Case control study measuring influenza vaccine effectiveness in Ireland 2011-2012

Final report

Health Protection Surveillance Centre, Dublin: Ms. Javiera Rebolledo, Dr. Joan O’Donnell, Dr. Lisa DómeGAN, Ms Aoibheann O’Malley, Dr. Suzanne Cotter and Dr. Darina O’Flanagan.

Irish College of General Practitioners: Dr. Claire Collins (Director of Research), Dr. Michael Joyce (GP co-ordinator).

National Virus Reference Laboratory, University College, Dublin: Dr. Suzie Coughlan, Grainne Tuite, Dr. Allison Waters, Professor William Hall.
Contents

1. Background .......................................................................................................................... 4

2. Study Objectives .............................................................................................................. 5
   2.1. Primary objective .......................................................................................................... 5
   2.2. Secondary objectives .................................................................................................... 5

3. Methods ............................................................................................................................... 6
   3.1. Study design ................................................................................................................ 6
   3.2. Study timeline ............................................................................................................. 6
   3.3. Study population ......................................................................................................... 6
       3.3.1. Inclusion criteria .................................................................................................. 7
       3.3.2. Exclusion criteria ............................................................................................... 7
   3.4. Laboratory confirmation ............................................................................................. 8
   3.5. Definition of cases and controls group ....................................................................... 8
       3.5.1. Influenza cases ..................................................................................................... 8
       3.5.2. Control group ...................................................................................................... 8
   3.6. Exposure ..................................................................................................................... 8
       3.6.1. 2011/2012 influenza vaccination campaign in Ireland ........................................... 8
       3.6.2. Definition of being vaccinated .............................................................................. 9
       3.6.3. Ascertainment of vaccination status .................................................................... 9
   3.7. Potential confounding factors and effect modifiers ..................................................... 9
       3.7.1. Underlying medical conditions ............................................................................ 10
       3.7.2. Pregnancy ........................................................................................................... 10
       3.7.3. Smoking history .................................................................................................. 10
       3.7.4. Vaccination history .............................................................................................. 10
       3.7.5. Functional status ................................................................................................ 11
       3.7.6. Total number of GP consultations in the previous year ........................................ 11
   3.8. Data flow ..................................................................................................................... 11
       3.8.1. Data collection ..................................................................................................... 11
       3.8.2. Data transmission ............................................................................................... 11
       3.8.3. Data entry and validation .................................................................................... 11
       3.8.4. Data confidentiality ............................................................................................. 12
   3.9. Sample size calculation ............................................................................................... 12
3.10. Analysis ................................................................................................................................. 12
  3.10.1. Recoding and categorisation of variables ................................................................. 12
  3.10.2. Exclusion ......................................................................................................................... 13
  3.10.3. Descriptive analysis ....................................................................................................... 14
  3.10.4. Univariable analysis ........................................................................................................ 14
  3.10.5. Multivariable analysis ..................................................................................................... 14
  3.10.6. Sensitivity analysis ......................................................................................................... 14

3.11. Ethical considerations ........................................................................................................... 15

3.12. Logistical aspects .................................................................................................................. 15

4. Results ........................................................................................................................................ 16
  4.1. Participating GPs .................................................................................................................. 16
    4.1.1. Contact with GPs ........................................................................................................... 16
    4.1.2. Participating GPs ........................................................................................................... 16
    4.1.3. Representativeness of GPs ............................................................................................ 17
    4.1.4. Material sent to GPs ...................................................................................................... 18
    4.1.5. GP participation ............................................................................................................ 18
  4.2. Description of participants in the VE study ........................................................................ 20
    4.2.1. Recruitment .................................................................................................................... 20
    4.2.2. Description of patients included in the final analysis (N=93) ..................................... 21
    4.2.3. Description of patients vaccinated against seasonal influenza in 2011/12 ............. 24
    4.2.4. Description of case and control groups ....................................................................... 24
  4.3. Measure of effect ................................................................................................................... 27
    4.3.1. Crude VE ......................................................................................................................... 27
    4.3.2. Stratified analysis .......................................................................................................... 28
    4.3.3. Multivariable analysis .................................................................................................... 29
    4.3.4. VE in patients targeted for influenza vaccination in 2011/2012 ............................... 29
  4.4. Phylogenetic analyses .......................................................................................................... 29

5. Discussion .................................................................................................................................... 30
  5.1. Summary of results .............................................................................................................. 30
  5.2. Main achievements .............................................................................................................. 31
  5.3. Main challenges .................................................................................................................... 31

6. Conclusion and recommendations ............................................................................................ 34

Acknowledgements ...................................................................................................................... 36
1. Background

As influenza viruses constantly evolve and vaccines are reformulated every year, influenza vaccine effectiveness (IVE) from previous years cannot be used to estimate vaccine effectiveness (VE) in subsequent years. Also, 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

For the 2011/2012 influenza season the World Health Organization (WHO) recommended the following viruses to be used for influenza vaccines 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.

In Ireland, no study had ever been conducted to measure the influenza vaccine effectiveness prior to the 2009/2010 influenza season. The first study measuring influenza vaccine effectiveness in Ireland was conducted in the framework of the I-MOVE project, which aimed to monitor and estimate seasonal and pandemic influenza vaccine effectiveness against laboratory-confirmed medically-attended influenza-like illness (ILI) in the European Union (EU) and European Economic
Area. Since then, Ireland has participated in the I-MOVE project during the 2010/2011 and 2011/2012 influenza seasons.

As part of the I-MOVE project, 10 European countries have conducted 11 influenza VE studies using a case-control (8 studies) or a cohort design (3 studies). Also, a multicentre case-control study was undertaken pooling the results of the eight case-control studies. Preliminary results of the pooled vaccine effectiveness were published in an international journal (1).

This year, again, 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 (HSE-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 40-2011 to week 20-2012.

2. Study Objectives

2.1. Primary objective

The main study objective was to estimate the trivalent influenza VE in Ireland during the 2011/2012 influenza season.

2.2. Secondary objectives

- To estimate VE among the target population for influenza vaccination, as recommended by the Irish National Immunisation Advisory Committee (NIAC) (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 40-2011 and week 20-2012. Annex B shows the influenza outbreak timeline and the description of influenza activity during the 2011/2012 season. According to data collected through the national influenza surveillance scheme, the epidemic peak occurred in week 8.

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).

For the second year in succession, 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 during the study period

Each practice was asked to provide a nasal/throat swab specimen for influenza testing, as per routine surveillance.

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 ILI definition, presented within seven days of symptom onset and consented 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 or 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 National Virus Reference Laboratory (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.

3.5. Definition of cases and controls group

3.5.1. Influenza cases
Influenza cases were defined as ILI (EU definition) 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 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 2011/2012.

3.6.1. 2011/2012 influenza vaccination campaign in Ireland
The influenza vaccination campaign in Ireland was launched by the National Immunisation Office on the 17th of October 2011. Recommendations for influenza vaccine for the 2011/2012 season are described in Annex A.
This year, in Ireland, only one brand of seasonal trivalent influenza vaccine was used, namely Inactivated Influenza Vaccine (Split Virion) BP manufactured by Sanofi Pasteur MSD. This is a non-adjuvanted vaccine.

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

Preliminary estimations of influenza vaccination coverage in 2011/2012 are presented in Annex E.

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. Influenza vaccination status will be obtained from the GP records in the vast majority of cases and in some instances will be asked directly to the patient. Therefore, 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 using a questionnaire. 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)

People with these conditions all belong to the target groups for the vaccine. Others e.g. health care workers, carers, etc. are also included in the target groups (Annex A).

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 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 influenza during the 2010/2011 influenza season. 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 (Annex F). 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 prior to 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. Depending on their preference, GPs could use either a paper questionnaire (Annex F) or a web-based questionnaire created on the Booroo website (http://booroo.com/s.asp?sid=54exeah9y5gtz1w15219).

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 the Booroo website. Laboratory results were transmitted directly by NVRL to HPSC once a week by email. A GP code and a unique patient 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 sought.
3.8.4. Data confidentiality

Data were extracted anonymously from the patient record by the GP. Information which could identify 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 the GP clients and a ratio controls/cases of 1, a sample size of 1112 (556 cases and 556 controls) would be 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%. For 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 2011/12
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 onset of symptoms before week 46-2011 or after week 19-2012 (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 2011/2012 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 had been 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 2011/2012.
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 28th September 2011 (Annex G).

3.12. Logistical aspects

The project was led by Ms. Javiera Rebolledo, EPIET Fellow at HPSC, and Dr. Joan O’Donnell Specialist 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. Dr. Lisa Domegan, responsible for data management of sentinel clinical and virology data liaised with the NVRL regarding the laboratory results.
4. Results

4.1. Participating GPs

4.1.1. Contact with GPs

On 21\textsuperscript{st} September 2011, a letter was sent by the Irish College of General Practitioners (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, 29 expressed interest in participating in the study and 16 (27\% of all practices) recruited at least one IILI patient. GPs reported that 37 GPs were working in these 16 practices during the 2011/2012 season. Figure 1 shows the geographical distribution of the participating GP practices. All HSE areas were covered apart from HSE-Midlands and HSE-South (Cork and Kerry).

![Figure 1: Geographical distribution of the 16 GP practices participating in the influenza vaccine effectiveness study in Ireland, 2011/2012](image)
4.1.3. **Representativeness of GPs**

The population covered by the 16 participating practices was 92,078 persons and represents 2.1% of the Irish population (based on the 2011 census).

Compared to the 2011 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 Eastern and South-Eastern areas (Table 1).

**Table 1:** Population covered by participating GP practices by HSE Areas, Influenza vaccine effectiveness study in Ireland, 2011/2012

<table>
<thead>
<tr>
<th>HSE-Area</th>
<th>Population</th>
<th>% Census population (n=4,588,252)</th>
<th>Number of Participating practices</th>
<th>Population covered</th>
<th>% Patient population (n=92,078)</th>
<th>% Census population (n=4,588,252)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSE-E</td>
<td>1,620,021</td>
<td>35.3</td>
<td>6</td>
<td>28,901</td>
<td>31.4</td>
<td>0.63</td>
</tr>
<tr>
<td>HSE-M</td>
<td>282,410</td>
<td>6.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HSE-MW</td>
<td>379,327</td>
<td>8.3</td>
<td>2</td>
<td>6,329</td>
<td>6.9</td>
<td>0.14</td>
</tr>
<tr>
<td>HSE-NE</td>
<td>440,698</td>
<td>9.6</td>
<td>2</td>
<td>8,602</td>
<td>9.3</td>
<td>0.19</td>
</tr>
<tr>
<td>HSE-NW</td>
<td>258,328</td>
<td>5.6</td>
<td>1</td>
<td>2,122</td>
<td>2.3</td>
<td>0.05</td>
</tr>
<tr>
<td>HSE-SE</td>
<td>497,578</td>
<td>10.8</td>
<td>4</td>
<td>44,324</td>
<td>48.1</td>
<td>0.97</td>
</tr>
<tr>
<td>HSE-S</td>
<td>664,534</td>
<td>14.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HSE-W</td>
<td>445,356</td>
<td>9.7</td>
<td>1</td>
<td>1,800</td>
<td>2</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4,588,252</strong></td>
<td><strong>100</strong></td>
<td><strong>16</strong></td>
<td><strong>92,078</strong></td>
<td><strong>100</strong></td>
<td><strong>2.1</strong></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 to all GP practices who wished to participate in the study:

- Introduction letter
- Recommendations for influenza vaccination in 2011/2012 (Annex A)
- Abridged version of the study protocol
- Flow chart for patient recruitment and swabbing procedures (Annex H)
- Questionnaires (Annex F)
- Study labels
- Stamped addressed envelopes.

Swab containers and laboratory forms were obtained by GPs from NVRL as per routine influenza surveillance.

4.1.5. GP participation

During the whole study period, the 16 participating GP practices recruited in total 137 patients. A median of 4 patients was recruited per GP practice (min = 1; max = 33). Table 2 shows the number of patients recruited into the study and included in the analysis (n=93) by week and by GP practice, from week 46-2011 to week 12-2012. GP practice number 15 and 16 recruited patients (total = 2), but they were excluded from the analysis at a later stage because they did not meet the inclusion criteria.
Table 2: Number of patients recruited and included in the analysis by participating sentinel practices in the influenza vaccine effectiveness study in Ireland, weeks 46-2011 to 12-2012 (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>46</td>
<td>47</td>
</tr>
<tr>
<td>GP 1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>GP 2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GP 3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GP 4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GP 5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GP 6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GP 7</td>
<td>0</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>0</td>
</tr>
<tr>
<td>GP 11</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>GP 12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GP 13</td>
<td>0</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>
</tbody>
</table>

Of 16 participating GP practices, 10 (62.5%) used the Booroo online questionnaire, one used both Booroo and paper based questionnaire (6.3%) and 6 (33.5%) used the paper-based questionnaire exclusively.
4.2. Description of participants in the VE study

4.2.1. Recruitment

From week 45-2011 to week 18-2012, 137 ILI patients were recruited into the study. No refusals were reported by participating GPs and the participation rate was 100%.

Of these 137 patients, 44 patients were excluded. Figure 2 outlines the flowchart of data exclusion. Eventually, 93 patients were included in the analyses.

![Flowchart of data exclusion](image)

Figure 2: Flow chart of data exclusion, Influenza vaccine effectiveness study in Ireland, 2011/2012
As shown in Figure 2, 17 of 130 patients (13.1%) did not meet the EU ILI definition of whom six (35.2%) had tested positive for influenza, of which 5 were Influenza A(H3) and one Influenza B.

Of 17 patients who did not meet the EU ILI definition:
- 7 (41.2%) did not have sudden onset of symptoms of whom 3 (42.9%) tested positive for influenza;
- 3 (17.7%) did not have any systemic symptoms but none of these tested positive for influenza;
- 9 (52.9%) did not have any respiratory symptoms of whom 3 (33%) tested positive for influenza

4.2.2. Description of patients included in the final analysis (N=93)

Laboratory result
Of 93 patients, 41 (44.1%) tested negative for any influenza virus and 52 (55.9%) were laboratory confirmed with influenza, of whom:
- 48 (92.3%) with influenza A(H3)
- 3 (5.8%) with influenza B
- 1 (1.9%) with influenza A(H1N1)2009

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 8 and there were two main circulating influenza subtypes i.e. A (H3) with a smaller proportion of influenza B noted later in the season.

In our study, the peak positivity rate occurred in week 9-2012. Our sample also shows the predominance of Influenza A(H3) throughout this season.
Figure 3: Distribution of ILI patients (N=93) and positivity rate by week of onset of symptoms and by virus subtype, Influenza vaccine effectiveness study in Ireland, 2011/2012

Patient information
The median age of patients was 33 years old (range: 2 months to 78 years) and the sex ratio of females to male was 1.5.

Symptoms and clinical details
Table 3 outlines all symptoms reported by patients. The most frequently reported systemic symptom was malaise (95.7%) and the most frequently reported respiratory symptom was cough (76.3%).

The median delay between the onset of symptoms and swabbing was 2 days (range: 0-7 days); 76 patients (81.7%) were swabbed within 3 days of onset of symptoms.
Table 3: Symptoms reported by patients (N=93), Influenza vaccine effectiveness study in Ireland, 2011/2012

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients (N=93)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Systemic symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Malaise</td>
<td>89 (95.7)</td>
</tr>
<tr>
<td>Fever</td>
<td>74 (79.6)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>70 (75.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>51 (54.8)</td>
</tr>
<tr>
<td><strong>Respiratory symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>71 (76.3)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>58 (62.4)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>4 (4.3)</td>
</tr>
</tbody>
</table>

**Risk factors**

In total, 15 patients (16.1%) presented with at least one underlying medical condition, the most frequent were respiratory disease (n=6, 40%) and diabetes (n=4, 26.7%). Five patients had been hospitalised at least once for their chronic illness in the previous year.

No patient reported being pregnant.

With regard to smoking status, 9 (9.7%) patients were former smokers, 8 (8.6%) were current smokers and 76 (81.7%) had never smoked.

**Functional status**

Three patients (3.3%) were reported to need help with bathing. No patient was reported to need help with walking.

**Antiviral treatment**

Twelve patients (12.9%) received antiviral treatment, mostly (n=11, 91.7%) Tamiflu and one received Relenza.
Care history
Of 93 patients for whom information was available, the median number of GP consultations in the previous year was 2 (range: 0-21).

History of influenza vaccination in 2010/2011
Of 88 patients for whom information was available, twenty patients (22.7%) reported to have received the seasonal influenza vaccine in the previous influenza season 2010/11.

4.2.3. Description of patients vaccinated against seasonal influenza in 2011/12
Twenty-two patients (23.7%) were reported as belonging to a target group for influenza vaccination (Annex A).

Of the 93 patients, 15 (16.1%) had received the 2011/2012 trivalent seasonal vaccine more than 14 days before symptom onset. Of these, one had received the vaccine in September 2011, ten in October 2011 and four in November 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). Having at least one medical condition was not statistically significant. Also, when looking at all the medical conditions individually, there were no significant differences between cases and controls.

The number of GP visits in the previous year was not significantly different between controls and influenza cases.
Table 4: Description of cases and controls by baseline characteristics, Influenza vaccine effectiveness study in Ireland, 2011/2012

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Influenza cases (N=52)</th>
<th>Controls (N=41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (q25 – q75)</td>
<td>32 (12 - 48)</td>
<td>36.6 (25- 51)</td>
<td>0.19</td>
</tr>
<tr>
<td>Age group (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>8 (15.4)</td>
<td>4 (9.8)</td>
<td>0.20</td>
</tr>
<tr>
<td>5-14</td>
<td>9 (17.3)</td>
<td>3 (7.3)</td>
<td></td>
</tr>
<tr>
<td>15-64</td>
<td>28 (53.9)</td>
<td>31 (75.6)</td>
<td></td>
</tr>
<tr>
<td>≥ 65</td>
<td>7 (13.5)</td>
<td>3 (7.3)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22 (42.3)</td>
<td>15 (36.6)</td>
<td>0.37</td>
</tr>
<tr>
<td>Female</td>
<td>30 (57.7)</td>
<td>26 (63.4)</td>
<td></td>
</tr>
<tr>
<td>At least one underlying medical condition</td>
<td>8 (15.4)</td>
<td>7 (17.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>Any hospitalisation for underlying medical condition</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Need help for bathing or walking</td>
<td>3 (5.8)</td>
<td>0</td>
<td>0.17</td>
</tr>
<tr>
<td>Median number of GP consultations in the last year</td>
<td>2 (1-4)</td>
<td>3 (2-4)</td>
<td>0.26</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>44 (84.6)</td>
<td>32 (78.1)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>3 (5.8)</td>
<td>5 (12.2)</td>
<td>0.57</td>
</tr>
<tr>
<td>Current</td>
<td>5 (9.6)</td>
<td>4 (9.8)</td>
<td></td>
</tr>
</tbody>
</table>
Clinical symptoms

With regard to systemic symptoms, fever was significantly more frequently reported in influenza cases compared to controls. Regarding respiratory symptoms, cough and sore throat were reported more frequently in influenza cases compared to controls and this was also significant (table 5).

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 cases (N=52)</th>
<th>Controls (N=41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td><strong>Systemic symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaise</td>
<td>49 (94.2)</td>
<td>40 (97.6)</td>
<td>0.40</td>
</tr>
<tr>
<td>Fever</td>
<td>47 (90.4)</td>
<td>27 (65.9)</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td>Myalgia</td>
<td>39 (75)</td>
<td>31 (75.6)</td>
<td>0.57</td>
</tr>
<tr>
<td>Headache</td>
<td>28 (53.9)</td>
<td>23 (56.1)</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Respiratory symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>47 (90.4)</td>
<td>24 (58.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sore throat</td>
<td>28 (53.9)</td>
<td>30 (73.2)</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>1 (1.9)</td>
<td>3 (7.3)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Influenza vaccination history

As shown in Table 6, seven controls and eight influenza cases had received the seasonal trivalent vaccine in 2011/2012. All vaccinated cases were confirmed as influenza A(H3).

Regarding history of vaccination, in the previous season controls seemed more likely than influenza cases to have been vaccinated with the seasonal vaccine in 2010/2011, but this slight difference is not significant.
Table 6: Description of cases and controls by influenza vaccination history, Influenza vaccine effectiveness study in Ireland, 2011/2012

<table>
<thead>
<tr>
<th>Vaccination</th>
<th>Influenza cases (N=52)</th>
<th>Controls (N=41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated against seasonal influenza in 2010/11</td>
<td>9 (17.7)</td>
<td>11 (29.7)</td>
<td>0.14</td>
</tr>
<tr>
<td>Vaccinated against seasonal influenza in 2011/12</td>
<td>8 (15.4)</td>
<td>7 (17.1)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

4.3. Measure of effect

4.3.1. Crude VE

VE against all influenza subtype (N=93)

The crude OR of being vaccinated with the trivalent vaccine in 2011/2012 was 0.88 [95% CI: 0.25 – 3.18], giving a crude VE of 11.7% [-167.63 – 70.86%] against any influenza subtype.

VE against influenza A(H3) (N=89)

The crude OR of being vaccinated with the trivalent vaccine in 2011/2012 was 0.97 [95% CI: 0.32 – 2.95], giving a crude VE of 3% [-195.55 – 68.07%] against influenza A(H3).

VE against influenza B (N=44)

There were no influenza B cases who were vaccinated; hence it was not possible to estimate the vaccine effectiveness for this subtype.
### 4.3.2. Stratified analysis

Table 7 shows the results of the stratified analysis by age group, risk factor and onset month.

**Table 7: Stratification for potential confounding variables, Influenza vaccine effectiveness study in Ireland, 2011/2012.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Vaccinated cases / total cases</th>
<th>Vaccinated controls / total controls</th>
<th>OR by stratum [CI 95%]</th>
<th>Mantel-Haenszel Adjusted OR [CI 95%]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>0/8</td>
<td>0/4</td>
<td>-</td>
<td>0.49 [0.09;2.52]</td>
</tr>
<tr>
<td>5-14</td>
<td>0/9</td>
<td>0/3</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>15-64</td>
<td>1/28</td>
<td>5/31</td>
<td>0.19 [0.004-1.93]</td>
<td></td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>7/7</td>
<td>2/3</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>At least one risk factor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4/8</td>
<td>5/7</td>
<td>1.6 [0.21; 18.64]</td>
<td>0.92 [0.25;3.38]</td>
</tr>
<tr>
<td>No</td>
<td>4/44</td>
<td>2/34</td>
<td>0.4 [0.02; 5.03]</td>
<td></td>
</tr>
<tr>
<td><strong>Onset month</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>November</td>
<td>0/1</td>
<td>1/4</td>
<td>-</td>
<td>0.81 [0.25;2.68]</td>
</tr>
<tr>
<td>December</td>
<td>1/3</td>
<td>1/8</td>
<td>3.5 [0.03;313.1]</td>
<td></td>
</tr>
<tr>
<td>January</td>
<td>0/7</td>
<td>0/7</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>February</td>
<td>6/26</td>
<td>4/14</td>
<td>0.8 [0.14;4.5]</td>
<td></td>
</tr>
<tr>
<td>March</td>
<td>1/15</td>
<td>1/8</td>
<td>0.5 [0.006;44.8]</td>
<td></td>
</tr>
</tbody>
</table>
4.3.3. Multivariable analysis

Because of the small sample size, only limited multivariable analyses could be performed. Very few variables could only be included in the model. As the most important confounder appeared to be age, this variable as well as month of onset were included in the model. Therefore, with logistic regression, adjusted for age and month of onset the OR of being vaccinated with the trivalent vaccine in 2011/2012 was 0.34 [95% CI: 0.05 – 2.14], giving a VE estimated of 66% [-113.99 – 94.6] against any influenza subtype.

4.3.4. VE in patients targeted for influenza vaccination in 2011/2012

VE against all influenza subtypes (N=22)

Nine controls and 13 cases were reported as belonging to a target group for influenza vaccination in 2011/2012. Of those belonging to a target group, six controls (27%) and seven influenza cases (32%) had received the trivalent seasonal vaccine in 2011/2012. The crude OR of being vaccinated with the trivalent vaccine in 2011/2012 was 0.58 [95% CI: 0.10 – 3.40], giving a crude VE of 42% [-240% – 90%] against any influenza subtype.

4.4. Phylogenetic analyses

A total of 11 specimens were sent to NVRL for phylogenetic characterisation of which eight were specimens from the vaccine failure cases and the remaining three belonged to each of the following age groups (0-4, 5-14 and 15-64). There were no specimens taken from those aged ≥65 years.

Of the eleven specimens, two could not be amplified or sequenced. All nine specimens genetically characterised belonged to the A/Vic/208/2009 Influenza clade, of which two were within England/259/2011 genetic group and seven were within Stockholm18/2011 genetic group. The strain, A/Vic/208/2009 Influenza identified from the specimens did not match the influenza A(H3) strain, A/Perth/16/2009 (H3N2)-like virus in the seasonal influenza vaccine (2011/2012).
5. Discussion

5.1. Summary of results

The crude VE of the 2011/2012 trivalent influenza vaccine in Ireland was estimated to be:

- 11.7% [-167.63 – 70.86%] against any influenza subtype
- 3% [-195.55 – 68.07%] against influenza A(H3)
- None of the influenza B cases were vaccinated so it was not possible to estimate the vaccine effectiveness for this subtype

The crude VE of the 2011/2012 trivalent influenza vaccine in Ireland was estimated to be: 66% [-113.99 – 94.6] against any influenza subtype.

These results should be interpreted with caution given the very wide confidence intervals observed but they suggest that the 2011/2012 trivalent influenza vaccine provided low protection against medically-attended laboratory confirmed influenza. This result is consistent with a low to moderate match between the vaccine strain and the circulating strain as suggested in the I MOVE pooled analysis. (1).

Because of the small sample size, only limited multivariable analysis could be performed. Due to the small number of vaccinated cases we could not perform more detailed stratified analyses, for example by presence of underlying medical condition or smoking status.

Influenza cases and controls were similar for most baseline characteristics. When there were differences these were not statistically significant. For the multivariable analysis, the main confounder appeared to be age.
5.2. Main achievements

Following three seasons of undertaking the IMOVE study in Ireland, GP practices have become familiar with study procedures including sending swabs to the laboratory and collection of data. Also, the proportion of missing data was much lower than in previous years as a result of the active involvement of GPs as well as careful monitoring of data by HPSC.

This resulted in data which was more homogeneous with other countries participating in the IMOVE multicentre case-control study facilitating a better pooled analysis.

5.3. Main challenges

The main difficulty was the power of the analyses due to a small sample size. As shown in Table 9, in the sample size calculations, the following items were overestimated: number of participating GP practices, number of patients recruited by week and vaccination coverage, hence the sample size was overestimated. Each item will be explored individually 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, 2011-2012

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Expected * (sample size calculations)</th>
<th>Observed in 2011/2012 †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination coverage</td>
<td>20%</td>
<td>16%</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>1,112</strong></td>
<td><strong>93</strong></td>
</tr>
<tr>
<td>Duration of influenza outbreak (weeks) ‡</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>No. patients/week</td>
<td>139</td>
<td>5</td>
</tr>
<tr>
<td>No. participating practices</td>
<td>28§</td>
<td>16</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, 29 expressed interest in participating in the study and eventually only 16 (27%) recruited at least one ILI patient into the study. The participation this season was similar to the participation observed during the 2010/2011 and 2009/2010 seasons (28% in 2010/2011 and 27% in 2009/2010). However, this participation rate is lower than in other countries participating in I-MOVE. Although this year, higher numbers of GP practices expressed interest in participating in the study, ultimately a much smaller number actually recruited patients. Reasons for the rather low participation rate observed in Ireland and the discrepancy between the number of GP practices who expressed interest in participating and the number who actually recruited patients needs to be explored and will be discussed with the ICGP study coordinators. Ways for increasing GP participation will need to 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 procedure and the majority did not recruit more than two patients per week. Although activity was very low during this influenza season, reasons for low recruitment need to be explored further.

The small sample size while due to low numbers of recruited patient was also affected by having to exclude patients who did not meet the inclusion criteria. In particular 17 patients were excluded because they did not meet the EU ILI definition, although this definition was outlined on the questionnaire and despite its second year of application. Also, missing data still remains an important reason for excluding patients.
In 2012/2013, the importance of the inclusion criteria should be emphasised more strongly in order to optimise recruitment and it should be highlighted that missing data may lead to the exclusion of patients from the analysis. Also, as outlined last year, changing the method of payment for participating GP practices may 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 38% of patients who did not meet the EU ILI definition tested positive for influenza. It appears that sudden onset of symptoms was the least sensitive criterion: 42.9% of patients who did not present with a sudden onset of symptoms tested positive for influenza. The same phenomenon was observed during the two previous study seasons in relation to this criterion. This criterion seems to be difficult to assess and there is no clear and standardised definition for it at present. The assessment is left to the GP and could vary considerably dependant on GPs’ subjectivity.

Finally, another issue related to the recruitment strategy is that the population eligible for vaccine does not appear to be captured effectively using the current strategy. For example, only 24% of recruited patients were reported as eligible for vaccination. Also many outbreaks in those aged 65 years and over occurred late in the season in nursing homes, however, none of these were captured by sentinel GPs.

**Vaccination coverage**

Only 24% 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 59% versus 16.3% in all ILI patients (regardless of their target group status). Restricting the recruitment to ILI patients targeted by
influenza vaccination could increase the vaccination coverage, hence the power of the analyses. However, conversely this may also further restrict the sample size.

6. Conclusion and recommendations

For the third successive influenza season the I MOVE case-control study conducted in Ireland has allowed us to measure influenza VE. However, estimates were imprecise and not reliable due to the small sample size.

In Ireland, once again, this season, only limited multivariable analyses could be performed and confounding bias for some of the covariates could not be ruled out. Therefore, pooling of data within I-MOVE remains essential to obtain precise and reliable VE estimates.

As recommended in previous years, for future influenza VE studies, the priority should be to increase the sample size on order to increase the power of the analyses. Different methods need to be explored to encourage more GP participation in the study and to facilitate the recruitment of the expected number of patients. One way may be to change the payment process by paying GPs per recruited eligible patient rather than an agreed fee for simply participating to the study. This approach may encourage them to recruit more patients and thus help to achieve the expected sample size.

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). Although, a limited number of covariates are collected on this form at the moment, this may help to decrease the perception of duplicated work, as many of these covariates are also collected in the I MOVE questionnaire. The possibility of adding new data items to the sentinel surveillance form should be further explored as well as the quality of information provided in order to improve this if needed.
If we opt to use the method alluded to in the previous paragraph, for measuring IVE, we could introduce bias as under the current routine surveillance, recruitment is left to the GPs’ discretion. At present, GPs carry out ad-hoc sampling; therefore they may be more likely to recruit a certain age group or patients with underlying medical conditions. In addition, it would not be possible to determine a delay of less than 8 days between symptom onset and swabbing since this information is not collected on the current form. As, only 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.

Finally, it would also be of great value if molecular analyses were 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.
**Acknowledgements**

We would like to greatly acknowledge:

- All participating GPs
- Lisa Domegan, Aoibheann O’Malley, Suzanne Cotter, Sarah Gee, Jolita Mereckiene, Piaras O’Lorcan, Orla Bannon and Darina O Flanagan (HPSC)
- Esther Kissling, Alain Moren, Camelia Savulescu, Marta Valenciano and Ariane Halm (Epiconcept)
Reference List

### Annexes

<table>
<thead>
<tr>
<th>Annex</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Recommendations for seasonal influenza vaccine 2011/2012</td>
<td>2</td>
</tr>
<tr>
<td>B</td>
<td>Description of 2011/2012 influenza season in Ireland</td>
<td>3</td>
</tr>
<tr>
<td>C</td>
<td>Description of ICGP sentinel general practitioners</td>
<td>7</td>
</tr>
<tr>
<td>D</td>
<td>Collection and transportation of specimens</td>
<td>9</td>
</tr>
<tr>
<td>E</td>
<td>Estimations of influenza vaccination coverage in Ireland</td>
<td>11</td>
</tr>
<tr>
<td>F</td>
<td>Case/Control Questionnaire</td>
<td>14</td>
</tr>
<tr>
<td>G</td>
<td>Approval of Ethics Committee</td>
<td>16</td>
</tr>
<tr>
<td>H</td>
<td>Flow chart of instructions for the influenza vaccine effectiveness</td>
<td>17</td>
</tr>
</tbody>
</table>
Annex A: Recommendations for seasonal influenza vaccine 2011/2012
(updated in September 2011)

The 2011/2012 seasonal influenza vaccine is strongly recommended for:

- All those aged 65 years and older
- 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
heritary 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 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
- Children and teenagers on long-term aspirin therapy (because of the risk of
Reyes syndrome)
- Those with morbid obesity i.e. Body Mass Index ≥ 40
- All pregnant women. The vaccine can be given at any stage of pregnancy.
  This year influenza vaccine is not recommended for those women up to six
  weeks post partum
- Healthcare workers
- Residents of nursing homes, and other long stay institutions
- Carers
- People who have close, regular contact with pigs, poultry or water fowl
Annex B: Description of 2011/2012 influenza season in Ireland

ILI consultation rate and laboratory confirmation

Figure B1 shows the sentinel GP influenza-like illness (ILI) consultation rates, the baseline threshold rate and the number of confirmed influenza positive specimens detected by the NVRL for the 2011/2012 influenza season.

In Ireland, as in other European countries, the influenza season began very late compared to previous years, only increasing above the Irish baseline threshold (25.86 per 100,000 population) for the first time during week 7 2012. Influenza activity was also at very low levels compared to previous seasons, with ILI rates peaking at 41.3 per 100,000 population (during week 8 2012). Apart from the three weeks (weeks 7 to 9) around the peak of ILI activity the ILI rate remained below the baseline for the remainder of the season. For comparison, the ILI rate (per 100,000 population) peaked at 201.3 during the 2009/2010 pandemic period and 202.1 during the 2010/2011 season.

To date this season, the NVRL has detected 557 influenza positive specimens from all sources: 481 A (H3), 1 A (H1) 2009, 45 A (unsubtyped) and 30 B. The predominant circulating influenza type/subtype during the 2011/2012 season was influenza A (H3).
**Figure B1.** ILI GP consultation rates per 100,000 population, baseline threshold rate and number of positive influenza specimens, Week 40-2011 to Week 20-2012 *(Source: NVRL laboratory data and ICGP ILI clinical data)*

As shown in figure B2, the highest ILI rates were observed in those aged 0-4 years old.
Figure B2. Age specific sentinel GP consultation rate for ILI per 100,000 population, Week 40-2011 to Week 20-2012 (Source: ICGP ILI clinical data)

Phylogenetic characterisation

Influenza virus characterisation was carried out at the NVRL, which is the National Influenza Centre for Ireland and at the WHO Collaborating Centre (WHO CC), Mill Hill, U.K. A selection of the circulating influenza strains were chosen for genetic and antigenic characterisation throughout the 2011/2012 respiratory season. The data provided evidence that Influenza B, which includes Victoria-like and Yamagata-like lineages, were antigenically and genetically similar to the vaccine strain and other strains circulating in Europe, respectively. A single Influenza A H1pdm09 virus was detected during the 2011/2012 influenza season and was deemed antigenically similar to vaccine strain also. Of particular note, was the characterisation of Influenza A H3, which was the predominant strain for this season. All Influenza A H3 strains characterised belonged to the A/Victoria/208 genetic clade, which is genetically distinct from the vaccine strain, A/Perth/16/2009. Furthermore antigenic characterisation determined the
The majority of this season’s Influenza A H3 strain gave titres distinct from those determined for the vaccine antigen. The WHO has recommended the inclusion of influenza A H3 A/Victoria/2008-like and influenza B Yamagata-like viral strains in the 2012/2013 influenza vaccine.

**Severity**

As of 24\textsuperscript{th} May 2012, 135 (22.3\%) of the 605 confirmed influenza cases notified on Ireland’s Computerised Infectious Disease Reporting System (CIDR)\textsuperscript{1} this influenza season were hospitalised. Of the 135 hospitalised cases, 71 (52.6\%) were influenza A (H3), 56 (41.5\%) influenza A (unsubtyped) and 8 (5.9\%) influenza B. The highest cumulative age specific rate for influenza confirmed hospitalised cases for the 2011/2012 influenza season to date is in the 0-4 year age group (15.5 per 100,000 population), followed by those aged 65 years or older (7.1 per 100,000).

As of 24\textsuperscript{th} May 2012, HPSC has been notified of 15 hospitalised patients admitted to critical care units with confirmed influenza (14 A H3 and 1 A unsubtyped) between week 40 2011 and week 20 2012. The highest age specific ICU admission rates per 100,000 population this season were reported in the 0-4 year age group (1.3 per 100,000) and in those aged 65 years or older (1.3 per 100,000).

As of 24\textsuperscript{th} May 2011, 11 influenza-associated deaths have been reported to HPSC, all in patients aged 65 years or older.

\textsuperscript{1} Influenza data reported on CIDR for the 2011/2012 season are provisional and may be subject to change once validation has been completed.
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\(^2\) 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 Health Services Executives (HSE) areas (Figure 1) and cover 5.7% of the national population (calculations based on the 2011 census data). Table 1 shows the population covered by the sentinel scheme by HSE Areas.

During the 2011/2012 influenza season, all sentinel GPs were requested to obtain one swab from one ILI patient per week. GPs participating in the IVE study were requested to obtain swabs on 5 ILI patients per week. The NVRL undertakes testing for influenza on all specimens (swabs) received from sentinel GPs.

The EU ILI definition was implemented for the first time in the sentinel system during the 2010/2011 season\(^3\). The 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.

\(^2\) Sixty general practices participated in the scheme at the start of the 2011/2012 season. It should however be noted that one sentinel GP retired during the season.

\(^3\) Prior to the 2010/2011 season, the Irish ILI case definition was used by sentinel GPs.
**Figure 1.** Map of Sentinel GP Practices by location

*Table 1:* Population covered by GP influenza sentinel scheme by HSE-Area for the 2011/2012 season, 23/09/2011.

<table>
<thead>
<tr>
<th>HSE-Area</th>
<th>Population</th>
<th>% Census population</th>
<th>No. practices</th>
<th>No. GPs</th>
<th>Patient population</th>
<th>% Patient population</th>
<th>% Census population</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSE-E</td>
<td>1,620,021</td>
<td>35.3</td>
<td>19</td>
<td>44</td>
<td>85,030</td>
<td>32.3</td>
<td>5.7</td>
</tr>
<tr>
<td>HSE-M</td>
<td>282,410</td>
<td>6.2</td>
<td>2</td>
<td>4</td>
<td>7,156</td>
<td>2.7</td>
<td>2.8</td>
</tr>
<tr>
<td>HSE-MW</td>
<td>379,327</td>
<td>8.3</td>
<td>8</td>
<td>14</td>
<td>25,944</td>
<td>9.9</td>
<td>7.2</td>
</tr>
<tr>
<td>HSE-NE</td>
<td>440,698</td>
<td>9.6</td>
<td>6</td>
<td>17</td>
<td>31,255</td>
<td>11.9</td>
<td>7.9</td>
</tr>
<tr>
<td>HSE-NW</td>
<td>258,328</td>
<td>5.6</td>
<td>4</td>
<td>9</td>
<td>14,727</td>
<td>5.6</td>
<td>6.2</td>
</tr>
<tr>
<td>HSE-SE</td>
<td>497,578</td>
<td>10.8</td>
<td>7</td>
<td>22</td>
<td>56,072</td>
<td>21.3</td>
<td>12.2</td>
</tr>
<tr>
<td>HSE-S</td>
<td>664,534</td>
<td>14.5</td>
<td>10</td>
<td>19</td>
<td>31,775</td>
<td>12.1</td>
<td>5.1</td>
</tr>
<tr>
<td>HSE-W</td>
<td>445,356</td>
<td>9.7</td>
<td>4</td>
<td>6</td>
<td>11,276</td>
<td>4.3</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4,588,252</strong></td>
<td><strong>100</strong></td>
<td><strong>60</strong></td>
<td><strong>135</strong></td>
<td><strong>263,235</strong></td>
<td><strong>100.0</strong></td>
<td><strong>6.2</strong></td>
</tr>
</tbody>
</table>
Annex D: Collection and transportation of specimens

Influenza Surveillance Unit,
National Virus Reference Laboratory,
University College Dublin,
Belfield, Dublin 4
T: 01 716 1323/1358/1341
F: 01 2697611
nvrl@ucd.ie

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: Estimations of influenza vaccination coverage in Ireland

Note: Due to lack of formal vaccination coverage register, influenza vaccination coverage is only available this season for those aged ≥65 years.

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

- On February 1\textsuperscript{st} 2012, 441,573 (82.5\%) of the population aged 65 years or older had either a medical card or a GP visit card. Approximately, 58.3\% of the population aged 65 to 69 years have a medical card or a GP visit card. Source: PCRS and 2011 CSO population census.

- The average uptake for influenza vaccination nationally during the period September 2011 to February 2012 in those aged 65 years and older was 56.6\% (Table F1). Variation in vaccination coverage was observed between age groups, with the highest uptake (61.7\%) in those aged 75 years or older (Table F1). Slight variation in vaccination coverage was also observed between HSE areas, ranging from 53.4\% in HSE-NE to 58.0\% in HSE-E and -SE (Figure F1). Table F2 shows the evolution of vaccine uptake over time.

| Table F1: Cumulative percentage seasonal influenza vaccine uptake in Medical Card and GP visit Card Holders aged 65 years and older, September 2011 – February 2012 |
|---|---|---|---|---|
| Age group (years) | No. vaccinated | No. medical & GP visit card holders* | % Uptake |
| 65-69 | 70-74 | ≥75 | ≥65 |
| No. vaccinated | 43058 | 62443 | 143652 | 249153 |
| No. medical & GP visit card holders* | 91749.33 | 113045.67 | 235543.33 | 440338.3 |
| % Uptake | 46.9 | 55.2 | 61.7 | 56.6 |

* The number of Medical card holders and GP visit card holders represents the average number of card holders for the period September 2011 – February 2012
Table F2: Cumulative percentage seasonal influenza vaccine uptake in Medical Card and GP visit Card Holders aged 65 years and older by season for the period September to February.

<table>
<thead>
<tr>
<th></th>
<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>249153</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>440338</td>
<td>429974</td>
<td>415457</td>
<td>425902</td>
<td>417509</td>
<td>403548</td>
<td>393707</td>
<td>382918</td>
<td>409859</td>
</tr>
<tr>
<td>% Influenza vaccine uptake</td>
<td>56.6 59.9 51.4 57.3 56.8 59.8 62.0 60.5 58.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The number of Medical card holders and GP visit card holders represents the average number of card holders for the period September–February.
Figure F1: Cumulative percentage seasonal influenza vaccine uptake in medical card and GP visit card holders aged 65 years and older by HSE area of GP, September 2011 – February 2012.
Annex F: Case/Control Questionnaire

### Influenza Vaccine Effectiveness Study 2011/2012

**Case/Control Questionnaire**

**Reminder - Only recruit persons who meet the following 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. Participated  Yes [ ]  No [ ]  
2. GP name  

3. 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,...)  [ ]

Please place the study label here:

### II - Patient information

4. Date of Birth:  ____________  
5. Sex:  F [ ]  M [ ]

### III - Symptoms & Clinical details

6. Sudden onset?  Yes [ ]  No [ ]
7. Date of Onset:  ____________  

8. Symptoms
   - High fever (≥38°C)  [ ]
   - Malaise  [ ]
   - Headache  [ ]
   - Myalgia  [ ]

9. Date of swab:  ____________  

For HPSC official use only
NVRL specimen ID  ____________  

### IV - Influenza vaccination

10. Vaccination this flu season (2011/2012)
   - Seasonal influenza vaccine  Yes [ ]  No [ ]  Not known [ ]

   **If yes** date of vaccination (dd/mm/yyyy):  ____________  

   Brand name of vaccine:  Sanofi Pasteur MSD [ ]
   Other brand:  

11. Vaccination last flu season (2010/2011)  Yes [ ]  No [ ]  Not known [ ]
### V - Care History

12. How many times approximately has the patient attended the GP in the last 12 months?  

### VI - Treatment

13. Was antiviral treatment commenced?  
   Yes [ ]  No [ ]  

   If yes, name of antiviral:  
   - Oseltamivir phosphate (Tamiflu) [ ]  
   - Zanamivir (Relenza) [ ]  
   - Oseltamivir phosphate (Tamiflu) & Zanamivir (Relenza) [ ]  
   - Other antiviral [ ]  

14. Date of antiviral administration:  

### VII - Risk Factors

15. Does the patient belong to a target group for influenza vaccination?  
   Yes [ ]  No [ ]  
   (e.g. ≥ 65 years, underlying medical conditions, health care workers, carer, etc...)  
   Please refer to influenza vaccination recommendation list in the pack which you received  

16. Does the patient have an underlying medical condition for influenza vaccine?  
   Yes [ ]  No [ ]  

   If yes, please tick the relevant box(es):  
   - Diabetes Mellitus [ ]  
   - Chronic respiratory disease [ ]  
   - Chronic heart disease [ ]  
   - Chronic liver disease [ ]  
   - Chronic neurological disease [ ]  
   - Chronic renal disease [ ]  
   - Immunosuppression [ ]  
   - Severely obese (BMI ≥ 40) [ ]  
   - Other(s) [ ]  

17. How many times has the patient been hospitalised for their chronic illness in the last 12 months?  

18. Pregnant:  
   Yes [ ]  No [ ]  

19. Smoking status  
   - Current smoker [ ]  
   - Never smoked [ ]  
   - Former smoker [ ]  
   (stopped smoking at least 5yr before inclusion in study)  

### VIII - Functional Status

20. Does the patient usually need help with walking?  
   Yes [ ]  No [ ]  

21. Does the patient usually need help with bathing?  
   Yes [ ]  No [ ]
28th September 2011

Dr 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 Dr O'Donnell,

I wish to confirm that the Research Ethics Committee approved your request to repeat the above study for the 2011/2012 influenza season.

If you have any queries please contact - janet.stafford@icgp.ie

Yours sincerely,

[Signature]

Prof. Colin Bradley
Chair Research Ethics Committee
Annex H: Flow chart of instructions for the influenza vaccine effectiveness (IMOVE) study: (2011/2012)

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

  Yes                                No
  Participate

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
  - **Paper** OR **Web-based**
    - Place a study label on the 1st sheet of the questionnaire
    - Fill out the questionnaire
    - Send the completed questionnaire to Javiera Rebolledo (HPSC) using the stamped addressed envelope supplied
    - Complete a questionnaire on Booroo website: [http://booroo.com/s.asp?sid=54ex4ah9y5gtz1w15219](http://booroo.com/s.asp?sid=54ex4ah9y5gtz1w15219)

  - Document the reasons for non participation on the paper or web-based questionnaire

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