

RAPID COMMUNICATIONS

Early estimates of seasonal influenza vaccine effectiveness in Europe: results from the I-MOVE multicentre case–control study, 2012/13

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We conducted a test-negative case–control study based in five European sentinel surveillance networks. The early 2012/13 adjusted influenza vaccine effectiveness was 78.2% (95% 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) and 50.4% (95% CI: –20.7 to 79.6) against all influenza types in the target groups for vaccination. Efforts to improve influenza vaccines should continue to better protect those at risk of severe illness or complications.

Background

Since 2008/9, the Influenza Monitoring Vaccine Effectiveness (I-MOVE) network has estimated the effectiveness of seasonal influenza vaccine to prevent medically attended influenza-like illness (ILI) laboratory confirmed as influenza [1–7]. One of the components of I-MOVE is a multicentre case–control study based on practitioners participating in the European Influenza Surveillance Network (EISN) [8].

This season, six study sites are participating in the multicentre study: Germany, Ireland, Poland, Portugal, Romania and Spain.

Here we provide early season estimates of the 2012/13 influenza vaccine based on data collected from week 43 2012 to week 3 2013. Poland is not included in the early season estimates as there were no vaccinated individuals among the patients recruited.

Estimating influenza vaccine effectiveness

The methods of the multicentre case–control study have been described previously [1–4,9].

Participating practitioners swabbed and interviewed all or a systematic sample of patients consulting for ILI. The common variables collected in all study sites were symptoms, date of onset and swabbing, 2012/13 seasonal vaccination status and date of vaccination, sex, age, presence of chronic conditions and number

of hospitalisations for the chronic condition in the past 12 months. Four of the five study sites included a question on belonging to the target groups for vaccination. In Portugal, this information was gathered using information on age, chronic conditions, pregnancy, whether the patient was a health professional or carer and a household member or carer of an at-risk patient aged less than six months.

In the pooled analysis, we included patients with a nasopharyngeal swab taken less than eight days after symptom onset and meeting the European Union case definition for ILI: sudden onset of symptoms, at least one of four systemic symptoms (fever or feverishness, malaise, headache, myalgia) and at least one of three respiratory symptoms (cough, sore throat, shortness of breath) [10]. 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 or culture. Controls were ILI patients who tested negative for any influenza virus.

We defined a person as vaccinated if he or she had received at least one dose of a 2012/13 seasonal influenza vaccine more than 14 days before ILI symptom onset. All the others were classified as unvaccinated.

For each study site we included ILI patients with symptom onset up to the end of week 3 2013 and more than 14 days after the start of national or regional influenza vaccination campaigns.

We conducted a complete case analysis excluding individuals with missing information on key confounders. We estimated the pooled 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.

TABLE 1

Study details, multicentre case-control study, study sites in five European Union countries, week 43/2012-week 3/2013

Study site	Week of start of influenza season ^a	Number of practitioners participating in the study	Number of practitioners recruiting at least one ILI patient ^b	Number of ILI patients ^c recruited by practitioners	Inclusion period for the preliminary analysis (ISO weeks) ^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
Germany	Week 50/2012	150	109	863	Week 43/2012-week 3/2013	267	8	556	38
Ireland	Week 50/2012	28	20	126	Week 48/2012-week 3/2013	81	3	45	4
Portugal	Not started within study period	62	21	43	Week 51/2012-week 3/2013	10	0	33	5
Romania	Week 3/2013	75	7	7	Week 2/2013-week 3/2013	4	1	3	1
Spain	Week 3/2013	239	66	122	Week 50/2012-week 3/2013	54	0	68	5
Total	-	554	223	1,161	-	416	12	705	53

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

^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 less than eight days after onset of symptoms within the study period.

^c From 15 days after the start of the vaccination campaign to week 3/2013. We excluded controls with an onset of symptoms in the weeks before the first influenza case in the study site.

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

We used a logistic regression model to adjust for presence of at least one chronic disease, sex, age group and month of symptom onset.

We estimated VE against all laboratory-confirmed influenza, and individually against influenza A(H3N2), A(H1N1)pdm09 and influenza B. For each study site, we excluded controls with symptom onset in the weeks before symptom onset of the first influenza type/subtype case depending on the outcome used. We also estimated VE restricted to the target groups for vaccination.

Early estimates of 2012/13 influenza vaccine effectiveness

In the five countries, the influenza season, as defined by national thresholds, started at different times – in week 50 2012 in Germany and Ireland, week 3 2013 in Spain and Romania (Table 1). In week 3, the ILI incidence in Portugal was still below the threshold defining the start of the season. The first study site to recruit cases was Germany (in week 43 2012) and the last Romania (in week 2 2013).

Among 554 practitioners, 223 recruited at least one ILI patient (Table 1).

Of the 1,161 ILI patients enrolled, 271 tested positive for influenza A (23.3%), 162 for influenza B (14.0%) and one tested positive for both influenza B and influenza A(H1)pdm09. Among the 269 influenza A viruses that could be subtyped, 146 (54.3%) were A(H1)pdm09 and 123 (45.7%) were A(H3N2). Influenza A virus was predominant in Germany, and influenza B in Ireland and Spain (Table 2).

The proportion of patients who were vaccinated was 2.9% (12/416) among cases and 7.5% (53/705) among controls.

After excluding patients with missing information on 2012/13 influenza vaccination (n=40), age (n=2), sex (n=11), presence of chronic conditions (n=62), we included 1,046 individuals (396 cases and 650 controls) in the complete case analysis (Figure). There were 12 vaccinated cases: five positive for influenza A(H3N2), four for A(H1)pdm09 and three for B.

The adjusted VE was 62.2% (95% CI: 21.1 to 81.9) for influenza A and B combined, 78.2% (95% CI: 18.0 to 94.2) for influenza B, 62.1% (95% CI: -22.9 to 88.3) for A(H1)pdm09 and 41.9 (95% CI: -67.1 to 79.8) for A(H3N2) (Table 3). Among the target groups for vaccination, the VE against influenza A and B combined was 50.4% (95% CI: -20.7 to 79.6).

Discussion

These early estimates suggest a moderate VE against all influenza viruses. By type and subtype, the highest VE was against influenza B and the lowest against influenza A(H3N2).

TABLE 2

Details for influenza B (n=163), A(H3N2) (n=123), A(H1)pdm09 (n=146) cases and controls^a (n=727) considered for mid-2012/13 season trivalent influenza vaccine effectiveness analysis, study sites in five European Union countries, week 40/2012–week 3/2013 (n=1,161^{b,c})

Variables	Number of test-negative controls ^c /total n (%)	Number of influenza B cases ^b /total n (%)	Number of influenza A(H3N2) cases/total n (%)	Number of influenza A(H1)pdm09 cases ^b /total n (%)
Median age (years)	20	31	11	25.5
Age groups (years)				
0–4	184/725 (25.4)	16/163 (9.8)	33/123 (26.8)	25/146 (17.1)
5–14	130/725 (17.9)	51/163 (31.3)	38/123 (30.9)	35/146 (24.0)
15–59	350/725 (48.3)	84/163 (51.5)	41/123 (33.3)	79/146 (54.1)
≥60	61/725 (8.4)	12/163 (7.4)	11/123 (8.9)	7/146 (4.8)
Sex				
Female	368/714 (51.5)	84/162 (51.9)	56/122 (45.9)	85/146 (58.2)
Days between symptom onset and swabbing				
0	60/727 (8.3)	6/163 (3.7)	2/123 (1.6)	8/146 (5.5)
1	294/727 (40.4)	34/163 (20.9)	52/123 (42.3)	55/146 (37.7)
2	171/727 (23.5)	41/163 (25.2)	34/123 (27.6)	37/146 (25.3)
3	112/727 (15.4)	43/163 (26.4)	17/123 (13.8)	23/146 (15.8)
4–7	90/727 (12.4)	39/163 (23.9)	18/123 (14.6)	23/146 (15.8)
Seasonal vaccination ^d 2012/13	53/705 (7.5)	3/161 (1.9)	5/117 (4.3)	4/136 (2.9)
At least one chronic condition	143/676 (21.2)	29/161 (18.0)	14/114 (12.3)	18/134 (13.4)
At least one hospitalisation in the previous 12 months for chronic conditions	11/584 (1.9)	2/152 (1.3)	2/103 (1.9)	0/122 (0.0)
Belongs to target groups for vaccination	175/711 (24.6)	35/163 (21.5)	22/117 (18.8)	23/143 (16.1)
Study sites				
Germany	578/727 (79.5)	51/163 (31.3)	112/123 (91.1)	122/146 (83.6)
Ireland	45/727 (6.2)	66/163 (40.5)	9/123 (7.3)	5/146 (3.4)
Portugal	33/727 (4.5)	4/163 (2.5)	0/123 (0.0)	6/146 (4.1)
Romania	3/727 (0.4)	2/163 (1.2)	0/123 (0.0)	2/146 (1.4)
Spain	68/727 (9.4)	40/163 (24.5)	2/123 (1.6)	11/146 (7.5)

^a Controls used to compare with all influenza cases.

^b One influenza case positive for influenza B and for influenza A(H1)pdm09 was included in both analyses.

^c The virus from three influenza A cases could not be subtyped: these cases are not included in the descriptive analysis.

^d Vaccination more than 14 days before onset of influenza-like illness symptoms.

TABLE 3

Pooled crude and adjusted 2012/13 seasonal vaccine effectiveness against laboratory confirmed influenza by influenza type/subtype, overall and among target groups for vaccination. Multicentre case–control study in five European Union study sites, week 43 (2012)–week 3 (2013), influenza season 2012/13

Influenza type/subtype	Crude vs adjusted model	Cases and controls (n/n)	Vaccinated cases and controls (n/n)	Vaccine effectiveness (%)	95% confidence intervals
All population					
A and B	Crude ^a	396/650	12/48	62.8	27.3 to 80.9
	Adjusted ^b	396/650	12/48	62.2	21.1 to 81.9
A(H1)pdm09	Crude ^a	125/477	4/37	66.1	-2.7 to 88.8
	Adjusted ^c	125/477	4/37	62.1	-22.9 to 88.3
A(H3N2)	Crude ^a	111/577	5/39	34.7	-70.1 to 74.9
	Adjusted ^b	111/577	5/39	41.9	-67.1 to 79.8
B	Crude ^a	158/523	3/41	79.8	29.2 to 94.2
	Adjusted ^b	158/523	3/41	78.2	18.0 to 94.2
Target population					
A and B	Crude ^a	73/157	9/32	46.5	-23.0 to 76.8
	Adjusted ^d	73/154	9/32	50.4	-20.7 to 79.6

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

^b Model adjusted for presence of at least one chronic disease, sex, 10-year age group and month of symptom onset.

^c Model adjusted for presence of at least one chronic disease, sex, 10-year age group until age 60, where age is coded as ≥60 years and month of symptom onset.

^d Model adjusted for presence of at least one chronic disease, sex, age group (0–14; 15–59 and ≥60 years) and month of symptom onset. Three records were excluded for October.

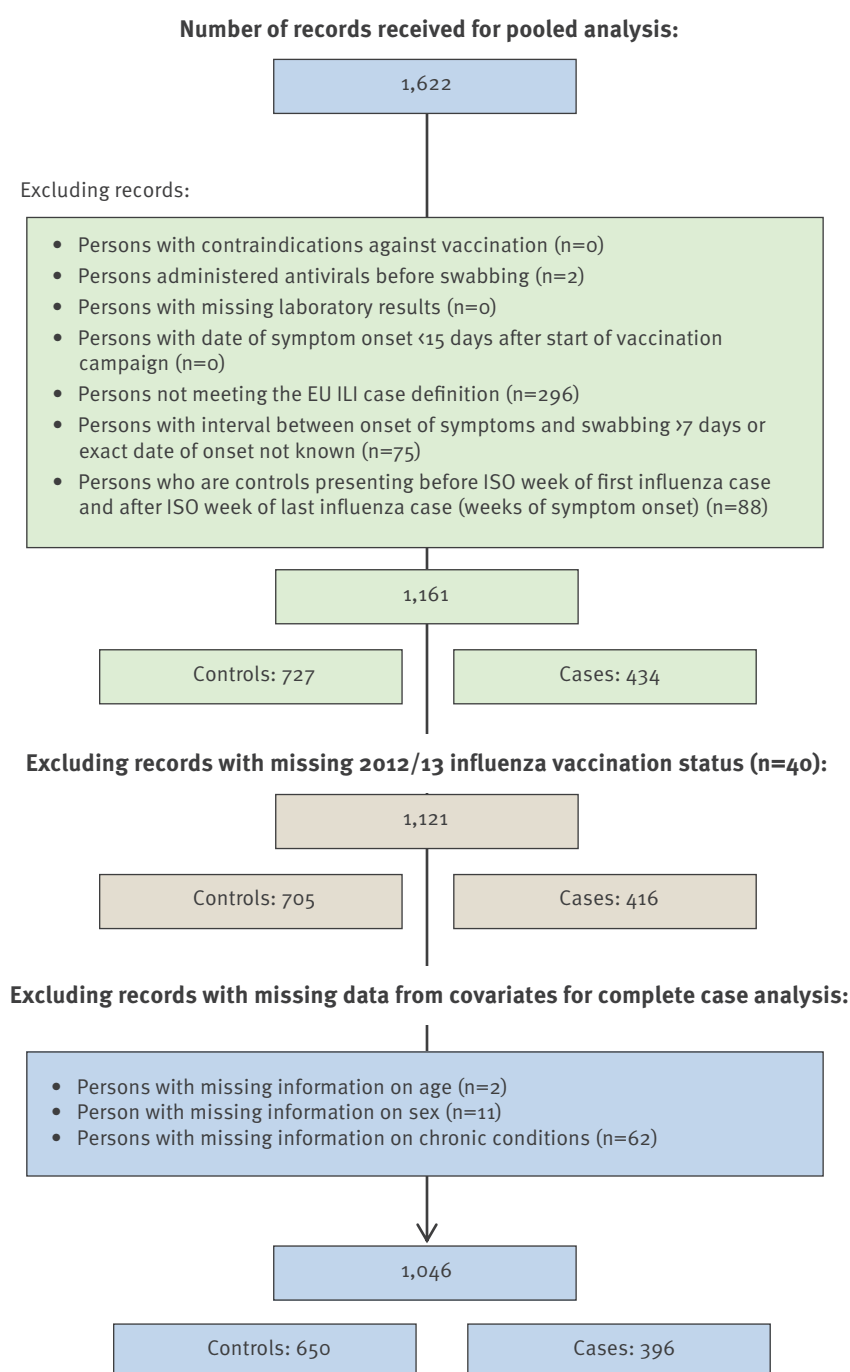
During the study period, as of week 3-2013, two of the participating countries reported a low ILI/ARI activity (Portugal, Romania) and three medium activity (Germany, Ireland, Spain) [11]. The sample size varied by study site. As most patients (863/1,161, 74.3%) were enrolled in Germany, the pooled estimates are highly influenced by the German data. When restricting the analysis to Ireland, Portugal, Romania and Spain (n=296, four vaccinated cases), the adjusted point VE against all influenza was higher (73.5%; 95% CI: 8.7

to 92.3) than the adjusted point VE including the five study sites.

As in 2011/12, the results suggests a low-to-moderate VE for influenza A(H3N2) [9]. Our point estimate is lower than that reported by Canada [12] and the United States [13], countries with a predominance of this subtype in the early phase of the 2012/13 season. Most of the influenza A(H3N2) cases included in our study were German patients. In Germany, most of

FIGURE

Flowchart of data exclusion for pooled analysis, I-MOVE multicentre case-control study, influenza season 2012/13



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

the 103 influenza A(H3N2) viruses characterised at the national reference centre for influenza were similar to the A/Victoria/361/2011(H3N2) vaccine virus for the 2012/13 season [14]. This similarity was also reported by the Community Network of Reference Laboratories for Human Influenza in Europe (CNRL) [15]. This discrepancy between the apparently well-matched vaccine strain/circulating strains and low VE has also been noted this season in Canada [12].

Our 2013 early point VE estimates for influenza B are similar to estimates from the United States [13] and higher than those reported in the United Kingdom [16]. All the influenza B virus isolates genetically characterised from influenza cases enrolled in the Irish (three isolates), Portuguese (three isolates) and Spanish (four isolates) study sites were B/Yamagata, the lineage included in the 2012/13 vaccine. Data from the German national reference centre for influenza indicated that among 75 influenza B strains characterised, 68 were Yamagata and 7 Victoria.

The sample size did not allow VE estimation by type and subtype among the target population for vaccination. The low VE against all influenza types in this population is similar to the estimates the I-MOVE multicentre case-control study provided last season against influenza A(H3) [3].

This season, in which different influenza viruses are co-circulating in Europe, the I-MOVE multicentre case-control study provided early adjusted VE estimates for influenza B, A(H3N2) and A(H1N1)pdm09 viruses. However, due to small sample size, the precision around these estimates is low and should be taken into account when interpreting these preliminary results.

The results underscore the importance of providing early VE estimates against virus subtype regardless of the reported relatedness between circulating viruses and administered vaccines. The early VE estimates could be useful when defining the recommendations for next season's vaccine composition.

In conclusion, our early season estimates suggest that the 2012/13 influenza vaccine is effective in preventing medically attended laboratory-confirmed influenza, with a higher VE against influenza B than against influenza A subtypes. The lower VE among the target groups and against influenza A(H3N2) underlines that efforts to improve the influenza vaccine should continue in order to better protect those at risk of severe illness or complications.

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Conflict of interest

None declared. EpiConcept analyses pooled data of a hospital-network multicentre case-control (HNMCC) study measuring influenza VE. The HNMCC analysis is co-funded by Pasteur, Sanofi Pasteur MSD, GlaxoSmithKline and EpiConcept.

Authors' contributions

Marta Valenciano led the writing of the rapid communication. Esther Kissling undertook the statistical analysis on which the rapid communication is based. All authors participated in the interpretation of the study and contributed to the revision of the draft manuscript and approving the final version. Alain Moren, Marta Valenciano, Esther Kissling were involved in the original methodological design of the multicentre case-control study. Amparo Larrauri, Silvia Jiménez-Jorge, Joan O'Donnell, Emilia Lupulescu, Daniela Pitigoi, Baltazar Nunes, Ausenda Machado, Annicka Reuss, Udo Buchholz have had a role in modification of this design over the years.

Germany: Annicka Reuss, Udo Buchholz and Silke Buda are responsible for validation of data and interpretation of results. **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. Lisa Domegan was involved in collection, collation and analysis of clinical and virological data from all sentinel GPs. Darina O'Flanagan was involved in the original initiation of the ILI surveillance system and approved the final communication. Claire Collins was involved in the original study design. In this round, she contributed to the preparation of the ethical submission and coordinated the invitation letter to participating GPs and the GP payments. Michael Joyce was involved in the collection and collation of the data. Joanne Moran and Suzie Coughlan - Extraction of sentinel influenza I-MOVE data from the National Virus Reference Laboratory information system (NVRL LIMs) on a weekly basis for distribution to the Health Protection Surveillance Centre (HPSC). **Portugal:** Baltazar Nunes, Ausenda Machado, Raquel Guiomar and Pedro Pechirra were responsible for the study design in Portugal study site. Ausenda Machado, Inês Batista, were responsible for the field work, study monitoring, data validations and preparation. Pedro Pechirra, Paula Cristovão and Patricia Conde were responsible for the laboratory analysis: virus sub-typing, genotyping and laboratory data validation. **Romania:** Daniela Pitigoi, Emilia Lupulescu, Viorel Alexandrescu coordinated the Romanian study. Daniela Pitigoi and Emilia Lupulescu were responsible for the study design in Romania study site. Daniela Pitigoi, Emilia Lupulescu, Gheorghe Necula collected data. Daniela Pitigoi, Alina Ivanciuc enrolled patients. **Spain:** Amparo Larrauri and Silvia Jiménez-Jorge participated in the coordination of the Spanish study and the national database. Salvador de Mateo was involved in the interpretation and analysis of the Spanish study. Francisco Pozo and Inmaculada Casas were involved in genetic characterisation of influenza virus from the Spanish Influenza Surveillance System.

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