Case control study measuring influenza vaccine effectiveness in Ireland 2010/2011

Final report

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1. Background

As influenza viruses constantly evolve and vaccines are reformulated every year, influenza vaccine effectiveness (VE) from previous years cannot be used to estimate VE in subsequent years. Having vaccine effectiveness estimates as soon as possible and monitoring the effectiveness along the course of an influenza season is essential to:

- Decide on recommendations for the use of the vaccine
- Target complementary or alternative public health measures (e.g. antivirals) for population subgroups for whom vaccine is less effective
- Allow for precise estimates of the impact of the current vaccination strategies on the burden of disease to support vaccination campaigns
- Trigger further investigation on seasonal and pandemic vaccines (improve composition, use of adjuvants, need for booster doses)
- Better manage and respond to expected reports of vaccine failures
- Counterbalance the reports of adverse events following immunisation by providing elements for an adequate risk management and cost effectiveness analysis

In February 2010, the World Health Organization (WHO) recommended the following viruses to be used for influenza vaccines in the 2010/2011 influenza season in the northern hemisphere:

- an A/California/7/2009 (H1N1)-like virus;
- an A/Perth/16/2009 (H3N2)-like virus;
- a B/Brisbane/60/2008-like virus.

Following these recommendations, trivalent influenza vaccines were developed by manufacturers and provided to the Irish population at the beginning of the 2010/2011 influenza season.

The first study measuring the influenza vaccine effectiveness in Ireland was conducted in 2009/2010. It aimed to estimate the pandemic influenza vaccine effectiveness against medically-attended influenza-like illness (ILI) laboratory-confirmed as pandemic (H1N1) 2009. A multicentre case-control study was undertaken using sentinel practitioner surveillance networks from seven European countries. Results of country-specific and pooled vaccine effectiveness were published in national (1) and international journals (2).
In 2010/11, a multicentre case-control study was conducted in eight European countries including Ireland. In Ireland, this study was undertaken as a collaboration between the Health Protection Surveillance Centre (HPSC), the Irish College of General Practitioners (ICGP) and the National Virus Reference Laboratory (NVRL).

This report presents the final results of the case-control study conducted in Ireland using the data collected from week 39-2010 to week 16-2011.

2. Study Objectives

2.1. Primary objective

The main objective was to estimate the trivalent influenza vaccine effectiveness in Ireland.

2.2. Secondary objectives

- To estimate VE among the target population for influenza vaccination, as recommended by the Irish National Immunisation Advisory Committee (NIAC) (Recommendations for influenza vaccine during the 2010/2011 season are described in Annex A)
- To provide intra-seasonal VE estimates
- To estimate VE in risk groups
- To estimate VE by influenza subtype
- To monitor VE estimates every year
3. Methods

3.1. Study design

A case-control study was conducted within the framework of the GP influenza sentinel surveillance system.

3.2. Study timeline

We conducted the case-control study between week 38-2010 and week 16-2011. Annex B shows the influenza outbreak timeline and the description of influenza activity during the 2010/2011 season. According to data collected through the national influenza surveillance scheme, the epidemic peak occurred in week 1.

3.3. Study population

The study population comprised individuals with no contraindications for influenza vaccine who were consulting at a participating GP practice and presenting with influenza-like-illness (ILI). GPs were asked to use the European Union (EU) ILI definition, as follows:

- sudden onset of symptoms;
- at least one of the following four systemic symptoms: fever, malaise, headache, myalgia;
- at least one of the following three respiratory symptoms: cough, sore throat, shortness of breath.

All age groups were included. Each practice was asked to recruit ILI patients as follow:

- the first three patients aged <65 years presenting with ILI each week
- all patients aged ≥65 years old presenting with ILI

Participating GPs were members of the sentinel general practice influenza surveillance network. The description of the GPs participating in the sentinel influenza network is outlined in Annex C.
3.3.1. Inclusion criteria
Patients were eligible if they met the EU ILI definition, if they presented within seven days of symptom onset and if they agreed to participate. Oral informed consent was obtained from participating patients or from parents/guardians of patients aged 16 years and under.

3.3.2. Exclusion criteria
Patients were excluded if they:
- Refused to participate in the study
- Were not eligible for influenza vaccination as suffering from a condition listed as a contraindication for the vaccine in the summary of product characteristics
- Lived in a residential home
- Were unable to give informed consent or to follow the interview in the native language because of aphasia or reduced consciousness.

Reasons for exclusion were documented.

3.4. Laboratory confirmation
For each patient recruited into the study, a nasal/throat swab specimen was collected for influenza testing. Specimens were sent to the NVRL as per routine influenza surveillance. Influenza laboratory confirmation was done using RT-PCR.

Mode of collection, storage and transport of specimens are listed in Annex D.
The algorithm for influenza testing is shown in Annex E.

Molecular analyses were performed on a systematic subset of specimens. The first positive specimen per week was selected, from week 48-2010 to week 5-2011 for influenza A(H1N1)2009 and from week 50-2010 to week 12-2011 for influenza B. Analyses comprised nucleotide sequencing and phylogenetic analysis of haemagglutinin gene.
3.5. Definition of cases and controls group

3.5.1. Influenza cases
Influenza cases were defined as ILI patients with a respiratory sample positive for influenza during the influenza season.

3.5.2. Control group
Controls were defined as ILI patients with a respiratory sample negative for all influenza viruses whose week of symptom onset was:
- During or after the week of onset of the first laboratory-confirmed influenza case
- Prior to or during to the week of onset of the last laboratory-confirmed influenza case

3.6. Exposure
The exposure of interest in this study is a history of vaccination with the trivalent influenza vaccine in 2010/2011.

3.6.1. 2010/2011 influenza vaccination campaign in Ireland
The annual seasonal influenza vaccination campaign was launched on 6th October 2010. Recommendations for influenza vaccine during the 2010/2011 season are described in Annex A.

Two vaccine brands were marketed in Ireland in 2010/2011: Influvac (Solvay) and the inactivated influenza vaccine Split Virion (Sanofi Pasteur MSD). Both were non-adjuvanted.

Vaccines could be administered either in GP practices, occupational health departments (healthcare facilities or workplaces) or in Boots Pharmacies. The vaccine was provided free of charge for all those aged 65 years and over, those in at-risk groups and healthcare staff. Moreover, those who did not have a medical card or a GP visit card were liable for a consultation fee.

Preliminary estimations of influenza vaccination coverage in 2010/2011 are presented in Annex F.
3.6.2. Definition of being vaccinated
An individual was considered as vaccinated against influenza if the vaccination had occurred more than 14 days before onset of ILI symptoms.

3.6.3. Ascertainment of vaccination status
In Ireland, there is no formal national immunisation coverage register for influenza vaccine. An individual was considered as vaccinated against influenza if he/she reported having received an influenza vaccination during the current season or he/she was recorded as being vaccinated during the current season in the GP record. Date of administration and brand name were also collected.

3.7. Potential confounding factors and effect modifiers
Potential confounders or effect modifiers were documented by GPs. The list of collected covariates is described below.

3.7.1. Underlying medical conditions
Definition
A limited list of underlying medical conditions was documented by GPs. It included the following:

- Diabetes mellitus
- Chronic respiratory disease
- Chronic heart disease
- Chronic liver disease
- Chronic neurological disease
- Chronic renal disease
- Immunosuppression due to disease or treatment, including asplenia or splenic dysfunction
- Severe obesity (BMI ≥ 40)

Severity
The severity of the underlying condition(s) was measured by the number of hospital admissions due to the underlying condition(s) in the year prior to study inclusion.
3.7.2. Pregnancy
Pregnancy status, including six weeks post partum, was collected.

3.7.3. Smoking history
Smoking history was collected and coded as never smoked, former smoker (stopped smoking at least one year before inclusion in the study) and current smoker.

3.7.4. Vaccination history
Vaccination history included vaccinations against seasonal and pandemic influenza in 2009/2010. An individual was considered as vaccinated if he/she reported having received an influenza vaccination or he/she was recorded as being vaccinated in the GP record.

3.7.5. Functional status
Two questions were used as a proxy to estimate functional status in the elderly. Poor functional status was defined as the need of assistance for bathing and walking.

3.7.6. Total number of GP consultations in the previous year
To document and control for access to care, GPs documented the number of visits to the GP in the year before inclusion in the study.

3.8. Data flow

3.8.1. Data collection
Data were collected face-to-face by GPs using a standardised questionnaire (Annex G). According to their preference, GPs could use either a paper questionnaire or a web-based questionnaire created on the SurveyMonkey website.

3.8.2. Data transmission
Completed paper questionnaires were transmitted to the study coordinator at the HPSC by post or electronically for those GPs using SurveyMonkey. Laboratory results were transmitted directly by
NVRL to HPSC once a week by email. A GP code and a patient unique identification number were used to link the results to the questionnaire.

3.8.3. Data entry and validation
EpiData Entry was used for data entry. Data were entered directly at HPSC during the study period. Validation and data cleaning were also performed and GPs were contacted if clarifications were needed.

3.8.4. Data confidentiality
Data were extracted anonymously from the patient record by the GP. Information which could identify the individual patients was not sought on the data form and was not shared with any of the study team.

All answers given were completely confidential and protected by the Data Protection Act 2003. Data security and confidentiality was maintained at all times at the Health Protection Surveillance Centre, which is accredited for Information Security Management IS17799. The study was used for public health purposes only.

3.9. Sample size calculation
For an estimated vaccine coverage of 20% among GP clients and a ratio of controls/cases of 1, a sample size of 1,111 (556 cases and 556 controls) was needed for the detection of a vaccine effectiveness of 50% (OR=0.5) with a precision of 20%, for a power of 80% and an alpha error of 5%. Giving an influenza outbreak duration of 8 weeks, 139 ILI patients would have to be recruited each week. With a sampling frame of 5 ILI patients per week per GP practice, 28 practices would have to participate in the study (46% of all sentinel GP practices).

3.10. Analysis
Analysis was performed using Stata 11.0.
3.10.1. Recoding and categorisation of variables

Age
Age at the date of symptom onset was calculated and recoded to four age groups according to age groups used by the European Influenza Surveillance Network (0-4, 5-14, 15-64, 65 years and over).

ILI definition
Using the symptoms reported in the questionnaire, a variable was defined to determine whether the patient met the EU ILI definition.

Presence of at least one underlying medical condition
A binary variable was created to determine if the patient presented with at least one underlying medical condition.

Hospitalisations for underlying disease in the last year
A binary variable was created to determine if the patient had been hospitalised for their underlying disease in the past year.

Trivalent influenza vaccination status 2010/11
The time between the date of vaccination and the date of onset of symptoms was calculated. A binary variable was created and coded 1 if the patient had received 1 dose of vaccine more than 14 days before the onset of symptoms.

3.10.2. Exclusion
Patients were excluded from the analysis if they:
- did not meet the EU ILI definition;
- were swabbed eight days or more after symptom onset;
- had the onset of symptoms before week 48-2010 or after week 12-2011 (respectively week of onset of first and last confirmed influenza cases);
- received antiviral treatment prior to swabbing;
- had an unknown date of onset or date of swabbing;
- had an unknown or missing 2010/2011 seasonal vaccination status
- had unknown or missing laboratory result

### 3.10.3. Descriptive analysis

The proportion of eligible ILI patients who agreed to participate in the study was calculated. Patients were described by baseline characteristics.

### 3.10.4. Univariable analysis

**Association between baseline characteristics and outcome**

Baseline characteristics of cases and controls were compared using the chi-square test or Fisher’s exact test for categorical variables and the Student test or Mann-Whitney test for quantitative variables. Significance level was set to 0.05.

**Measure of effect**

The vaccine effectiveness was computed as $VE = 1 – \text{Odds Ratio for vaccination}$. An exact 95% confidence interval was computed around the point estimate.

**Stratification**

The vaccine effectiveness was calculated by influenza subtype and taking into account influenza vaccination history in previous years.

### 3.10.5. Multivariable analysis

If the sample size was sufficient, we had planned to conduct logistic regression to control for negative and positive confounding.

### 3.10.6. Sensitivity analysis

We conducted an analysis restricted to patients who were reported as belonging to a target group for influenza vaccination in 2010/2011.
3.11. Ethical considerations

This study was undertaken as part of the existing ICGP Influenza Sentinel Surveillance System and ethical approval was obtained from the ICGP Research Ethics Committee on 1st July 2010 (Annex H).

3.12. Logistical aspects

The project was led by Ms. Anne-Sophie Barret, EPIET Fellow at HPSC, and Drs. Joan O'Donnell and Aidan O’Hora, Specialists in Public Health Medicine at HPSC.

Ms. Aoibheann O’Malley, administrative assistant at HPSC, was responsible for managing the day-to-day issues that arose. In particular, she liaised with the ICGP and with participating GPs with regard to data management. She also liaised with the NVRL regarding the laboratory results.
4. Results

4.1. Participating GPs

4.1.1. Contact with GPs

On 30\textsuperscript{th} August 2010, a letter was sent by ICGP to all 60 sentinel GP practices inviting them to participate in the study.

4.1.2. Participating GPs

Of the 60 practices that were contacted, 22 expressed interest in participating in the study and 17 (28% of all practices) recruited at least one ILI patient. GPs reported that 37 GPs were working in these 17 practices during the 2010/2011 season. Figure 1 shows the geographical distribution of the participating GP practices. All HSE areas were covered apart from HSE-Midlands.

Figure 1: Geographical distribution of the 17 GP practices participating in the influenza vaccine effectiveness study in Ireland, 2010/2011
4.1.3. Representativeness of GPs

The population covered by the 17 participating practices was 78,350 persons and represents 1.8% of the Irish population (based on the 2006 census).

Compared to the 2006 census population distribution, the population covered by the participating practices was under-represented in the Midlands, Southern and Western areas of the country and over-represented in the North-Eastern and South-Eastern areas (Table 1).

Table 1: Population covered by participating GP practices by HSE Areas, Influenza vaccine effectiveness study in Ireland, 2010/2011

<table>
<thead>
<tr>
<th>HSE-Area</th>
<th>Population</th>
<th>% Census population</th>
<th>Number of participating practices</th>
<th>Population covered</th>
<th>% Patient population</th>
<th>% Census population</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSE-E</td>
<td>1,499,705</td>
<td>35.4</td>
<td>5</td>
<td>27,362</td>
<td>34.9</td>
<td>1.8</td>
</tr>
<tr>
<td>HSE-M</td>
<td>251,664</td>
<td>5.9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HSE-MW</td>
<td>361,028</td>
<td>8.5</td>
<td>2</td>
<td>6,329</td>
<td>8.1</td>
<td>1.8</td>
</tr>
<tr>
<td>HSE-NE</td>
<td>394,098</td>
<td>9.3</td>
<td>3</td>
<td>12,553</td>
<td>16.0</td>
<td>3.2</td>
</tr>
<tr>
<td>HSE-NW</td>
<td>237,108</td>
<td>5.6</td>
<td>2</td>
<td>4,425</td>
<td>5.6</td>
<td>1.9</td>
</tr>
<tr>
<td>HSE-SE</td>
<td>460,838</td>
<td>10.9</td>
<td>2</td>
<td>19,256</td>
<td>24.6</td>
<td>4.2</td>
</tr>
<tr>
<td>HSE-S</td>
<td>621,130</td>
<td>14.6</td>
<td>2</td>
<td>6,625</td>
<td>8.5</td>
<td>1.1</td>
</tr>
<tr>
<td>HSE-W</td>
<td>414,277</td>
<td>9.8</td>
<td>1</td>
<td>1,800</td>
<td>2.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Total</td>
<td>4,239,848</td>
<td>100.0</td>
<td>17</td>
<td>78,350</td>
<td>100.0</td>
<td>1.8</td>
</tr>
</tbody>
</table>

4.1.4. Material sent to GPs

Once the practices had expressed interest in participating in the study, a pack containing the following was sent by post:

- Abridged version of the study protocol
- Recommendations for influenza vaccination in 2010/2011
- Flow chart for patient recruitment and swabbing procedures (Annex I)
- Questionnaires
- Study labels
• Stamped addressed envelopes
Swab containers were obtained from NVRL as per routine influenza surveillance.

4.1.5. GP participation

Table 2 shows the number of patients recruited in the study by week and by GP practice from week 50-2010 to week 9-2011 when the IILI consultation rate was above the baseline rate. The number of patients recruited by each GP practice by week was greater than or equal to 2 in 28.5% of instances (given week and practice).

Table 2: Number of patients recruited by participating sentinel practices in the influenza vaccine effectiveness study in Ireland, weeks 50-2010 to 9-2011 (Cells are highlighted if the number of recruited patients is greater or equal to two)

<table>
<thead>
<tr>
<th>GP practice</th>
<th>Week of swabbing</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50</td>
<td>51</td>
</tr>
<tr>
<td>GP 1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GP 2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GP 3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>GP 4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>GP 5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GP 6</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>GP 7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>GP 8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>GP 9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GP 10</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>GP 11</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>GP 12</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>GP 13</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>GP 14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GP 15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GP 16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GP 17</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Of 17 participating GP practices, 14 (82.4%) used the paper-based questionnaire only and three used SurveyMonkey. On average, 16 patients per practice were recruited by those using the paper questionnaire versus 18 patients for those using SurveyMonkey.
4.2. Description of participants in the VE study

4.2.1. Recruitment

From week 39-2010 to week 16-2011, 288 ILI patients were recruited into the study. No refusal was notified by participating GPs and the participation rate was 100%.

Of these 288 patients, 97 patients were excluded. Figure 2 shows the flowchart of data exclusion. Finally, 191 patients were included in the analyses.

**Figure 2**: Flow chart of data exclusion, Influenza vaccine effectiveness study in Ireland, 2010/2011
As shown in Figure 3, after applying all other exclusion criteria, 35 of 226 patients (15.5%) did not meet the EU ILI definition but 14 of them (40.0%) tested positive for influenza. There were 10 patients positive for influenza A(H1N1)2009 and 4 positive for influenza B.

Of 35 patients who did not meet the EU ILI definition:
- 11 (31.4%) did not have sudden onset of symptoms (or missing) of whom 5 (45%) tested positive for influenza;
- 7 (20.0%) did not have any systemic symptoms of whom 1 (14%) tested positive for influenza;
- 21 (60.0%) did not have any respiratory symptoms of whom 8 (38%) tested positive for influenza

4.2.2. Description of patients included in the final analysis (N=191)

Laboratory result
Of 191 patients, 85 tested negative for any influenza virus and 106 (55.5%) were laboratory confirmed with influenza, of whom:
- 56 (52.8%) with influenza A(H1N1)2009
- 47 (44.3%) with influenza B
- 2 influenza A unsubtyped
- 1 influenza A(H3)

Figure 3 shows the distribution of ILI patients by week of symptom onset. As observed in data collected through sentinel surveillance in Ireland (Annex B), the epidemic peak of the ILI consultation rate occurred during week 1 and there were two main circulating influenza subtypes. Influenza A(H1N1)2009 was detected in patients with symptom onset between week 48-2010 and week 5-2011. Influenza B was identified in patients with symptom onset between week 50-2010 and week 12-2011.

In our sample, the peak of positivity rate occurred in week 52-2010 for influenza A(H1N1)2009 and in week 6-2011 for influenza B.
Figure 3: Distribution of ILI patients (N=191) and positivity rate by week of onset of symptoms (ISO week number) and by virus subtype, Influenza vaccine effectiveness study in Ireland, 2010/2011

Patient information
The median age of patients was 26 years old (range: 10 months to 89 years) and the sex ratio of females to male was 0.9.

Symptoms and clinical details
Table 3 outlines all symptoms reported by patients. The most frequently reported systemic symptoms were malaise (84.3%) and fever (75.9%). The most frequently reported respiratory symptom was cough (84.8%).

The median delay between the onset of symptoms and swabbing was 2 days (range: 0-7 days); 147 patients (77%) were swabbed within 3 days of onset of symptoms.
Table 3: Symptoms reported by patients (N=191), Influenza vaccine effectiveness study in Ireland, 2010/2011

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=191</td>
</tr>
<tr>
<td><strong>Systemic symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Malaise</td>
<td>161 (84.3)</td>
</tr>
<tr>
<td>Fever</td>
<td>145 (75.9)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>133 (69.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>130 (68.1)</td>
</tr>
<tr>
<td><strong>Respiratory symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>162 (84.8)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>145 (75.9)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>24 (12.6)</td>
</tr>
</tbody>
</table>

**Risk factors**
In total, 35 patients (18.3%) presented with at least one underlying medical condition, the most frequent were respiratory disease (n=22, 63%) and diabetes (n=7, 20%). Five patients had been hospitalised at least once for their chronic illness in the previous year.

Three patients (1.6%) were reported as pregnant or within six weeks post-partum.

Regarding smoking status, 17 patients (8.9%) were former smokers and 31 (16.2%) were current smokers.

**Functional status**
Three patients (1.6%) were reported to need help with walking.

**Antiviral treatment**
Twenty-seven patients (14.1%) had received antiviral treatment, mostly (n=23, 85%) Tamiflu.
Care history
Of 190 patients for whom information was available, the median number of GP consultations in the previous year was 2 (range: 0-40).

History of influenza vaccination in 2009/2010
Eleven patients (5.8%) reported to have received the seasonal influenza vaccine in 2009/10. Forty-eight patients (25.1%) reported to have received the pandemic vaccine in 2009/10.

4.2.3. Description of patients vaccinated against seasonal influenza in 2010/11
Forty-one patients (21.5%) were reported as belonging to a target group for influenza vaccination (as detailed in Annex A).

Of the 191 patients, 10 (5.2%) received the 2010/2011 trivalent seasonal vaccine but only eight (4.2%) had received it more than 14 days before symptom onset.

Of these eight patients, five had received the inactivated Split Virion-Sanofi Pasteur MSD, two had received Solvay-Influvac and for one, the brand name was unknown. Two had received the vaccine in September 2010, four in October 2010 and two in January 2011.

4.2.4. Description of case and control groups
Baseline characteristics
The distribution of baseline characteristics was not significantly different between cases and controls (Table 4), apart from the proportion of patients with diabetes. Controls were more likely to have diabetes than cases.

When comparing influenza virus subtypes, age was the only characteristic associated with influenza confirmation. Confirmed influenza B cases were more likely to be younger than controls (12 years versus 31 years, p=0.001) whereas influenza A(H1N1)2009 cases had a similar age distribution to controls (29 years versus 31 years, p=0.76).
Table 4: Description of cases and controls by baseline characteristics, Influenza vaccine effectiveness study in Ireland, 2010/2011

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Influenza cases (N=106)</th>
<th>Controls (N=85)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (q25 – q75)</td>
<td>26 (10 - 37)</td>
<td>30 (17- 41)</td>
<td>0.10</td>
</tr>
<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>11 (10.4)</td>
<td>8 (9.4)</td>
<td>0.33</td>
</tr>
<tr>
<td>5-14</td>
<td>23 (21.7)</td>
<td>11 (12.9)</td>
<td></td>
</tr>
<tr>
<td>15-64</td>
<td>69 (65.1)</td>
<td>61 (71.7)</td>
<td></td>
</tr>
<tr>
<td>≥ 65</td>
<td>3 (2.8)</td>
<td>5 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>51 (48.1)</td>
<td>45 (52.9)</td>
<td>0.50</td>
</tr>
<tr>
<td>Female</td>
<td>55 (51.9)</td>
<td>40 (47.1)</td>
<td></td>
</tr>
<tr>
<td>At least one underlying medical condition</td>
<td>19 (17.9)</td>
<td>16 (18.8)</td>
<td>0.87</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (0.9)</td>
<td>6 (7.1)</td>
<td>0.04</td>
</tr>
<tr>
<td>Any hospitalisation for underlying medical condition in the previous year</td>
<td>3 (2.9)</td>
<td>0</td>
<td>0.25</td>
</tr>
<tr>
<td>Need help for bathing or walking</td>
<td>1 (0.9)</td>
<td>2 (2.4)</td>
<td>0.59</td>
</tr>
<tr>
<td>Median number of GP consultations in the last year (q25 – q75)</td>
<td>2 (0-3)</td>
<td>2 (1-5)</td>
<td>0.10</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>Never</td>
<td>82 (77.4)</td>
<td>61 (71.8)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>7 (6.6)</td>
<td>10 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>17 (16.0)</td>
<td>14 (16.5)</td>
<td></td>
</tr>
</tbody>
</table>
Clinical symptoms
Two symptoms were significantly associated with influenza confirmation: headache and cough (Table 5). Influenza A(H1N1)2009 cases presented more frequently with headache whereas this symptom was less frequent among influenza B cases. Cough was reported more frequently in influenza cases compared to controls.

The number of GP visits in the previous year was not significantly different between controls and influenza cases. It was two among controls (q25-q75: 1-3), two among influenza A(H1N1)2009 cases (q25-q75: 2-4) and two among influenza B cases (q25-q75: 1-3).

Table 5: Description of cases and controls by clinical symptoms, Influenza vaccine effectiveness study in Ireland, 2010/2011

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Influenza A(H1N1)2009 (N=56)</th>
<th>Influenza B cases (N=47)</th>
<th>Controls (N=85)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaise</td>
<td>48 (85.7)</td>
<td>38 (80.9)</td>
<td>72 (84.7)</td>
<td>0.78</td>
</tr>
<tr>
<td>Fever</td>
<td>44 (78.6)</td>
<td>38 (80.9)</td>
<td>62 (72.9)</td>
<td>0.54</td>
</tr>
<tr>
<td>Myalgia</td>
<td>39 (69.6)</td>
<td>31 (66.0)</td>
<td>61 (71.7)</td>
<td>0.79</td>
</tr>
<tr>
<td>Headache</td>
<td>45 (80.4)</td>
<td>27 (57.4)</td>
<td>57 (67.1)</td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>54 (96.4)</td>
<td>40 (85.1)</td>
<td>65 (76.5)</td>
<td><strong>0.006</strong></td>
</tr>
<tr>
<td>Sore throat</td>
<td>38 (67.9)</td>
<td>38 (80.9)</td>
<td>66 (77.7)</td>
<td>0.26</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>8 (14.3)</td>
<td>4 (8.5)</td>
<td>12 (14.1)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Influenza vaccination history
As shown in Table 6, seven controls and one influenza case had received the seasonal trivalent vaccine in 2010/2011. The vaccinated case was confirmed as influenza B. This patient was a male aged 22 years old with chronic neurological disease.
Regarding history of vaccination in previous years, controls were more likely than influenza cases to have been vaccinated with the seasonal vaccine in 2009/2010. There was no difference between the two groups for pandemic vaccination in 2009/2010.

Table 6: Description of cases and controls by influenza vaccination history, Influenza vaccine effectiveness study in Ireland, 2010/2011

<table>
<thead>
<tr>
<th>Vaccination</th>
<th>Influenza cases (N=106)</th>
<th>Controls (N=85) n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated against seasonal influenza in 2009/10</td>
<td>1 (0.9)</td>
<td>10 (11.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>Vaccinated against pandemic influenza in 2009/10</td>
<td>23 (21.7)</td>
<td>25 (29.4)</td>
<td>0.22</td>
</tr>
<tr>
<td>Vaccinated against seasonal influenza in 2010/11 &gt;14 days before symptom onset</td>
<td>1 (0.9)</td>
<td>7 (8.2)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

4.3. Measure of effect

4.3.1. Crude VE

- **VE against all influenza subtype (N=191)**

The crude OR of being vaccinated with the trivalent vaccine in 2010/2011 was 0.10 [95% CI: 0.002; 0.861], giving a crude VE of 89.4% [13.8; 99.8%] against any influenza subtype.

- **VE against influenza A(H1N1)2009 (N=121)**

The crude OR of being vaccinated with the trivalent vaccine in 2010/2011 was 0 [95% CI: 0; 1.08], giving a crude VE of 100% [-8; 100%] against influenza A(H1N1)2009.

Table 7 shows the vaccine effectiveness against influenza A(H1N1)2009 stratified by vaccination history.
Table 7: VE of 2010/2011 trivalent influenza vaccine and 2009/2010 monovalent influenza vaccine against influenza A(H1N1)2009, Influenza vaccine effectiveness study in Ireland, 2010-2011

<table>
<thead>
<tr>
<th>Vaccination</th>
<th>Influenza A(H1N1)2009 cases (N=56) n (%)</th>
<th>Controls* (N=65) n (%)</th>
<th>VE [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not vaccinated</td>
<td>50 (89.3)</td>
<td>45 (69.2)</td>
<td>-</td>
</tr>
<tr>
<td>Only pandemic vaccine in 2009/10</td>
<td>6 (10.7)</td>
<td>16 (24.6)</td>
<td>66% [6%; 88%]</td>
</tr>
<tr>
<td>Only seasonal vaccine in 2010/11</td>
<td>0</td>
<td>2 (3.1)</td>
<td>-</td>
</tr>
<tr>
<td>Pandemic vaccine in 2009/10 AND seasonal vaccine in 2010/11†</td>
<td>0</td>
<td>2 (3.1)</td>
<td>-</td>
</tr>
</tbody>
</table>

* Including controls with week of onset after week 48-2010 and before week 5-2011 (respectively week of onset of first and last confirmed influenza A(H1N1)2009 case)
† Vaccinated more than 14 days before symptom onset

- **VE against influenza B (N=128)**

The crude OR of being vaccinated with the trivalent vaccine in 2010/2011 was 0.23 [95% CI: 0.004; 1.90], giving a crude VE of 77% [-90.0%; 99.5%] against influenza B.

### 4.3.2. Multivariable analysis

Because of the small number of vaccinated cases, multivariable and stratified analyses other than by influenza subtype could not be performed.

### 4.3.3. VE in patients targeted for influenza vaccination in 2010/2011

- **VE against all influenza subtypes (N=41)**

Eighteen controls and 23 cases were reported as belonging to a target group for influenza vaccination in 2010/2011. Of those, 7 controls (39%) and one influenza case (4%) had received
the trivalent seasonal vaccine in 2010/2011. The crude OR of being vaccinated with the trivalent vaccine in 2010/2011 was 0.07 [95% CI: 0.001; 0.709], giving a crude VE of 92.9% [29.1; 99.8%] against any influenza subtype.

- **VE against influenza A(H1N1)2009 (N=23)**

Twelve controls and 11 influenza A(H1N1)2009 cases were reported as belonging to a target group for influenza vaccination in 2010/2011 between week 48-2010 and week 5-2011. Of those, 4 controls (33%) and none of the influenza cases (0%) had received the trivalent seasonal vaccine in 2010/2011. The crude OR of being vaccinated with the trivalent vaccine in 2010/2011 was 0 [95% CI: 0; 0.84], giving a crude VE of 100% [15.8; 100%] against influenza A(H1N1)2009.

- **VE against influenza B (N=28)**

Eighteen controls and 10 influenza B cases were reported as belonging to a target group for influenza vaccination in 2010/2011 between week 50-2010 and week 12-2011. Of those, 7 controls (39%) and one influenza case (10%) had received the trivalent seasonal vaccine in 2010/2011. The crude OR of being vaccinated with the trivalent vaccine in 2010/2011 was 0.17 [95% CI: 0.003; 1.901], giving a crude VE of 83% [-90.1%; 99.6%] against influenza A(H1N1)2009.

### 4.4. Phylogenetic analyses

A total of 18 specimens underwent phylogenetic characterization: 11 influenza A(H1N1)2009 and 7 influenza B. The specimen isolated in the patient with vaccine failure could not be sequenced because there was not enough sample for analysis.

As shown in Figure 4, all influenza A(H1N1)2009 strains sequenced in 2010/2011 were clustered with reference sequences and Irish sequences from 2009/2010. Few changes have occurred in the sequence of the influenza A(H1N1)2009 strain between the two seasons. Important mutations are shown in Table 8. According to data from the Community Network of Reference Laboratories for Human Influenza in Europe, the S815T group is showing the widest geographic spread (3). This is also true for the Irish sequences.
Figure 4: Influenza A(H1N1)2009 neighbour-joining phylogenetic tree containing reference sequences and Irish sequences from 2009, 2010 and 2011 (I-MOVE specimens from 2010/2011 season are highlighted in green)
Table 8: Listing of the important mutations detected in the 2010/2011 influenza A(H1N1)2009 sequences

<table>
<thead>
<tr>
<th></th>
<th>N31D</th>
<th>D97N</th>
<th>A134T</th>
<th>S143G</th>
<th>S162N</th>
<th>S183P</th>
<th>S185T</th>
<th>A186T</th>
<th>S204T</th>
<th>R205K</th>
<th>I216V</th>
<th>V249L</th>
<th>V272I</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N</td>
<td>N</td>
<td>A</td>
<td>S</td>
<td>S</td>
<td>P</td>
<td>T</td>
<td>A</td>
<td>T</td>
<td>R</td>
<td>I</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>A</td>
<td>S</td>
<td>S</td>
<td>P</td>
<td>T</td>
<td>A</td>
<td>T</td>
<td>R</td>
<td>I</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>-</td>
<td>A</td>
<td>S</td>
<td>S</td>
<td>P</td>
<td>T</td>
<td>A</td>
<td>T</td>
<td>R</td>
<td>I</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>-</td>
<td>A</td>
<td>S</td>
<td>S</td>
<td>P</td>
<td>T</td>
<td>A</td>
<td>T</td>
<td>R</td>
<td>I</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>5*</td>
<td>-</td>
<td>-</td>
<td>A</td>
<td>G</td>
<td>S</td>
<td>P</td>
<td>T</td>
<td>A</td>
<td>T</td>
<td>R</td>
<td>I</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>-</td>
<td>A</td>
<td>S</td>
<td>S</td>
<td>P</td>
<td>T</td>
<td>A</td>
<td>T</td>
<td>R</td>
<td>I</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>N</td>
<td>A</td>
<td>S</td>
<td>S</td>
<td>P</td>
<td>T</td>
<td>A</td>
<td>T</td>
<td>R</td>
<td>I</td>
<td>V</td>
<td>V</td>
</tr>
<tr>
<td>8*</td>
<td>-</td>
<td>D</td>
<td>T</td>
<td>S</td>
<td>S</td>
<td>P</td>
<td>S</td>
<td>A</td>
<td>T</td>
<td>R</td>
<td>I</td>
<td>V</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>N</td>
<td>A</td>
<td>S</td>
<td>S</td>
<td>P</td>
<td>T</td>
<td>A</td>
<td>T</td>
<td>R</td>
<td>I</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10*</td>
<td>-</td>
<td>D</td>
<td>T</td>
<td>S</td>
<td>S</td>
<td>P</td>
<td>S</td>
<td>A</td>
<td>T</td>
<td>R</td>
<td>I</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>-</td>
<td>A</td>
<td>S</td>
<td>S</td>
<td>P</td>
<td>T</td>
<td>A</td>
<td>T</td>
<td>R</td>
<td>I</td>
<td>V</td>
<td>V</td>
</tr>
</tbody>
</table>

* Separate branch due to N97, T134 and S185 mutations  
† Separate branch due to 143G and S185T mutations

Regarding influenza B, two different strains of influenza B were detected. Six sequences were clustered as Victoria-like strains, indicating that they are genetically similar to the 2010/2011 vaccine strain. One sequence was clustered as a Yamagata-like strain, which was not included in the 2010/2011 influenza vaccine.
Figure 5: Influenza B neighbour-joining phylogenetic tree containing reference sequences and Irish sequences from 2010 and 2011 (I-MOVE specimens from 2010/2011 season are highlighted in green)
5. Discussion

5.1. Summary of results

The crude VE of the 2010/2011 trivalent influenza vaccine was estimated to be:

- 89.4% [13.8; 99.8%] against any influenza subtype
- 100% [-8; 100%] against influenza A(H1N1)2009
- 77% [-90.0%; 99.5%] against influenza B

These results should be interpreted with caution given the wide confidence intervals but they suggest that the 2010/2011 trivalent influenza vaccine provided good protection against medically-attended laboratory confirmed influenza. This result is consistent with a good match between the vaccine and the circulating strain as demonstrated in the phylogenetic analyses undertaken in the I-MOVE study and those which are part of the WHO Global Influenza Surveillance Programme (Annex B).

The crude VE of the 2009/2010 pandemic vaccine only (without vaccination in 2010/2011) was 66% [6; 88%], suggesting some residual protection from the vaccine administered last season. Because of the small number of vaccinated cases, we could not perform multivariable analyses nor stratified analyses by age group, by vaccine brand or by presence of underlying medical condition.

Influenza cases and controls were similar for most baseline characteristics. The only individual factors associated with the influenza outcome were the age (influenza B cases were younger than controls) and diabetes (controls were more likely than influenza cases to have diabetes). These results suggest that cases and controls are comparable and confounding did not seem to play an important role in VE estimates.

5.2. Main achievements

Following the study conducted in 2009/2010, some improvements were made in the methods to avoid any biases and to make them more homogeneous with other countries participating in the I-MOVE multicentre case-control study. In particular, we implemented the EU ILI definition for the
first time in the influenza sentinel surveillance system. Participating GPs were also asked to use systematic sampling to recruit patients.

In addition, we were better prepared for the study in 2010/2011 as compared to 2009/2010. Materials were sent to participating GPs well before the influenza outbreak started. Participating GPs had enough time to get familiar with instructions and materials and ask for clarifications.

The proportion of missing data was low as a result of the active involvement of GPs as well as careful monitoring of data performed at HPSC.

5.3. Main difficulties

The main difficulty was the power of the analyses due to a small sample size coupled with low vaccination coverage. As shown in Table 9, in the sample size calculations, the following figures were overestimated: number of participating GP practices, number of patients recruited by week, vaccination coverage, and hence sample size. Each figure will be explored below to understand the reasons for this discrepancy.

Table 9: Comparison of expected and observed figures influencing the power of the analyses, Influenza vaccine effectiveness study in Ireland, 2010-2011

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Expected * (sample size calculations)</th>
<th>Observed in 2010/2011†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination coverage</td>
<td>20%</td>
<td>4%</td>
</tr>
<tr>
<td>Ratio controls/cases</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td><strong>1,111</strong></td>
<td><strong>191</strong></td>
</tr>
<tr>
<td>Duration of influenza outbreak (weeks)‡</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>No. patients/week</td>
<td>139</td>
<td>10</td>
</tr>
<tr>
<td>No. participating practices</td>
<td>28§</td>
<td>17</td>
</tr>
</tbody>
</table>

* Sample size calculated for a precision of 20%, power of 20% and alpha error of 5%
† Considering only ILI patients who met the inclusion criteria
‡ Number of weeks between the first and the last confirmed influenza case included in the study
§ Considering that each practice recruits 5 patients per week
Number of participating GP practices
Of 60 GP practices participating in the sentinel influenza surveillance system in Ireland, 22 expressed interest in the study and 17 (28%) recruited at least one ILI patient in the study. The participation in the 2010/2011 season was similar to the participation observed during the 2009/2010 season (27%) but it was lower than in other countries participating in I-MOVE. In four countries for which GP participation rate was presented at the annual I-MOVE meeting (Madrid, 11-14 April 2011), the average participation rate was 71%. The reasons for the rather low participation rate observed in Ireland should be discussed with coordinators of the ICGP influenza sentinel surveillance system. Ways for increasing the GP participation could also be considered.

Number of recruited patients per week
GP practices were asked to recruit ILI patients as follow:
- first three patients aged <65 years each week
- all patients aged ≥65 years

Our results indicate that not all GP practices followed this instruction and most of them did not recruit more than two patients per week, even when influenza activity was quite intense.

This was coupled with quite a lot of patients being excluded because they did not meet the inclusion criteria. In particular, 17 patients were excluded because they were swabbed more than seven days after symptom onset and 35 patients were excluded because they did not meet the EU ILI definition. The EU ILI definition was outlined on the questionnaire and reminders about inclusion criteria were sent through newsletters but these reminders do not appear to have been sufficient.

In 2011/2012, inclusion criteria should be emphasised more strongly in order to optimise recruitment. Changing the method of payment for participating GP practices could also have an impact on the number of recruited patients. At the moment, participating GP practices receive €500 for participating in the study regardless of the number of patients recruited, however, paying them per eligible patient included instead could increase the sample size.

Patients who did not meet the EU ILI definition could be explained by errors in symptoms reported by GPs or by the sensitivity of this definition. Indeed 40% of patients who did not meet the EU ILI definition tested positive for influenza (versus 55.5% in ILI patients who met the EU ILI definition). It
seems that sudden onset of symptoms was the least sensitive criteria: 45.4% of patients who did not present with a sudden onset of symptoms tested positive for influenza.

We observed the same problem last season with the sudden onset criterion. This criterion appears to be difficult to assess and there is no clear and standardised definition for it at the moment. The assessment is left to the GP and could vary a lot according to GPs’ subjectivity.

Moreover, if vaccination was linked to symptoms (e.g. vaccination could induce milder ILI symptoms), the VE could be overestimated when excluding patients with mild symptoms such as absence of sudden onset. In our sample, the vaccination coverage for having received the 2010/2011 trivalent influenza vaccine (anytime before symptom onset) was 27.3% in patients who did not present with sudden onset of symptoms and 5.6% in those who presented with sudden onset of symptoms (p=0.03).

When including patients who did not present with sudden onset of symptoms, the VE of the 2010/2011 trivalent influenza vaccine was estimated to 79% [-16; 98%] against any influenza subtype. This point estimate was lower than the one found excluding patients who did not meet the EU ILI definition (89.4%).

**Vaccination coverage**

Only 21.5% of patients included in the analysis were reported as belonging to a target group for influenza vaccination. In this group, the vaccination coverage for having received an influenza vaccine more than 14 days before symptom onset was 19.5% versus 4.2% in all ILI patients (regardless of their status of target group for influenza vaccination). Restricting the recruitment to ILI patients targeted by influenza vaccination would increase the vaccination coverage, hence the power of the analyses.

Interestingly, using only data collected from ILI patients who were reported as belonging to a target group for influenza vaccination, the crude VE of the 2010/2011 trivalent influenza vaccine was estimated as:

- 92.2% [29.1; 99.8%] against any influenza strain
- 100% [15.8; 100%] against influenza A(H1N1)2009
- 83% [-90.1%; 99.6%] against influenza B
Although the sample sizes were much lower, these estimates were similar to the ones found using all ILI patients regardless of whether or not they belonged to a target group for influenza vaccination.

It suggests that restricting the recruitment to ILI patients targeted for influenza vaccination would not bias the VE while it would increase the power of the analyses.

6. Conclusion and recommendations

During the last two influenza seasons, the case-control studies conducted in Ireland allowed us to measure influenza VE but estimates were imprecise and not reliable because of the small sample size. Influenza cases and controls were comparable for most baseline characteristics but stratified and multivariable analyses could not be performed and therefore, confounding bias could not be ruled out. Pooling of data within I-MOVE was essential to obtain precise and reliable VE estimates.

For the coming influenza season, the priority would be to increase the power of the analyses, by increasing both sample size and vaccination coverage. To obtain precise VE estimates for Ireland, we would probably need to change the recruitment strategy and to recruit only patients who belong to a target group for influenza vaccination. Moreover vaccine policy makers are probably more interested to know VE in groups for whom influenza vaccination is recommended than in those for whom it is not.

Different ways could be explored to encourage more GPs to participate in the study and so to facilitate recruitment of the expected number of patients into the study. Paying them per recruited eligible patient could help to achieve the expected sample size. As last year, dissemination of results to all sentinel GPs (through newsletter, journals and conferences) would be another way to make them aware of the importance of participating in the study.

Another way to increase the sample size would be to apply the test-negative design using routine surveillance data collected on the laboratory form for each influenza test requested by GP practices participating in the sentinel system in Ireland (60 practices in total).
A limited number of covariates are collected on the form at the moment and the quality of information should be further explored with the purpose of improving this. Studies could be conducted using data collected in previous seasons to calculate VE and compare these estimates to the matching between the circulating and the vaccine strain, as well as VE estimates found in other countries.

If these data are of good enough quality, they could be used to monitor VE adjusted for age, sex and risk group for influenza complications. However, using these data could introduce some selection and confounding biases, unless the current sentinel surveillance system is modified.

Indeed, in the current system, recruitment is left to the GPs discretion using ad-hoc sampling which could introduce a bias if some GPs were more likely to recruit a certain age group or patients with underlying medical conditions. In addition, it would not be possible to apply restriction criteria such as EU ILI definition or a delay of less than 8 days between symptom onset and swabbing since this information is not collected on the current form. As a limited number of potential confounders can be included on the laboratory form, we could not guarantee that there would not be any residual confounding in the VE estimate. Regarding vaccination status, GPs should be asked to report information as accurately as possible and to report vaccine brand and date of vaccination (which are not collected at the moment).

Possibilities of modifying the recruitment strategy and including more information on the laboratory form will be discussed with the ICGP and NVRL. If this is considered too labour intensive, data entry for additional information could be performed at HPSC if NVRL are in agreement.

Ideally, molecular analyses should be performed during the influenza season in order to have real-time surveillance of circulating strains and to add some complementary information to the VE estimated throughout the season. Funding would be required to do this. It could be done using a systematic sampling strategy planned prior to the season (e.g. first positive isolate per week). However it may not be possible to plan the number of specimens that would undergo molecular analyses as this depends on the duration of the influenza outbreak and the circulating strains.
Finally, ILI patients testing negative for influenza should be further characterized and if possible, tested for other respiratory viruses. It would be interesting to compare ILI patients negative for any respiratory viruses and ILI patients negative for influenza but positive for other respiratory viruses.

Acknowledgements

We would like to greatly acknowledge:

- All participating GPs
- Orla Bannon, Lisa Domegan, Suzanne Cotter, Sarah Gee, Jolita Mereckiene, Piaras O’Lorcan, Aoibheann O’Malley (HPSC)
- Esther Kissling, Alain Moren, Camelia Savulescu, Marta Valenciano (Epiconcept)
- Biagio Pedalino (EPIET coordinator, Institut de Veille Sanitaire, Paris, France)
Reference List


(3) European Centre for Disease Prevention and Control, Community Network of Reference Laboratories for Human Influenza in Europe. Influenza virus characterisation. Summary Europe, April 2011.
Annexes

<table>
<thead>
<tr>
<th>Annex</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
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<td>6</td>
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<td>19</td>
</tr>
</tbody>
</table>

The 2010/2011 seasonal influenza vaccine is recommended for:

- **Persons aged 50 years and older**¹
- Adults and children over 6 months of age with any of the following
  - chronic illness requiring regular follow up (e.g. chronic respiratory disease including cystic fibrosis, moderate or severe asthma, chronic heart disease, chronic neurological disease, diabetes mellitus, *chronic liver disease*, *chronic neurological disease including multiple sclerosis*, *hereditary and degenerative disorders of the central nervous system* etc)
  - those who are immunosuppressed due to disease or treatment including those with missing or non functioning spleens
- Children and teenagers on long-term aspirin therapy
- Children with any condition (e.g. cognitive dysfunction, spinal cord injury, seizure disorder, or other neuromuscular disorder) that can compromise respiratory function especially those attending special schools/day centres
- **Those with morbid obesity** i.e. Body Mass Index ≥40
- Residents of nursing homes, old peoples’ homes and other long stay facilities where rapid spread is likely to follow introduction of infection
- Healthcare workers
- People who have close, regular contact with pigs, poultry or water fowl
- All pregnant women and those up to 6 weeks post partum

**BOLD indicates new groups for 2010/2011**

¹ Vaccines were provided free of charge only to those aged 65 years and over
Annex B: Description of 2010/2011 influenza season in Ireland

ILI consultation rate and laboratory confirmation

Figure B1 shows the sentinel GP ILI consultation rates, the baseline threshold rate and the number of positive specimens detected by the NVRL.

The baseline threshold (17.9 / 100,000 pop) was crossed in week 50-2010 and the epidemic peak was reached in week 1-2011 with an ILI rate of 202.1 per 100,000 population. The ILI rate decreased below the threshold in week 10-2011. For comparison, the ILI rate (per 100,000 population) at epidemic peak was 120.6 in 2008/2009 and 201.3 in 2009/2010.

Influenza A(H1N1)2009, A(H3) and influenza B were all detected during the season. The beginning of the influenza season was dominated by A(H1N1)2009 whereas from week 4-2011 onwards, influenza B became the dominant circulating subtype.

Figure B1. ILI GP consultation rates per 100,000 population, baseline threshold rate and number of positive influenza specimens, Week 40-2010 to Week 20-2011

Source: NVRL laboratory data and ICGP ILI clinical data
As shown in figure B2, the highest ILI rates were observed in those aged 15-64 years old when A(H1N1)2009 was the main circulating subtype and in those aged 5-14 years old when influenza B was the main circulating subtype.

![Image of a graph showing age-specific ILI rates per 100,000 population from Week 40-2010 to Week 20-2011. The graph has four lines representing different age groups: 0-4 years, 5-14 years, 15-64 years, and ≥ 65 years. The peaks of the curves are observed in different weeks, indicating the timing of the influenza season.](image)

**Figure B2.** Age specific sentinel GP consultation rate for ILI per 100,000 population, Week 40-2010 to Week 20-2011

*Source: ICGP ILI clinical data*

### Phylogenetic characterisation

As part of the WHO Global Influenza Surveillance Programme, a proportion of influenza viruses (10 A (H1N1) 2009 and 2 B viruses) circulating in Ireland during the 2010/2011 season were submitted to the WHO Collaborating Centre for Reference and Research on Influenza (Mill Hill, London) for characterisation. Antigenic results for the circulating influenza A (H1N1 2009) and for the influenza B isolates showed good reactivity with the A/California/7/2009 and the B/Brisbane/60/2008 vaccine strains, respectively. Both strains were included in the 2010/2011 influenza vaccine.
Severity

As of 25\textsuperscript{th} May 2011, 945 (42.3\%) of the 2233 confirmed influenza cases notified on CIDR this influenza season were hospitalised. Of the 945 hospitalised cases, 601 (63.6\%) were influenza A(H1N1)2009 cases, 7 (0.7\%) were influenza A (H3) cases, 109 (11.5\%) were influenza A (unsubtyped) and 228 (24.1\%) were influenza B cases. The highest cumulative age specific rate for influenza confirmed hospitalised cases for the 2010/2011 influenza season to date is currently in the 0-4 year age group (61.9 per 100,000 population).

As of 25\textsuperscript{th} May 2011, HPSC has been notified of 122 hospitalised patients admitted to critical care units with confirmed influenza, 108 of whom are adults and 14 are paediatric cases. The last confirmed influenza case admitted to ICU was on February 17\textsuperscript{th} 2011.

Ninety-one of the 122 (74.6\%) cases have underlying medical conditions, 82 adults and nine paediatric cases. The underlying medical conditions include: chronic respiratory disease, chronic heart disease, immunosuppression, pregnancy, metabolic disorders and morbid obesity.
Annex C: Description of ICGP sentinel general practitioners

The National Influenza Surveillance Scheme is a collaborative initiative between the National Virus Reference Laboratory (NVRL), the Health Protection Surveillance Centre (HPSC), the Irish College of General Practitioners (ICGP) and the Departments of Public Health (DPH) that aims to combine clinical and virological data to assess the incidence of influenza and influenza like illness through a sentinel surveillance programme.

The scheme has been in operation since October 2000 and comprises a group of 135 general practitioners grouped in 60 practices who report consultations of influenza-like illness (ILI) on a weekly basis. The scheme runs all year round.

Sentinel GP practices are dispersed throughout all HSE areas (Figure 1) and cover 6.2% of the national population (calculations based on the 2006 census data). Table 1 shows the population covered by the sentinel scheme by HSE Areas.

During the pandemic, sentinel GPs sent a combined nasal and throat swab, to the NVRL, on five patients per week where a clinical diagnosis of ILI is made. This reverted back to swabs on 1-2 patients during the 2010-2011 influenza season. The NVRL undertakes testing for influenza on all swabs received from sentinel GPs.

The EU ILI definition was implemented for the first time in the sentinel system during the 2010/2011 season. EU ILI definition is:

- sudden onset of symptoms;
- at least one of the following four systemic symptoms: fever, malaise, headache, myalgia;
- at least one of the following three respiratory symptoms: cough, sore throat, shortness of breath.
Table C1. Population covered by sentinel scheme by HSE Areas

<table>
<thead>
<tr>
<th>HSE-Area</th>
<th>Population (2006 census)</th>
<th>% Census population (n=4,239,848)</th>
<th>No. practices</th>
<th>No. GPs</th>
<th>Patient population (n=263,235)</th>
<th>% Patient population</th>
<th>% Census population (n=4,239,848)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSE-E</td>
<td>1,499,705</td>
<td>35.4</td>
<td>19</td>
<td>44</td>
<td>85,030</td>
<td>33.2</td>
<td>5.7</td>
</tr>
<tr>
<td>HSE-M</td>
<td>251,664</td>
<td>5.9</td>
<td>2</td>
<td>4</td>
<td>7,156</td>
<td>3.5</td>
<td>2.8</td>
</tr>
<tr>
<td>HSE-MW</td>
<td>361,028</td>
<td>8.5</td>
<td>8</td>
<td>14</td>
<td>25,944</td>
<td>9.3</td>
<td>7.2</td>
</tr>
<tr>
<td>HSE-NE</td>
<td>394,098</td>
<td>9.3</td>
<td>6</td>
<td>17</td>
<td>31,255</td>
<td>12.5</td>
<td>7.9</td>
</tr>
<tr>
<td>HSE-NW</td>
<td>237,108</td>
<td>5.6</td>
<td>4</td>
<td>9</td>
<td>14,727</td>
<td>5.8</td>
<td>6.2</td>
</tr>
<tr>
<td>HSE-SE</td>
<td>460,838</td>
<td>10.9</td>
<td>7</td>
<td>22</td>
<td>56,072</td>
<td>20.7</td>
<td>12.2</td>
</tr>
<tr>
<td>HSE-S</td>
<td>621,130</td>
<td>14.6</td>
<td>10</td>
<td>19</td>
<td>31,775</td>
<td>11.8</td>
<td>5.1</td>
</tr>
<tr>
<td>HSE-W</td>
<td>414,277</td>
<td>9.8</td>
<td>4</td>
<td>6</td>
<td>11,276</td>
<td>3.1</td>
<td>2.7</td>
</tr>
<tr>
<td>Total</td>
<td>4,239,848</td>
<td>100.0</td>
<td>60</td>
<td>135</td>
<td>263,235</td>
<td>100.00</td>
<td>6.2</td>
</tr>
</tbody>
</table>
Influenza Surveillance Programme
Collection and Transportation of Specimens for Influenza Virus detection.

GPs participating in this programme should ensure that they have been supplied with an influenza specimen collection kit containing the following: (a) wire swabs, (b) flocked (plastic) swabs with transport media, (c) patient information forms, (d) plastic containers and (e) transport box. The National Virus Reference Laboratory provides these kits free of charge.

Protocol:
GPs are required to provide a combined nose and throat swab specimen from cases presenting with suspected influenza or influenza like illness.

Taking the specimen and filling in the forms:
1. The flocked (plastic) swab is used to abrade the tonsils and pharynx (see diagram).
2. The swab is then broken off into a bottle containing the transport medium.
3. The flexible wire swab is inserted into the nostril and rubbed against and above the nasal turbinate.
4. The swab is then agitated thoroughly into the same bottle as the flocked swab to release virus infected cells. The wire swab may then be withdrawn and discarded safely.
5. Ensure that the bottle lid is secured tightly onto the bottle to prevent leakages.
6. Label the bottle with Patient’s Name and Date of Birth.
7. It is important to complete fully and legibly the patient information form provided.
Packaging and transportation to the laboratory:

1. GP’s should be familiar with the regulations pertaining to conditions of posting for pathological specimens.

2. The labelled primary container /specimen bottle should be placed in the plastic mailing container provided (1 specimen per container). There should be sufficient absorbent wrapping to ensure that the specimen cannot move about the plastic container.

3. The container and the completed form should then be placed into transport box provided. (Two containers maximum per transport box)

4. The name and address of the sender should be clearly marked on the outside of the transport box to ensure they are contactable in case of damage or leaks.

5. The package should be addressed:

   Influenza Surveillance Unit
   National Virus Reference Laboratory
   University College Dublin
   Belfield
   Dublin 4.

6. Specimen should reach the laboratory within 24 hours.

7. Where unavoidable delays are envisaged, specimens should be stored at 4°C and sent to the NVRL as soon as possible.
Annex E: Influenza testing algorithm 2010/11

Respiratory sample e.g. combined nose and throat swab, BAL, NPA

Preparation of respiratory swabs
LP/VIR/002

RT-PCR for Influenza A and B
LP/MVIR/090
VFLU

Positive A
$RT-PCR$ for Influenza A and B

Positive A*

RT-PCR for Seasonal Influenza H1 or H3
LP/MVIR/099
ISUB

OR

RT-PCR for Pandemic H1N1
LP/MVIR/106
SOH1

Negative*

Negative

Positive^*Refer to ALG/MVIR/029 for further testing requirements

Choice of subtyping assay for Influenza A should depend on circulating viruses in given season. Review after first 50 influenza A positives. Consider antiviral resistance on antiviral failures. Review cases with clinical team.

Samples of interest for genetic characterisation include early and late season positives, known vaccine failures and suspected cases of antiviral resistance.

*Selection of positive A and B samples for genetic characterisation HA gene
LP/MVIR/044
MSEQ

Report as positive for influenza A

Report as positive for influenza B

Report as either resistant or sensitive to NAIs

Report to HPSC/CNRL as either as resistant or sensitive to NAIs

Report to HPSC/CNRL as positive for pandemic H1N1 2009

Consult with BL3 staff and consider alternative testing H2/H5/H7

Report as negative for influenza A and B

Report as positive for influenza A

Report to HPSC/CNRL as positive for seasonal influenza H1 or H3

Report as negative for influenza B

Report as positive for influenza B

Report as positive for influenza A

Report as negative for influenza A and B

^Antiviral resistance determination using NA sequencing
LP/MVIR/044
MSEQ
Annex F: Estimations of influenza vaccination coverage in Ireland

Vaccine uptake in medical cardholders and GP visit cardholders aged 65 years and older

- On October 1st, 2010, 427,406 (91.3%) of the population aged 65 years or older had either a medical card or a GP visit card (source: PCRS and 2006 CSO population census). Approximately, 58.4% of the population aged 65 to 69 years have a medical card or a GP visit card.

- The average uptake for influenza vaccination nationally during the period September to February 2011 in those aged 65 years and older was 59.9% (Table F1). This is the highest recorded rate for this period since the 2005/2006 influenza season when uptake reached 62.0% (Table F2). Variation in vaccination coverage was observed between age groups, with the highest uptake (63.7%) in those aged 75 years or older (Table F1). Variation in vaccination coverage was also observed between HSE areas, ranging from 57.8% in HSE-NW to 62.9% in HSE-SE (Figure F1). Figure F2 shows the evolution of vaccine uptake over time.

Table F1: Cumulative percentage seasonal influenza vaccine uptake in Medical Card Holders aged 65 years and older, September 2010 – February 2011

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>65-69</th>
<th>70-74</th>
<th>≥75</th>
<th>≥65</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. vaccinated</td>
<td>43523</td>
<td>67366</td>
<td>146493</td>
<td>257382</td>
</tr>
<tr>
<td>No. Medical card holders*</td>
<td>85142.8</td>
<td>115014.0</td>
<td>229817.8</td>
<td>429974.7</td>
</tr>
<tr>
<td>% Uptake</td>
<td>51.1</td>
<td>58.6</td>
<td>63.7</td>
<td>59.9</td>
</tr>
</tbody>
</table>

* The number of Medical card holders includes GP visit card holders and represents the average number of card holders for the period September 2010 – February 2011

2 The inclusion of the 493 vaccinations of pandemrix in this analysis increased the average uptake for influenza vaccination nationally during the period September 2010 to February 2011 in those aged 65 years and older from 59.7% to 59.9%.
### Table F2: Cumulative percentage seasonal influenza vaccine uptake in Medical Card Holders aged 65 years and older by year (September 2010 – February 2011)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. vaccinated</td>
<td>257382</td>
<td>213587</td>
<td>244208</td>
<td>236989</td>
<td>241349</td>
<td>244151</td>
<td>231638</td>
<td>238472</td>
</tr>
<tr>
<td>No. Medical card holders*</td>
<td>429974.7</td>
<td>415457.3</td>
<td>425902.5</td>
<td>417509.3</td>
<td>403547.7</td>
<td>393707.0</td>
<td>382918.0</td>
<td>409859.5</td>
</tr>
<tr>
<td>% Influenza vaccine uptake</td>
<td>59.9</td>
<td>51.4</td>
<td>57.3</td>
<td>56.8</td>
<td>59.8</td>
<td>62.0</td>
<td>60.5</td>
<td>58.2</td>
</tr>
</tbody>
</table>

* The number of Medical card holders includes GP visit card holders and represents the average number of card holders for the period September 2010 – February 2011.

### Figure F1: Cumulative percentage seasonal influenza vaccine uptake in medical card holders aged 65 years and older by HSE area of GP, September 2010 – February 2011
Figure F2: Seasonal influenza vaccine uptake in medical card holders aged 65 years and older by month of vaccination, September 2010 to February 2011

**Vaccine uptake in boots pharmacies**

- Between 02/10/2010 and 18/02/2011, 4730 winter influenza vaccines were administered by 48 Boots pharmacy stores nationwide. This usage represents approximately 68% of the 7,000 of the vaccines originally distributed to the Boots chain for the current winter influenza vaccine campaign programme.

- Of the 4730 vaccinations, 4724 had details of the vaccine brand used: 3949 (83.6%) ‘Fluvarix’ and 775 (16.4%) ‘Influvac’, a ratio of 5.1:1.

- Figure F2 presents a weekly profile of the number and brand of vaccine administered as of 18th of February. Some vaccines were administered prior to the official launch date (1.5%; n=72/4730).
Figure F2: Weekly number of vaccinations by brand in Boots pharmacies in Ireland between 02/10/2010 and 18/02/2011

- More female clients than males were vaccinated against influenza with a ratio of 1.3:1.
- Clients over 65 years of age accounted for 11% (n=520/4730) of the total number of vaccines administered.
- 48.7% of clients (n=2302/4730) were reported to be at increased medical risk for influenza complications; 44.4% (n=2082/4730) of clients cited one risk factor only; 4.7% of clients (n=221/4730) had more than one risk factor recorded (Table 5). First recorded risk categories are outlined in table F3.
**Table F3:** Number of vaccines administered by client's *first* recorded risk category and gender* between 02/10/2010 and 18/02/2011

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
<th>% Males</th>
<th>% Females</th>
<th>% Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over 50 years of age</td>
<td>849</td>
<td>1132</td>
<td>1986</td>
<td>41.3%</td>
<td>42.5%</td>
<td>42.0%</td>
</tr>
<tr>
<td>Chronic Respiratory Disease</td>
<td>59</td>
<td>99</td>
<td>158</td>
<td>2.9%</td>
<td>3.7%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Chronic Heart Disease</td>
<td>11</td>
<td>9</td>
<td>20</td>
<td>0.5%</td>
<td>0.3%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Chronic Renal Disease</td>
<td>5</td>
<td>3</td>
<td>8</td>
<td>0.2%</td>
<td>0.1%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Chronic Liver Disease</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>0.0%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Chronic Neurological Disease</td>
<td>2</td>
<td>6</td>
<td>8</td>
<td>0.1%</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>14</td>
<td>9</td>
<td>23</td>
<td>0.7%</td>
<td>0.3%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>28</td>
<td>22</td>
<td>50</td>
<td>1.4%</td>
<td>0.8%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Haemoglobinopathy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Morbidly Obese</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Resident of Long Stay Facility</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>At increased risk, undefined</td>
<td>17</td>
<td>26</td>
<td>43</td>
<td>0.8%</td>
<td>1.0%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Not at increased risk</td>
<td>1071</td>
<td>1352</td>
<td>2428</td>
<td>52.0%</td>
<td>50.8%</td>
<td>51.3%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2058</strong></td>
<td><strong>2662</strong></td>
<td><strong>4730</strong></td>
<td><strong>100%</strong></td>
<td><strong>100%</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

*Clients with no gender details reported not shown*
**Annex G: Case/Control Questionnaire**

### Influenza Vaccine Effectiveness Study 2010/2011

**Case/Control Questionnaire**

#### Reminder - EU Influenza-like illness (ILI) definition

- Sudden onset of symptoms
- At least one of the following systemic symptoms: fever, malaise, headache, myalgia
- At least one of the following respiratory symptoms: cough, sore throat, shortness of breath

#### I - Participation

1. Date of consultation
2. GP name
3. Participated Yes [ ] No [ ]
4. If no, please tick the exclusion criteria:
   - Refusal to participate
   - Influenza vaccine contraindicated
   - Lives in a residential home
   - Unable to give consent or to follow the interview (aphasia, reduced consciousness,…)

#### II - Patient information

5. Date of Birth: [ ] [ ] [ ] [ ] [ ] [ ]
6. Sex: F [ ] M [ ]

#### III - Symptoms & Clinical details

7. Sudden onset? Yes [ ] No [ ]
8. Date of Onset: [ ] [ ] [ ] [ ] [ ] [ ]
9. Symptoms
   - High fever (≥ 38°C)
   - Malaise
   - Headache
   - Myalgia
   - Cough
   - Sore throat
   - Shortness of breath
10. Swab taken Yes [ ] No [ ]
11. Date of swab: [ ] [ ] [ ] [ ] [ ] [ ]

#### IV - Influenza vaccination

12. Does the patient belong to a target group for influenza vaccination? Yes [ ] No [ ]
   - Trivalent seasonal vaccine Yes [ ] No [ ] Not known [ ]
   - If yes, date of vaccination (dd/mm/yyyy): [ ] [ ] [ ] [ ] [ ] [ ] [ ]
   - Brand name of vaccine: Solvay Influvac Sanofi Pasteur MSD Other brand:
   - Seasonal vaccine Yes [ ] No [ ] Not known [ ]
   - Pandemic vaccine Yes [ ] No [ ] Not known [ ]
<table>
<thead>
<tr>
<th>Section</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>V - Functional Status</td>
<td>15. Does the patient usually need help with walking?  Yes ☐ No ☐</td>
</tr>
<tr>
<td></td>
<td>16. Does the patient usually need help with bathing? Yes ☐ No ☐</td>
</tr>
<tr>
<td>VI - Care history</td>
<td>17. How many times approximately has the patient attended the GP in the last 12 months?</td>
</tr>
<tr>
<td>VII - Risk Factors</td>
<td>18. Does the patient have an underlying medical condition for influenza vaccine? Yes ☐ No ☐</td>
</tr>
<tr>
<td></td>
<td>If yes, please tick the relevant box(es):</td>
</tr>
<tr>
<td></td>
<td>Diabetes Mellitus ☐</td>
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<tr>
<td></td>
<td>Chronic respiratory disease ☐</td>
</tr>
<tr>
<td></td>
<td>Chronic heart disease ☐</td>
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<tr>
<td></td>
<td>Chronic liver disease ☐</td>
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<td>Chronic neurological disease ☐</td>
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<td></td>
<td>Chronic renal disease ☐</td>
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<tr>
<td></td>
<td>Immunosuppression ☐</td>
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<tr>
<td></td>
<td>Severely obese (BMI ≥ 40) ☐</td>
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<tr>
<td></td>
<td>Other(s)</td>
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<tr>
<td></td>
<td>19. How many times has the patient been hospitalised for their chronic illness in the last 12 months?</td>
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<tr>
<td></td>
<td>20. Pregnant (including six weeks post partum) Yes ☐ No ☐</td>
</tr>
<tr>
<td></td>
<td>21. Smoking status</td>
</tr>
<tr>
<td></td>
<td>Current smoker ☐</td>
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<tr>
<td></td>
<td>Never smoked ☐</td>
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<tr>
<td></td>
<td>Former smoker (stopped smoking at least 1yr before inclusion in study)</td>
</tr>
<tr>
<td>VIII - Treatment</td>
<td>22. Was antiviral treatment commenced? Yes ☐ No ☐</td>
</tr>
<tr>
<td></td>
<td>If yes, name of antiviral:</td>
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<tr>
<td></td>
<td>Oseltamivir phosphate (Tamiflu) ☐</td>
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<tr>
<td></td>
<td>Zanamivir (Relenza)</td>
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<tr>
<td></td>
<td>Oseltamivir phosphate (Tamiflu) &amp; Zanamivir (Relenza) ☐</td>
</tr>
<tr>
<td></td>
<td>Other antiviral</td>
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<tr>
<td></td>
<td>23. Date of antiviral administration:</td>
</tr>
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</tbody>
</table>
1st July 2010

Mrs Joan O'Donnell  
Health Protection Surveillance Centre, 
25-27 Middle Gardiner Street, 
Dublin 1

Re: I-MOVE (Influenza Monitoring of Vaccine Effectiveness) European Project: Case control study monitoring influenza (seasonal and influenza) vaccine effectiveness in Ireland

Dear Mrs O'Donnell,

I wish to confirm that the Research Ethics Committee approved your request to repeat the above study next year.

If you have any queries please contact Ms Pauline Tierney - pauline.tierney@icgp.ie

Yours sincerely,

Prof. Colin Bradley 
Chair Research Ethics Committee
Annex I: Flowchart for patient recruitment and swabbing

Patient with ILI (European Union case definition)
- Explain to the patient the purpose of the study
- Ask for oral consent

Yes  Participate  No

Swabbing
- Take the nasal/throat swab
- Label the specimen bottle with Patient and GP Practice details as per routine
- Fill in the lab request form as per routine surveillance (i.e. Patient’s details, etc.)

- **Place a study label on the lab request form only**
- Send the swab to NVRL as per routine surveillance
  (Details in Annex A: Collection and Transportation of Specimens)

Questionnaire
- Place a study label on the 1st sheet of the questionnaire
- Fill out the questionnaire
- Send the completed questionnaire to Anne-Sophie Barret (HPSC) using the stamped addressed envelope supplied

<table>
<thead>
<tr>
<th>Paper</th>
<th>OR</th>
<th>Web-based</th>
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- **Document the reasons for non participation on the questionnaire**

Complete a questionnaire on SurveyMonkey website
https://www.surveymonkey.com/s/JM7T9QW

List (GP use)
- Place a study label on a separate list with patient’s name and date of birth
- Keep the list in GP practice for GP use only