Early 2016/17 vaccine effectiveness estimates against influenza A(H3N2): I-MOVE multicentre case control studies at primary care and hospital levels in Europe

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Abstract

We measured early 2016/17 season influenza vaccine effectiveness (IVE) against influenza A(H3N2) in Europe using multicentre case control studies at primary care and hospital levels. IVE at primary care level was 44.1%, 46.9% and 23.4% among 0–14, 15–64 and ≥ 65 year-olds, and 25.7% in the influenza vaccination target group. At hospital level, IVE was 2.5%, 7.9% and 2.4% among ≥ 65, 65–79 and ≥ 80 year-olds. As in previous seasons, we observed suboptimal IVE against influenza A(H3N2).

Keywords: influenza, influenza like illness, ILI, severe acute respiratory infection, SARI, vaccine effectiveness, vaccines, immunisation

The 2016/17 influenza season in Europe is marked by the predominant circulation of influenza A(H3N2) viruses [1], with significant pressure on hospitals, mostly due to patients aged 65 years and older developing severe disease [1]. Many European countries have reported excess all-cause mortality [2]. Initial estimates based on Swedish and Finnish electronic databases suggest low influenza vaccine effectiveness (IVE) among older adults [3, 4]. We measured early IVE at primary care and hospital levels against laboratory-confirmed influenza A(H3N2) in Europe.
We conducted separate multicentre primary care and hospital-based case–control studies and analyses using the test-negative design (TND). We have described the methods in detail previously [5-7].

In the primary care study, comprising 893 practitioners (including general practitioners and paediatricians) in 12 countries, we included a systematic sample of all community-dwelling patients presenting to their practitioner with influenza-like illness (ILI), as defined by the European Union ILI case definition (sudden onset of symptoms and at least one of the following systemic symptoms: fever or feverishness, malaise, headache, myalgia, and at least one of the following respiratory symptoms: cough, sore throat, shortness of breath). In the hospital study, comprising 27 hospitals from 11 countries, we included community-dwelling patients aged 65 years and older admitted to hospital for influenza-related clinical conditions with symptoms compatible with severe acute respiratory infection (SARI). Each study site adapted a generic protocol to their local setting [8,9].

At each study site, the study period commenced more than 14 days after the start of the vaccination campaign and lasted from the week of the first influenza case to the date of sending data for the interim analysis at the end of January 2017.

A case of confirmed influenza was an ILI (primary care) or SARI (hospital) patient who was swabbed and tested positive for influenza A(H3N2) virus using real-time RT-PCR. Controls were ILI (primary care) or SARI (hospital) patients who tested negative for any influenza virus using RT-PCR.

We excluded patients with contraindications for influenza vaccination, SARI patients discharged from a previous hospital stay within 48 hours of symptom onset (hospital), those with a previous laboratory-confirmed influenza in the season, those refusing to participate or unable to consent, those who had received antiviral drugs before swabbing (primary care), those swabbed more than 7 days after symptom onset, patients with missing laboratory results and any patients positive to any influenza virus other than influenza A(H3N2).

Practitioners and hospital teams collected clinical and epidemiological information including date of symptom onset and date of swabbing, 2016/17 seasonal vaccination status, date of vaccination and vaccine product administered, 2015/16 seasonal vaccination status, sex, age, presence of chronic conditions, whether the patient belonged to a target group for influenza vaccination (primary care) and number of hospitalisations for chronic conditions in the past 12 months.

We defined individuals as vaccinated if they had received at least one dose of the 2016/17 influenza vaccine at least 15 days before ILI/SARI symptom onset. We excluded individuals vaccinated less than 15 days before symptom onset and individuals with unknown vaccination date.

At primary care level, nine study sites (France, Germany, Hungary, Ireland, the Netherlands, Portugal, Romania, Spain and Sweden) participated in a sub-study using an in-depth laboratory protocol, and randomly selected positive influenza A(H3N2) specimens for genetic sequencing.
We pooled individual patient data in each study and computed the pooled IVE as \((1-\text{OR of vaccination between cases and controls}) \times 100\) using logistic regression with study site as a fixed effect. We conducted a complete case analysis excluding patients with missing values for any of the variables in the model. All IVE estimates were adjusted for study site, calendar time of onset and age (where sample size allowed). Further potential confounding factors included sex, underlying chronic conditions and hospitalisations in the past year.

We stratified IVE by age group. We measured IVE among the target groups for influenza vaccination at primary care level, defined as older adults (aged over 54, 59 or 64 years depending on study site), individuals with chronic conditions and other groups for whom the vaccine was recommended in a given country (e.g. pregnant women, healthcare workers and other professional groups, depending on the study site).

Influenza vaccine effectiveness in primary care

In the primary care analysis, we included 2,250 cases of influenza A(H3N2) and 2,773 negative controls.

The 2016/17 seasonal influenza vaccine coverage was 10.3% among influenza A(H3N2) cases and 10.9% among controls. Compared with cases, a greater proportion of controls belonged to the age group of 0–4-year-olds (26.1% vs 12.3%) and a lower proportion belonged to the age group of 5–14-year-olds (12.1% vs 22.7%) (Table 1).

Nine study sites sequenced 204 randomly selected specimens out of 1,817 (11.2%) (Table 2). Of these, 156 (76.5%) belonged to the 3C.2a1 clade A/Bolzano/7/2016, 46 (22.5%) to A/Hong Kong/4801/2014 (3C.2a) and two (1.0%) to A/Switzerland/9715293/2013 (3C.3a).

Among the 156 viruses of the 3C.2a1 clade, further genetic groups have emerged in 108 (69.2%) (Table 2). These include 34 viruses in group 1 (22%), harbouring the I140M substitution located in the antigenic site A of the haemagglutinin, in addition to changes in amino acid positions 171 and 121, both located in the antigenic site D. Eleven viruses belonged to group 2 (7%), carrying the T135K mutation located in the antigenic site A and resulting in the loss of a glycosylation site, in addition to the already mentioned changes in positions 171 and 121. Twenty-eight viruses belonged to genetic group 3 (18%), carrying the K92R and H311Q substitutions located in the antigenic sites E and C, respectively, in addition to changes in positions 171 and 121. Finally, 35 viruses belonged to group 4 (22%), carrying the R142G mutation located in the antigenic site A and the N171K substitution. Thirty-one viruses (67%) belonging to the 3C.2a clade (A/HongKong/4801/2014) carried the substitutions N121K and S144K, the latter located in the antigenic site position A.

Adjusted IVE against influenza A(H3N2) across all age groups was 38.0% (95% CI: 21.3 to 51.2). It was 44.1% (95% CI: −12.3 to 72.2), 46.9% (95% CI: 25.2 to 62.3) and 23.4% (95% CI: −15.4 to 49.1) in 0–14, 15–64 and ≥ 65 year-olds, respectively. The IVE in the target group for vaccination was 25.7% (95% CI: 1.5 to 43.9) (Table 3).

Influenza vaccine effectiveness at hospital level

In the hospital study, we included 267 cases of influenza A(H3N2) and 368 negative controls.
Early 2016/17 vaccine effectiveness estimates against influenza A(H3N2): I-MOVE multicentre case control studies at primary care.

The 2016/17 seasonal influenza vaccine coverage was 40.4% among influenza A(H3N2) cases and 51.9% among controls. A higher proportion of controls were vaccinated with inactivated split-virion vaccine group (20.6% vs 12.3%). A higher proportion of controls had been hospitalised for chronic conditions in the past twelve months (43.7% vs 26.7%) (Table 1).

Adjusted IVE against influenza A(H3N2) among those aged 65 years and older was 2.5% (95% CI: −43.6 to 33.8), it was 7.9% (95% CI: −67.3 to 49.3) among those aged 65 to 79 years and 2.4% (95% CI: −81.3 to 47.5) among those aged 80 years and older (Table 3).

Discussion

In primary care, early estimates suggest moderate IVE against influenza A(H3N2) among 0–64-year-olds and low IVE in the target group for influenza vaccination. Among those aged 65 years and older, IVE was low at both primary care and hospital level, however precision was low.

Viruses of the 3C.2a1 clade (A/Bolzano/7/2016) predominated in the study sites participating in the laboratory protocol. Compared to the vaccine virus A/HongKong/4801/2014, they had the N171K substitution and in addition, most of them had the N121K substitution. This clade appears to be antigenically similar to the A(H3N2) vaccine component. However, our sequencing results suggest that this cluster is continuing to evolve: 70% of sequenced viruses had further mutations, forming clusters defined by new HA1 amino acid substitutions in antigenic sites, including antigenic site A. We did not measure IVE against A/Bolzano/7/2016 viruses, as estimates were not robust because of the small sample size.

The 2016/17 early primary care IVE estimate among all ages was 38% (95% CI: 21.3 to 51.2), similar to the early estimates from the Canadian Sentinel Practitioner Surveillance [10] and comparable to early estimates against influenza A(H3N2) in previous seasons: 43% (95% CI: -0.4 to 67.7) in 2011/12 and 41.9% (95% CI: −67.1 to 79.8) in 2012/13 [11,12]. This season, we reached better precision thanks to a larger sample size.

The IVE estimates among those aged 65 years and older and target groups for vaccination were low and, despite low precision, reinforce the risk assessment from the European Centre for Disease Prevention and Control (ECDC), which suggests to consider administering antiviral drugs to populations vulnerable to severe influenza irrespective of vaccination status, in line with national and international recommendations [1].

These early results are included in the Global Influenza Vaccine Effectiveness (GIVE) report to contribute to the World Health Organization consultation and information meeting on the composition of influenza virus vaccines for use in the 2017/18 northern hemisphere influenza season [13].

Conclusion

The early season estimates presented here corroborate the suboptimal performance of inactivated influenza vaccine against influenza A(H3N2) that the I-MOVE team and others have reported in the previous post-2009 pandemic seasons [14,15].

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# Figures and Tables

## Table 1

Influenza A(H3N2) cases and controls included in the 2016/17 season influenza vaccine effectiveness analysis, I-MOVE/I-MOVE+ multicentre case control studies (primary care (n = 5,023) and hospital (n = 635) levels) Europe, influenza season 2016/17

| Variables                                | Primary care level | Hospital level |
|------------------------------------------|--------------------|----------------|
|                                          | Number of A(H3N2) n = 2,250 | Number of controls n = 2,773 | Number of A(H3N2) n = 267 | Number of controls n = 368 |
| Median age (years)                       | n  | Total | %   | n  | Total | %   | n  | Total | %   | n  | Total | %   |
|                                          | 29 | 28    | 79  | 80 |
| Age groups (years)                       |     |       |     |     |
| 0–4                                      | 276 | 2,242 | 12.3| NA | NA |
| 5–14                                     | 508 | 2,242 | 22.7| NA | NA |
| 15–64                                    | 1,177 | 2,242 | 52.5| NA | NA |
| 65–79                                    | 234 | 2,242 | 10.4| 138 | 267 | 51.7| 185 | 368 |
| ≥80                                      | 47  | 2,242 | 2.1 | 129 | 267 | 48.3| 183 | 368 |
| Missing                                  | 8   | 7     | 0   | 0  |
| Sex                                      |     |       |     |     |
| Female                                   | 1,126 | 2,237 | 50.3| 1,407 | 2,758 | 51.0| 141 | 267 | 52.8| 190 | 368 |
| Missing                                  | 13  | 15    | 0   | 0  |
| Chronic conditions                       |     |       |     |     |
| At least one chronic condition           | 451 | 2,237 | 20.2| 542 | 2,743 | 19.8| 237 | 255 | 92.9| 321 | 344 |
| Missing                                  | 13  | 30    | 12  | 24 |
| At least one hospitalisation in the previous 12 months for chronic conditions | 26 | 2,196 | 1.2 | 57 | 2,686 | 2.1 | 66 | 247 | 26.7 | 146 | 334 |
| Missing                                  | 54  | 87    | 20  | 34 |
| Target group for vaccination             |     |       |     |     |
| Belongs to a target group for vaccination| 616 | 2,241 | 27.5| 706 | 2,755 | 25.6| 267 | 267 | 100.0| 368 | 368 |
NA: Not applicable.

Table 2

Influenza A(H3N2) viruses characterised by clade, amino acid substitutions and study site, at nine participating laboratories, I-MOVE/I-MOVE+ primary care multicentre case control study, Europe, influenza season 2016/17 (n = 1,817)

| Characterised viruses (clade) | Germany n = 289 | France n = 584 | Hungary n = 39 | Ireland n = 135 | The Netherland n = 47 |
|------------------------------|-----------------|---------------|----------------|-----------------|-----------------------|
|                              | n  | %  | n  | %  | n  | %  | n  | %  | n  | %  |
| A/HongKong/4801/2014 (3C.2a) | 10 | 6  | 3  | 0  | 8  | 1  |
| N121K + S144K                | 3  | 30 | 6  | 100| 3  | 100| 0  | 1  | 7  |
| A/Bolzano/7/2016 (3C.2a1)    | 33 | 19 | 3  | 5  | 20 |  |
| N171K + N121K + I140M        | 10 | 30 | 0  | 0  | 0  | 7  |
| N171K + N121K + T135K        | 2  | 6  | 0  | 67 | 0  | 3  |
| N171K + N121K + K92R + H311Q | 8  | 24 | 0  | 33 | 1  | 20 | 4  |
| N171K + R142G                | 7  | 21 | 3  | 16 | 0  | 60 | 3  |
| A/Switzerland/9715293/2013 (3C.3a) | 0  | 0  | 0  | 2  | 0  |  |
| Total sequenced/total A(H3N2)| 43 | 15 | 25 | 4  | 15 | 7  | 5  | 28 |
Pooled adjusted seasonal vaccine effectiveness against laboratory-confirmed influenza A(H3N2) by age group and target group for vaccination, I-MOVE/I-MOVE+ multicentre case control studies (primary care (n = 4,937) and hospital (n = 635)), influenza season 2016/17

| Analyses                  | Adjustment / stratification                                                                 | Cases       | Controls       | Adjusted VE | 95% CI       |
|---------------------------|---------------------------------------------------------------------------------------------|-------------|----------------|-------------|-------------|
|                           |                                                                                             | All | Vaccinated | % | All | Vaccinated | % |               |
| Primary care              | Adjusted by study site only                                                                  | 2,216 | 229 | 10 | 2,721 | 297 | 11 | 10.9 | -8.3 to 29.1 |
|                           | Adjusted by calendar time and study site                                                    | 2,216 | 229 | 10 | 2,721 | 297 | 11 | 27.9 | 13.9 to 41.9 |
|                           | Adjusted by calendar time, age and study site                                                | 2,216 | 229 | 10 | 2,721 | 297 | 11 | 38.4 | 22.2 to 54.6 |
|                           | Fully adjusted: calendar time, age, study site, presence of chronic conditions, sex         | 2,216 | 229 | 10 | 2,721 | 297 | 11 | 38.0 | 21.3 to 54.7 |
| All ages                  | By age group (years) a                                                                       |               |               |               |               |               |               |               |
|                           | 0–14                                                                                        | 773 | 20 | 3 | 1,043 | 27 | 3 | 44.1 | -12.3 to 90.4 |
|                           | 15–64                                                                                       | 1,164 | 69 | 6 | 1,410 | 126 | 9 | 46.9 | 25.2 to 68.5 |
|                           | ≥ 65                                                                                       | 278 | 140 | 50 | 268 | 144 | 54 | 23.4 | -15.4 to 62.2 |
| Target group for vaccination a | All ages                                                                                    | 606 | 201 | 33 | 698 | 235 | 34 | 25.7 | 1.5 to 49.9  |
| Hospital                  | Adjusted by study site only                                                                  | 267 | 108 | 40 | 368 | 191 | 52 | -0.7 | -46.8 to 35.5 |
|                           | Adjusted by calendar time and study site                                                    | 267 | 108 | 40 | 368 | 191 | 52 | 3 | -42.2 to 36.7 |
|                           | Adjusted by calendar time, age and study site                                                | 267 | 108 | 40 | 368 | 191 | 52 | 2.5 | -43.6 to 48.6 |

CI: confidence interval; VE: vaccine effectiveness at hospital level.

a Adjusted by study site, age, calendar time, presence of chronic conditions and sex.
Adjusted by calendar time, age and study site.