

# Early estimates of seasonal influenza vaccine effectiveness in Europe, 2010/11: I-MOVE, a multicentre case–control study

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We present early estimates (up to week 4 of 2011) of the 2010/11 seasonal influenza vaccine effectiveness in preventing medically attended influenza-like illness (ILI) laboratory confirmed as influenza. Practitioners from seven European sentinel networks systematically swabbed ILI patients. We included patients meeting the European Union ILI case definition and swabbed less than eight days after symptom onset. Laboratory-confirmed influenza cases were compared with negative controls. The adjusted vaccine effectiveness was 42.3% (95% CI: –7.3 to 69.0%), suggesting moderate protection of the seasonal vaccine.

## Background

The Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) network was established in 2007 by the European Centre for Disease Prevention and Control (ECDC) to monitor seasonal and pandemic influenza vaccine effectiveness [1–3]. In the 2010/11 season, to estimate the effectiveness of the seasonal vaccine in preventing medically attended influenza-like illness (ILI) laboratory confirmed as influenza we undertook a multicentre case–control study based on sentinel practitioner surveillance networks from eight study sites (France, Hungary, Ireland, Italy, Romania, Poland, Portugal and Spain). We report the preliminary results from seven study sites (data from France are not included in this preliminary analysis as data collection is ongoing).

## Data collection and analysis

We used similar methods to those used in the first two seasons of I-MOVE [1,3]. The studies were conducted within the context of the existing European Influenza Surveillance Network (EISN) [4].

The study population consisted of patients consulting a participating practitioner for ILI within eight days after symptom onset. Practitioners systematically selected ILI patients to swab.

A case of confirmed influenza was an ILI patient (defined according to the European Union case definition [5])

who was swabbed and tested positive for influenza using real-time polymerase chain reaction (PCR) or culture. Controls were ILI patients who were swabbed and tested negative for any influenza virus.

Individuals were considered vaccinated if they had received a dose of the seasonal vaccine more than 14 days before the date of onset of ILI symptoms. Participating sentinel practitioners interviewed ILI patients to collect information on ILI signs and symptoms, date of onset of symptoms, current vaccination status (including date of vaccination), prior seasonal and pandemic influenza vaccination status and a list of potential confounding factors: age, sex, presence of chronic condition(s), severity of chronic disease(s) using the number of hospitalisations for the chronic disease(s) in the previous 12 months as a proxy, smoking history (non-smoker, past, current smoker), number of practitioner visits in the previous 12 months. We included in the study patients recruited up to the end of week 4 of 2011, meeting the European ILI case definition with onset of symptoms more than 14 days after the start of national 2010/11 influenza vaccination campaigns. In each study, we excluded controls with symptom onset in the weeks before the week of symptom onset of the first confirmed influenza case of the season and individuals with missing information on laboratory results. In addition, for effectiveness of the vaccine in preventing influenza A(H1N1)2009 virus infection, we excluded any individual positive for other influenza virus types and excluded controls with symptom onset in the weeks before the week of symptom onset of the first case of influenza A(H1N1)2009 virus infection recruited in the 2010/11 season.

We estimated the pooled seasonal influenza vaccine effectiveness as one 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 vaccine effectiveness, we used logistic regression models including all potential confounding factors.

We first conducted the analysis excluding all individuals with at least one missing value (complete case analysis). We then estimated missing data for vaccination status and covariates using the multiple multivariate imputation by chained equations procedure in Stata [6]. We used missing at random assumptions. We used all predictors together to impute the missing values and independently analysed 20 copies of the data using 30 cycles of regression.

## Estimates of seasonal influenza vaccine effectiveness

A total of 585 practitioners agreed to participate in the study; 352 of them (60%) recruited at least one ILI patient (Table 1). After excluding 71 individuals with missing information on laboratory results, a total of 1,671 ILI patients were included in the analysis: 846 cases and 825 controls (Figure 1). Among the cases, 649 (76.7%) were positive for influenza A(H1N1)2009 virus, nine (1.1%) for influenza A(H3N2) virus, 15 (1.8%) were positive for influenza A virus that could not be subtyped and 173 (20.5%) were positive for influenza B virus.

Among 1,658 individuals with information on vaccination status and vaccination date for seasonal vaccination in 2010/11, 116 (7.0%) were vaccinated (ranging from 2.2% in Poland and Ireland to 19.9% in Italy).

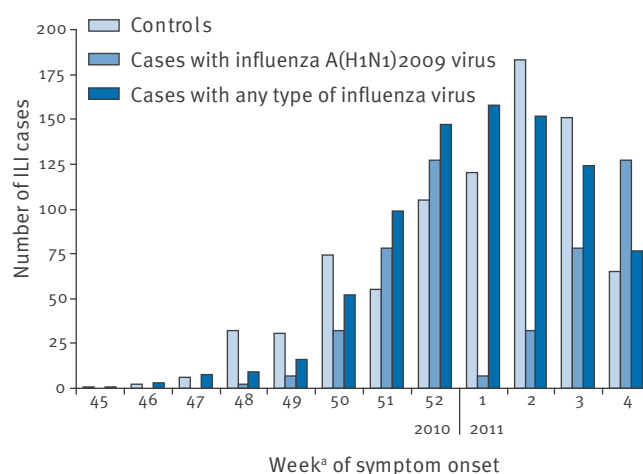
The median age was lower in cases (29 years, standard deviation (SD): 18 years) than in controls (34 years, SD: 21 years) (Table 2). The delay between onset of symptoms and swabbing was slightly shorter in cases (mean: 1.8 days, range: 0–7 days) than in controls (mean: 1.9 days, range: 0–7 days). The proportion of individuals presenting with fever, malaise, headache, myalgia or cough was higher among cases than among controls (Table 2). Compared with cases, a higher proportion of

controls had diabetes, heart disease or were hospitalised at least once for their chronic disease in the previous 12 months. A higher proportion of controls were current or past smokers, vaccinated with the 2009/10 seasonal influenza vaccine, and vaccinated with the 2009/10 pandemic influenza vaccine. The median number of practitioner visits in the previous 12 months was two for cases (ranging from 0 to 26) and three for controls (ranging from 0 to 60) (Table 2).

A total of 34 cases were vaccinated with the 2010/11 seasonal vaccine. In two of the seven studies there

**FIGURE**

Influenza A(H1N1)2009 cases (n=649), all influenza cases (n=846) and influenza-negative controls (n=825) recruited by week of symptom onset, multicentre case-control study, seven European Union country study sites, week 45 (2010)–week 4 (2011)



ILI: influenza-like illness.

<sup>a</sup> International Organization for Standardization (ISO) definition of a week.

**TABLE 1**

Practitioners' participation, influenza-like illness (ILI) patients recruited by case-control status, vaccination status and study site, multicentre case-control study, seven European Union country study sites, week 45 (2010)–week 4 (2011)

Study site	Number of practitioners accepting to participate in the study	Number of practitioners recruiting at least one ILI patient <sup>a</sup>	Number of ILI patients <sup>a</sup> recruited by practitioners	Inclusion period for the study	Number of ILI patients included in the study positive for any influenza virus <sup>c</sup>		Number of ILI patients included in the study negative for any influenza virus <sup>c</sup>	
					Total	Vaccinated	Total	Vaccinated
Hungary	98	64	242	50 (2010)–4 (2011)	47	1	195	11
Ireland	22	17	160	48 (2010)–4 (2011)	84	0	54	3
Italy	38	31	220	48 (2010)–4 (2011)	40	7	126	26
Poland	34	16	46	48 (2010)–4 (2011)	24	0	21	1
Portugal	58	30	186	45 (2010)–4 (2011)	117	5	69	11
Romania	89	40	69	52 (2010)–4 (2011)	32	2	37	5
Spain	246	154	819	49 (2010)–4 (2011)	498	19	314	25
<b>Total</b>	<b>585</b>	<b>352</b>	<b>1,742</b>	–	<b>842</b>	<b>34</b>	<b>816</b>	<b>82</b>

ISO : International Organization for Standardization.

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

<sup>b</sup> From 15 days after the start of the seasonal influenza vaccination campaign to the week of symptom onset of the last case recruited. Controls with an onset of symptoms in the weeks before the first case were excluded.

<sup>c</sup> ILI patients in the study after excluding those with missing information on laboratory results, vaccination status or date of vaccination.

were no vaccinated individuals among the recruited cases.

In the pooled complete case analysis the adjusted vaccine effectiveness was 35.1% (95% CI: -23.0 to 65.8) in preventing influenza caused by all types of influenza viruses and 34.9% (95% CI: -37.5 to 69.2%) in preventing influenza A(H1N1)2009 virus infection (Table 3).

In the pooled analysis with imputed data, the adjusted vaccine effectiveness against all influenza strains was 42.3% (95% CI: -7.3 to 69.0%), and 44.1% (95% CI: -14.3 to 72.7%) against influenza A(H1N1)2009 virus (Table 3).

## Discussion

Our early pooled estimates suggest that the 2010/11 seasonal vaccine conferred moderate protection against medically attended laboratory-confirmed influenza. These results should be interpreted with caution, however, for reasons including low vaccine coverage and potential biases due to the test-negative design, confounding factors, missing values and small sample size due to the early estimation in the season. Those biases have been described elsewhere in detail [3,7].

Our estimates of the 2010/11 seasonal vaccine effectiveness apply to the study period (until the end of week 4 of 2011). They are based on data from seven European study sites sharing the same protocol and definition of variables. The pooled point estimates of vaccine effectiveness were between 35% (adjusted) and 61% (crude).

**TABLE 2**

Characteristics of influenza cases (n=846) and test-negative controls (n=825) included, multicentre case-control study, seven European Union country study sites, week 45 (2010)–week 4 (2011)

Characteristic	Influenza cases No./total no. (%) <sup>a</sup>	Test-negative controls No./total no. (%) <sup>a</sup>	P value
<b>Median age</b>	29 years	34 years	< 0.001 <sup>b</sup>
<b>Age group (years)</b>			
0–4	49/845 (5.8)	57/825 (6.9)	< 0.001 <sup>c</sup>
5–14	146/845 (17.3)	88/825 (10.7)	
15–64	621/845 (73.5)	591/825 (71.6)	
≥65	29/845 (3.4)	89/825 (10.8)	
<b>Female</b>	443/844 (52.5)	433/825 (52.5)	1.000 <sup>c</sup>
<b>Symptoms</b>			
Fever	818/845 (96.8)	763/819 (93.2)	0.001 <sup>c</sup>
Malaise	791/846 (93.5)	745/822 (90.6)	0.037 <sup>c</sup>
Headache	653/830 (78.7)	596/809 (73.7)	0.020 <sup>c</sup>
Myalgia	683/827 (82.6)	626/806 (77.7)	0.013 <sup>c</sup>
Cough	797/846 (94.2)	686/818 (83.9)	<0.001 <sup>c</sup>
<b>Number of days between symptom onset and swabbing</b>			
0	49/846 (5.8)	39/825 (4.7)	0.327 <sup>c</sup>
1	376/846 (44.4)	352/825 (42.7)	
2	247/846 (29.2)	242/825 (29.3)	
3	108/846 (12.8)	105/825 (12.7)	
≥4	66/846 (7.8)	87/825 (10.5)	
<b>Seasonal vaccination, 2010/11</b>	34/842 (4.0)	82/816 (10.0)	<0.001 <sup>c</sup>
<b>Pandemic vaccination, 2009/10</b>	53/826 (6.4)	88/784 (11.2)	0.001 <sup>c</sup>
<b>Seasonal vaccination, 2009/10</b>	58/825 (7.0)	109/780 (14.0)	<0.001 <sup>c</sup>
<b>Diabetes</b>	15/741 (2.0)	38/774 (4.9)	0.003 <sup>c</sup>
<b>Heart disease</b>	24/740 (3.2)	84/774 (10.9)	<0.001 <sup>c</sup>
<b>Smoker status</b>			
Current	88/822 (10.7)	123/786 (15.6)	<0.001 <sup>c</sup>
Former	52/822 (6.3)	79/786 (10.1)	
Never	682/822 (83.0)	584/786 (74.3)	
<b>Median number of GP visits in the previous 12 months</b>	2	3	0.005 <sup>b</sup>
<b>Any hospitalisation in the previous 12 months for chronic diseases</b>	1/846 (1.1)	23/823 (2.6)	0.026 <sup>c</sup>

GP: general practitioner.

<sup>a</sup> Unless otherwise indicated.

<sup>b</sup> Non-parametric test of the median.

<sup>c</sup> Two-sided Fisher's exact test.

We adjusted for most of the confounding factors described in the literature (see, for example, [7]). The adjusted vaccine effectiveness was lower than the crude vaccine effectiveness (absolute differences ranging from 16.2% to 24.7%), suggesting some positive confounding. The main confounders identified were seasonal influenza vaccination in the previous season and age group.

This is the third season the I-MOVE programme has estimated influenza vaccine effectiveness using laboratory-confirmed outcomes. Compared with the I-MOVE estimates of last season, the 2010/11 seasonal vaccine seems to have a lower effectiveness against influenza A(H1N1)2009 virus infection than the monovalent pandemic vaccine of 2009/10 [3]. This may be explained by antigenic drift, by a different distribution of adjuvanted versus non-adjuvanted vaccines in some study sites [8] or by a different study population. The ILI cases included in the 2009/10 I-MOVE multicentre case-control study were younger (mean age: 12 years for cases and 24 for controls) than those included in this 2010/11 early analysis.

The pooled early estimates are similar to those observed in the United Kingdom [9], the Navarre region in Spain [8] and the cycEVA study in Spain [10]. Later in the season, the larger sample size per country will allow us to conduct precise pooled and stratified analyses and to further explore the difference in effectiveness of the seasonal vaccine with that of the 2009/10 pandemic vaccine. In addition, the use of validation subsets in France, in which we collect more accurate and additional information in a subsample of the ILI patients, will enable to base our estimates on data from eight countries.

I-MOVE is a unique network in Europe able to measure seasonal and pandemic vaccine effectiveness. The early estimates presented here suggest that the seasonal vaccine has a lower effectiveness than that observed with the monovalent pandemic vaccine [3].

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**TABLE 3**

Pooled crude and adjusted 2010/11 seasonal vaccine effectiveness, by type of outcome and type of analysis, multicentre case-control study, seven European Union country study sites, week 45 (2010)–week 4 (2011)

Outcome	Crude vs adjusted	Complete vs imputed data analysis	Number of ILI cases included	Vaccine effectiveness	
				%	95% CI
Infection with any influenza virus	Crude <sup>a</sup>	Complete case analysis <sup>b</sup>	1,390	56.9	32.2 to 72.6
		Imputed data <sup>c</sup>	1,671	58.5	35.7 to 73.2
	Adjusted model <sup>d</sup>	Complete case analysis <sup>b</sup>	1,390	35.1	-23.0 to 65.8
		Imputed data <sup>c</sup>	1,671	42.3	-7.3 to 69.0
Infection with influenza A(H1N1)2009 virus	Crude <sup>a</sup>	Complete case analysis <sup>b</sup>	1,158	59.6	32.6 to 75.8
		Imputed data <sup>c</sup>	1,407	60.5	35.3 to 75.8
	Adjusted model <sup>d</sup>	Complete case analysis <sup>b</sup>	1,158	34.9	-37.5 to 69.2
		Imputed data <sup>c</sup>	1,407	44.1	-14.3 to 72.7

ILI: influenza-like illness.

<sup>a</sup> Study site included in the model as fixed effect.

<sup>b</sup> Excluding individuals with missing values.

<sup>c</sup> Missing data imputed using imputation by chained equations.

<sup>d</sup> Model adjusted for 2009/10 seasonal and pandemic influenza vaccination, presence of at least one chronic disease, sex, at least one hospitalisation for chronic disease in the previous 12 months, current smoker, age group, visits to a general practitioner in previous 12 months (0–1, 2–4 and ≥5 visits) and week of symptom onset.

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11. Savulescu C, Jiménez-Jorge S, de Mateo S, Ledesma J, Pozo F, Casas I, et al. Effectiveness of the 2010/11 seasonal trivalent influenza vaccine in Spain: preliminary results of a case-control study. *Euro Surveill.* 2011;16(11):pii=19820. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19820>

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#### References

1. Kissling E, Valenciano M, Falcao J, Larrauri A, Widgren K, Pitigoi D, et al. "I-MOVE" towards monitoring seasonal and pandemic influenza vaccine effectiveness: lessons learnt from a pilot multi-centric case-control study in Europe, 2008-9. *Euro Surveill.* 2009;14(44):pii=19388. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19388>
2. Savulescu C, Valenciano M, de Mateo S, Larrauri A; cycEVA Study Team. Estimating the influenza vaccine effectiveness in elderly on a yearly basis using the Spanish influenza surveillance network-pilot case-control studies using different control groups, 2008-2009 season, Spain. *Vaccine.* 2010;28(16):2903-7.
3. Valenciano M, Kissling E, Cohen JM, Oroszi B, Barret AS, Rizzo C, et al. Estimates of pandemic influenza vaccine effectiveness in Europe, 2009-2010: results of Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) multicentre case-control study. *PLoS Med.* 2011;8(1):e1000388.
4. European Centre for Disease Prevention and Control (ECDC). European Influenza Surveillance Network (EISN). [Accessed 16 Mar 2011]. Stockholm, ECDC. Available from: <http://ecdc.europa.eu/en/activities/surveillance/eisn/pages/index.aspx>
5. European Commission. Commission Decision of 30 April 2009 amending Decision 2002/253/EC laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Council. Luxembourg: Publications Office of the European Union. 15.2009. L 110/58. Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:110:0058:0059:EN:PDF>
6. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ.* 2009;338:b2393.
7. Valenciano M, Kissling E, Ciancio BC, Moren A. Study designs for timely estimation of influenza vaccine effectiveness using European sentinel practitioner networks. *Vaccine.* 2010;28(46):7381-8.
8. Castilla J, Moran J, Martínez-Artola V, Reina G, Martínez-Baz I, García Cenoz M, et al. Effectiveness of trivalent seasonal and monovalent influenza A(H1N1)2009 vaccines in population with major chronic conditions of Navarre, Spain: 2010/11 mid-season analysis. *Euro Surveill.* 2011;16(7):pii=19799. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19799>
9. Pebody R, Hardelid P, Fleming D, McMenamin J, Andrews N, Robertson C, et al. Effectiveness of seasonal 2010/11 and pandemic influenza A(H1N1)2009 vaccines in preventing influenza infection in the United Kingdom: mid-season analysis 2010/11. *Euro Surveill.* 2011;16(6):pii=19791. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19791>