination campaigns and we excluded controls presenting before the onset week of the first influenza type/subtype-specific case. ILI patients presenting in weeks of onset after two or more consecutive weeks of no cases and influenza A cases that were not further subtyped were also excluded from the analysis.

For each study site, we computed the odds ratio (OR) of being vaccinated in cases vs controls. We conducted a complete analysis excluding patients with missing values for any of the variables in the model measuring adjusted VE. Using Cochran’s Q-test and the I² index, we tested the heterogeneity between study sites.8 We estimated the pooled type/subtype influenza VE as (1 minus the OR)×100 using a one-stage model with study site as a fixed effect.

Using a logistic regression model, we calculated VE including potential confounding factors: date of symptom onset (modelled as a restricted cubic spline with 4 knots where sample size allowed), age (modelled as a restricted cubic spline with 4 knots or age groups depending on the analysis), sex and presence of at least one chronic medical condition (including pregnancy and obesity where available). We used the one in ten rule of predictor degrees of freedom to events to determine the maximum number of covariates to include in analyses with low sample sizes in order to avoid overfitting the model.9,10

To study the effect of prior (2014/15) vaccination on the 2015/16 VE, we conducted an indicator analysis using four categories: individuals unvaccinated in both seasons (reference category), vaccinated in 2014/15 only, vaccinated in 2015/16 only and vaccinated in both seasons. We did not measure effect of prior (2014/15) vaccination among children aged <9 years as their vaccination definition is based on previous vaccination history (children older than 6 months and less than 9 years old who have not been vaccinated in the previous influenza season should receive two doses of the seasonal influenza vaccine). We also conducted a stratified analysis, measuring VE of the 2015/16 vaccine among those vaccinated in 2014/15 and separately among those not vaccinated in 2014/15.

We measured VE by age group (0-14, 15-64 and 65 years and older), by type of vaccine (inactivated subunit and inactivated split virus) and in the target group for vaccination. We tested for interaction between vaccination and age group, chronic medical condition, onset month and sex, using the likelihood ratio test to compare the additive model with the interaction.

To study the effects of waning on the vaccine effect within a season, we further estimated VE by time since vaccination, modelling days between vaccination and symptom onset as a restricted cubic spline with 4 knots.11 In this analysis, we additionally included patients vaccinated 14 days or less before symptom onset (excluded from the main analysis).

Nine study sites participated in a laboratory pilot project (DE, FR, HU, IE, PT, RO, SE, ES and NL) for sequencing at least the haemagglutinin gene segment for each influenza type/subtype. In this laboratory pilot project, either all specimens were selected for sequencing or a proportion of specimens were randomly selected for sequencing to ensure representativity. The proportion of specimens randomly selected for sequencing could vary over time (eg, higher early in the season and lower during the peak) and a sampling fraction was calculated for each study site and time unit. The specimens were sent to the corresponding National Influenza Centre, where influenza diagnosis was confirmed, and viruses were characterised by sequencing the HA1 coding portion of the haemagglutinin gene. Analysis of the nucleotide and amino acid sequences of the HA1 coding portion of the haemagglutinin gene was performed in MEGA6 to determine clade distribution.

We weighted the genetic group-specific VE analysis using the reciprocal of the sequencing sampling fraction for each time period and study site and used robust standard errors.

Data management and statistical analyses were carried out using Stata 14 (StataCorp. 2015. College Station, TX, USA).

3 RESULTS

The 2015/16 influenza season in Europe was characterised by the cocirculation of influenza A(H1N1)pdm09 and influenza B viruses (Figure 1). Influenza A(H3N2) viruses circulated at very low levels. The
study period ranged from week 44/2015 to week 18/2016 for influenza A(H1N1)pdm09 with cases peaking in week 4/2016 and from week 45/2015 to week 19/2016 for influenza B, with cases peaking in week 9/2016.

Of the 14,294 ILI patients recruited, 11,430 met the eligibility criteria (5,410 cases and 6,020 controls). In the influenza type/subtype-specific analysis, 2,272 cases of influenza A(H1N1)pdm09 and 2,901 cases of influenza B were included (Figure 2). We did not include the 172 patients testing positive for influenza A(H3N2) in the analysis due to small sample size.

The proportion vaccinated with the 2015/16 influenza vaccine was 9.7% among controls, 6.7% among influenza A(H1N1)pdm09 cases and 6.3% among influenza B cases (Table 1).

The median age of influenza A(H1N1)pdm09 cases was 35 years, of controls 29 years and of influenza B cases 12 years (Table 2). Compared to influenza A(H1N1)pdm09, a higher proportion of influenza B cases were less than 15 years (55.3% vs 30.3%) and a lower proportion were 15-64 years old (40.8% vs 63.5%). The proportion of patients aged 65 and older varied between controls, influenza A(H1N1)pdm09 and influenza B cases with 9.5%, 6.2% and 3.9%, respectively.

The proportion of patients with at least one chronic condition was similar between controls and influenza A(H1N1)pdm09 cases (20.2% and 17.6%, respectively), but lower among influenza B cases (11.9%).

Among controls, 81.7% were swabbed within 3 days of symptom onset compared to 84.9% and 85.2% of influenza A(H1N1)pdm09 and influenza B cases, respectively. Among controls, 6.5% were swabbed on the day of symptom onset, compared to 4.2% and 4.3% of influenza A(H1N1)pdm09 and influenza B cases, respectively.

In total, 10.6% of controls had received both the 2014/15 and the 2015/16 vaccines compared to 7.3% and 6.2% of influenza A(H1N1) pdm09 and B cases, respectively. The proportion of unvaccinated in the current and previous season was 89.2% for influenza A(H1N1)pdm09 and influenza B cases, respectively.

Information on vaccine type received was available for 470 (83.3%) of vaccinated controls, 130 (86.7%) vaccinated influenza A(H1N1)pdm09 and 149 (82.2%) vaccinated influenza B cases. Trivalent inactivated subunit and trivalent inactivated split virion vaccines were used among 43.4% and 43.0% of vaccinated controls, 43.8% and 49.2% of vaccinated influenza A(H1N1)pdm09 cases and 45.9% and 48.0% of vaccinated influenza B cases, respectively.

From the 11,430 patients meeting the eligibility criteria, we further excluded patients with missing information on 2015/16 seasonal vaccination status or date, onset/swab date, age, sex or presence of chronic condition. We included 7,358 patients for the complete case analysis of VE against influenza A(H1N1)pdm09 and 7,400 patients for the analysis against influenza B among all ages (Figure 2). For the complete case analysis restricted to the target group for vaccination, we included 1,953 patients (520 influenza A(H1N1)pdm09 cases) in the analysis of VE against A(H1N1)pdm09 and 1,578 patients (409 influenza B cases) in the analysis of VE against influenza B.

### 3.1 | Influenza A(H1N1)pdm09

Statistical heterogeneity between VE estimates against influenza A(H1N1)pdm09 by study site was low overall (among all ages) and among those aged 15-64 years ($I^2$ index 0% and 10%, respectively). Due to small sample sizes, it was not possible to estimate heterogeneity among other age groups.

The adjusted VE in the total population (all ages) against influenza A(H1N1)pdm09 was 32.9% (95% CI: 15.5-46.7) (Table 2). The adjusted VE against influenza A(H1N1)pdm09 was 31.9% (95% CI: −32.3 to 65.0) among the 0- to 14-year-olds and 41.4% (95% CI: 20.5-56.7) among the 15- to 64-year-olds. Among the target group for vaccination, VE (all ages) was 33.0% (95% CI: 10.8-49.7). It was 55.5% (95% CI: −35.1 to 85.3) and 42.9% (95% CI: 14.5-61.9) among those aged 0-14 and 15-64 years, respectively. Among those aged 65 years and older, VE adjusted for age and study site was 13.2% (95% CI: −38.0 to 45.3).

The adjusted VE for trivalent inactivated subunit vaccine against influenza A(H1N1)pdm09 (all ages) was 33.9% (95% CI: 6.7-53.1) and for trivalent inactivated split virion vaccine 36.9% (95% CI: 10.8-54.5) (Table 2).

Information on prior vaccination status was missing among 6.7% of ILI patients (restricting to those 9 years and older). When using the indicator analysis, with the reference of those not vaccinated in the current or previous season, the VE among those aged 9 years and...
older against influenza A(H1N1)pdm09 was 54.7% for those who received 2015/16 seasonal influenza vaccine only (95% CI: 19.6-74.5), 8.0 (95% CI: -39.3 to 39.2) for those who received prior (2014/15) vaccine only and 28.4% (95% CI: 6.2-45.4) for those who received both 2015/16 and 2014/15 season vaccine (Table 2).

In the stratified analysis, the VE of current influenza vaccination against A(H1N1)pdm09 among those aged 9 years and older was 56.2% (full model adjusted, 95% CI: 22.2-75.3) among those not vaccinated in 2014/15 and 6.9% (adjusted by age and study size, 95% CI: -51.5 to 42.8) among those vaccinated in 2014/15.

When modelling VE by time since vaccination, VE against influenza A(H1N1)pdm09 among all ages increased to 49.8% at 45 days since vaccination and declined to 9.3% at 218 days since vaccination (Figure 3).

During the study period where specimens were sequenced, the nine sites participating in the laboratory pilot season genetically characterised 723 of 2087 (34.6%) influenza A(H1N1)pdm09 specimens among all ages. Of these, 15 (2.1%) belonged to the genetic group represented by A/England/377/2015 (genetic group 6B.2), 56 (7.7%) to the genetic group represented by A/SouthAfrica/3626/2013.
### TABLE 1

Details for influenza A(H1N1)pdm09 (n = 2272) and influenza B cases (n = 2901) and controls (n = 1650) included in the 2015/16 season influenza vaccine effectiveness analysis (week 41/2015-week 19/2016), I-MOVE/I-MOVE+ multicentre case-control study

| Variables | Number of test-negative controls /total n (% | Number of influenza A(H1N1) pdm09/total n (%) | Number of influenza B cases/total n (%) |
|-----------|---------------------------------------------|---------------------------------------------|-----------------------------------------|
| Median age (years) | 29.0 | 35.0 | 12.0 |
| Age groups | | | |
| 0-4 | 1437/6004 (23.9) | 365/2268 (16.1) | 536/2894 (18.5) |
| 5-14 | 739/6004 (12.3) | 321/2268 (14.2) | 1064/2894 (36.8) |
| 15-64 | 3255/6004 (54.2) | 1441/2268 (63.5) | 1182/2894 (40.8) |
| ≥65 | 573/6004 (9.5) | 141/2268 (6.2) | 112/2894 (3.9) |
| Missing | 16 | 4 | 7 |
| Sex | | | |
| Female | 3159/5975 (52.9) | 1137/2259 (50.3) | 1456/2871 (50.7) |
| Missing | 45 | 13 | 30 |
| Days between onset of symptoms and swabbing | | | |
| 0 | 389/6020 (6.5) | 95/2272 (4.2) | 126/2901 (4.3) |
| 1 | 2008/6020 (33.4) | 824/2272 (36.3) | 907/2901 (31.3) |
| 2 | 1589/6020 (26.4) | 663/2272 (29.2) | 899/2901 (31.0) |
| 3 | 934/6020 (15.5) | 348/2272 (15.3) | 539/2901 (18.6) |
| 4-7 | 1100/6020 (18.3) | 342/2272 (15.1) | 430/2901 (14.8) |
| Seasonal vaccination, 2015/16 | | | |
| Vaccinated <15 d before onset of symptoms | 17 | 0 | 0 |
| Missing | 201 | 49 | 60 |
| Prior season influenza vaccinationb | | | |
| Not vaccinated in any season | 3259/3896 (83.6) | 1421/1593 (89.2) | 1481/1635 (90.1) |
| Current season (2015/16) vaccination only | 87/3896 (2.2) | 17/1593 (1.1) | 19/1635 (1.2) |
| Prior (2014/15) season vaccination only | 138/3896 (3.5) | 39/1593 (2.4) | 33/1635 (2.0) |
| Current and prior season vaccination | 412/3896 (10.6) | 116/1593 (7.3) | 102/1635 (6.2) |
| Missing or vaccinated <15 d before onset | 279 | 109 | 69 |
| Seasonal vaccination type | | | |
| Not vaccinated | 5255/5819 (90.3) | 2073/2203 (93.3) | 2661/2809 (93.7) |
| Inactivated subunit | 204/5819 (3.5) | 57/2203 (2.6) | 68/2809 (2.4) |
| Inactivated split virion trivalent | 202/5819 (3.5) | 64/2203 (2.9) | 71/2809 (2.5) |
| Adjuvantedc | 60/5819 (1.0) | 6/2203 (0.3) | 6/2809 (0.2) |
| Inactivated cell-derived trivalent | 1/5819 (0.0) | 0/2203 (0.0) | 0/2809 (0) |
| Quadrivalent vaccine | 3/5819 (0.1) | 3/2203 (0.1) | 3/2809 (0.1) |
| Unknown vaccine type | 94/5819 (1.6) | 20/2203 (0.9) | 32/2809 (1.1) |
| Missing vaccination status or date or vaccinated <15 d before onset | 81 | 49 | 60 |
| At least one chronic condition | 1194/5900 (20.2) | 391/2227 (17.6) | 341/2870 (11.9) |
| Missing | 120 | 45 | 31 |
| At least one hospitalisation in the previous 12mo for chronic conditions | 110/5857 (1.9) | 26/2214 (1.2) | 21/2854 (0.7) |
| Missing | 163 | 58 | 47 |
| Belongs to the target group for vaccination | 1648/5931 (27.8) | 544/2236 (24.3) | 434/2873 (15.1) |
| Missing | 89 | 36 | 28 |
| Study sites | | | |
| Croatia | 39/6020 (0.6) | 15/2272 (0.7) | 19/2901 (0.7) |
and 40.1% (95% CI: −12.9 to 68.3) among 15- to 64-year-old age groups (Table 2). The sample size was too small to calculate VE among the 15- to 64-year-olds (Table 2). Crude VE was 9.3% (95% CI: −4.1 to 56.7) overall for all age groups, 51.3% (95% CI: 33.5 to 74.7) among the 0- to 14-year-old groups, 15.6 to 29.2) among the 0- to 14-year-old and 40.1% (95% CI: −12.9 to 68.3) among the 15- to 64-year-old age groups (Table 2). The sample size was too small to calculate VE for those aged 65 years and older.

### 3.2 Influenza B

The $I^2$ index for heterogeneity between VE estimates against influenza B by study site was 56% among all ages and 0% among those aged 15-64 years. Due to small sample size, it was not possible to estimate heterogeneity among those aged 65 years and older. Among children, we could measure the $I^2$ between three countries (DE, FR and IT; in all other countries, less than 5 children were vaccinated), which was 0%.

The adjusted VE against influenza B was $-47.6\%$ (95% CI: $-124.9$ to $3.1$) among the 0- to 14-year-olds and 27.3% (95% CI: $-4.6$ to $49.4$) among the 15- to 64-year-olds (Table 2). Crude VE was 9.3% (95% CI: $-44.1$ to $42.9$) among those aged 65 years and older (all belong to the target group for vaccination only), and the small sample size did not allow for adjusted VE estimates. The chi-square of the likelihood ratio test for interaction between vaccine and age group was 0.001. Due to this strong interaction between age group and vaccine, we did not attempt to calculate an overall (all ages) VE. The adjusted VE among the target group for vaccination was 1.7% (95% CI: $-94.5$ to $50.3$) and 38.4% (95% CI: $-6.6$ to $64.4$) among those aged 0-14 and 15-64 years, respectively.

The adjusted VE for trivalent inactivated subunit vaccine against influenza B among those aged 0-14 years was $-56.4\%$ (95% CI: $-202.1$ to $19.0$) and for split virion vaccine $-83.5\%$ (95% CI: $-232.9$ to $1.1$) (Table 3). For those aged 15-64 years, it was $17.7\%$ (95% CI: $-48.0$ to $54.3$) for subunit vaccine and $44.4\%$ (95% CI: $-2.8$ to $70.0$) for split virion vaccine.

Information on prior vaccination status was missing in 5.1% of ILI patients (restricting to those 9 years and older). When using the indicator analysis, with the reference of those not vaccinated in the current or previous season, the VE among 15- to 64-year-olds receiving the current 2015/16 seasonal influenza vaccine only was $28.3\%$ (95% CI: $-40.2$ to $63.3$), $41.3\%$ (95% CI: $-8.7$ to $68.3$) among those receiving prior season (2014/15) vaccine only and $23.7\%$ (95% CI: $-16.8$ to $50.2$) among those who received both 2015/16 and prior season (2014/15) vaccine (Table 2).

In the stratified analysis, the VE of current influenza vaccination against influenza B among 15- to 64-year-olds was $28.7\%$ (95% CI: $-39.6$ to $63.5$) among those who did not receive prior season (2014/15) vaccine. We could not compute VE of current influenza vaccination among those who received prior season (2014/15) due to small sample size.

When modelling VE by time since vaccination among those aged 15 years and older, VE against influenza B ranged from 2.3% at 218 days to 36.6% at 60 days (Figure 3).

Of the 2901 influenza B cases (all ages), 2132 (73.5%) had known B lineage. Among these, $2.7\%$ were B/Yamagata lineage (57) and $77.3\%$ were B/Victoria lineage (2075). Among the 8 of 9 pilot laboratory study sites that sequenced B-positive specimens, 321 of 2416 were sequenced (13.3%) (Table 3). Twelve (3.7%) belonged to the genetic group represented by B/Phuket/3073/2013 (Yamagata lineage) group 3. Among the 309 (96.3%) that belonged to the genetic group represented by B/Phuket/3073/2013 (Yamagata lineage), all belonged to genetic group 1A, and 308 of them had N129D amino acid substitutions, and one had K56N and V124A amino acid substitutions.

### Table 1 (Continued)

| Variables       | Number of test-negative controls /total n (%) | Number of influenza A(H1N1)pdm09/total n (%) | Number of influenza B cases/total n (%) |
|-----------------|---------------------------------------------|---------------------------------------------|----------------------------------------|
| France          | 1471/6020 (24.4)                            | 508/2272 (22.4)                             | 1294/2901 (44.4)                       |
| Germany         | 1726/6020 (28.7)                            | 436/2272 (19.2)                             | 571/2901 (19.7)                       |
| Hungary         | 593/6020 (9.9)                              | 54/2272 (2.4)                               | 112/2901 (3.9)                       |
| Ireland         | 241/6020 (4.0)                              | 181/2272 (8)                               | 130/2901 (4.5)                       |
| Italy           | 498/6020 (8.3)                              | 34/2272 (1.5)                               | 390/2901 (13.4)                       |
| Poland          | 312/6020 (5.2)                              | 136/2272 (6.0)                             | 65/2901 (2.2)                       |
| Portugal        | 186/6020 (3.1)                              | 111/2272 (4.9)                             | 11/2901 (0.4)                        |
| Romania         | 80/6020 (1.3)                               | 61/2272 (2.7)                               | 0/2901 (0.0)                        |
| Spain           | 286/6020 (4.8)                              | 447/2272 (19.7)                             | 165/2901 (5.7)                       |
| Sweden          | 376/6020 (6.2)                              | 175/2272 (7.7)                             | 65/2901 (2.2)                        |
| The Netherlands | 212/6020 (3.5)                              | 114/2272 (5.0)                             | 79/2901 (2.7)                       |

*a Controls for "any influenza" used here (number of controls differs slightly for influenza A(H1N1)pdm09 and B analyses, due to the inclusion criteria).

*b Among patients aged 9 y and over.

*c Includes squalene (MF59), virosome and aluminium phosphate gel adjuvants.

*d Includes Fluenz Tetra (nasal spray) as well as Fluarix Tetra (injectable).
| Type/subtype | Analysis scenario | N | Cases; vacc/Controls; vacc | Crude VE | CI | Adjusted VE | CI |
|--------------|-------------------|---|---------------------------|---------|----|-------------|----|
| A(H1N1) pdm09 | By age            |   |                           |         |    |             |    |
|               | All ages          | 7358 | 2176:148/5182:527 | 41.9 | 28.9-52.6 | 32.9 | 15.5-46.7 |
|               | 0-14 y           | 2424 | 648:14/1776:56 | 25.4 | -39.1 to 60.0 | 31.9 | -32.3 to 65.0 |
|               | 15-64 y          | 4308 | 1394:73/2914:230 | 40.8 | 21.1-55.6 | 41.4 | 20.5-56.7 |
|               | 65+ y            | 625 | 134:61/491:240 | 26.8 | -14.4 to 53.1 | 13.2c | -38.0 to 45.3 |
| Target group for vaccination | All ages | 1953 | 520:114/1433:425 | 44.3 | 27.4-57.2 | 33.0 | 10.8-49.7 |
|               | 0-14 y           | 253 | 70:6/183:24 | 48.7 | -46.7 to 82.1 | 55.5f | -35.1 to 85.3 |
|               | 15-64 y          | 1061 | 315:47/746:155 | 45.2 | 18.9-62.9 | 42.9 | 14.5-61.9 |
| By vaccine type—all ages | Unvaccinated (ref) | 6683 | 2028:4655 | 39.3 | 16.2-56.1 | 33.9 | 6.7-53.1 |
|               | Subunit vaccine  | 242 | 57/185 | 47.6 | 28.6-61.5 | 36.3 | 10.8-54.5 |
|               | Split virion vaccine | 255 | 62/193 | 46.2 | -68.5 to 82.8 | 51.1 | -55.8 to 84.6 |
| By vaccine type—0- to 14- y-olds | Unvaccinated (ref) | 2354 | 634:1720 | Ref |  |  |  |
|               | Subunit vaccine  | 24 | 4/20 | 37.5 | -144.8 to 65.1 | 16.3 | -137.2 to 70.4 |
|               | Split virion vaccine | 28 | 6/22 | 7.6 | 10.1-75.3 | 5.7 | 0.4-30.7 |
| By vaccine type—15- to 64- y-olds | Unvaccinated (ref) | 4005 | 1321:2684 | Ref |  |  |  |
|               | Subunit vaccine  | 112 | 27/85 | 43.5 | 9.9-64.6 | 45.6 | 12.1-66.4 |
|               | Split virion vaccine | 106 | 28/78 | 45.7 | 14.2-65.6 | 45.2 | 11.8-65.9 |
| By prior (2014/15) influenza vaccination status—≥9- y-olds | Neither | 4378 | 1404:2974 | Ref |  | Ref |  |
|               | 2015/16 season only | 100 | 17/83 | 59.2 | 28.8-76.6 | 54.7 | 19.6-74.5 |
|               | 2014/15 season only | 146 | 38/108 | 19.0 | -20.3 to 45.5 | 8.0 | -39.3 to 39.2 |
|               | Study and previous season | 497 | 114:383 | 43.0 | 28.0-54.9 | 28.4 | 6.2-45.4 |
| By prior (2014/15) influenza vaccination status—≥9- y-olds, target group | Neither | 1106 | 335:771 |  |  |  |  |
|               | 2015/16 season only | 67 | 10/57 | 66.5 | 30.8-83.8 | 60.4 | 16.0-81.3 |
|               | 2014/15 season only | 85 | 14/71 | 53.6 | 12.8-75.3 | 46.4 | -2.4 to 72.0 |
|               | Study and previous season | 428 | 95:333 | 46.4 | 28.0-60.1 | 31.8 | 5.7-50.7 |
| By prior (2014/15) influenza vaccination status—15- to 64- y-olds | Neither | 3707 | 1244:2483 |  |  |  |  |
|               | 2015/16 season only | 66 | 10/56 | 70.3 | 39.5-85.4 | 68.2 | 34.4-84.6 |
|               | 2014/15 season only | 102 | 30/72 | 11.0 | -40.1 to 43.4 | 12.7 | -38.9 to 45.1 |
|               | Study and previous season | 220 | 58:162 | 32.4 | 6.5-51.2 | 32.1 | 4.2-51.8 |
| A(H1N1)pdm09 clade 6B.1 | All ages | 4779 | 645:46/4134:434 | 45.5 | 18.4-63.5 | 32.8 | -4.1 to 56.7 |
|               | 0-14 y           | 1505 | 191:5/1314:43 | 38.6 | -74.8 to 78.4 | 51.3 | -33.5 to 82.3 |
|               | 15-64 y          | 2840 | 417:19/2423:197 | 42.5 | -8.2 to 69.4 | 40.1 | -12.9 to 68.3 |

(Continues)
| Type/subtype            | Analysis scenario | N     | Cases; vacc/Controls; vacc | Crude VE | Adjusted VE |
|------------------------|-------------------|-------|---------------------------|----------|-------------|
|                        | Influenza B ²     |       |                          |          |             |
| 0-14 y                 | By age            | 304   | 15/54; 32/47; 92/52      | -31.4    | -77.6       |
|                        |                   | 360   | 11/39; 49/24; 48/36      | -81.4    | -159.2      |
|                        |                   | 488   | 1/10; 46/34; 186/86      | -93.3    | -21.3       |
|                        |                   | 38/141| 35/136; 82/175         | -121.0   | -26.9       |
|                        |                   | 375   | 15/63; 22/58; 121/211   | -11/4-68 | 38/4        |
|                        |                   | 1/19  | 1/10; 46/34; 186/86      | -16/9    | -83/5       |
|                        |                   | 31/19 | 1/10; 46/34; 186/86      | -93.7    | -26/0       |
|                        |                   | 67    | 44/23; 186/86; 210/277   | -106.9   | -124/9      |
|                        |                   | 39/16 | 10/39; 46/34; 186/86      | 47/1     | 8/4-64/9    |
|                        |                   | 84    | 15/69; 186/86; 210/277   | 47/1     | 25/2-76/3   |
|                        |                   | 314   | 15/69; 186/86; 210/277   | 39/16    | 44/4-64/9   |
|                        |                   | 59    | 13/46; 186/86; 210/277   | 37/8     | 28/3        |
|                        |                   | 77    | 16/61; 186/86; 210/277   | 91/49    | 10/71/2     |
|                        |                   | 176   | 35/141; 186/86; 210/277  | 49/0     | 24/6-64/4   |

TABLE 2

Continued

| Type/subtype            | Analysis scenario | N     | Cases; vacc/Controls; vacc | Crude VE | Adjusted VE |
|------------------------|-------------------|-------|---------------------------|----------|-------------|
|                        |                   |       |                          |          |             |

Notes:

- 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), sex, chronic condition and study site unless otherwise indicated.
- d Study sites included in B 0-14 y analysis: DE, ES, FR, IT, NL, PL, PT, SE; study sites included in B 15-64 y analysis: DE, ES, FR, IT, NL, PL, PT, SE; study sites included in B ≥65 y analysis: DE, ES, NL, PT, SE.
- e Adjusted by age and study site only.
- f Due to heterogeneity of VE estimates against influenza B between age groups, no "all ages" estimate against influenza B was attempted.
- g Adjusted by age and study site only.
- h Study sites included in B 0-14 y analysis: DE, ES, FR, IT, NL, PL, SE.
- i Study sites included in B 15-64 y analysis: DE, ES, FR, IT, NL, PL, PT, SE; study sites included in B ≥65 y analysis: DE, ES, NL, PT, SE.
- j Adjusted by time and study site only.
4 | DISCUSSION

The 2015/16 influenza VE against medically attended ILI due to influenza A(H1N1)pdm09 in the I-MOVE/I-MOVE+ multicentre case-control study in Europe ranged from 13.2% to 55.5% in the total and target population, depending on age group. There was a very low VE or no protective effect against influenza B among the 0- to 14-year-olds and VE among the 15- to 64-year-olds among the total and target population ranged from 27.3% to 38.4%.

In the 2015/16 season, twelve study sites contributed to the I-MOVE multicentre case-control study and 11,430 individuals were included. This is the largest sample size since the network began in 2008/09. The number of vaccinated patients remains low, even among the target group for vaccination, with 29%-30% of controls vaccinated. Despite the large sample size, this results in a reduced precision, which is one of the limitations of the study.

Vaccine effectiveness (VE) point estimates against influenza A(H1N1)pdm09 were lower in 2015/16 than in 2014/15, overall and by each age group (54.2, 73.1, 59.7 and 22.4 for all ages, 0- to 14-year-olds, 15- to 59-year-olds and those aged 60 and older, respectively). Vaccine effectiveness (VE) point estimates against A(H1N1)pdm09 were also lower in Canada and in the USA, compared to 2013/14, the last year where influenza A(H1N1)pdm09 was a dominant or codominant circulating strain in these countries.12-15 We observed a low influenza A(H1N1)pdm09 VE point estimate among those aged 65 years and older that was not seen in other studies in
TABLE 3 Influenza A(H1N1)pdm09, influenza B/Yamagata and influenza B/Victoria viruses characterised by clade and study site, I-MOVE multicentre case-control study, Europe, influenza season 2015/6 (week 41/2015–week 16/2016)
case-control study. The VE was 56.3% in the UK among those children receiving the (predominantly trivalent) inactivated injectable vaccine, and in the USA, the VE was 64% against B/Yamagata and 56% against B/Victoria among those children receiving the (predominantly quadrivalent) inactivated injectable vaccine. A low VE among children was seen in Finland receiving the (predominantly trivalent) inactivated injectable vaccine (~1%). In the USA, there is a universal vaccination recommendation, and in the UK and Finland, vaccine is recommended in certain age groups in children. However, in the countries participating in the I-MOVE/I-MOVE+ multicentre case-control study, vaccine is recommended only to children with chronic conditions, with the exception of Poland where vaccination is recommended among those aged 6 months to 18 years.

The low VE against influenza B in children in the I-MOVE/I-MOVE+ multicentre case-control study in the 2015/16 season is in contrast to 2014/15 where VE against influenza B was 62.1% (95% CI: 14.9-83.1). While a selection bias among children could explain the low VE against influenza B, the higher VE against influenza A(H1N1)pdm09 among children (31.9%) and the high VE in the 2014/15 season suggest otherwise. Few children in the 2015/16 study were vaccinated with the quadrivalent vaccine (4.4% among those vaccinated with known vaccine product).

The crude VE against influenza B in those aged 65 years and older was low as observed in the UK (~20.2%), in Danish interim estimates (4.1%; hospital-based patients included) and in the USA (~34%; B Flannery, personal communication, 8 March 2017) 2015-16 season.

In the 2015/16 season, the circulating strains were antigenically distinct from the strain selected for the influenza B component in the trivalent influenza vaccine. Nevertheless, there was VE of 27.3% among the 15- to 64-year-olds. Varying levels of cross-protection have been reported previously. In the 2015/16 season, our VE point estimates are less than 10% among those aged 0-14 years and those aged 65 years and above. Among older adults and children, the differences observed in VE in a season of mismatch between the vaccine and circulating strains may be explained by a combination of immune system properties specific to children and the elderly, as well as by the role of previous vaccinations and previous infections.

The VE point estimate was higher for subunit vaccine than for split virion vaccine among children, but precision was low. Both estimates were low, indicating that the low VE was not due to a vaccine type-specific issue. Among 15- to 64-year-olds, split virion VE point estimate was higher than subunit vaccine, but again precision was low.

In our study, there is residual protection of the prior (2014/15) season vaccine against influenza B among the 15- to 64-year-olds. The 2014/15 trivalent vaccine also contained a B/Yamagata virus, mismatched with regard to the lineage circulating in 2015/16. Vaccination in current and previous season resulted in a similar VE against influenza B among 15- to 59-year-olds as vaccination with current vaccine only.

In the 2015/16 influenza season, the results of I-MOVE/I-MOVE+ study suggest a lower VE against influenza A(H1N1)pdm09 and influenza B than in previous seasons. Both the low VE against influenza B in children and older adults and the low to moderate VE against influenza B among younger adults may be important in the context of cost-effectiveness studies looking into recommendations for quadrivalent vaccines and for more precise data need to be collected. Lower VE against influenza A(H1N1)pdm09 in the 2015/16 season, as well as the indications of the effects of previous vaccination seen here and elsewhere need to be evaluated in subsequent seasons together with virological and immunological results.

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CONFLICT OF INTEREST

None.

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