

Early estimates of seasonal influenza vaccine effectiveness in Europe among target groups for vaccination: results from the I-MOVE multicentre case–control study, 2011/12

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To provide an early estimate of 2011/12 influenza vaccine effectiveness (VE), we conducted a multicentre case–control study based on seven sentinel surveillance networks. We included influenza-like illness cases up to week 7/2012 from the vaccination target groups, swabbed less than eight days after symptom onset. Laboratory-confirmed influenza A(H3) cases were compared to negative controls. Adjusted VE was 43% (95% confidence interval: -0.4 to 67.7), suggesting low to moderate VE against influenza A(H3) in the early 2011/12 season.

Introduction

In the context of the Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) Network we estimated the effectiveness of the 2011/12 trivalent vaccine against medically attended influenza-like illness (ILI) that was laboratory-confirmed as influenza. We undertook a multicentre case–control study based on the European Influenza Sentinel Practitioner Surveillance Networks (EISN) [1] from eight study sites (France, Hungary, Ireland, Italy, Poland, Portugal, Romania and Spain).

Data were collected from week 48/2011 to week 7/2012. During these 12 weeks of data collection, 867 (92.7%) of 935 laboratory-confirmed influenza cases recruited in the study were identified as influenza A(H3). This finding was consistent with data from the Community Network of Reference Laboratories (CNRL) for Human Influenza in Europe: of the 11,159 viruses detected from week 40/2011 to week 7/2012, 95.9% were influenza type A, and of 6,238 influenza A viruses subtyped, 97.5% were influenza A(H3) [2].

We provide early season estimates of the effectiveness of the 2011/12 vaccine against influenza A(H3) virus among those subpopulations identified as target groups for vaccination in the respective countries (Table 1) [3–10].

Methods

The study population consisted of non-institutionalised patients of all ages (over the age of 17 years in Hungary) consulting a participating practitioner for ILI and having a naso-pharyngeal swab taken less than eight days after symptom onset. Recruitment of ILI patients was based on exhaustive (Romania), systematic (Hungary, Ireland, Italy, Poland, Portugal, Spain) or quota sampling (France) [11]. The European Union case definition for ILI was used: sudden onset of symptoms, at least one of these four systemic symptoms (fever or feverishness, malaise, headache, myalgia) and at least one of these three respiratory symptoms (cough, sore throat, shortness of breath) [12]. A case of confirmed influenza A(H3) was an ILI patient who was swabbed and tested positive for influenza A(H3) virus using RT-PCR or culture. Controls were ILI patients who tested negative for any influenza virus.

Individuals were considered vaccinated if they had received a dose of the 2011/12 seasonal vaccine more than 14 days before the date of onset of ILI symptoms, and unvaccinated if they had received no vaccine or the vaccine was given less than 15 days before the onset of ILI symptoms. The variables collected during this season were the same as in 2010/11 [13], except for pandemic vaccination (not collected in 2011/12) and smoking (not collected in France). In each country we included ILI patients who presented to the practitioner up to the end of week 7/2012 who belonged to a target group for vaccination, with onset of symptoms more than 14 days after the start of national or regional influenza vaccination campaigns. For each study site, we excluded controls with symptom onset in the weeks before symptom onset of the first influenza A(H3) case, as well as cases infected with any non-A(H3) influenza virus.

We conducted a complete case analysis excluding individuals with missing values. We estimated the pooled

TABLE 1

Target groups for influenza vaccination in eight European Union countries, influenza season 2011/12

Country	Target groups for vaccination
France	<ul style="list-style-type: none"> • People aged 65 years and older • >6 months with chronic conditions (chronic respiratory disease, chronic respiratory failure, bronchopulmonary dysplasia, cystic fibrosis, chronic cardiac failure, cardiovascular disease, diabetes type 1 and type 2, severe neurological and muscular disease, chronic renal disease, body mass index >30) • Pregnant women in second and third trimester • Residents of long-term care facilities • Healthcare workers • Carers in direct contact with at-risk patients • Household contacts of at-risk children under the age of 6 months • Personnel working on cruise ships or planes, and tour guides
Hungary	<ul style="list-style-type: none"> • People aged 65 years and older • >6 months with chronic conditions (respiratory illness, body mass index ≥ 35, neuromuscular disease, cardiovascular disease except well treated hypertension, congenital or acquired immunodeficiency including HIV infection and cancer, chronic hepatic or renal disease, chronic metabolic disease including diabetes) • Pregnant women or women planning to be pregnant during the influenza season • Healthcare and social workers
Ireland	<ul style="list-style-type: none"> • People aged 65 years and older • >6 months with chronic conditions (chronic respiratory disease, chronic heart disease, neurological disease, diabetes mellitus, liver disease, neurological disease including sclerosis, hereditary and degenerative disorders of the central nervous system, body mass index ≥ 40, immunosuppression due to disease or treatment including those with missing or non-functioning spleen) • Pregnant women (any stage and up to 6 weeks post partum) • Children with any condition that can compromise respiratory function, especially those attending special schools/day centres • Children and teenagers on long-term aspirin therapy (risk of Reyes syndrome) • Residents of nursing homes and other long-stay institutions • Carers in direct contact with at-risk patients • People in close, regular contact with pigs, poultry or water fowl • Healthcare workers
Italy	<ul style="list-style-type: none"> • People aged 65 years and older • >6 months with chronic conditions (chronic respiratory disease, chronic cardiovascular disease, neurological disease, diabetes mellitus and metabolic diseases including obesity with body mass index >30, liver disease, renal disease, immunosuppression and HIV infection, chronic inflammatory diseases, tumours, pathologies of the hematopoietic organs, pathologies for which an important surgical intervention is planned, pathologies producing an increased risk of respiratory aspirations) • Pregnant women in second and third pregnancy trimester • People working in essential public services • People working with animals that could be infected with influenza • Residents of nursing homes and long-term care facilities • Household contacts of at-risk persons • Healthcare workers • Children with long-term salicylate therapy
Poland	<ul style="list-style-type: none"> • People aged 55 years and older • >6 months with chronic condition (asthma, diabetes, cardiovascular or respiratory disease, renal failure, hepatic disease, neurological disease, congenital or acquired immunodeficiency, organ transplantation, body mass index ≥ 40) • Healthcare, school, trade and transport workers and other staff exposed to large numbers of people • Healthy children between 6 months and 18 years of age
Portugal	<ul style="list-style-type: none"> • People aged 65 years and older (but also recommended to those over the age of 60 years) • >6 months with chronic conditions (chronic respiratory disease, cardiovascular disease, metabolic disorders, renal or hepatic disease, congenital or acquired immunodeficiency, chronic neurological or neuromuscular disorders, any other condition impairing immunity or respiratory function, body mass index ≥ 30) • Pregnant women in second trimester • Household contacts and carers of children under the age of 6 months with high risk of developing complications • Health professionals, care givers in nursing homes and domiciliary service
Romania	<ul style="list-style-type: none"> • People aged 65 years and older • >6 months with chronic conditions (respiratory, cardiovascular, renal or hepatic diseases, diabetes, metabolic disorders, HIV infection, obesity) • Pregnant women • Persons institutionalised for social care • Healthcare workers
Spain	<ul style="list-style-type: none"> • People aged 59 years and older or 64 years and older, depending on the region • >6 months with chronic conditions (diabetes, cardiovascular, lung, kidney or hepatic diseases, immunodeficiency, body mass index ≥ 40) • Pregnant women • Children <15 years under salicylate therapy • Healthcare workers, people in contact with high-risk groups, essential civil servants, people in contact with birds

HIV: human immunodeficiency virus.

seasonal influenza vaccine effectiveness (VE) as 1 minus the odds ratio (OR) expressed as a percentage, using a one-stage method with the study site as fixed effect in the model.

To estimate adjusted VE, we used logistic regression models including the following potential confounding factors: age groups (10-year age bands), sex, week of symptom onset, chronic disease (at least one), hospitalisations associated with a chronic disease in the last 12 months, and number of visits to a general practitioner or paediatrician in the last 12 months.

Results

Among the 1,056 practitioners who agreed to participate, 528 (50%) recruited at least one ILI case (Table 2).

Of the 2,090 ILI cases recruited, 575 belonged to a target group for vaccination. After excluding the weeks before symptom onset of the first influenza A(H3) case at each of the study sites and 10 cases positive for other influenza viruses, we included 208 influenza A(H3) cases and 330 influenza-negative controls (Figure). Poland is not included in this preliminary analysis as no influenza A(H3) case was detected.

The first study site to recruit an influenza A(H3) case in the target group for vaccination was Italy (week 48/2011), and the last sites were France, Romania and Spain (week 52/2011) (Table 2). The median number of

weeks during which patients were recruited for the preliminary analysis was nine, ranging from six in France to 12 in Italy (Table 2).

Differences in the characteristics of influenza A(H3) cases and controls are presented in Table 3.

Among 533 individuals for whom vaccination status was available, 179 (33.5%) were vaccinated. The median time since vaccination was 105 and 74 days for cases and controls, respectively ($p=0.031$).

The complete case analysis was done for 530 individuals after excluding those with missing information on 2011/12 seasonal vaccination ($n=5$), on hospitalisations for chronic disease in the previous year ($n=2$) and on practitioners' visits in the previous year ($n=1$). The crude VE against influenza A(H3) was 42.9 (95% confidence interval (CI): 10.3 to 63.6) and the adjusted 43% (95% CI: -0.4 to 67.7) (Table 4).

Discussion

Our pooled early estimates suggest that the point estimate of the of the 2011/12 influenza vaccine against influenza A(H3) in the target group for vaccination was below 50%. These results are consistent with the VE against influenza A(H3) estimated in Australia for the season 2011 (58%, 95% CI: -53 to 89) [14] and with the Spanish early estimates of the 2011/12 VE against influenza A(H3) among target group for vaccination (54%, 95% CI: 1 to 79) [15].

TABLE 2

Participating practitioners and recruited influenza-like illness patients, by A(H3) influenza case-control status, vaccination status and study site, multicentre case-control study, study sites in eight European Union countries, week 48/2011–week 7/2012

Study site	Number of practitioners participating in the study	Number of practitioners recruiting at least one ILI patient ^a	Number of ILI patients recruited by practitioners	Inclusion period for the preliminary analysis (ISO weeks) ^b	Number of included ILI patients positive for influenza A(H3) and with known vaccination status ^c		Number of included ILI patients negative for any influenza and with known vaccination status ^c	
					Total	Vaccinated	Total	Vaccinated
France	499	169	325	Week 52/2011–week 6/2012	4	1	24	12
Hungary	94	63	354	Week 49/2011–week 7/2012	2	0	112	41
Ireland	28	11	60	Week 50/2011–week 7/2012	5	4	3	3
Italy	10	10	143	Week 48/2011–week 7/2012	18	6	33	15
Poland	35	15	45	Not included in preliminary analysis (no influenza A(H3) cases)	0			
Portugal	59	30	149	Week 51/2011–week 7/2012	23	5	47	24
Romania	100	56	128	Week 52/2011–week 7/2012	18	1	31	6
Spain	231	174	886	Week 52/2011–week 7/2012	136	37	77	24
Total	1,056	528	2,090		206	54	327	125

ILI: influenza-like illness; ISO: International Organization for Standardization.

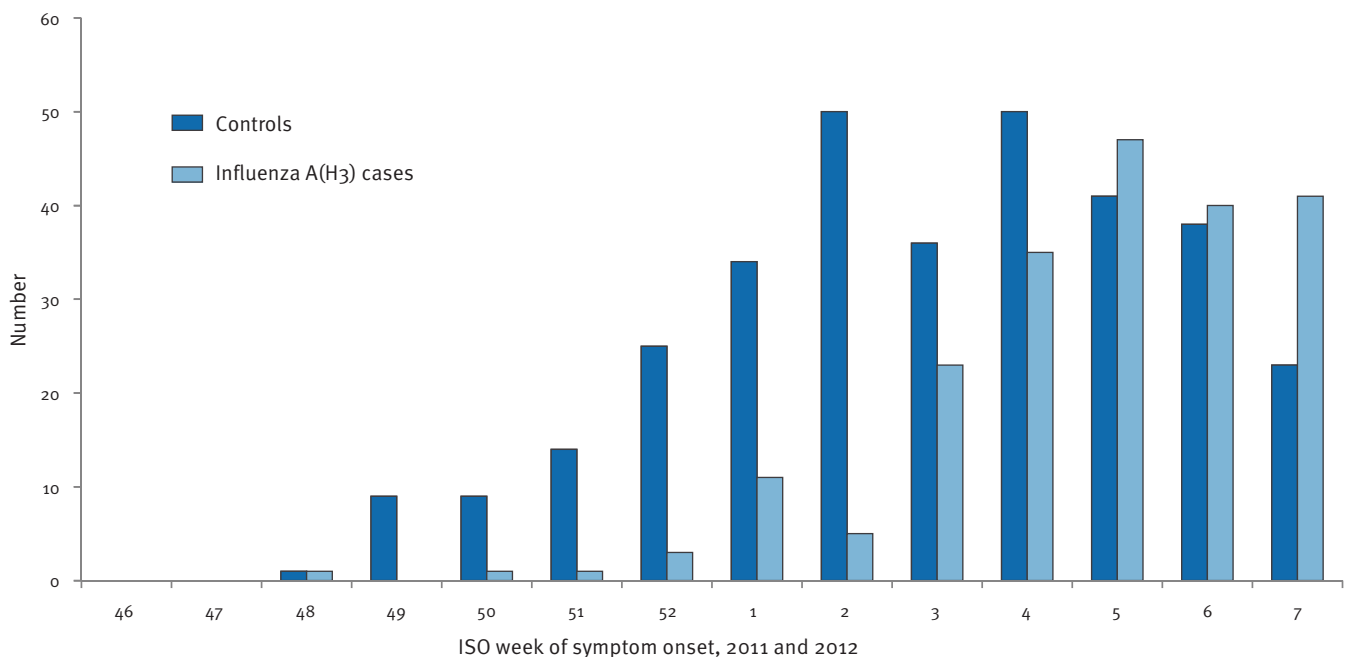
^a ILI patients meeting the European Union case definition, swabbed less than eight days after onset of symptoms within the study period.

^b From 15 days after the start of the vaccination campaign to week 7/2012; we excluded controls with an onset of symptoms in the weeks before the first influenza A(H3) case in the study site.

^c ILI patients in a vaccination target group included in the study, after excluding those with missing information on laboratory results, vaccination status or date of vaccination.

FIGURE

Influenza A(H3) cases (n=208) and influenza-negative controls (n=330) in vaccination target groups recruited at study sites in seven European Union countries, by week of symptom onset, week 48/2011–week 7/2012



International Organization for Standardization (ISO) definition of a week.

The late start of the 2011/12 season in Europe [2] and the low influenza incidence in some of the eight countries participating in the multicentre case–control season limited the sample size for this preliminary analysis. By week 7/2012, four of the eight countries participating in the study had not reached the peak of the influenza season.

We included ILI patients swabbed less than eight days after symptom onset. Due to the small sample size we did not assess potential misclassification (false influenza A(H3)-negatives because of late swabbing) by restricting the analysis to those swabbed less than four days after ILI onset. However, only 12% of the ILI patients included in this preliminary analysis were swabbed more than three days after onset of ILI symptoms (Table 2). This will be addressed in the final analysis.

There were important differences between target groups for vaccination and non-target groups (data not shown). The vaccine coverage was 2.8% in the non-target groups compared to 33.8% in the target groups and the median age was 26 years and 56 years respectively. In this preliminary analysis our results are restricted to the population for which the vaccine is recommended. We collected information on the main potential confounding factors described in the literature [16]. The crude and adjusted VE were similar, suggesting that within this subpopulation and using a specific laboratory-confirmed outcome, the presence of known confounding was minimised.

The low to moderate VE we observed may be explained by a limited match identified between the circulating influenza A(H3) virus strains and the vaccine strain [2]. In February 2012, the vaccine strain selection committee at the World Health Organization (WHO) concluded that there was evidence of increasing antigenic and genetic drift in circulating influenza A(H3N2) and consequently recommended to include a different influenza A(H3) vaccine strain in the 2012/13 seasonal vaccine [17].

In the 2011/12 season, the time lag between the beginning of the vaccination campaigns and the start of the influenza season was longer than in previous seasons. In our preliminary analysis, the delay from vaccination to onset of symptoms was longer in cases than in controls. This may suggest that waning immunity has contributed to the moderate VE observed. However, with the sample available for this preliminary analysis, we could not verify this hypothesis.

Our preliminary estimates suggest that, among the target groups for vaccination, the effectiveness of the 2011/12 influenza vaccine is low to moderate against medically-attended ILI confirmed as influenza A(H3). At the end of the season, a larger sample size per study site may allow us to estimate also the VE against other influenza viruses, by age group, and to further explore hypotheses on the reasons for the low VE observed early in the season.

TABLE 3

Characteristics of A(H3) influenza cases (n=208) and test-negative controls (n=330) in vaccination target groups included from study sites in seven European Union countries, week 48/2011–week 7/2012

Characteristic	Number of influenza cases/ total n (%) ^a	Number of test-negative controls/total n (%) ^a	P value
Median age	56.0	56.0	1.000 ^b
Age group (years)			
0-4	6/208 (2.9)	13/330 (4.0)	0.050 ^c
5-14	17/208 (8.2)	10/330 (3.2)	
15-64	115/208 (55.3)	201/330 (61.0)	
≥65	70/208 (33.7)	106/330 (32.1)	
Females	117/208 (56.3)	208/330 (53.6)	0.124 ^c
Symptoms			
Fever	198/206 (96.1)	293/320 (89.1.7)	0.003 ^c
Malaise	194/202 (96.0)	277/304 (91.1)	0.033 ^c
Headache	179/207 (86.5)	243/327 (74.3)	0.001 ^c
Myalgia	185/207 (89.4)	258/327 (78.9)	0.002 ^c
Days between onset of symptoms and swabbing			
0	8/208 (3.9)	21/330 (6.4)	0.101 ^c
1	74/208 (35.6)	113/330 (34.2)	
2	63/208 (30.3)	100/330 (30.3)	
3	44/208 (21.2)	48/330 (14.6)	
≥4	19/208 (9.1)	48/330 (14.6)	
Seasonal influenza vaccination ^d , 2011/12	54/206 (26.2)	125/327 (38.2)	0.005 ^c
Seasonal influenza vaccination, 2010/11	50/206 (24.3)	126/323 (39.0)	<0.001 ^c
Obese	21/207 (10.1)	57/330 (17.3)	0.024 ^c
Heart diseases	36/208 (17.3)	107/330 (32.4)	<0.001 ^c
At least one chronic disease	121/208 (58.2)	254/330 (77.0)	<0.001 ^c
Smoker			
Current	30/202 (14.9)	49/302(16.2)	0.087 ^c
Former	22/202 (10.9)	53/302(17.5)	
Never	150/202 (74.3)	200/302(66.2)	
Median number of practitioners' visits in the previous 12 months	4	5	0.031 ^b
Any hospitalisation in the previous 12 months for chronic diseases	9/208 (4.3)	23/327 (7.0)	0.262 ^c
Median number of days from vaccination ^d to onset of ILI symptoms	105	74	<0.001 ^b

ILI: influenza-like illness.

^a Unless otherwise indicated.

^b Non-parametric test of the median.

^c Two-sided Fisher's exact test.

^d Vaccination more than 14 days before onset of ILI symptoms.

TABLE 4

Pooled crude (n=530) and adjusted (n=521) 2011/12 seasonal influenza vaccine effectiveness against laboratory-confirmed A(H3) influenza in target groups for vaccination at study sites in seven European Union countries, week 48/2011–week 7/2012

Crude versus adjusted	Cases/controls	Vaccinated cases/controls	Vaccine effectiveness (%)	95% confidence intervals
Crude ^a	206/324	54/123	42.9	10.3 to 63.6
Adjusted model ^{b, c}			43.0	-0.4 to 67.7

^a Study site included in the model as fixed effect.

^b Model adjusted for presence of at least one chronic disease, sex, at least one hospitalisation for chronic disease in the previous 12 months, age group, practitioners' visits in the previous 12 months (0-1, 2-4 and ≥5 visits) and week of symptom onset.

^c Onset week 49 dropped due to no cases (nine records dropped).

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