“I-MOVE” TOWARDS MONITORING SEASONAL AND PANDEMIC INFLUENZA VACCINE EFFECTIVENESS: LESSONS LEARNT FROM A PILOT MULTI-CENTRIC CASE-CONTROL STUDY IN EUROPE, 2008-9

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Within I-MOVE (European programme to monitor seasonal and pandemic influenza vaccine effectiveness (IVE)) five countries conducted IVE pilot case-control studies in 2008-9. One hundred and sixty sentinel general practitioners (GP) swabbed all elderly consulting for influenza-like illness (ILI). Influenza confirmed cases were compared to influenza negative controls. We conducted a pooled analysis to obtain a summary IVE in the age group of ≥65 years. We measured IVE in each study and assessed heterogeneity between studies qualitatively and using the I2 index. We used a one-stage pooled model with study as a fixed effect. We adjusted estimates for age-group, sex, chronic diseases, smoking, functional status, previous influenza vaccinations and previous hospitalisations. The pooled analysis included 138 cases and 189 test-negative controls. There was no statistical heterogeneity (I2=0) between studies but IVE case definition, previous hospitalisations and functional status were slightly different. The adjusted IVE was 59.1% (95% CI: 15.3-80.3%). IVE was 65.4% (95% CI: 15.6-85.8%) in the 65-74, 59.6% (95% CI: -72.6-90.6%) in the age group of ≥75 and 56.4% (95% CI: -0.2-81.3%) for A(H3).

Therefore, influenza vaccine effectiveness (IVE) can vary from year to year according to the degree of match between the selected vaccine strains and those actually circulating. Hence, IVE should be measured and monitored every year. In a pandemic situation, strain specific vaccines become available only four to six months after beginning the development of the vaccine. Consequently, when the vaccines start to be administered, the virus is already circulating and IVE results are needed rapidly. In addition, vaccine availability is likely to increase over time according to the speed of vaccine production and the licensing of additional vaccines, meaning that IVE measurements need to be repeated over time during the pandemic.

Many factors affect IVE in observational studies. IVE estimates vary according to the specificity of the outcome, the influenza incidence, the population targeted for vaccination and the confounding factors taken into account. Many of the case-control studies reported in the literature measured IVE against clinical outcomes (i.e., hospitalisations for pneumonia or influenza, acute respiratory infections, influenza-like illness (ILI)). Clinical outcomes for influenza are non-specific and likely to underestimate the IVE when the vaccines start to be administered, the virus is already circulating and IVE results are needed rapidly. In addition, vaccine availability is likely to increase over time according to the speed of vaccine production and the licensing of additional vaccines, meaning that IVE measurements need to be repeated over time during the pandemic.

Confounding affects IVE observational studies. IVE is underestimated when individuals at higher risk of acquiring influenza are more likely to be vaccinated than individuals at lower risk (negative confounding by indication) [6,7]. IVE is overestimated if individuals more cautious about their health and at lower risk of acquiring influenza are more likely to be vaccinated (positive confounding due to healthy vaccinee effect) [7,8].
In general practitioners (GP) based case-control studies, individuals who use health services more often are more likely to be vaccinated and more likely to consult their GP with influenza symptoms. Vaccinated individuals with influenza symptoms will have a higher probability of being included in the study than vaccinated individuals with no influenza symptoms. This would underestimate the IVE. To control for health seeking behaviour, recent studies suggested comparing individuals who consult for ILI and are influenza positive to individuals consulting for ILI who test negative for influenza (test-negative controls) [3-5;9]. The assumption is that test-negative controls have the same vaccination coverage as the source population giving rise to the influenza cases detected at the GP practice.

I-MOVE started in 2007 with the aim to measure IVE against seasonal and pandemic influenza in the European Union (EU) and the European Economic Area (EEA). Two cohort and five case-control studies to measure IVE were piloted in the 2008-9 season. In order to develop a sustainable system, the studies were conducted in the framework of existing GP-based influenza sentinel surveillance systems. All the country teams conducting I-MOVE pilot studies are members of the European Influenza Surveillance Network (EISN) [14]. The successor of the Commission-funded network, EISS, EISN collects and exchanges timely information on influenza activity in Europe [11]. National Reference Laboratories participating in EISN are evaluated periodically through external inter-laboratory quality control assessments. All the EU Member States recommend seasonal vaccine for the elderly either defined as 65 years old and older or as 60 years old and older [12].

In the pilot case-control studies, we measured IVE against laboratory-confirmed influenza and collected variables to control for positive and negative confounding in the analysis. We restricted the study population to community-dwelling elderly. To increase the precision of the estimates and to provide a summary IVE for the five participating European countries. Age groups included were community-dwelling elderly individuals consulting for ILI during the previous two seasons.

IVE estimates were obtained using the formula: 1 - odds ratio, with 95% exact confidence intervals (CI) [10,15].
We computed study specific crude IVE and adjusted for the pre-defined set of confounders (including age, sex, chronic disease, smoking, previous influenza vaccination and functional status) where possible, using logistic regression. We evaluated heterogeneity between studies qualitatively by assessing the standardisation of the case and covariate definitions. We evaluated statistical heterogeneity using the Q-test and the I² index [16,17]. To estimate a pooled IVE, we used a one-stage method with study as fixed effect in the model. Results were stratified according to influenza strain and two age groups: 65-74 and >74 years.

According to country specific requirements for ethical approval, all participants provided oral or written consent.

**Figure 1**
Influenza-like illness (ILI) incidence (cases per 100,000 population) reported by the national influenza sentinel surveillance systems in Denmark, Hungary, Portugal, Romania, and Spain, influenza season 2008-9*

**Table 1**
General practitioner (GP) participation and influenza-like illness (ILI) cases recruitment by study, Denmark, Hungary, Portugal, Romania, and Spain, influenza season 2008-9
Table 2
Influenza cases and test-negative controls by study and characteristic, Denmark, Hungary, Portugal, Romania, and Spain, influenza season 2008-9

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Country</th>
<th>ILI patients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Influenza cases</td>
<td>Test-negative controls</td>
</tr>
<tr>
<td>Interval from symptom onset to swab sample collection (mean in days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Denmark</td>
<td>3.05</td>
<td>4.25</td>
</tr>
<tr>
<td></td>
<td>Hungary</td>
<td>2.1</td>
<td>3.08</td>
</tr>
<tr>
<td></td>
<td>Portugal</td>
<td>1.5</td>
<td>2.33</td>
</tr>
<tr>
<td>Mean age</td>
<td>Portugal</td>
<td>70</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any influenza vaccination in past 2 seasons</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Portugal</td>
<td>4/14</td>
<td>10/14</td>
</tr>
<tr>
<td></td>
<td>Spain</td>
<td>28/43</td>
<td>33/36</td>
</tr>
<tr>
<td></td>
<td>Denmark</td>
<td>19/20</td>
<td>14/21</td>
</tr>
<tr>
<td></td>
<td>Romania</td>
<td>30/30</td>
<td>57/68</td>
</tr>
<tr>
<td>Cough</td>
<td>Denmark</td>
<td>20/20</td>
<td>16/21</td>
</tr>
<tr>
<td></td>
<td>Romania</td>
<td>1/30</td>
<td>13/68</td>
</tr>
</tbody>
</table>

*Mann-Whitney U test, **Chi square
Results

In the participating pilot countries, the 2008-9 seasonal influenza epidemic started in Portugal at the end of 2008 (epidemiological week 49) and spread to the east of Europe (Hungary) in spring 2009 (week 4) (Figure 1).

The duration of the epidemic period ranged from seven weeks in Denmark to 13 weeks in Romania. The influenza peaks were reached between week 52 in 2008 (Portugal) and week 10 in 2009 (Romania).

In the five participating countries, the population was vaccinated with a trivalent inactivated influenza vaccine. In the 2008-9 influenza season, different vaccine brands were used in each of the countries. The number of GPs enrolled in each of the studies ranged from 40 in Denmark to 164 in Spain. Overall, 160 GPs recruited at least one patient ranging from 21% in Portugal to 73% in Denmark (Table 1). GPs swabbed and interviewed a total of 455 ILI patients. Among them, 159 (35%) were positive for influenza (from 29% in Romania to 43% in Spain). The completeness of the variables in the returned questionnaires varied from 85% to 100%.

Among 147 isolates typed before the restriction criteria were applied, 131 (89%) were influenza A and 16 (11%) B. Ninety-five of the A isolates were H3N2. All H3N2 strains genetically characterised were A/Brisbane/10/07 similar to the H3N2 vaccine component of the 2008-9 northern hemisphere vaccine. The B strain included in the 2008-9 vaccine did not match the circulating strain. Eight out of the 16 type B isolates were from cases enrolled in Hungary.

After applying the study restriction criteria we included 138 cases and 189 test-negative controls in the analysis (Figure 2).

### Table 3
Vaccination coverage for the seasonal 2008-9 influenza vaccine by control group and country study, Denmark, Hungary, Portugal, Romania, and Spain, 2008-9

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccine coverage (%) in ILI positive cases</th>
<th>Vaccine coverage (%) in test-negative controls</th>
<th>Vaccine coverage (%) in non-ILI GP patients</th>
<th>Vaccine coverage in community controls</th>
<th>Vaccine coverage in participating GPs catchment area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>55</td>
<td>71.4</td>
<td>N/A</td>
<td>53.6**</td>
<td>N/A</td>
</tr>
<tr>
<td>Hungary***</td>
<td>41.9</td>
<td>48.7</td>
<td>42.7</td>
<td>N/A</td>
<td>38.5</td>
</tr>
<tr>
<td>Portugal</td>
<td>42.9</td>
<td>53.3</td>
<td>70</td>
<td>54.4*</td>
<td>N/A</td>
</tr>
<tr>
<td>Romania</td>
<td>46.7</td>
<td>67.6</td>
<td>N/A</td>
<td>N/A</td>
<td>86.9</td>
</tr>
<tr>
<td>Spain</td>
<td>61.4</td>
<td>89.2</td>
<td>80.7</td>
<td>N/A</td>
<td>65.3</td>
</tr>
</tbody>
</table>

N/A: not applicable
*Community controls sample selected for national telephone survey (Lisboa: Instituto Nacional de Saúde Dr. Ricardo Jorge. Observatório Nacional de Saúde)
** Community controls randomly selected from the Danish population register
*** Results apply to ages 65 years and above, apart from Hungary where the study was carried out for 60 year-olds and older

### Table 4
Country specific and pooled crude and adjusted vaccine effectiveness (VE), Denmark, Hungary, Portugal, Romania, and Spain, influenza season 2008-9

<table>
<thead>
<tr>
<th>Country specific estimates</th>
<th>Crude analysis</th>
<th>Adjusted analysis</th>
<th>Variables used for adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N  VE  95% CI</td>
<td>N  VE  95% CI</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>81  80.8  36.0 - 94.2</td>
<td>76  82.9  30.6 - 95.8</td>
<td>age, sex, chronic disease, smoking, functional status</td>
</tr>
<tr>
<td>Portugal</td>
<td>29  34.4  -184.3 - 84.9</td>
<td>28  82.3  -70.5 - 98.2</td>
<td>age, sex, chronic disease, smoking</td>
</tr>
<tr>
<td>Denmark</td>
<td>41  51.1  -78.2 - 86.6</td>
<td>34  90.9  -43 - 99.4</td>
<td>age, sex, chronic disease, smoking, previous influenza vaccination</td>
</tr>
<tr>
<td>Romania</td>
<td>98  58.2  -0.8 - 82.6</td>
<td>92  86.8  38.0 - 97.2</td>
<td>age, sex, chronic disease, smoking, previous influenza vaccination</td>
</tr>
<tr>
<td>Hungary</td>
<td>78  28.6  -78.6 - 71.5</td>
<td>72  43.6  -119.8 - 85.6</td>
<td>age, sex, chronic disease, smoking, previous influenza vaccination</td>
</tr>
<tr>
<td>Pooled estimates</td>
<td>65+</td>
<td>327  55.1  27.8 - 72.1</td>
<td>292  59.1  15.3 - 80.3</td>
</tr>
<tr>
<td></td>
<td>65-74 years</td>
<td>196  65.4  15.6 - 85.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75+ years</td>
<td>96  59.6  -72.6 - 90.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A(H3) strain</td>
<td>259  56.4  -0.2 - 81.0</td>
<td></td>
</tr>
</tbody>
</table>
In Romania and Denmark, the proportion of ILI patients presenting with fever was higher among cases than among test-negative controls (Table 2). In Denmark, all of the cases and three quarters of the controls had a cough (p=0.02). In Romania, the proportion of ILI patients with pulmonary chronic disease was lower among cases than among controls (3% vs. 19%).

The mean delay between onset of symptoms and swab collection was shorter for cases than for test-negative controls in Portugal, Denmark and Romania (Table 2). In Spain and Portugal, the proportion of people having received influenza vaccines in at least one of the two previous seasons was lower among cases than among test-negative controls.

Vaccination coverage among controls varied according to country and control group; no specific pattern was identified (Table 3).

The country specific adjusted VE estimates ranged from 43.6% (95% CI: -119.8 - 85.6) in Hungary to 90.9% (95% CI: -42.6 - 99.4) in Denmark (Table 4).

In terms of heterogeneity between studies, two out of the five studies used a different ILI definition. Three variables (number of hospitalisations, presence of chronic diseases and functional status) were collected differently in the five studies. The Q test for heterogeneity was 2.87 (p = 0.579) and the I2 index was 0%.

In the pooled analysis the crude IVE was 55.1% (95% CI: 27.8-72.1%). The IVE adjusted for study, age, sex, presence of chronic conditions, previous hospitalisations, smoking history, functional status, and previous influenza vaccination was 59.1% (95% CI: 15.3-80.3%) (Table 4).

The adjusted IVE was 65.4% (95% CI: 15.6-85.8%) in the 65-74 year-olds and 59.6% (95% CI: -72.6 -90.6%) in the age-group of ≥75 years. The adjusted IVE against the A(H3) strain was 56.4% (95% CI: -0.2-81.0%).

Discussion

We estimated influenza VE against laboratory-confirmed medically attended influenza using test-negative controls, within existing sentinel GP networks in five EU countries. The country specific and the pooled IVE estimates suggest a protective effect of the 2008-9 seasonal vaccine in the elderly population in a year with a good match between the seasonal vaccine and the A(H3) strain predominantly circulating in Europe [18]. However, the estimates have wide confidence intervals.

The case-control design using test-negative controls was performed easily in the framework of the established GP sentinel surveillance networks. Participating GPs had previous experience in collecting swabs and in completing a form for each patient swabbed. Among the GPs who accepted to participate in the study, less than half interviewed and swabbed ILI patients. This may be explained by the overall low incidence of ILI in the elderly in 2008-9 [18] rather than a low acceptability of GPs, as swabbing and interviewing ILI patients is a simple way of recruiting cases and test-negative controls. The questionnaires used for data collection were short leading to a high completeness of all variables. At the end of the season, the study coordinators in Denmark, Romania, and Spain interviewed GPs who participated in the 2008-9 study. Most of them (95% in Spain, 78% in Romania, 74% in Denmark) would be willing to participate in the study in 2009-10 (data not shown). In 2006 in Denmark (one of the current study sites), Mazick et al. showed similar acceptability results following an influenza VE case-control study based on the sentinel GP network [19].

We took into account the main confounding factors identified in the literature. Most of them were based on patients’ report for which validity is unknown. The pooled crude and adjusted IVE were similar suggesting a low distortion of effect due to confounding. In our study, a small proportion of ILI patients had indicators of frailty (4.3% had poor functional status and 6.4% were hospitalised in the previous year). Elderly ILI patients consulting GPs at their office may have a better health status than those not consulting. Therefore, functional status and severity may not be relevant confounding factors within this study population and study design. Our results may also reflect that using specific outcomes decrease the amount of confounding observed [5,7]. In Canada, using the same study design, IVE did not change when adjusting for chronic diseases [20].

The recruitment procedure minimised selection bias as all ILI cases were swabbed. Furthermore, GPs did not know the case or control status when recruiting ILI patients. This was the first season in which the EU ILI case definition was introduced into the sentinel GP networks. For most ILI patients recruited, the case definition was correctly used: of 455 ILI patients reported, only 17 were excluded because they did not match the EU ILI case definition. However, we cannot rule out that some GPs did not include all patients corresponding to the EU case definition. If the sensitivity of GPs’ ILI case definition were dependent on the vaccination status, IVE might have been over- or underestimated.

Various studies suggest that ILI test-negative controls represent the source population of influenza cases seen at GPs offices and that the study design adjusts for propensity to seek care. This would mean that the propensity to seek care is equal between ILI patients who test positive and those testing negative for influenza. Our results indicate that in three out of the five studies, the delay between onset of symptoms and swabbing was shorter for cases than for test-negative controls. Similar results were found in the Wisconsin study [3]. This may indicate a different health-seeking behaviour or a different severity of ILI in cases and in controls. Health-seeking behaviour of ILI cases and ILI test-negative controls should be further studied and compared.

To further assess the representativity of test-negative controls, we measured the vaccine coverage in other potential control groups. The vaccine coverage differed by control group (test-negative controls, non-ILI GP controls, community controls) and between countries with no specific pattern. This could suggest that the source population of influenza cases consulting a GP may be country specific. In general, the vaccine coverage in the community or in the GPs’ catchment area was lower than the vaccine coverage of GP clients indicating that community controls do not represent a good control group for medically-attended ILI influenza cases. In a recent study in Wisconsin, VE for laboratory confirmed medically attended-ILI was estimated for three seasons using two control groups: test-negative controls and controls randomly selected from individuals in the source population who did not have a clinical encounter for acute respiratory illness prior to the week of recruitment [3]. In the three seasons, the vaccination coverage of the test-negative controls was higher than among the other controls.

We estimated influenza VE against laboratory-confirmed medically attended influenza using test-negative controls, within existing sentinel GP networks in five EU countries. The country specific and the pooled IVE estimates suggest a protective effect of the 2008-9 seasonal vaccine in the elderly population in a year with a good match between the seasonal vaccine and the A(H3) strain predominantly circulating in Europe [18]. However, the estimates have wide confidence intervals.

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The excellent collaboration between the study teams made the pooling of data from the five studies possible. Pooling increased the precision of the estimates. Given the small samples sizes of the individual studies, we used a one-stage pooling model that assumes that the effect of the exposure (the seasonal vaccine) and the effect of the covariates are the same in all the studies. We do not know if the difference in virus circulation in the various countries and a potential different health-seeking behaviour may violate this assumption. The pooled estimates of the pilot phase have to be interpreted with caution as heterogeneity between studies may exist. Furthermore, different vaccine brands were used. However, the aim of I-MOVE is not to guide the Member States in deciding which seasonal vaccine to purchase. In order to assess VE for the various vaccine brands, the sample size would have to be increased significantly. The definitions of some covariates were not exactly the same in the different studies. Tests for interaction between study and covariates did not suggest the presence of heterogeneity. However, the small sample size may have led to an insufficient power to detect heterogeneity.

Conclusions

In 2008-9 the match between the seasonal influenza vaccine and the predominant circulating strains was good and the IVE in the elderly relatively high. Our results suggest that GP based case-control studies using test-negative controls to estimate seasonal IVE against laboratory-confirmed medically- attended influenza, are feasible in Europe. The use of a laboratory confirmed outcome may reduce the magnitude of confounding. If other studies confirm this, the number of confounders documented may be reduced, thus simplifying the data collection. The representativity of test-negative controls should be further evaluated.

Pooling of country specific data is needed to have early seasonal or pandemic VE estimates and to increase the precision of the estimates for subgroup analysis. In 2009-10 we will increase the sample size, by increasing the number of countries participating in the study and including more GPs per country. The larger sample size will allow the use of a two-stage model that better takes into account the potential heterogeneity between studies (18,21). The studies will use common definitions for all variables to minimise heterogeneity between studies. During H1N1 influenza pandemic, interim analyses will be conducted in different periods according to the available sample size. The timing for conducting each of the interim analyses will depend on the time necessary to reach the appropriate sample size. This will depend mainly on the ILL incidence, the influenza incidence and the vaccination coverage.

The suitability of the case-control studies based on sentinel GPs to measure pandemic IVE will depend on the vaccination and control strategy. If pandemic cases are seen by the sentinel GPs and GPs have the possibility to ascertain patient vaccination status, then the case-control design piloted in 2008-9 would be adequate to estimate pandemic VE. All age and risk groups targeted by the vaccine should be included in the study. The design will be adapted to reduce the GPs' workload by simplifying the questionnaire and revising the procedure to select patients to swab.

Acknowledgements

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