Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Case Control Study Monitoring Influenza Vaccine Effectiveness in Ireland

November 2009

Health Protection Surveillance Centre, Dublin:
Ms. Anne-Sophie Barret, Dr. Joan O'Donnell, Dr. Aidan O' Hora, Dr. Darina O Flanagan and Dr. Derval Igoe

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

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

Contents

Introduction/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.

In light of the emergence of a new pandemic virus, having vaccine effectiveness estimates as soon as possible and monitoring the effectiveness along the course of the pandemic 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 in which 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 (especially during a pandemic)
- Counterbalance the reports of adverse events following immunisation by providing elements for an adequate risk management and cost effectiveness analysis.

Study Objectives

Primary objective

- To measure pandemic influenza vaccine effectiveness among the target population for vaccination, as listed below:

  At risk groups (1st group)

  - Anyone aged 6 months to 65 years with:

- Chronic respiratory disease (including asthma and cystic fibrosis)
- Chronic heart disease
- Chronic renal disease
- Chronic liver disease
- Chronic neurological disease
- Congenital or acquired immunodeficiency and their household contacts
- Diabetes mellitus
- Haemoglobinopathies
- Morbid obesity (BMI ≥ 40)

– All pregnant women in the 2nd and 3rd trimester (of 14 weeks gestation and over) and those in the first 6 weeks postpartum period.

– Pregnant women in the 1st trimester (less than 14 weeks gestation) who are also in another risk group (as listed above).

Other groups

– Healthcare workers

– Children aged 3 - 18 years

– Adults aged 65 years or older

– All others

- To measure seasonal influenza vaccine effectiveness among the usual risk groups for seasonal influenza i.e. people aged ≥65 years and others (see Immunisation Guidelines for Ireland, Chapter 7).

Secondary objectives

- To estimate VE by risk group
- To estimate VE by age group
- To estimate VE by influenza subtype (including pandemic)
- To monitor VE estimates every year
- To provide intra-seasonal VE estimates

Methods

A case control study will be undertaken with influenza-like illness (ILI) positive cases and ILI negative controls. This study is a collaboration between the Health Protection Surveillance Centre (HPSC), the National Virus Reference Laboratory (NVRL) and the Irish College of General Practitioners (ICGP). Ireland is willing to participate in a multicentre case control study with other countries.

Study period

The study period will start from Week 46 2009 starting on November 9th (beginning of influenza season) and extend until Week 20 2010 (end of influenza season).

Study population

The study population is individuals with no contraindication for neither pandemic influenza vaccine nor seasonal influenza vaccine who are consulting at a participating GP practice and presenting with ILI. All age groups should be included.

According to the ICGP agreement (used in this protocol), samples from **at least five patients** with ILI will be selected by participating GPs each week and asked to provide a nasal/throat swab specimen for influenza testing.

Inclusion criteria

Patients will be eligible if they meet the ILI definition used for routine sentinel surveillance and accept to participate. They will be requested to give oral consent. For patients aged 16 years and under, oral consent will be asked from parents/guardians.

Exclusion criteria

Patients will be excluded if they:

- Refuse to participate in the study
- Are not eligible for influenza vaccination as suffering from a condition listed in the summary of product characteristics
- Live in a residential home
- Are unable to give informed consent or to follow the interview in the native language because of aphasia or reduced consciousness.

Laboratory confirmation

Specimens will be collected from ILI cases and sent to NVRL as per current practice for sentinel surveillance (study code on specimen and lab request form, see section Coding system). Mode of specimen collection, storage and transport are listed in Annex A.

Influenza laboratory confirmation will be done using RT-PCR. ILI cases who tested positive for influenza will be included in the case group. ILI cases who tested negative for influenza will be

included in the control group.

Coding system

Three identification numbers will be assigned for this study:

- Study code (I-MOVE 09)
- GP Code (the same as sentinel code)
- Patient Number (in sequence as seen e.g. first=01, second=02, etc.)

These codes (3 components) will be printed on sticky labels. Three labels will be provided per patient as follows:

- the first will be placed on the questionnaire;
- the second will be placed on the swab container;
- the third will be stored by the GP with the patient's name and date of birth in order to identify the patient later on if needed. The list with the patient number and his/her name will be kept by the GP and not communicated to HPSC.

The NVRL will send the swab results to the GP as per current clinical practice and also to HPSC with the study ID number (study code, practice code and patient code) in order to link the result to the questionnaire.

Data

Data on cases and controls will be collected at GP office level using a standardised structured questionnaire (Annex B). The completed questionnaires will be forwarded to the study coordinator (Anne-Sophie Barret[1]) at HPSC. This will be done posting the paper forms to HPSC using stamped addressed envelopes.

[1] Contact details: annesophie.barret@hse.ie or 01 876 53 00

Information collected in the questionnaire will include:

- Study identification: country and GP
- Case / control demographics
- Symtoms & clinical details
- Medical risk factors
- Functional status (using the Rankin score)
- Antiviral treatment
- Vaccination history (for both pandemic and seasonal vaccine)
- Access to care

All answers given will be completely confidential and protected by the Data Protection Act 2003. Information which could identify the individual patients is not being sought on the data form and will not be shared with any of the study team. Data security and confidentiality will be maintained at all times at the Health Protection Surveillance Centre, which is accredited for Information Security Management IS17799. The study will be used for public health purposes only.

Analysis

Analysis of Irish data will be performed at HPSC and a pooled analysis for European countries will be conducted by Epiconcept, an independent team of public health research experts contracted by ECDC and based in Paris. During the influenza season 2008-2009, Epiconcept coordinated a pilot study to monitor seasonal influenza vaccine effectiveness[2,3].

[2] Valenciano M, Ciancio B, Moren A. First steps in the design of a system to monitor vaccine effectiveness during seasonal and pandemic influenza in EU/EEA Member States. Euro Surveill 2008 October 23;13(43)

[3] Kissling E, Valenciano M, Falcão JM, Larrauri A, Widgren K, Pitigoi D, Oroszi B, Nunes B, Savulescu C, Mazick A, Lupulescu E, Ciancio B, Moren A. I-MOVE" towards monitoring seasonal and pandemic influenza vaccine effectiveness: Lessons learnt from a pilot multi-centric case-control study in Europe, 2008-9. Euro Surveill 2009 Nov (in press)

First VE estimates (intra-seasonal) will be disseminated as soon as they are available. Final estimates will follow at the end of the influenza season. The results of the study may be published in scientific journals or presented at scientific conferences.

Annex A: Collection and Transportation of Specimens

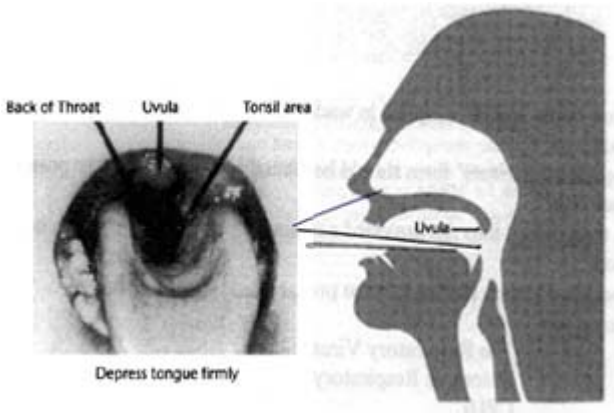
Collection and Transport of Specimens

GPs participating in the Influenza Surveillance Scheme should ensure that they have been supplied with an influenza specimen-collection kit from the NVRL containing the following: (a) swabs, (b) transport media, (c) patient information forms, (d) plastic specimen bags, (e) pre – addressed & sender labels, (f) plastic containers and (g) outer wrapper.

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 throat swab is used to abrade the tonsils and pharynx (see diagram).



Swabbing the throat

Transport bottle containing swab

2. The swab is then broken off into a bottle containing virus transport medium.
3. The flexible wire nasal swab is inserted into the nostril and rubbed against and above the nasal turbinates.
4. The swab is then agitated thoroughly into the same bottle as the throat swab to release virus infected cells. The nasal 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 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 specimens per container). There should be sufficient absorbent wrapping to ensue that the specimens cannot move about the plastic container.
3. The container should then be placed into a plastic specimen bag with the completed patient information form positioned in the special pouch section.
4. The outer wrapper must be conspicuously marked "Pathological Specimen – Fragile with Care"
5. It must also show the name and address of the sender to be contacted in case of damage or leaks.
6. The package should be addressed :

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

7. Specimen should reach the laboratory within 24 hours.
8. Where unavoidable delays are envisaged, specimens should be stored at 4*C and sent to the NVRL as soon as possible.

Annex B: Case/Control Questionnaire

Influenza Vaccine Effectiveness Study

Case/Control Questionnaire

Date

GP name

Please place here the study label

PATIENT INFORMATION

Date of Birth:

Sex: F M

Is the patient a health-care worker? Yes No

Does the case have occupational exposure to pigs? Yes No

Symptoms & Signs

Sudden onset? Yes No Date of Onset:

Symptoms (please tick relevant boxes)

- High fever (≥ 38ºC)
- Malaise
- Headache
- Myalgia
- Cough
- Sore throat
- Shortness of breath

Swab taken Yes No Date of swab:

Risk Factors

Does the patient have any of the following underlying illnesses?
Please tick the relevant box(es)

- Diabetes Mellitus
- Chronic respiratory disease (excluding asthma)
- Heart disease
- Chronic liver disease
- Chronic neurological disease
- Pregnancy
- Chronic renal disease
- Immunosuppression
- Haemoglobinopathies
- People on medication for asthma
- Severely obese (BMI ≥ 40)

If pregnant, please state week of gestation at date of onset of symptoms Week(s)

Post partum ≤ 6 weeks Yes No

If patient has other chronic illness, please specify

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

Smoking status

- Current smoker
- Never smoked
- Former smoker (stopped smoking 1yr before inclusion in study)

Influenza Vaccine Effectiveness Study

Case/Control Questionnaire

Functional Status

MODIFIED RANKIN SCALE (MRS) Score (See Annex 1 for description)
Please fill score accordingly 0 - 6
Choose one score only.

1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐

Treatment

Was antiviral treatment commenced? **Yes** ☐ **No** ☐ **Not Known** ☐

If yes, name of antiviral:

- Oseltamivir phosphate (Tamiflu) ☐
- Zanamivir (Relenza) ☐
- Oseltamivir phosphate (Tamiflu) & Zanamivir (Relenza) ☐
- Other antiviral ☐

Date of antivirals administration: |_|_|_|_|_|_|

Vaccination History

Pandemic influenza

Has the patient been vaccinated against pandemic influenza (H1N1)? **Yes** ☐ **No** ☐ **Not Known** ☐

If yes, give date of vaccination (dd/mm/yyyy):

1st dose |_|_|_|_|_|_| 2nd dose *(if applied)* |_|_|_|_|_|_|

If vaccination date is unknown, was the patient vaccinated more than 14 days ago? **Yes** ☐ **No** ☐ **Not Known** ☐

Where has the patient been vaccinated?

- GP ☐
- Vaccination clinics ☐
- Not known ☐

Seasonal influenza

Has the patient been vaccinated against seasonal influenza this season (2009-2010)? **Yes** ☐ **No** ☐ **Not Known** ☐

If yes, give date of vaccination (dd/mm/yyyy): |_|_|_|_|_|_|

Brand name: _____ Batch number if available: _____

If vaccination date is unknown, was the patient vaccinated more than 14 days ago? **Yes** ☐ **No** ☐ **Not Known** ☐

Has the patient been vaccinated against influenza in the last 2 years?

- 2006-2007: **Yes** ☐ **No** ☐ **Not Known** ☐
- 2008-2009: **Yes** ☐ **No** ☐ **Not Known** ☐

Care history

Has the patient ever been lab-confirmed with H1N1? **Yes** ☐ **No** ☐ **Not Known** ☐

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

Influenza Vaccine Effectiveness Study

Laboratory Results - For HPSC use only

Positive RT-PCR for Influenza? Yes ☐ No ☐ Not Known ☐

	Yes	No	Not Known
Influenza A	☐	☐	☐
Influenza B	☐	☐	☐
Influenza A(H1N1)	☐	☐	☐
Other	☐	☐	☐

If other, please specify: ☐

Phylogenetic typing Yes ☐ No ☐ If Yes, please specify strain identified ☐

Classification of Patient - For HPSC use only

ILI negative	Control	☐
ILI positive	Pandemic H1N1 case	☐
	Seasonal influenza case	☐

Annex 1 - MODIFIED RANKIN SCALE (MRS) Score Description

Score	
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

References

Provided by the Internet Stroke Center - www.strokecenter.org

Rankin J. "Cerebral vascular accidents in patients over the age of 60." *Scott Med J* 1957;2:200-15

Bonita R, Beaglehole R. "Modification of Rankin Scale: Recovery of motor function after stroke." Stroke 1988 Dec;19(12):1497-1500

Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. "Interobserver agreement for the assessment of handicap in stroke patients." Stroke 1988;19(5):604-7