

# **Influenza Vaccine Effectiveness in Portugal**

Season 2011-12

**Final Report**

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## Summary

The EuroEVA project is the Portuguese component of the multicentre I-MOVE study and aims to obtain estimates of the seasonal and pandemic vaccine effectiveness during and after the influenza season.

Since the 2008/2009 influenza season Portugal, along with other European countries, has implemented a common protocol using a case-control study design, where influenza-like illness cases which are laboratory confirmed as influenza (ILI+) are compared to a control group consisting of ILI patients which test negative for influenza (ILI-) (Case-control Test negative design).

The results presented in this report relate to the EuroEVA 2011-2012 season and aim to estimate the seasonal influenza vaccine effectiveness for the age group 60+ years and in all age groups, using two approaches: ***Case-control Test negative design*** and ***Screening Method***.

## Materials and Methods

### Test Negative Design

ILI cases were identified among patients that presented ILI symptoms to a participating EuroEVA General Medical Practitioner (GP). On a weekly basis, each GP systematically selected ILI patients (two per week with less than 60 years and all ILI patients with 60 years and more) using the EU ILI case definition. Data on potential confounding factors and effect modifiers was collected using a standardized questionnaire which included information on socio-demographic variables (age, gender, education and co-inhabitants), previous (2010-11) influenza vaccination, chronic conditions and related hospitalizations, current smoking habits, belonging to GP list and number of consultations in the previous year. An ILI patient was considered vaccinated if he/she had received one dose of the 2011/2012 trivalent influenza vaccine at least 14 days prior to onset of symptoms. VE was estimated as one minus the odds ratio of being vaccinated in cases versus controls adjusted for confounders by logistic regression. Potential confounders were investigated and included if: they changed crude OR estimate in at least 10% after adjustment by the Mantel-Haenszel method, were associated both to being a case (in the absence of the exposure factor) and to the seasonal vaccination.

### Screening Method

ILI cases and ILI laboratory confirmed influenza cases were recruited in the context of the National I-MOVE case-control study (EuroEVA). Vaccine coverage in the population was obtained from a sample of 1074 households stratified by region (homogeneous allocation) selected from a dual sample frame: random digit dialling mobile and landline phones (ECOS sample). Relevant information was collected by CATI (Computer Assisted Telephone interview) – one respondent by household (proxy for the rest of the household members). VE was estimated by comparing the proportion of vaccinated cases to the

vaccine coverage in the source population, using the Orenstein formula and the Farrington method to adjust for age group and target group for vaccination.

## Results

In Portugal, a later beginning of the 2011/2012 influenza epidemic was observed, starting in week 4/2012 and ending at week 12/2012. In this season both influenza B and A(H3) virus types were circulating, with predominance of the later.

### Test negative design

From the 59 GP's that accepted to participate in the study, 35 effectively participated in the study by selecting patients (which corresponds to a 59% participation rate). After excluding 79 ILI cases (for not adhering to the inclusion criteria) the final sample consisted on 273 ILI patients. Of the 134 cases which tested positive for influenza, 98.5% were positive for influenza A(H3) and the remaining for type B virus. The control group, consisting of 139 ILI patients who tested negative for influenza, was statistically different ( $p < 0.05$ ) from the ILI+ group in the following variables:

- **Clinical signs and symptoms: cough** (higher in cases than in controls: 95.5% vs. 89.2%, respectively) and **sore throat** (more frequent in controls, 89.2%, than in cases, 75.4%);
- **Age:** controls were older than cases (median age in controls was 52 yrs vs. 39 yrs in cases);
- **Any chronic disease:** the prevalence of at least one chronic condition relevant for influenza vaccination was higher in controls (41.7% vs 29.1%);
- **Seasonal vaccine in 2010-11:** controls were more often vaccinated against influenza in the last season than cases (30.2% vs. 14.4%);
- **Co-habitants:** the median number of co-habitants was higher in cases (3 vs. 2).

Considering all population, vaccine coverage (VC) in controls was 27.5% statistically higher than in cases (VC=13.4%). Similar results were obtained for the sub-group target for vaccination by the National Health Authorities (VC cases =24.6% and VC controls=46.1%,  $p=0.010$ ). These results indicate that crude VE estimates was 59.2% (95% CI: 21.1%-79.4%) in the general population and 61.8% (95% CI: 15.5% ;83.1%) in the target group for vaccination. After adjustment for co-inhabitants and month of onset of illness, VE adjusted estimates were 48.8% (95% CI: 0.0% ; 73.8%) and 51.6% (95% CI:-6.2%-77.9%) for the general population and for the target group, respectively.

### Screening Method

The ECOS telephone survey was conducted during April 2012, and information was obtained from a total of 2395 individuals. According to the results, individuals were vaccinated from October 2011 through January 2012, estimating a 16.4% (95% CI: 13.6-19.6) vaccine coverage (VC) in the population.



In the 60+ yrs age group, the VC was 37.3% (95% CI: 30.6-44.4) and for the individuals with chronic condition was 28.0% (95% CI: 23.0-33.7). The crude VE estimated with the Screening method for ILI+ as the outcome was 27.0% (95% CI: -19.9- 55.6) and -32.4% (95% CI: -77.7- 1.3) for ILI. Adjusted VE estimates varied from -90.4% (95% CI: -277.1- 3.9) (60+ yrs) to 6.1% (95% CI: -56.0- 43.4) (0-60 yrs) considering ILI as the outcome and from -58.6% (95% CI: -195.3- 14.8) to 56.9 (95% CI: -35.2- 86.3) for ILI positive outcomes (none were statistically significant).

### **Conclusions**

Given the 3 years experience in conducting this study, logistical and implementation aspects were straightforward.

The 2011-2012 season adjusted VE estimates were similar for the general population (48.8%) and for the target group (51.6%), although not statistical significant. When compared to the previous season, VE point estimate for the general population was lower (VE=58% in 2010-11), although the CI overlap.

The population studied this year was older than in the last season. The time between onset of symptoms and swabbing, was also different with marginally, non significant, differences between cases and controls.



## Introduction

Influenza virus circulates every year causing epidemics that are generally benign for the human population, but causes more severe disease with high impacts on mortality and hospitalizations<sup>1-3</sup>. This is particularly the case in specific population groups, such as the elderly and individuals with chronic conditions, which are at higher risk of becoming seriously affected.

Vaccination has been one of the main measures to mitigate influenza impacts, its role in reducing the risk of developing the disease and the occurrence of associated complications being well recognized<sup>4</sup>. In high-risk groups, influenza vaccine is recommended each year and, since the vaccine is also reformulated on a yearly basis, estimating influenza vaccine effectiveness (VE) in each season is of major importance to support public health decisions, both for the target group for vaccination and for the general population.

In Portugal, during the 2005/2006 and 2006/2007 influenza seasons, the Instituto Nacional de Saúde Doutor Ricardo Jorge (National Institute of Health - INSA) conducted two pilot studies with a cohort design (EVA I and EVA II), and the results obtained suggested that the estimation of effectiveness of the anti-influenza vaccine should be based on multicentre studies involving several European countries<sup>5</sup>. Thus, since 2008-2009, INSA has been participating in the project I-MOVE (Influenza – Monitoring Vaccine Effectiveness in Europe), funded by the European Centre for Disease Prevention and Control (ECDC) through its national component EuroEVA, (*Efectividade da Vacina Antigripal na Europa*). The I-MOVE project aims at monitoring influenza vaccine effectiveness during influenza seasons and pandemics in the European Union, with the participation of several countries<sup>6</sup>

The study conducted during the 2008-2009 season was essentially a pilot study to test if the case-control design would be able to measure influenza vaccine effectiveness in-season and at the end of the season, among people aged 65 years and above, using several control groups. One of the controls used was the laboratory influenza-negative cases (test negative design) and this method has been used since then<sup>7</sup>.

During the 2009-2010 influenza season, Portugal, Spain, Ireland, France, Italy, Hungary and Romania joined the I-MOVE multi-center case control study with a common protocol and with objective of estimating not only the seasonal influenza vaccine effectiveness but also the pandemic influenza VE, respectively in the elderly (65+) and in all age groups. In 2010-2011, 8 European countries participated in the multi-center case control study (Portugal, Spain, Italy, France, Poland, Hungary, Ireland and Romania) replicating the objectives and protocol used in 2009-10 season.

In the I-MOVE group, since 2009, 6 study sites (Portugal, Spain, England, Italy, France and Scotland) have been using the Screening method to estimate seasonal VE against medically attended influenza-like illness (ILI) cases and ILI laboratory confirmed influenza in primary care, general and ICU hospital wards. In Portugal, the Screening method was first used in the 2009/2010 season and this season it was once again used to estimate the 2011-12 seasonal influenza vaccine effectiveness against medically attended ILI cases and ILI laboratory confirmed influenza.

This report describes the data collected and analyzed for the EuroEVA 2011-2012 season, with the objective of estimating seasonal influenza vaccine effectiveness, both in the 60 and plus years old and in all age groups.

## **Objectives**

### **Main objective**

The primary objective was to estimate influenza vaccine effectiveness among people of all ages and those aged 60 years and more in Portugal.

### **Secondary objectives**

- To provide intra-seasonal VE estimates
- To estimate according to risk group
- To estimate VE according to influenza subtype



## Methods

### Study design

In this study, two approaches were used (Figure 1):

- 1) **Test negative design:** a case-control design approach in which laboratory confirmed influenza cases (ILI+) were compared to laboratory influenza-negative ILI patients (ILI-);
- 2) **Screening Method:** compares the proportion of cases who are vaccinated with the proportion vaccinated in a comparable group in the population. Information on cases derived from the Test negative design.

### Study population and sampling design

#### *Test Negative Design*

The study population was composed of individuals of all ages and with no known contraindication for influenza vaccination. Sampling was performed in two steps (Figure 1):

1. General practitioners (GPs) were contacted and selected from a list of medical general practitioners (GPs) that are, or were, members of the Rede Médicos Sentinela (Sentinel Network of Medical Practitioners). All GPs from this Portuguese Sentinel Network were invited to participate in the EuroEVA 2011-2012 study by ordinary mail and e-mail. The GPs were also asked to invite other GPs, not members of the Sentinel Network, to participate on the study, and these were contacted at a later stage. All GPs that participated on the previous EuroEVA 2010-2011 were invited.
2. Each GP that accepted to participate was asked to select each week two ILI cases (EU ILI definition) under 60 years, and all ILI cases from individuals aged 60 years or more, from their weekly medical appointments (either they were enrolled, or not, in the GP's list).

#### *Screening method*

In the **Screening Method**, the study population consisted of individuals of all ages with mobile and/or landline phones. The study was conducted as follows (Figure 1):

- 1) Selection of households, stratified by Administrative region, with homogeneous allocation, using random digit dialing mobile and landline phones (ECOS sample<sup>8</sup>).
- 2) One respondent in each household aged 18 or more (proxy information for the rest of the household members)

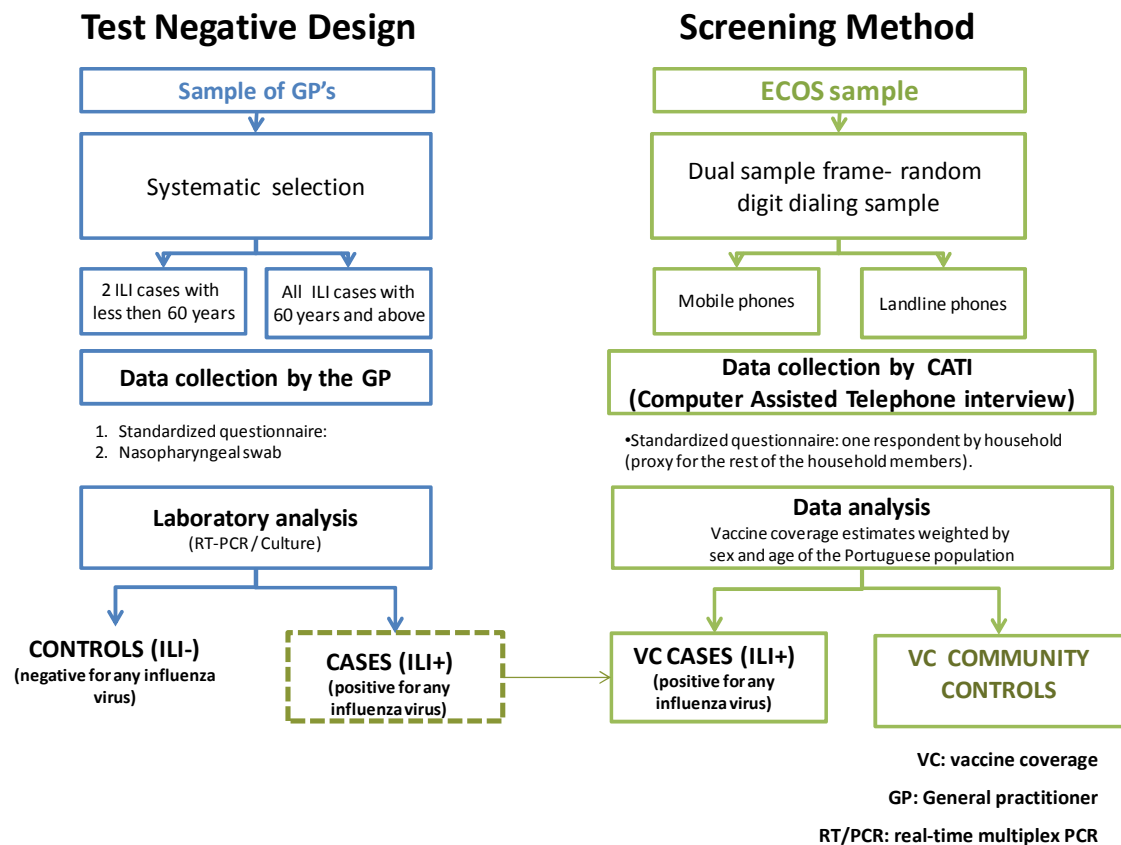


Figure 1: Schematic flow of the test negative design and Screening method for estimating seasonal vaccine effectiveness (VE).

## Study period

### Test Negative Design

In order to estimate seasonal VE, ILI cases were selected by GPs starting on 21st November 2011 (week 46). As previously established in the scientific protocol, a period of 2 weeks with no positive cases for influenza, after the epidemic period, would determine the end of the study. Data collection ended at 20th April 2012 (week 16), since from week 12 none of the enrolled ILI cases was positive for influenza.

### Screening method

Data collection on community controls (ECOS sample) took place during March-April 2012.

## Outcome (Test Negative Design and Screening Method)

For both methods, a confirmed case of influenza is defined as a person with an ILI with laboratory confirmation of infection with influenza B, A(H1N1), A(H3N2), or A(H1N1)pdm09, by one or more of the



following tests:

1. real-time RT-PCR
2. virus culture (MDCK-Siat1 cell line)

For the Screening Method, influenza like illness cases were also considered as an outcome.

### *Case definition*

Influenza-positive ILI cases were considered as **Cases** (for both methods) as well as ILI cases (for Screening Method only). An influenza like illness (ILI) was defined as an individual who consults a participating GP, presenting with a sudden onset of symptoms and at least one of the following four systemic symptoms (EU criteria)<sup>9</sup>:

- fever or feverishness;
- malaise;
- headache;
- myalgia;

AND at least one of the following three respiratory symptoms:

- cough;
- sore throat;
- shortness of breath.

### *Laboratory confirmation*

#### *Specimen's collection*

The success of virus diagnosis largely depends on the quality of the specimen collection and on the conditions of transport and storage, before it is processed in the laboratory.

Specimens were collected from ILI cases who attended their GP within 7 days after onset of clinical symptoms for influenza like illness.

Nasopharyngeal swabs, or a combined nasopharyngeal and oropharyngeal swab were acceptable. Specimens were collected into a suitable transport medium. This procedure was conducted by the GP himself or by a nurse under his supervision.

Each sample was identified anonymously with the ILI case code, and the information related to the patient, demographic data, characteristics of the disease and the data concerning the confounding variables were recorded on the notification form.

#### *Storage, transport*

The specimens on viral transport medium were kept at 0 to 4°C and transferred from the GP to the National Influenza Reference Laboratory by an express mail company within 24 hours, following the procedure already in place for the samples collected for routine surveillance of seasonal influenza.

#### *Laboratory Tests (RT-PCR / Culture)*

Laboratory confirmation of influenza infection was done using cell-tissue culture for influenza viruses and a real-time multiplex RT-PCR.

Virus isolation is a very useful technique for the diagnosis of influenza infection allowing for further antigenic and genetic characterization of isolates, and also for vaccine preparation or drug-susceptibility testing.

Isolates were characterized antigenically by haemagglutination inhibition tests (HAI), carried out using antisera and reference virus strains distributed by WHO Collaborating Center (London). Selected isolates were sent to the WHO Collaborating Center in London for further study.

The rapid detection and typing of seasonal influenza viruses was performed by a multiplex “in house” real-time RT-PCR targeted to the matrix and nucleoprotein genes of influenza A and B, respectively. This is a powerful technique for the identification of influenza virus genomes even when they are present at very low levels.

For influenza A subtyping, the Prodesse ProFAST+ Influenza A Subtyping assay (GEN-PROBE) was used.

In order to identify the influenza B lineage (Yamagata/88 and Victoria/87), a multiplex “in house” real-time RT-PCR was used.

#### *Strain characterization*

The phylogenetic analyses of the influenza virus isolates was performed by sequencing the coding region of the HA1 subunit of the haemagglutinin, for a subset of isolates from the beginning, the peak and the end of the season, representing 86.2% of the isolated strains, using the ClustalW Method for the multiple alignment and the Maximum Likelihood Method for the construction of the phylogenetic trees (MEGA Software).

### *Quality Control*

The National Influenza Reference Laboratory follows internal control procedures and also external quality control programs organized by the Global Influenza Surveillance and Response System (GISRS from WHO) and by the European Influenza Surveillance Network (EISN from ECDC).

### *Case finding*

#### *Procedures to select ILI cases*

ILI cases were identified among patients that presented ILI to a participating GP. For the purpose of estimating VE, GPs selected ILI cases of all ages and with 60 years or more. The ILI case could occur among GPs patient list or not, provided that an encounter patient/GP took place.

ILI cases were recruited using the EU case definition, respecting the exclusion criteria (described below) and using a non-randomized systematic sampling method. This systematic sampling procedure consisted on the selection, by each GP, of the first two ILI cases with less than 60 years of each week and all ILI cases with 60 years or more. To avoid bias regarding the weekday, the first day of the week for each GP was randomly assign (e.g. for GP1 the week starts at Thursday, GP2 Tuesday, GP3 Monday, etc.). In this way, each GP had a different starting day of the week and received a SMS reminder the day before the start of his/her "week".

#### *Case inclusion criteria*

Cases were eligible if they met the above case definition and accepted to participate. A written informed consent was requested to ILI cases after explaining the objectives of the study.

#### *Case exclusion criteria*

Cases were excluded if they:

- a) refused to participate in the study;
- b) were not eligible for influenza vaccination;
- c) were institutionalised;
- d) were unable to give informed consent or follow an interview in their native language because of aphasia, reduced consciousness, or other reasons.

All excluded cases were registered in an appropriated form.

## Control groups

### *Test negative design (ILI influenza negative controls)*

Considering the **Test negative design**, Controls corresponded to individuals that presented ILI symptoms to a participating GP but were laboratory negative for influenza infection with A(H1N1), A(H3N2), B and A(H1N1)pdm09 viruses.

As for Cases, Controls were systematically selected from the GP list or other, provided that an encounter patient/GP took place. The systematic sampling procedure was already described (for Cases). The exclusion criteria described for Cases were also applicable to Controls. Excluded controls were also registered in an appropriated form.

### *Screening method (Community controls)*

Within the **Screening Method**, controls were selected from an already implemented vaccine coverage monitoring survey<sup>8</sup>. Between 1999 until the present season, the Department of Epidemiology of the National Institute of Health held yearly telephone surveys to the panel of families ECOS (*Em Casa Observamos Saúde/ Observing Health at Home*) with the aim of studying the influenza vaccine coverage in the Portuguese mainland population.

Controls were selected from the ECOS sample, a population-based dual-frame sample of households with landline or mobile telephone. Data was collected via Computer Assisted Telephone Interview during March-April 2012.

## Exposure (vaccination)

### *Target groups, vaccines in use*

The target groups for vaccination were all individuals belonging to a risk group (see below).

During the 2011-2012 influenza season, seasonal vaccines were available at pharmacies and several brands were in use, namely:

- Chiroflu, Novartis Vaccines and Diagnostics (non adjuvant);
- Flud, Novartis Vaccines and Diagnostics (adjuvant) - individuals with 65 or more years of age;
- Fluarix GlaxoSmithKline (non adjuvant);
- Influvac, Solvay Farma (non adjuvant);
- Istivac, Sanofi Pasteur MSD (non adjuvant);

- Istivac Infantil, Sanofi Pasteur MSD (non adjuvant) – children with 6 to 35 months of age;
- Intanza, Sanofi Pasteur MSD (non adjuvant) – individuals with 60 or more years of age.

### *Vaccination campaign*

Seasonal vaccination campaign started on week 39 of 2011 (October 2011).

### *Definition of vaccinated individual*

Seasonal vaccinated individuals were those that had taken the seasonal vaccine (one of the available brands) 14 days before the disease onset.

### *Vaccine status ascertainment*

**Test negative design:** Inoculation with the 2011/2012 WHO approved influenza vaccine was ascertained by the GPs by consulting the patient’s record and confirming explicitly with the patient if the vaccine has been taken.

If no data existed in the clinical record, patients were asked about vaccine inoculation status. Flu patients were asked if the inoculation was through a “shot”. The day and month of inoculation were also asked and recorded.

**Screening method:** Vaccination status in the population was ascertained through a questionnaire. In each household one individual with 18 or more years provided information on his/her vaccination status and on the rest of the household elements. Thus the terminology "percent of vaccinated" used in this report refers to individuals whose vaccination status was either self-reported or reported by proxy. For validation purposes, individuals were asked if the inoculation was through a “shot”.

### **Risk groups**

Individuals were considered to belong to a risk group if in the GP records refer, or if the patient reports, they suffer from one of the underlying conditions included in the interview questionnaire.

Risk groups<sup>10</sup> individuals were all patients with at least one of the following underlying conditions:

- Diabetes: if treated for insulin or non-insulin-dependent diabetes;
- Cardiovascular disease (congenital heart disease, hypertensive heart disease, ischemic heart disease, chronic heart failure)
- Chronic renal disease (chronic renal failure and nephrotic syndrome);

- Chronic hepatic disease (cirrhosis, biliar atresia and chronic hepatitis);
- Obesity IMC $\geq$ 30;
- Chronic respiratory disease (asthma, chronic bronchitis, emphysema, bronchopulmonary dysplasia, cystic fibrosis, pneumoconiosis and pulmonary fibrosis) ;
- Immunodeficiency congenital or acquired (conditions that suppress the immune function due to underlying disease and/or therapy, e.g. chemotherapy, HIV infection);
- Neuromuscular disease.

An individual was considered to belong to the target group for vaccination if he belongs to at least one of the following groups:

- a) suffer from at least one of the chronic condition listed above;
- b) age  $\geq$ 65 years;
- c) pregnancy in the second and third trimester;
- d) occupation (health professional and care taker);
- e) caregiver or cohabitant of children with less than 6 months with chronic conditions

This season the influenza vaccination of the age group 60 to 64 years of age was recommended by the General Directorate of Health.

## Confounding factors and effect modifiers

### *Test negative design*

Data on potential confounding factors and effect modifiers were collected using a standardised questionnaire. For **Cases** and **Controls** enrolled at GP practices, data was collected by a face-to-face interview.

The questionnaire (annex B) was designed to collect information on risk groups plus the following variables:

- *Previous influenza vaccination (2010-2011)*: vaccination against seasonal influenza in the last season;
- *Patient is a health professional or care provider*: the patient is a health professional/ care provider or caregiver or cohabitant of children with less than 6 months with chronic

conditions. These variables plus the information on chronic condition allowed us to identify patients belongs to the 2011-2012 seasonal vaccine target group, according to the General Directorate for Health recommendations<sup>10</sup>;

- *Severity*: the severity of the underlying conditions was measured by the number of hospital admissions due to underlying conditions in the 12 months prior to inclusion in the study;
- *Smoking status*: smoking history was collected and coded as either “never-smoker”, “former smoker” (stopped smoking at least one year before inclusion in the study) or “current smoker”;
- *Number of GP visits in previous year*: in order to document and control for health seeking behavior the number of all GP visits in the 12 months before inclusion in the study.
- *Educational level*: number of completed years of education;
- *Co-inhabitants*: number of co-inhabitants was recorded considering the number of individuals that live in the same household with the patient (with or without family relations), excluding the patient;
- *Functional status*: low functional status was defined as needing help to bath;
- *Antiviral administration*: usage and type of antivirals was documented when applicable.

### Screening method

Data was collected via Computer Assisted Telephone Interview (CATI). Information with interest for the current study included vaccine status, influenza-like illness symptoms from September until the day of the interview (yes or no) and declared presence/absence of chronic conditions.

### Sample size calculation

The ILI cases sample size for the case control test negative design was set at 400.

This value was calculated aiming to estimate a vaccine effectiveness of 50% with a lower bound of the 95% confidence interval equal to 10%, assuming that the seasonal vaccine coverage in controls is 19% (all age groups) and that the proportion of ILI cases positive for influenza in the season was 45%. The expected vaccine effectiveness was set according to the 2010-2011 I-MOVE multicentre case control study. The assumed vaccine coverage in controls was the arithmetic average of vaccine coverage in the two previous seasons obtained by a telephone survey conducted in Portugal. The proportion of

positives for influenza was the average of the percentages observed in the two previous seasons in the Portuguese sentinel surveillance system.

It should be stated that with this sample size, if the expected vaccine effectiveness is higher, 70% the lower bound of the confidence interval will be 40%. The calculation formula was adapted from Lemeshow, Hosmer and Klar (1988)<sup>11</sup> who assumes a case control relation of 1:1 cases, in order to account for a chosen proportion of ILI cases positive for influenza, i.e. the case to control relation.

The sample size of ILI cases was given by:

$$n = \frac{Z_{1-\alpha/2}^2 \left\{ \frac{1}{p_1 p_I} + \frac{1}{(1-p_1) p_I} + \frac{1}{p_2 (1-p_I)} + \frac{1}{(1-p_2) (1-p_I)} \right\}}{[\ln(1 - \varepsilon)]^2}$$

Where:

$Z_{1-\alpha/2}$  is the standard Normal distribution  $1-\alpha/2$  percentile,

$p_2$  is the vaccination coverage in the controls,

$p_I$  is the proportion ILI cases positive for influenza,

$\varepsilon$  is relative precision,

$p_1 = \frac{(1-VE)p_2}{(1-VE)p_2 + (1-p_2)}$ , and VE is the expected vaccine effectiveness.

During the 2010-2011 study, 288 ILI cases were recruited by 35 GP's, which represents an average of approximately 8 ILI cases per GP. In this sense, to obtain the 400 ILI cases we the collaboration of 50 GP's. Considering the participation rate observed in last season (35/58=60%), our goal was to enroll 80 GP's to reach 50 participating GP's to collect 400 ILI cases (180 influenza positive cases and 220 ILI test negative controls).

### Screening method

For the **Screening method** the ECOS sample size is approximately 1000 household representing 3000 individuals in all age groups.

### Data collection

#### Test negative design

Data on **Cases** and **Controls** was collected at the GP offices. GPs interviewed the patients using a standardized questionnaire (in annex B). Each participating GP filled in the questionnaire that included data on:

1. study identification: country and GP;
2. case/control demographics;



3. ILI signs and symptoms;
4. date of onset of ILI;
5. date of swabbing;
6. laboratory results (filled in after the laboratory result);
7. patient is a health professional or care provider ;
8. selected underlying chronic conditions (including diabetes, heart disease, chronic obstructing pulmonary disorder, renal diseases and immunodeficiencies);
9. obesity (IMC>30);
10. number of hospitalizations for selected underlying chronic diseases in the previous 12 months;
11. total number of GP visits in the previous 12 months;
12. smoking history;
13. current season influenza vaccination including date and brand;
14. influenza vaccination in the previous season;
15. pregnancy status;
16. functional status;
17. antiviral administration

### *Screening method*

Collected information for the community control group included:

1. individual code
2. household code
3. sex
4. age
5. ILI signs and symptoms;
6. self reported underlying chronic conditions (including diabetes, heart disease, chronic obstructing pulmonary disorder, renal diseases, hepatic and immunodeficiencies).

### *Transmission*

In the **Test negative design**, biological material (from the swab collection) and data from ILI cases were sent on a daily basis by mail to the Instituto Nacional de Saúde Doutor Ricardo Jorge where it was centrally treated. Laboratory results obtained by the National Influenza Virus Laboratory team were sent to the Department of Epidemiology team with ILI case code and influenza test results on a weekly basis.

In order to perform the pooled analysis of the data gathered by all the participating countries, data was also transmitted to EpiConcept, after data anonymization and coding according to the list of variables, definitions and coding previously provided to EpiConcept.

Considering the **Screening Method**, the survey was conducted by an external company during one month. Database was sent to the Epidemiology Department where it was validated and analyzed.

### *Entry*

In the **Test negative design**, final data entry was performed at Department of Epidemiology of the Instituto Nacional de Saúde Doutor Ricardo Jorge on a STATA SE 11 database by typing in the answers from the questionnaires and laboratory results.

In the Screening method, data on the community controls were collected using CATI and entered in an Access data base.

### *Validation*

**Test negative design:** Before data entry, a visual verification of missing and inconsistent values was done by the research team. After data entry a validation script was also run on the database.

Validation procedures included verification of the presence of impossible values and of inconsistencies in and between variables. All missing or inconsistent values were clarified with the corresponding GP.

## **Analysis**

### *Test negative design: Coding and categorization of variables*

All categorical variables were previously coded<sup>12</sup> with exception of:

- the age group was created from the variable age and categorized in four classes: 0-4; 5-14; 15-59 and  $\geq 60$  years of age;
- the indicator variable of the delay between the onset of disease and swab less than 3 days data was computed from the number of days between the onset and the swab;
- the smoking status variable was recoded as 1- current smoker, and 0- former and never smoker;
- the variables diabetes, cardiovascular disease, chronic cardiac failure, chronic renal disease, chronic hepatic disease, chronic respiratory disease and immunodeficiency were recoded into 1- any chronic disease (at least one of the previous list) and 0 – no chronic diseases.

The variables treated as numerical (discrete or continuous) were age, days between the onset of the symptoms and swab, number of previous hospitalizations due to the underlying chronic diseases in the last 12 months, number of education years, number of co-habitants and number of GP consultations in the last 12 months.

Exposure to seasonal influenza vaccine variable:

*Vaccinated (coded 1)*- ILI case has taken the seasonal vaccine 14 days before the disease onset;

*Not vaccinated (coded 0)*-all others.

### *Comparison of group's characteristics*

In the **Test negative design**, Cases and Controls (ILI negative) were compared regarding the following variables: age, sex, pregnancy, morbid obesity, smoking status, diabetes, cardiovascular disease, heart failure, renal failure, chronic hepatic disease, immunodeficiency, any chronic condition, previous seasonal and pandemic vaccines (2009-2010), belong to target group, help for bathing, number of hospitalizations in the previous 12 months, years of education, patient belong to the GP list, number of GP consultation in the previous 12 months, number of co-habitants and ILI symptoms.

Statistical comparisons were performed considering that the samples were independent.

Association between variable **Case/Control** and all categorical variables was evaluated by the Chi-squared test. If at least one of the table cells presented expected frequencies lower than 5, the Chi-squared test was substitute by the Fisher's Exact test.

Comparisons of numerical variables between groups (**Case/Control**) were performed using the non parametric test of Mann-Whitney.

### *Measure of effect*

#### **Test negative design**

Vaccine effectiveness was computed as  $VE=1-OR$  (crude) and  $aVE=1-aOR$  (adjusted) where OR and aOR is respectively the crude and adjusted odds ratio of being vaccinated within **Cases** versus **Controls**.

For the crude estimate, the exact 95% confidence interval of VE (OR) was obtained by the method described in Sahai H and Khurshid<sup>13</sup>. The confidence interval for the aVE was computed by the respective method of adjustment (non conditional Logistic Regression).

## **Screening method**

Vaccine effectiveness (crude and adjusted for age group and presence of at least one chronic disease) was also computed by comparing the proportion of vaccinated **Cases** (ILI+ and ILI) with the vaccine coverage estimated on the Community control group using the Screening method as described by Farrington 1993<sup>14</sup>.

### *Stratified analysis*

Due to the small sample size stratified analysis was not executed in the **Test-negative design** study. For the **Screening method**, 2011-12 seasonal VE was estimated for: the age groups <60 and ≥60 years of age and according to the presence of at least one chronic condition.

### *Multivariable analysis*

The odds ratio of being vaccinated within **Cases** versus **Controls** was adjusted for possible confounders using non conditional logistic regression.

Potential confounders were included in the model if they changed crude vaccine OR estimate in at least 10% after adjustment by the Mantel-Haenszel (M-H) method, were associated to being a case (among the non-vaccinated) and were associated to the vaccine uptake.

### *Restricted analysis*

For each outcome, case and controls were respectively restricted to the period from the first to the last ILI patient positive.

### *Software used for data entry, statistical analysis.*

All the results were obtained using the package of statistical programs STATA/SE 11<sup>15</sup>.

## **Logistical aspects**

### *Consent*

Each GP had the responsibility of obtaining written consent from ILI cases, after giving adequate information on the general study characteristics.

### *Ethical approval*

The study protocol was submitted and authorized by the Comissão Nacional de Protecção de Dados

(National Committee for Data Protection) and submitted and approved by the Comissão de Ética (Ethics Committee) of Instituto Nacional de Saúde Doutor Ricardo Jorge, I.P (annex A).

### *Team*

*Department of Epidemiology, Instituto Nacional de Saúde Doutor Ricardo Jorge*

Ausenda Machado, Baltazar Nunes (coordinator), Inês Batista

*National Influenza Virus Laboratory of the Department of Infectious Diseases, Instituto Nacional de Saúde Doutor Ricardo Jorge*

Patrícia Conde, Paulo Gonçalves, Pedro Pechirra, Inês João, Raquel Guiomar (co-coordinator)

*General Directorate of Health*

Isabel Falcão

*MS network and others GP*

(see Acknowledgments' section)

### *Supervision*

A supervising committee was established with participating members of the Direcção-Geral da Saúde (General Directorate of Health), INFARMED (National Authority of Medicines and Health Products), CEFAR/ANF (National Pharmacies Association) and APMGF (Portuguese Association of General Practitioners).

### *Training*

After the selection procedure, to each one of the GPs that agreed to participate, a personal telephone contact was made by phone explaining the study and their participation. They also received the protocol, case definition questionnaires and laboratory swabbing procedures.

The following items were discussed:

- the design of the project;
- the EU case definition;
- the inclusion and exclusion criteria to select ILI cases and underlined that selection should be independent of vaccination status;

- definitions and concepts associated with each variable in the questionnaires and the way of answer or coding questions;
- to collect nasopharyngeal samples, and provide transportation to the National Influenza Reference laboratory in INSA;
- to accept data quality checks on the quality of some selected issues.

For these purposes several telephone calls have been made during the recruitment and development of the study. When necessary, some personal contacts or by e-mail have been made to clarify doubts.

## Results

### Influenza 2011/2012 season

Data collected through the National Influenza Surveillance Programme (Network of Sentinel General Practitioners- Rede Médicos Sentinela, Network of Emergency Units and National Laboratory Network for Influenza Diagnosis) reveals that the influenza activity in Portugal during the 2011-12 season was moderate-to-high, with a peak incidence during late-February through the beginning of March (Figure 2).

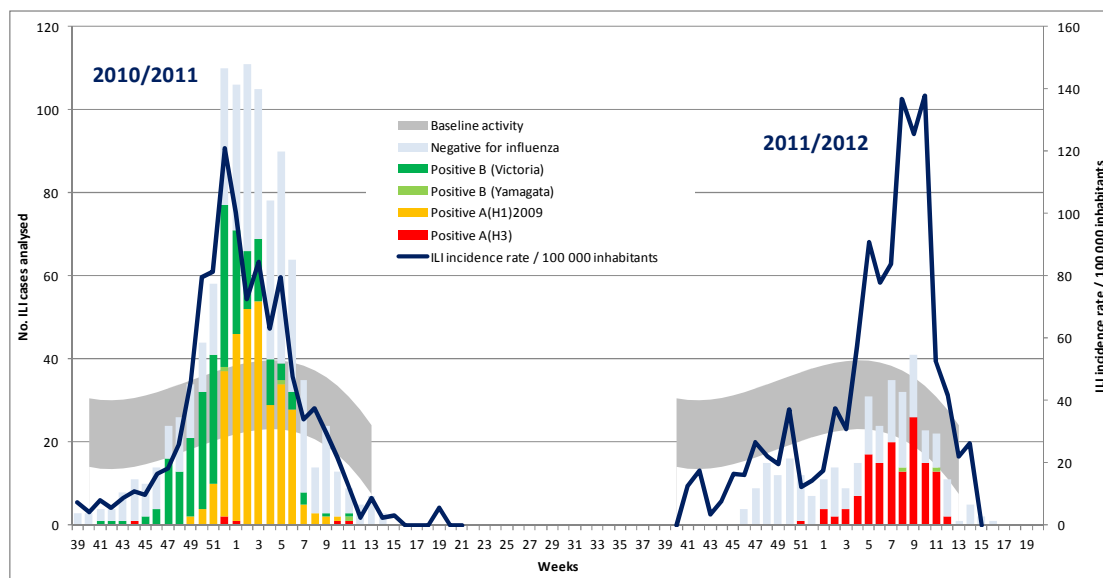


Figure 2: Distribution of ILI incidence rates, number of cases analyzed and number of viruses detected, by week during 2010-2011 and 2011-2012 influenza seasons (Data from the National Influenza Surveillance Programme).

### Duration

The ILI incidence rate was above the baseline threshold from week 4/2012 through week 12/2012. By week 4, the ILI incidence rate began to rise quickly, peaked at week 10/2012 with the value of 137.7 cases per 100 000 inhabitants, and decreased abruptly, falling below the baseline threshold from week 13 onward.

### ILI incidence

Comparing the epidemic period of 2011-2012 with the previous 2010-2011 season, the incidence rate peaked later during the 2011-2012 season (week 10/2012) than during 2010-2011 (week 52/2010), registering a maximum of 137.7 and 121.1 cases per 100 000 inhabitants, respectively.

ILI incidence rates were higher for the extreme age groups, *i.e.*, in infants (age group 0-4 years) and for the elderly ( $\geq 65$  years). This contrasts with the previous 2010/2011 season, when incidence rates were higher for the population aged 5-14 and 15-64 years (Figure 3).

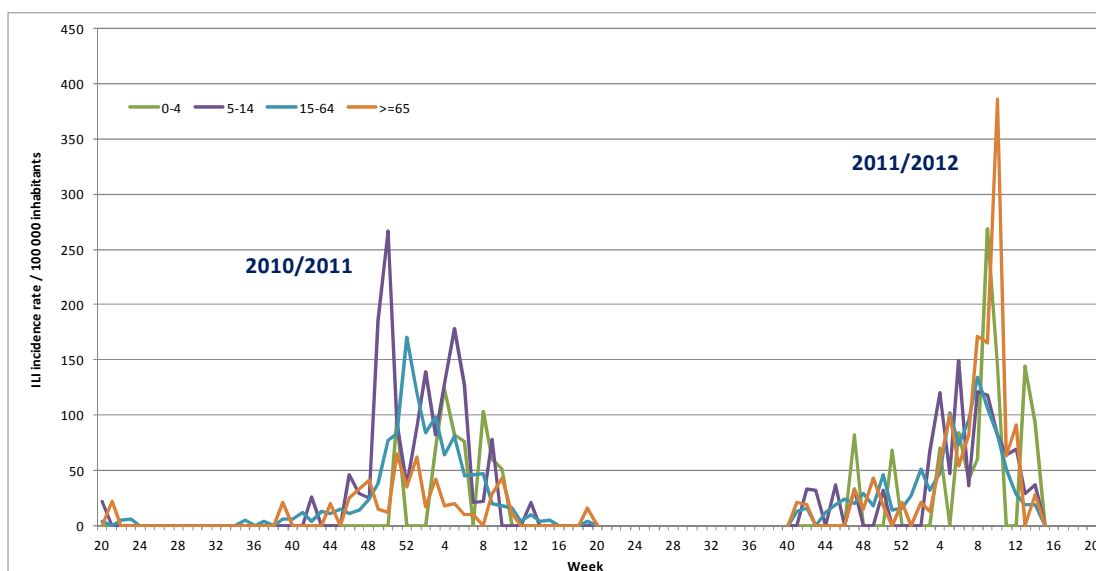


Figure 3: Distribution of ILI incidence rates by age group during 2010-2011 and 2011-2012 seasons.

### Virus circulation

Influenza subtype A(H3) was the predominant (97.7%) influenza virus circulating during the 2011-12 season. It was detected from week 51/2011 through week 18/2012, with a proportion of positive cases above 50% between weeks 3/2012 and 11/2012 (end of January through mid-March). Influenza viruses type B (Yamagata lineage) were detected sporadically during the second half of the season (weeks 7 through 11). This contrasts with the 2010-11 season, when Influenza B/Victoria and A(H1)pdm09 viruses co-circulated.



## Test Negative design

### Participating GP's:

After the selection procedure, 59 GP's agreed to participate. About 59% (35) participated in the study by selecting, collecting swabs and data on **Cases** and **Controls** (Table 1).

Table 1: Number of GPs that accepted to participate and those that selected at least one ILI patient.

	GPs currently participating in MS <sup>1</sup>	GPs ex-participants in MS or others <sup>1</sup>	Total
All GPs accepting to participate	26	33	59
GPs reporting valid data	20	15	35

<sup>1</sup>MS – "Médicos-Sentinela" network

All participating GPs work in a Health Center of the National Health Service (Ministry of Health) and have a stable list of patients. GPs that accepted to participate in EuroEVA were distributed by all 5 Administrative Regions and by 14 of the 18 Districts of mainland Portugal. GPs reporting ILI cases covered all 5 regions and 11 of the 18 Districts (Figure 4).

a)

b)

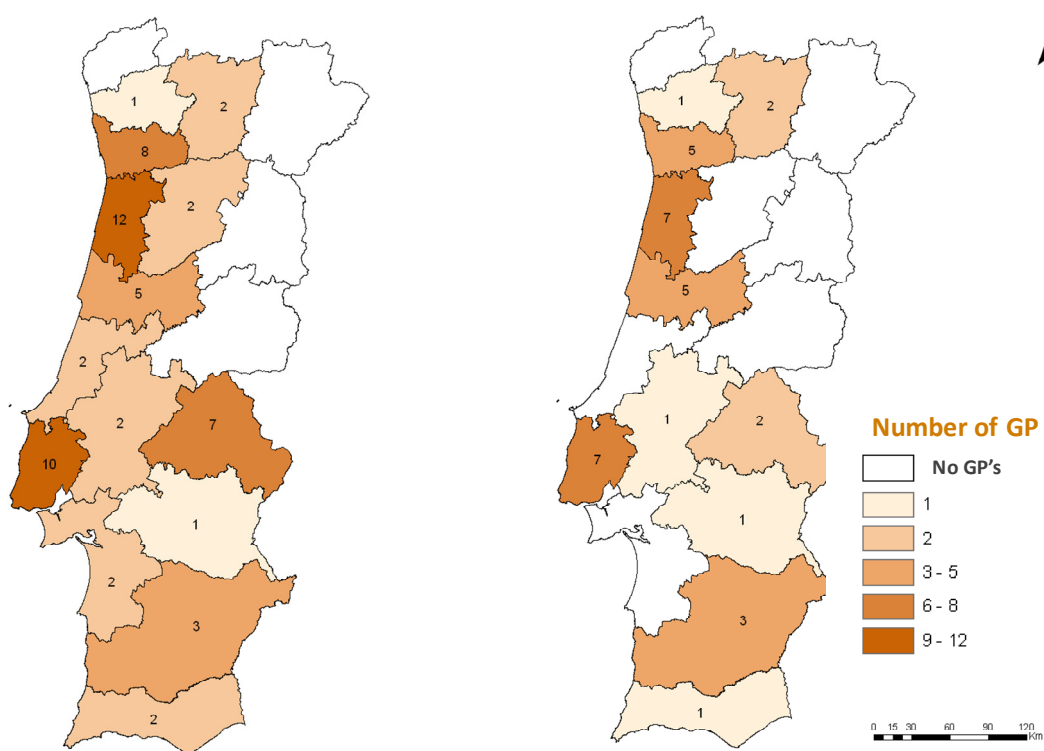


Figure 4: Distribution of participating a) and effectively reporting b) GPs.

### Description of participants

A total of 352 ILI cases were selected by the participating GP's during the study period. The final data set for analysis comprised 273 ILI cases. The flowchart of data inclusion/exclusion is presented in Figure 5.

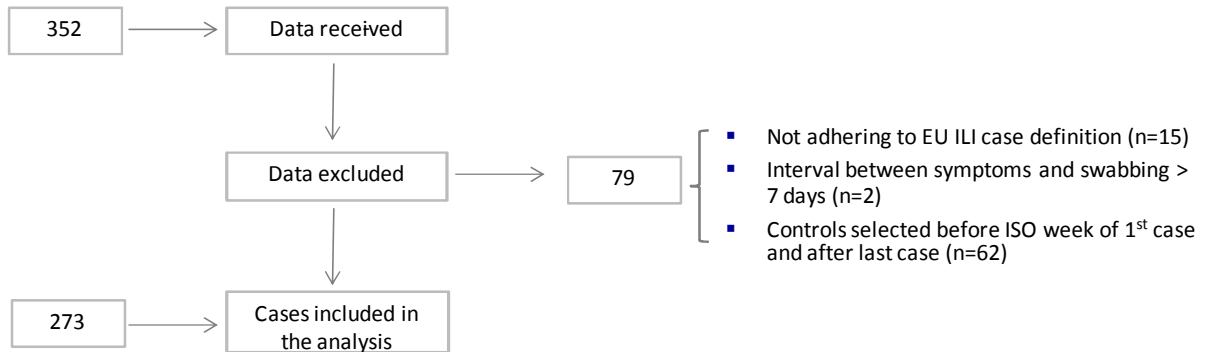


Figure 5: Flowchart of data inclusion/exclusion.

### Laboratory results

Specimens were collected for virological analysis at the National Influenza Reference Laboratory, from the 352 cases reported, between weeks 46/2011 and 16/2012 (Figure 6).

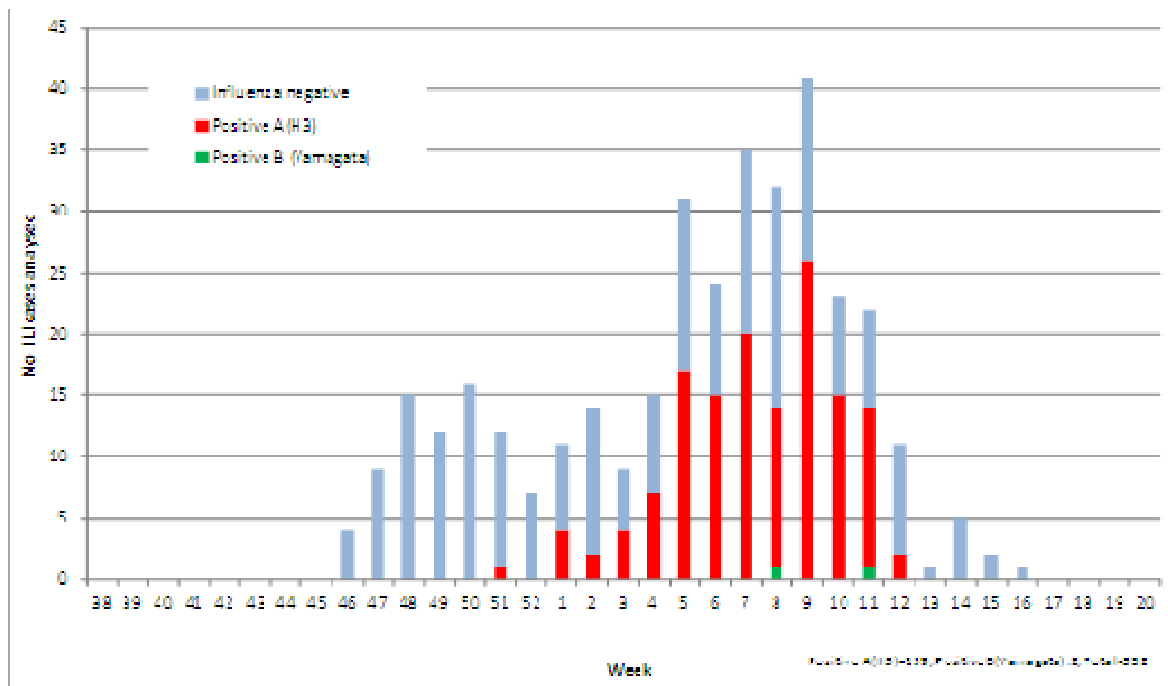


Figure 6: Weekly distribution of the 352 cases analyzed

Laboratory analysis shows that only 40.1% of all ILI cases were associated with infection with influenza viruses, the majority of which of the A(H3) subtype (Figure 7). Influenza B(Yamagata) viruses were detected sporadically.

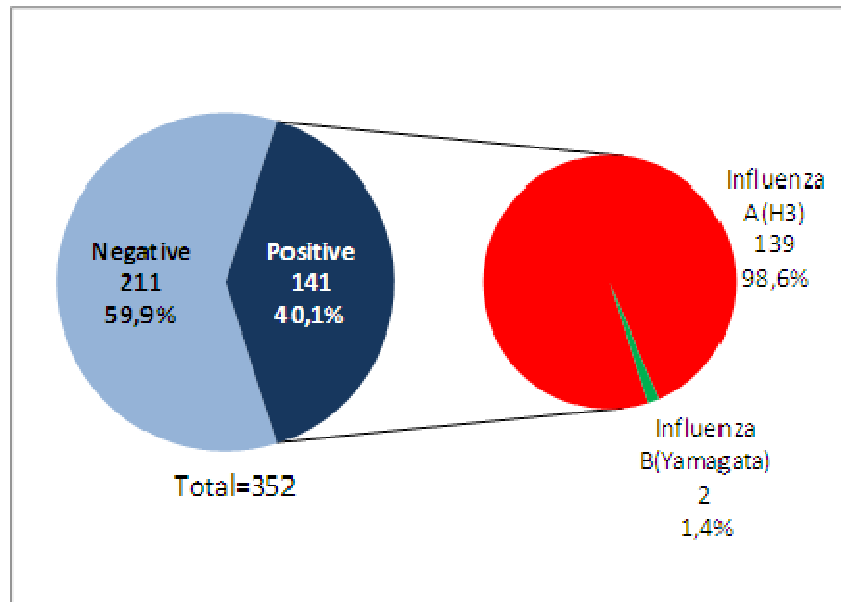


Figure 7: Virological characterization of influenza like-illness cases. Influenza-positive results account for 40.1% of the total of cases analysed.

As in the 2011/2012 influenza season, other respiratory viruses were also tested in the laboratory to further characterize the influenza-like syndrome. These included: respiratory syncytial virus types A and B, Rhinovirus, parainfluenza virus 1, 2 and 3, and adenovirus. The combined results are shown in Figure 8.

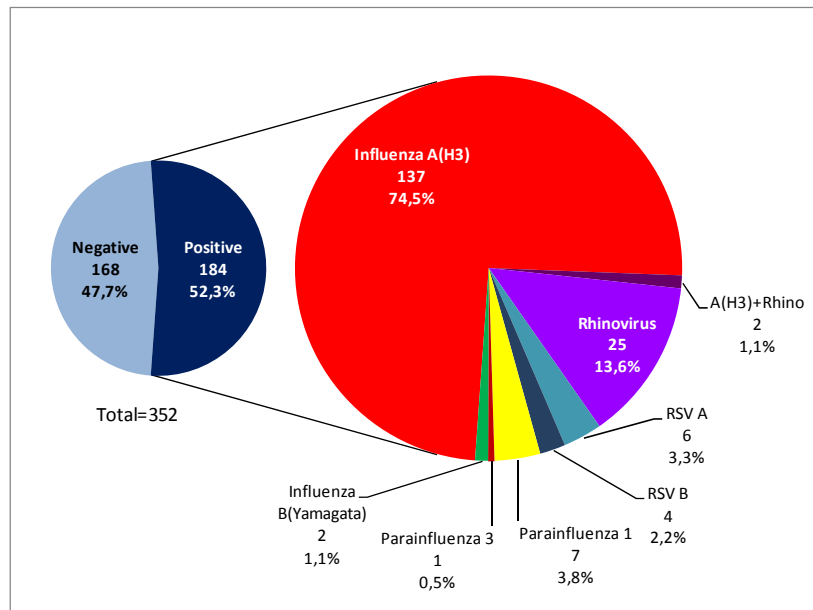


Figure 8: Virological characterization of ILI cases. Combined laboratory results for influenza A and B, RSV A and B, rhinovirus, parainfluenza 1, 2 and 3, and adenovirus.

One or more virus types were found in 52.3% of the ILI cases studied, the majority of which were influenza subtype A(H3) viruses (74.5%), followed by rhinoviruses (13.6%). RSV types A and B, and parainfluenza 1 and 3 were also found.

Specimen inoculation into cell-tissue culture resulted in the isolation of 29 strains of influenza virus, 27 influenza A(H3) and 2 influenza B (Yamagata) viruses. Although some antigenic variability was observed in influenza A(H3) viruses, they were all considered antigenically similar to the vaccine strain A/Perth/16/2009. The influenza B viruses were from a different lineage (Yamagata) comparing with the influenza B vaccine strain (Victoria lineage, strain B/Brisbane/60/2008).

Genetic analysis based on the HA1 subunit of the hemagglutinin gene was performed on 23 influenza A(H3) viruses (14 isolates and 9 clinical samples) and 2 influenza B strains.

Influenza A(H3) viruses clustered into 4 different genetic groups. Most of them (18 viruses) belong to clade 6 (represented by A/Iowa/19/2010). The remaining viruses clustered in clades 3 and 5 - two in subclade 3A, represented by A/Stockholm/18/2011, other two in subclade 3C, represented by the future vaccine strain A/Victoria/361/2011, and one virus in clade 5, represented by A/Perth/10/2010 (figure X). Comparing to the vaccine strain A/Perth/16/2009, most of the 2011/2012 influenza A(H3) viruses presented 10 amino acid substitutions (nine of them located in hemagglutinin antigenic sites).

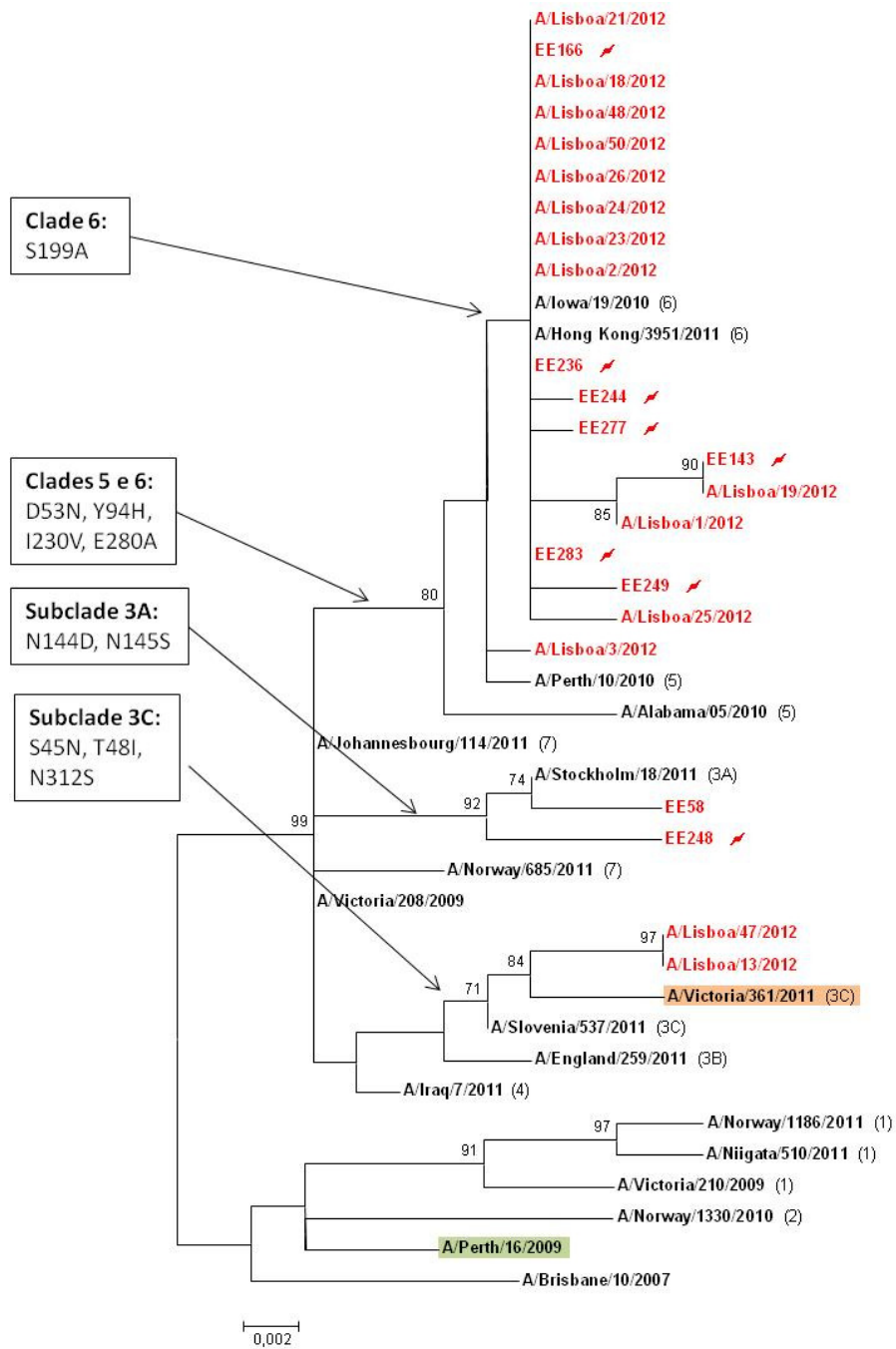


Figure 9: Phylogenetic tree of influenza A(H3) viruses based on the HA1 subunit. Bootstrapp values above 70 are shown. Viruses detected and characterised in this study are shown in red. Other reference and Portuguese strains are in black. The current and the future vaccine strains are highlighted in green and orange, respectively. ✂ - viruses detected in vaccinated individuals.

The two influenza B strains detected are of the Yamagata lineage, in contrast with the influenza B vaccine strain (B/Brisbane/60/2008) which belongs to the Victoria lineage. From the genetic characterization, they group into different clades of the Yamagata lineage, one virus clustered in clade 2,

represented by B/Brisbane/3/2007 (a group of strains which had previously circulated) and another virus in clade 3 (a more recent group), represented by B/Bangladesh/3333/2007 (Figure 10).

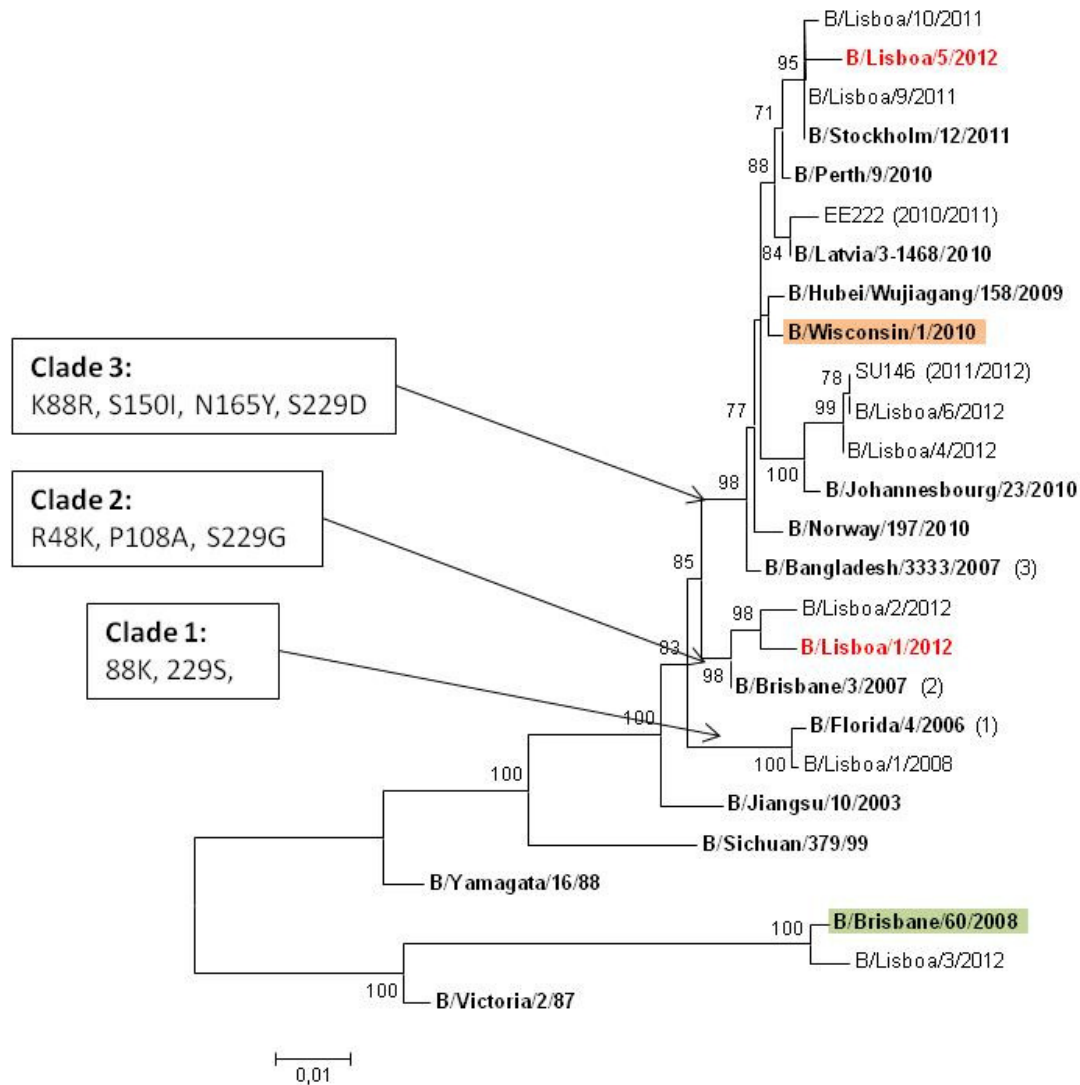


Figure 10: Phylogenetic tree of influenza B viruses based on the HA1 subunit. Bootstrapp values above 70 are shown. Viruses detected and characterised in this study are shown in red. Other reference and Portuguese strains are in black. The current and the future vaccine strains are highlighted in green and orange, respectively.

### Description of Cases and Controls

As referred, the data was restricted to the 273 ILI cases that fulfilled the inclusion/exclusion criteria. From these, 134 (49%) were positive for an influenza virus and were thus considered as cases in the analysis (132 were type AH3 and 2 were type B virus) and 139 (51%) tested negative for influenza and were thus considered as controls in the statistical analysis. For analysis purposes, the 134 were considered **Cases** and the 139 were considered as **Controls**. The comparison of cases and controls is presented in Tables 2 and 3.

Considering the delay between onset and swab collection, no significant differences were found between cases and controls when comparing either the median number of days or the proportion of individuals with swabs within the first 3 days after symptom onset (Table 2). For the clinical symptoms (Table 2), statistically significant differences were found for cough, with cases presenting a higher frequency, and sore throat (controls referred this symptoms more often than cases).

Table 2: Description of Cases and Control, from week 46 to week 12 during the 2011-2012 influenza season, according to time between the onset and swab, signs and symptoms, and treatment with antiviral

	Cases	Controls	p-value
<b>Time between onset and swab collection (days).</b>			
<i>median</i>	2.0	2.0	0.115
<i>less than 72h,%</i>	91.0 (134)	83.5 (139)	0.061
<b>Signs and symptoms, % (n)</b>			
<b>Fever</b>	89.3 (131)	83.2 (131)	0.151
<b>Malaise</b>	95.5 (133)	94.2 (139)	0.643
<b>Headache</b>	85.1 (134)	78.3 (138)	0.147
<b>Myalgia</b>	90.2 (132)	90.7 (139)	0.890
<b>Cough</b>	95.5 (134)	89.2 (139)	0.050
<b>Sore throat</b>	75.4 (134)	89.2 (139)	0.003
<b>Shortness of breath</b>	16.5 (133)	24.6 (138)	0.100
<b>Antiviral use</b>	0 (134)	0 (139)	-

(), number of valid answers; <sup>a</sup> Mann-Whitney test; <sup>b</sup> Fisher's Exact test; <sup>c</sup> Chi-squared test; - Not computed

In relation to demographic characteristics (Table 3), a significant difference was found in the age of the two groups (Cases were younger than Controls). For the remaining potential confounders (Table 3), the

following significant differences were identified when comparing cases to controls:

- ✓ **Controls** presented a higher prevalence of any chronic condition (41.7% vs 29.1% for **Cases**);
- ✓ Previous seasonal vaccine (2010-2011) was higher in **Controls** (30.2%) than in **Cases** (14.4%);
- ✓ Cases had a higher median number of co-habitants (Controls: 2 vs Cases: 3).

Table 3: Description of cases and controls, from week 46 to week 12 during 2011-2012 influenza season, according to demographic characteristics and potential confounders.

	Cases	Controls	p-value
<b>Demographic characteristics</b>			
<b>Age, median</b>	39 (129)	52 (130)	<0.001
<b>0-4 yrs, %</b>	0.8	0.7	0.021
<b>5-14 yrs, %</b>	14.2	7.9	
<b>15-60 yrs, %</b>	65.7	56.2	
<b>≥60 yrs, %</b>	19.4	35.3	
<b>Sex, men %</b>	47.0 (134)	40.3 (139)	0.262
<b>Potential confounders , %</b>			
<b>Belong to target group of vaccination</b>	45.5 (134)	55.4 (139)	0.103
<b>Any chronic disease</b>	29.1 (134)	41.7 (139)	0.029
<b>Seasonal vaccine 2010-11</b>	14.4 (132)	30.2 (139)	0.002
<b>Smokers</b>	14.2 (134)	13.0 (139)	0.767
<b>Help for bathing</b>	2.4 (124)	3.0 (135)	0.788
<b>Belongs GP patient list</b>	63.4 (134)	68.4 (139)	0.392
<b>GP consultations last 12 mo, median</b>	3 (130)	3 (139)	0.149
<b>Hospitalizations, median</b>	0 (134)	0 (139)	0.149
<b>Years of education, median</b>	7 (132)	6 (134)	0.716
<b>Co-inhabitants, median</b>	3 (134)	2 (138)	0.001

( ), number of valid answers; <sup>a</sup> Mann-Whitney test; <sup>b</sup> Fisher's Exact test, <sup>c</sup> Chi-squared test; - Not computed

### Vaccine coverage

In the 2011-2012 season, the seasonal vaccine coverage in Controls was significantly higher (27.5%) than in Cases (ILI+) (13.4%) (Figure 11). Restricting the analysis to individuals belonging to target groups for vaccination, vaccine coverage in controls was 46.1% significantly higher than in cases (24.6%).



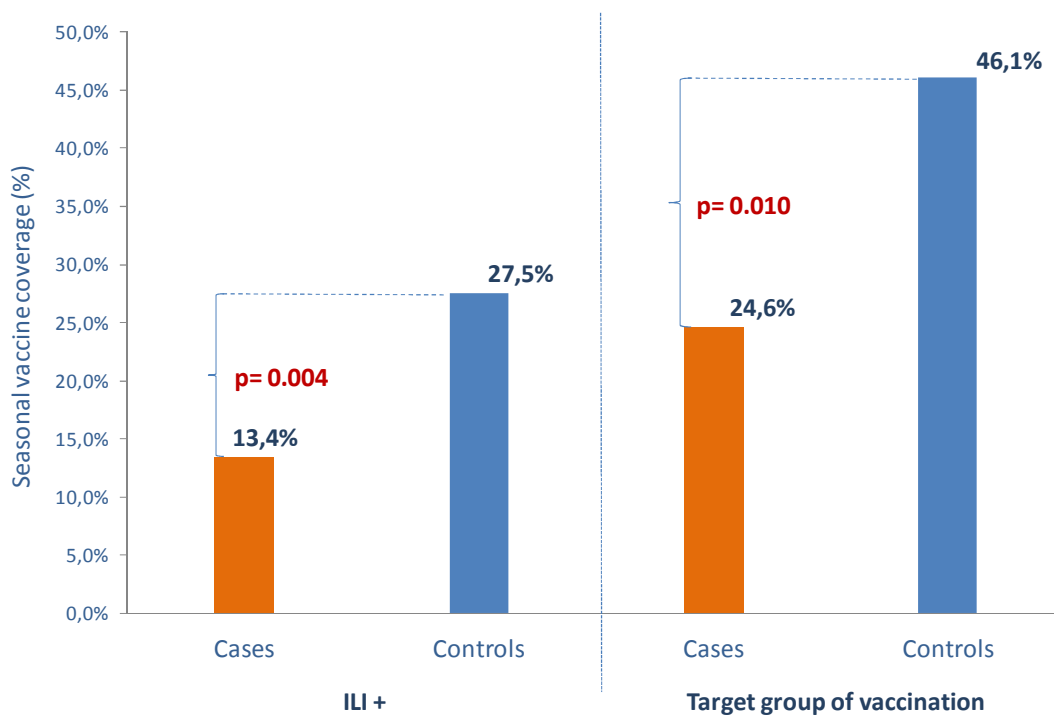


Figure 11: Comparison of vaccine coverage of Cases and Controls in all ILI+ cases and in the target group of vaccination.

### Vaccine effectiveness

Considering the odds of being vaccinated in cases compared with controls, VE crude estimates were computed (Table 6). The 2011-2012 seasonal VE estimate was 59.2% (CI95%: 21.1%: 79.4%). Considering the target group for vaccination, the crude VE was 61.8% (CI95%: 15.5%; 83.1%).

As mentioned in the *Material and Methods* section, in order to estimate adjusted VE, it was adopted a strategy that consisted in including only potential confounders that changed 2011-12 seasonal vaccine crude OR more than 10% after M-H adjustment, and were associated to being a case (among the non vaccinated) and were associated to the vaccine uptake. In Figure 12 it is presented the results of this analysis.

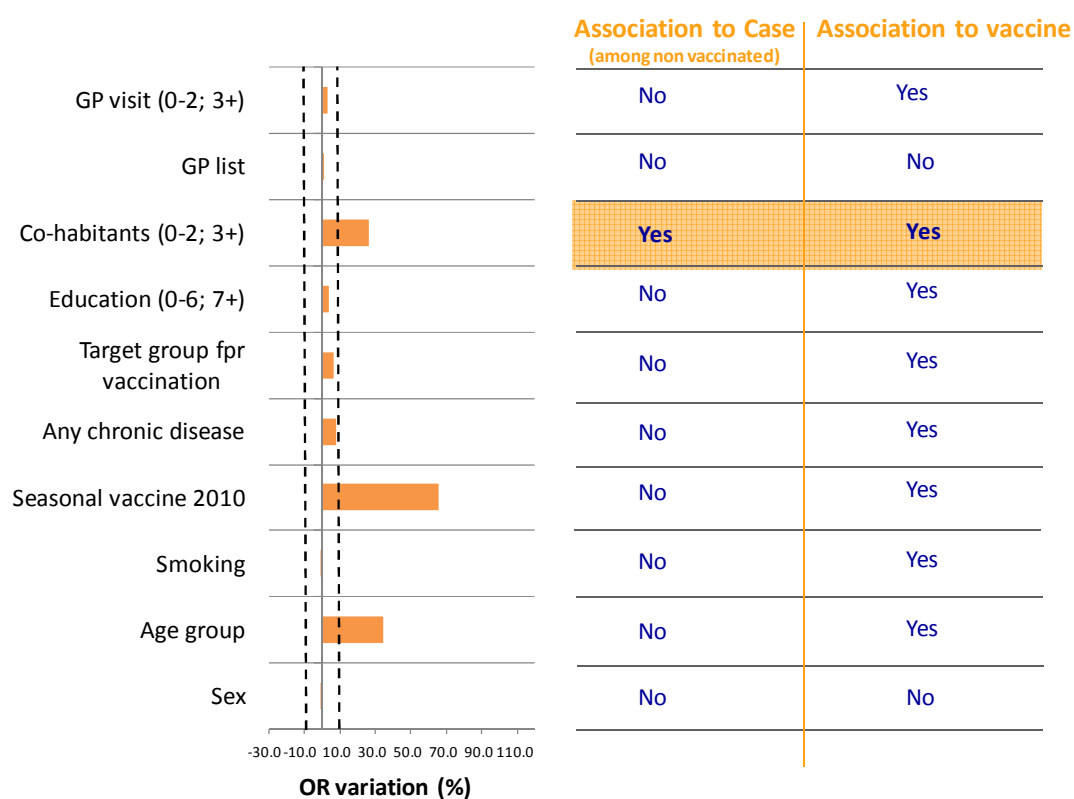


Figure 12: Seasonal vaccine 2011-12 OR change (%) after adjustment for potential confounding factors and association to ILI+ and vaccine uptake.

As showed by Figure 12, the only factor that fulfills all the three criteria was the number of Co-habitants (two categories: less than 3 co-habitants and 3 or more co-habitants). This result was used in order to obtain adjusted VE (Table 4).

Table 4: Crude and adjusted seasonal 2011-12 vaccine effectiveness against influenza, estimates based on comparison of laboratory-confirmed influenza cases and control individuals (test-negative method), 2011-12 influenza season, Portugal.

Population	Crude		Adjusted*	
	VE	CI95%	VE	CI95%
All	59.2%	21.1% ; 79.4%	48.8%	0.0% ; 73.8%
Target group of vaccination	61.8%	15.5% ; 83.1%	51.6%	-6.2% ; 77.9%

\* Data used in the estimates from week 46 till week 12; VE estimates adjusted for number of co-habitants and month of onset of symptoms.

After the adjustment for confounders, via non conditional logistic regression, the VE estimates for all population decreased to 48.8% and to 51.6% in the target group of vaccination. None of these estimates were statistical significant.

## Screening method

### Vaccine coverage

In Portugal, the vaccination campaign started on week 39 of 2011 and according to the results obtained with the yearly conducted dual-frame telephone survey, the vaccine coverage in 2011-2012 season was 16.4%.

Considering the population target group for vaccination, the vaccine coverage for the individuals with 60 or more years was 37.3% (CI95%: 30.6-44.4) and 28.0% (CI95%: 23.0-33.7) for individuals with at least one chronic condition.

Table 5: Influenza vaccine coverage (%) in the Portuguese population (All) and by age group and presence of a chronic condition.

	Vaccine Coverage,%	(95% CI)
<b>All</b>	16.4	(13.6-19.6)
<b>0-59 yrs</b>	9.3	(6.8,12.7)
<b>≥60 yrs</b>	37.3	(30.6-44.4)
<b>No chronic</b>	9.5	(7.1-12.6)
<b>Any chronic</b>	28.0	(23.0-33.7)

Considering the *Screening method* approach, and for **All individuals**, once again it was observed that the vaccine coverage in controls (from the community) was higher than the coverage in **ILI+** (Table 6).

Table 6: Influenza vaccine coverage (%) in the population and in ILI cases (total and ILI+).

	Population	ILI	(v/n)	ILI +	(v/n)
<b>All</b>	16.4	20.6	56/272	13.4	18/134
<b>0-59 yrs</b>	9.3	8.6	17/197	6.5	7/108
<b>≥60 yrs</b>	37.3	52.0	39/75	42.3	11/26
<b>No chronic</b>	9.5	15.9	28/176	13.7	13/95
<b>Any chronic</b>	28.0	29.2	28/96	12.8	5/39

v – nr of vaccinated; n – nr of cases

However, after restringing the analysis to individuals with 60 and more years of age, vaccine coverage in the ILI+ and ILI was higher than the corresponding coverage in Controls. The only result on favor of the hypothesis of a protective effect of the vaccine was on the ILI+, where the vaccine coverage was smaller in cases than in corresponding population controls.

### Vaccine effectiveness

Using the screening method approach, crude and adjusted VE were estimated (Table 7). According to these results, adjusted VE estimates varied from -90.4% (60+ yrs) to 6.1% (0-60 yrs) considering ILI as the outcome and from -58.6% to 56.9 for ILI positive outcomes (none were statistically significant). Crude and adjusted point estimates were higher considering only ILI positive for an influenza virus as the outcome measure, but estimative were very imprecise.

Table 7: Crude and adjusted seasonal vaccine effectiveness for all ILI cases and for ILI positive for an influenza virus (ILI+).

Outcome		Crude		Adjusted*	
		VE, %	CI95%	VE, %	CI95%
ILI+	All	27.0	-19.9; 55.6	4.2	-62.3; 43.4
	0-59 yrs	32.6	-44.9; 68.7	30.0	-52.2; 67.9
	≥60 yrs	-23.5	-267.9; 58.6	-40.2	-323.6; 53.6
	No chronic	-51.2	-171.4; 15.8	-58.6	-195.3; 14.8
	Any chronic	62.3	-156.8; 91.4	56.9	-35.2; 86.3
ILI	All	-32.4	-77.7; 1.3	-35.2	-86.2; 1.8
	0-59 yrs	8.2	-50.9; 44.2	6.1	-56.0; 43.4
	≥60 yrs	-82.4	-257.4; 6.9	-90.4	-277.1; 3.9
	No chronic	-80.4	-170.2; -20.5	-77.6	-173.8; -15.3
	Any chronic	-5.7	-92.0; 41.9	-3.1	-93.5; 45.1

\* Adjusted for confounding (age group and presence of chronic diseases) using the Farrington method

Estimates based on comparison of laboratory-confirmed influenza case subjects and community controls, influenza season 2011-12.

## Discussion

### Seasonal 2011-2012 Vaccine effectiveness against laboratory confirmed influenza cases and Influenza-like illness cases as outcome

#### *Laboratory confirmed influenza*

According to the results obtained using the test negative design data of the EuroEVA study, the 2011-2012 adjusted VE against medical attended laboratory confirmed influenza was 48.8% in the general population and 51.6% in the target group for vaccination. The results obtained in the target group are consistent with the 2011-2012 VE estimated within the I-MOVE multicentric study<sup>16</sup> (43%; 95% CI: -0.4 to 67.7) and with early estimates obtained in Spain<sup>17</sup> (55%; 95% CI: 3 - 79).

Comparing with results obtained with the Screening Method, VE estimates were considerably lower: 4% for the general population and -40% for individuals with 60 and more years of age. The only similar value was the one estimated for the individuals with at least one chronic condition, 56.9% (CI95%: -35.2-86.3). It should be stated that none of these estimates were statistical significant.

Since the two methods do not agree on the protective/ non protective effect of the 2011-12 influenza vaccine, some considerations should be done regarding these two estimates. According to Oreinstein *et al.* (1985)<sup>18</sup>, the Screening method only provides a rough guide of the VE point estimates and for this reason it should not be relied upon for precise estimates. For that reason, the Test Negative Design VE estimates should be more reliable. Nevertheless, it should be stated that the Screening method did detect a decrease in VE point estimate and thus, for monitoring purposes (providing that biases remain constant between seasons) the Screening method may be used for monitoring changes in VE over time and is useful for routine monitoring of VE<sup>18</sup>.

Within EuroEVA results, for the previous season 2010-11, VE from both methods were similar (59% Test Negative Design- TND, 63% Screening)<sup>19</sup>. For the 2011-2012 season, however, both VE estimative indicate different vaccine effect against ILI positive for influenza viruses. As reported for that season, the consistency between results was due to the similarity of vaccine coverage estimates between ILI laboratory influenza negative controls and the community controls from population sample ECOS<sup>19</sup>. This season, vaccine coverage in these two groups were different (Community controls ECOS 16.4%; TND controls 27.5%). The increase of the median age of TND controls this season may have played an important role in the discrepancy.

When compared to the last season, VE point estimate for the general population was lower in 2010-11 (VE=58% in 2010-11). However overlapping confidence intervals and the laboratory results may bring forward a possible explanation for this VE decrease.

Laboratory results, from the phylogenetic analysis by sequencing the coding region of the HA1 subunit of the haemagglutinin gene, showed that the majority of the influenza A(H3) viruses detected in vaccinated individuals grouped into clade 6 are represented by A/Iowa/19/2010 strain. Compared to the vaccine strain A/Perth/16/2009, most of the 2011/2012 influenza A(H3) viruses presented 10 amino acid substitutions (nine of them located in haemagglutinin antigenic sites). However, all strains were antigenically similar to the vaccine strain.

### *Influenza-like illness outcome*

Seasonal 2011-12 adjusted VE against influenza-like illness was -35.2% (CI95%: -86.2; 1.8) for the general population, and in the target population it varied between -90.4% (C95%:-277.1; 3.9) and -3.1% (CI95%: -93.5; 45.1), for the population with 60 and more yrs and with chronic condition, respectively. These VE estimates were only obtained through the Screening method, thus there is no comparison available within EuroEVA study.

Considering the Screening method, VE for ILI was lower than VE for ILI+, a result which was expected since ILI case is a less specific measure than laboratory confirmed influenza case.

### **Participation rate**

Overall 59 GP's were enrolled in EuroEVA 2011-12. Considering the sample size dimension<sup>20</sup> and the recommendations from season 2010-2011, the number of GP needed for the selection was 80 which means that, this season, the recruitment process was still short of the intended. Different approaches were tried to encourage participation, such as using informal contacts or previous mailing lists, but with limited success.

Participation rates remained at 59%, even though additional efforts to stimulate case collection were implemented, such as issuing a monthly newsletter (4 were issued) and weekly data validation by mobile phone.

Although the number of GP's planned was not achieved, the total number of ILI cases recruited was higher than would be expected with 35 GP's reporting ILI cases. In the planning phase the expected

number of ILI cases per GP was 6, given that we received 352 ILI cases the average number of ILI cases effectively recruited by GP was 10.

Participating GPs are volunteers for EuroEVA as they are for participating on the MS network. Therefore they do not represent the total group of GPs working in health centers, in Mainland Portugal.

### **ILI cases selection**

As in the previous studies, the EU ILI definition was used for the identification of ILI cases. From all the ILI cases enrolled with complete biological and clinical information, only 15 did not meet the EU ILI case definition (comparing with 17 last season). This result indicates that a correct ILI case selection has been maintained in the EuroEVA study. In part, this may be due to the long experience of most GPs in participating in the EuroEVA study.

A systematic ILI case selection scheme was again used this season, consisting of randomly attributing a different day of week to each GP (from Monday to Thursday) in which they would start selecting ILI cases, keeping the restriction of selecting only two ILI cases per week from individuals with less than 60 years of age, and no limit to the number of 60+ ILI cases selected. This strategy was intended to increase the previously observed low proportion of ILI cases with 65+ years of age, but proved relatively successful in practice.

### **Controls**

The ILI influenza negative cases and the community sample were once again used as controls. The ILI influenza negative controls were particularly interesting since they were obtained directly from the routine surveillance system, just adding a number of variables to be used mainly in stratified analysis, effect modification and confounding.

Also of substantial interest is the community control group selected from the Portuguese general population directly from an independent routine source that is easily accessed since is a national routine system to estimate seasonal vaccine coverage.

As stated before, no consistency was obtained between both methods this season and a probable explanation for this was the difference found in both controls groups. This result highlights one of the limitations of the Screening method.

In order to have a proper use of this method, coverage estimates should match the population from which the cases came<sup>21</sup>. Because the source population used is not the GP's catchment area population but a national sample of households with mobile and landline phone, controls from both methods differed (at least concerning the age).

Also a limitation of the Screening method, as used here, is the fact that the vaccine coverage used was assumed as known. However, it was also obtained from a population sample, so the variance of this estimate should be included in the 95% confidence interval VE estimate. This correction was not done because the Farrington method does not allow it. Further developments are needed to include this information in the VE estimate.

### **Vaccination status**

Considering the test negative design, the vaccination status was ascertained with the same approach for cases and controls. Along the data entered in the patient medical record, GPs were asked to confirm the inoculation of vaccine with the patient, and register the brand name of the vaccine. Complementarily, the GPs would also verify the mode of inoculation. It is improbable that GPs used different ascertainment criteria, especially between their own ILI cases and controls.

### **Information bias**

Data on variables used to characterize cases and controls were collected by direct interview conducted by the participating GP. As the questionnaires were similar for both cases and controls, and the GP's were only informed of the laboratory result at a later stage, it is unlikely that GPs collected data differently in cases and controls.

Regarding the Screening method, it must be cleared the fact that information on the vaccine uptake and presence of chronic condition was self-reported for respondents or given by *proxy* for the remaining household members. This could introduce bias since information on vaccination status differs from cases (collected and validated by the GP) and controls (self reported). In order to decrease bias, only controls that referred inoculation was made through a shot were considered as vaccinated.

### **Bias associated to the sensitivity of the case definition used in EuroEVA**

As declared before, cases were selected according to EU ILI definition. This EU ILI criterion consists in a very stringent combination of symptoms. It should be taken into consideration that, by using this kind of



case definition, some ILI cases with milder symptoms may be discarded in the selection and this could introduce bias in our VE estimate. For instance, if vaccination induces the occurrence of true cases of influenza with a smaller number and “mild” symptoms/signs, GPs would have a higher probability of failing to select such “mild”, but true cases, for lab confirmation, resulting in less sensitivity to select positive cases that had been vaccinated. This fact would underestimate vaccine coverage in cases and over estimate VE. Even though the possibility of this bias is recognized, is not possible to estimate its dimension in the context of EuroEVA.

### **Effects of adjustment**

In order to obtain adjusted VE point estimates, potential confounders were selected using a three step criteria that included: change more than 10% the crude seasonal vaccine OR, be associated to being a case (among non vaccinated) and to the vaccine uptake. With this kind of approach, it was possible to identify proper confounders and reduce an over adjustment. After this procedure, the number of co-habitants was the only identified confounder (positive effect).



## Conclusion

Considering the Test negative design, the 2011-2012 seasonal adjusted VE estimates were similar between the general population (48.8%) and target group (51.6%), but not statistically significant. When compared to last season, VE point estimates for the general population were lower (VE=58% in 2010-11) but with overlapping confidence intervals.

The Screening method provided lower estimates of the VE, 4% for the general population and -40% for individuals with 60 and more years. However, due to method limitations, these values should not be relied upon for exact estimate of vaccine effectiveness.

Laboratory results show the increasing antigenic and genetic variability among the influenza A(H3) studied during the 2011/2012 season, and also identify influenza B viruses circulating of a lineage different from that included in the 2011/2012 anti-influenza vaccine. These facts, alone or combined, may provide some explanation to the low/moderate VE estimates.

The 3-year experience in conducting this study was certainly a major contributor in streamlining the logistic aspects of this project.

Even though the total number of ILI cases recruited was higher than expected, the sample size for the 60+ yrs group does impose some limits in obtaining a more precise VE estimate for this age group.

As concluded in previous studies, these results still make evident the need for pooling data from a network of VE studies with a common protocol, such as I-MOVE.

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## Annexes

### Annex A -Project submission and approval to the Ethics committee of the Instituto Nacional de Saúde Doutor Ricardo Jorge



Comissão de Ética

Nota Interna N.º 2 /2012

De: Secretariado da Comissão de Ética

Data: 18 Janeiro 2012

Para: Baltazar Nunes


Assunto: Pedido de apreciação e parecer – projecto " Euroeva 2011-2012 "

No seguimento do seu pedido de apreciação e parecer, relativo ao projecto de investigação *EUROEVA 2011-2012*, vimos por este meio informar que o mesmo mereceu parecer positivo da Comissão de Ética deste Instituto, nos termos da autorização dada pela Comissão Nacional de Protecção de Dados.

Aproveitamos, ainda, para desejar o maior sucesso no desenvolvimento deste trabalho.

Com os melhores cumprimentos,

O Secretariado da Comissão de Ética

  
Comissão de Ética  
INSA, I.P.

## Annex A2 - Project submission and approval to the National Committee for Data Protection



Processo n.º 13472/2011

AUTORIZAÇÃO N.º 12404 /2011

### I. Do Pedido

O Instituto Nacional de Saúde Dr. Ricardo Jorge notificou à CNPD um tratamento de dados pessoais com a finalidade de elaborar um estudo observacional para analisar a efectividade da vacina antigripal durante e após a época de gripe de 2011/2012 na população em geral e no grupo etário de indivíduos com 65 anos ou mais anos de idade (Projecto EUROEVA).

O estudo terá a duração de três anos e pretende a inclusão de indivíduos com sinais e sintomas gripais, que recorram a consulta de Medicina Geral num dos centros participantes.

Aos participantes no estudo será pedido que respondam a um questionário, bem como será colhida uma amostra do exudado nasofaríngeo, para realização de análises laboratoriais.

As amostras biológicas, unicamente identificadas pelo código de participação atribuído no estudo, constituirão um biobanco, situado no Instituto Nacional de Saúde Dr. Ricardo Jorge.

O médico assistente, investigador no estudo, solicitará consentimento informado, cuja declaração será arquivada no processo clínico do doente.

Os dados serão recolhidos num caderno de dados em suporte papel. A informação codificada será enviada por correio expresso para o responsável pelo tratamento.

No "caderno de recolha de dados" não há identificação nominal do titular, sendo aposto um código de participante no estudo. A chave desta codificação só pode ser conhecida do médico assistente.

Os destinatários são ainda informados sobre a natureza facultativa da sua participação e garantida confidencialidade no tratamento.

Rua de São Bento, 148-3º • 1200-821 LISBOA  
Tel: 213 928 400 Fax: 213 976 832  
geral@cnpd.pt www.cnpd.pt

**21 393 00 39**  
LINHA PRIVACIDADE  
Das 09h às 13h  
dumdas@cnpd.pt



## II. Da Análise

A CNPD já se pronunciou na sua Deliberação n.º 227/2007 sobre o enquadramento legal, os fundamentos de legitimidade, os princípios orientadores para o correcto cumprimento da Lei de Protecção de Dados, bem como as condições gerais aplicáveis ao tratamento de dados pessoais para esta finalidade.

No caso em apreço, a notificação enquadra-se no âmbito tipificado por aquela Deliberação.

A informação tratada é recolhida de forma lícita (art.º 5º, n.º1 al. a) da Lei 67/98), para finalidades determinadas, explícitas e legítimas (cf. al. b) do mesmo artigo) e não é excessiva.

O fundamento de legitimidade é o consentimento expresso do titular dos dados.

Sallenta-se, que havendo absoluta necessidade de se usarem amostras identificadas ou identificáveis, estas devem ser codificadas, ficando os códigos armazenados separadamente, mas sempre em instituições públicas (Cfr. 19.º, n.º11 da Lei 12/2005, de 26 de Janeiro).

## III. Da Conclusão

Assim, de acordo com as disposições conjugadas do n.º 2 do artigo 7.º, n.º1 do artigo 27º, al. a) do n.º 1 do artigo 28º e art. 30º da Lei de Protecção de Dados, autoriza-se o tratamento, com as condições supra referidas, nos seguintes termos:

**Responsável pelo tratamento:** Instituto Nacional de Saúde Dr. Ricardo Jorge

**Finalidade:** Estudo observacional para analisar a efectividade da vacina antigripal durante e após a época de gripe de 2011/2012 na população em geral e no grupo etário de indivíduos com 65 anos ou mais anos de idade (Projecto EUROEVA).

**Categoria de Dados pessoais tratados:** código do doente, dados sócio-demográficos (Idade, sexo, n.º de anos de escolaridade e n.º de habitantes na unidade de alojamento), sinais e sintomas de síndrome gripal, resultado laboratorial de diagnóstico de gripe, vacinação anti-gripal, doenças crónicas, se é profissional de saúde, gravidez, hospitalizações nos últimos 12 meses, n.º de consultas de medicina geral e familiar nos últimos 12 meses, necessidade de assistência no banho, hábitos tabágicos, amostras biológicas e resultados laboratoriais ao exudado nasofaríngeo.

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**21 393 00 39**

LINHA PRIVACIDADE  
Das 10h às 13h  
duvidas@cnpd.pt

2



**Entidades a quem podem ser comunicados:** Não há.

**Formas de exercício do direito de acesso e rectificação:** Junto do médico assistente.

**Interconexões de tratamentos:** Não há.

**Transferências de dados para países terceiros:** Não há.

**Prazo de conservação:** O código do titular deve ser destruído um mês após o fim do estudo.

Dos termos e condições fixados na Deliberação n.º 227/2007 e na presente Autorização decorrem obrigações que o responsável deve cumprir. Deve, igualmente, dar conhecimento dessas condições a todos os intervenientes no circuito de informação.

Lisboa,  de Novembro de 2011

Ana Roque, Luís Paiva de Andrade, Vasco Almeida (Relator), Helena Delgado António, Carlos Campos Lobo, Luís Barroso

  
Luís Lingnau da Silveira (Presidente)

Annex B – Questionnaires

Nome: .....

N.º Cartão de utente/ Proc. Clínico ..... Código do caso: 0101\_001

(Destacar por aqui)

Instituto Nacional de Saúde  
www.insa.gov.pt



Código do caso: 0101\_001

**Efectividade da Vacina Antigripal EuroEVA - 2011/2012**

**Notificação Clínica da Síndrome Gripal**

**Colheita de Produto Biológico**

Centro de Saúde: .....	<b>A Preencher pelo INSA</b>
Hospital: .....	N.º Lab: ..... N.º Req: .....
Médico: .....	Data: ___/___/___ N.º Amostra: .....
(pode ser substituído pela vinheta)	<u>Pesquisa de vírus Influenza</u>
Telefone: .....	Resultado: .....
Data da colheita: ___/___/___	
Hora da colheita: ___:___	

**Informação Relativa ao Doente**

Sexo:  M  F      Idade: \_\_\_ | \_\_\_ | anos \_\_\_ | \_\_\_ | meses

<p><b>Síndrome Gripal</b>                  Nova definição de caso RQD: A+1 snt de B +1 snt de C                  Data de início dos sintomas: ___/___/___</p> <p><b>A</b> Início súbito (&lt;24h) ..... <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p><b>B</b> Febre ou febrícula _____ °C ..... <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p>Mal-estar geral, debilidade, prostração ..... <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p>Cefaleia ..... <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p>Mialgias, dores generalizadas ..... <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p><b>C</b> Tosse ..... <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p>Doz de garganta, inflamação da mucosa nasal e faríngea, sem sinais respiratórios relevantes ..... <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p>Dificuldade respiratória ..... <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p>Calafrios/Arrepios ..... <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p> <p>Contacto com doente com gripe ..... <input type="checkbox"/> S <input type="checkbox"/> N <input type="checkbox"/> D</p>	<p><b>Tomou antivirais durante os últimos 14 dias?</b></p> <p><input type="checkbox"/> Não</p> <p><input type="checkbox"/> Sim, o doente</p> <p><input type="checkbox"/> Sim, um co-habitante</p> <p><b>Nome do antiviral</b></p> <p><input type="checkbox"/> Oseltamivir (Tamiflu)</p> <p><input type="checkbox"/> Zanamivir (Relenza)</p> <p><input type="checkbox"/> Outro</p> <p>Colar na zaragatoa</p>
---	---

Legenda: M – Masculino F – Feminino S – Sim N – Não D – Desconhece

Questionário Síndrome Gripal (Confirmar as respostas directamente com o(a) doente)

EUROEVA

O doente não pertence à minha Ilha	<input type="checkbox"/>	Código do caso	0101_001			
Nesta época (2011/2012), o(a) doente foi <u>vacinado(a) contra a gripe?</u>	S	N	D			
Se sim, <u>vacinado em</u> (Se não sabe a data exacta, indique a mais aproximada)	_____ / _____ / _____					
Qual era o nome da vacina?	_____ Não sabe <input type="checkbox"/>					
O(a) doente foi vacinado(a) contra a gripe sazonal na época 2010/2011?	S	N	D			
O(a) doente é profissional de saúde ou cuidador num lar ou casa de idosos	S	N	D			
O(a) doente é co-habitante ou cuidador de crianças que tenham risco elevado de desenvolver complicações, cuja idade é < 6 meses	S	N	D			
A doente encontra-se grávida?	S	N	D	NA		
Se sim em que trimestre se encontra?	<input type="checkbox"/> Não sabe <input type="checkbox"/>					
História tabágica do(a) doente (Marcar com X a opção relevante): F (Fumador) ExF (Deixou de fumar há mais de um ano) NF (Nunca fumou) D (Desconhece)	F	ExF	NF	D		
Doenças crónicas:						
Diabetes	S	N	D			
Doenças cardiovasculares (cardiopatias congénitas, hipertensiva, isquémica e insuficiência cardíaca crónica)	S	N	D			
Doença renal crónica (insuficiência renal crónica, síndrome nefrótica)	S	N	D			
Doença hepática crónica (cirrose, atresia biliar, hepatite crónica)	S	N	D			
Obesidade (IMC >= 30)	S	N	D			
Doença respiratória crónica (asma, bronquite crónica, enfisema, fibrose quística, pneumoconioses, displasia broncopulmonar, fibrose pulmonar)	S	N	D			
Imunodeficiência congénita ou adquirida	S	N	D			
Doença neuromuscular com compromisso da função respiratória	S	N	D			
Nos últimos 12 meses, quantas vezes foi o(a) doente hospitalizado devido a uma destas doenças crónicas?	<input type="text"/> Não sabe <input type="checkbox"/>					
Número de consultas de Medicina Geral e Familiar, nos últimos 12 meses	<input type="text"/> Não sabe <input type="checkbox"/>					
Quantos anos de escolaridade o(a) doente completou com aproveitamento?	<input type="text"/> Não sabe <input type="checkbox"/>					
Quantas pessoas vivem na mesma casa com o(a) doente? (familiares ou não familiares, sem contar com o doente)	<input type="text"/> Não sabe <input type="checkbox"/>					
O(a) doente necessita de ajuda para tomar banho? (aplicável se tiver 10 ou mais anos de idade)	S	N	D	NA		

Legenda: S – Sim N – Não D – Desconhece NA – Não aplicável

Instituto **Nacional de Saúde**  
Doutor Ricardo Jorge



**EUROEVA**  
**“Efectividade da Vacina Antigripal”**  
**2011/2012**

Instituto **Nacional de Saúde**  
Doutor Ricardo Jorge



**INSTRUÇÕES**

O estudo visa estimar a efectividade da vacina contra a **gripe sazonal**, em indivíduos de **todas as idades** com particular enfoque em indivíduos com **idade igual ou superior a 60 anos**.

Este estudo tem um delineamento **caso-controlo** e terá início em **14 de Novembro de 2011**.

Gostaríamos que seleccionasse casos de síndrome gripal com **idade inferior a 60 anos** (até 2 casos por semana) bem como **TODOS** os casos de síndrome gripal com **60 e mais anos**.

A selecção de casos começa à **2ª feira**, com duração até ao final da época gripal, *i.e.*, semana 20 de 2012.

## AVALIAÇÃO DA EFECTIVIDADE DA VACINA DA GRIPE SAZONAL

### MÉTODO

Pretende-se verificar se há diferenças na percentagem de vacinados, entre os **2** grupos seguintes:

1. casos de síndrome gripal com resultado laboratorial **positivo** para gripe;
2. casos de síndrome gripal com resultado laboratorial **negativo** para gripe.

Para a Vigilância da Síndrome Gripal, os exames laboratoriais a efectuar consistem no isolamento e na detecção do RNA do vírus da gripe. Para o isolamento do vírus e a detecção do RNA viral é necessário:

- Um **exsudado da nasofaringe** colhido durante os primeiros **5 dias** de evolução da doença (de preferência até ao 2º ou 3º dia) em zaragatoa cedida pelo INSA e enviada rapidamente pela Alfaloc, Transportes Expresso.

### NOTA PARA MÉDICOS-SENTINELA

Se é **Médico-Sentinela** e já participa no programa de vigilância clínica e laboratorial da gripe, continue a fazê-lo como **habitualmente**. A única diferença é que, para este estudo, em **2 casos de síndrome gripal por semana com idade inferior a 60 anos e para TODOS os casos de síndrome gripal com 60 e mais anos**, terá de substituir a folha de preenchimento a que está habituado pela **folha do questionário**.

### PROCEDIMENTOS

A cada médico participante será fornecido um caderno com **instruções**, **16 questionários**, **40 folhas para o consentimento informado (a serem preenchidas em duplicado por cada caso)**, e uma **folha para a recusa/exclusão** de casos para o estudo (**folha branca**). O questionário deverá ser preenchido

sempre que identificar um caso de síndrome gripal na sua lista de utentes ou fora dela.

Note que os questionários estão pré-codificados com o **código de caso**, no canto superior direito, o que permite a respectiva identificação. Por favor registe, no cabeçalho do questionário, os dados de identificação pessoal de cada caso (Nome e Nº SNS ou do Processo Clínico).

Cada médico receberá também um “kit” para colheita de exsudado **nasofaríngeo que deverá também ser identificado com o código de caso** (o mesmo que se encontra no canto superior direito do questionário). Para tal, basta destacar a etiqueta como código de caso que se encontra no canto inferior direito do questionário e cole na zaragatoa.

## 1. Selecção dos casos de síndrome gripal

Selecione, na sua lista de utentes, ou fora dela, doentes com síndrome gripal. Deve identificar **2 casos de síndrome gripal com idade inferior a 60 anos e TODOS os casos de síndrome gripal com idade igual ou superior a 60 anos**, a partir de **2ª feira inclusive**, até ao final da época de gripe, i.e. finais de Abril. Se não identificar nenhum caso no dia da semana referido, tente nos dias seguintes, até conseguir. Os casos podem ser seleccionados onde for mais conveniente para si, i.e., em consultas, serviços de urgência, no domicílio, atendimentos complementares, etc.

A definição de síndrome gripal é a recomendada pelo Centro Europeu de Prevenção e Controlo de Doenças (ECDC):

**Grupo A + pelo menos 1 sinal ou sintoma do grupo B + pelo menos 1 sinal ou sintoma do grupo C**

### Grupo A

**Início súbito** (obrigatório)

### Grupo B

- Febre ou febrícula
- Mal-estar, debilidade, prostração
- Cefaleia
- Mialgias, dores generalizadas

### Grupo C

- Tosse
- Dor de garganta, inflamação da mucosa nasal e faríngea, sem sinais respiratórios relevantes
- Dificuldade respiratória

Se o doente estiver **a viver num lar ou residência para idosos** ou tiver **contra-indicação para a toma da vacina sazonal**, **exclua-o do estudo**, preencha a **folha branca** de recusa/exclusão e identifique outro caso de síndrome gripal.

O doente deve tomar conhecimento de que vai ser incluído neste estudo e concordar com essa participação, assinando em duplicado a folha de consentimento informado.

## 2. Colheita de dados

Preencha o questionário (folha amarela, frente e verso) que descreve a síndrome gripal (data de início dos sintomas, sintomas e sinais presentes, estado vacinal em 2011/12 e no ano anterior, toma de antivirais e estado de saúde ou doença do indivíduo). Assinale com um X sobre o espaço ou sobre a letra adequada.

Por favor, confirme directamente com o doente ou processo clínico as respostas que vai dar.

Destaque o questionário pelo picotado, sem o cabeçalho com a identificação do utente e envie-o juntamente com o exsudado nasofaríngeo cuja colheita se descreve a seguir.

O cabeçalho com a identificação do utente deve ficar no seu caderno de questionários para futura consulta, caso haja alguma dúvida sobre o caso enviado.

## 3. Colheita de exsudado da nasofaringe

- a) Recolha um exsudado nasofaríngeo de acordo com as instruções seguintes:
  1. Introduza a zaragatoa na narina (direita e esquerda) paralelamente ao palato e deixe nessa posição alguns segundos de forma a absorver as secreções;
  2. Introduza um pouco mais fundo na mucosa nasal (aproximadamente 2 a 3 centímetros no adulto e até o doente lacrimejar) e rode ligeiramente a zaragatoa;
  3. Retire a tampa do tubo de transporte e introduza a zaragatoa para que esta entre em contacto com a esponja existente no fundo do tubo;
  4. Pressione fortemente a parte inferior do tubo de modo a que o meio de transporte que embebe a esponja molhe o algodão da zaragatoa;
- b) Identifique o tubo com o código de caso (destaque a etiqueta e cole na zaragatoa).
- c) A amostra biológica deve ser conservada entre 4 a 8°C até à recolha pela transportadora, para envio ao laboratório.
- d) O tubo deve ser acondicionado individualmente, vedando a sua tampa com parafilm (segue com o restante material) e introduzindo-o num saco de plástico devidamente fechado. Este saco deve ser introduzido num envelope almofadado que, por sua vez, deve ser introduzido numa das bolsas plásticas (alfapack) fornecidas.

## 4. Envio do questionário e zaragatoa para o laboratório

A rapidez no envio das zaragatoas ao laboratório constitui um dos aspectos de maior relevância para a obtenção de resultados válidos no diagnóstico. Neste sentido, solicita-se que sejam enviados o mais brevemente possível.

Os pedidos de recolha à empresa transportadora poderão ser efectuados por telefone ou por e-mail, até às 12h00, de Segunda a Quinta-feira.

- **Por telefone:** o requerente deverá ligar para a linha **707 212 707** e solicitar a recolha de encomenda no âmbito do **Programa de Vigilância da Gripe** (a chamada será encaminhada para

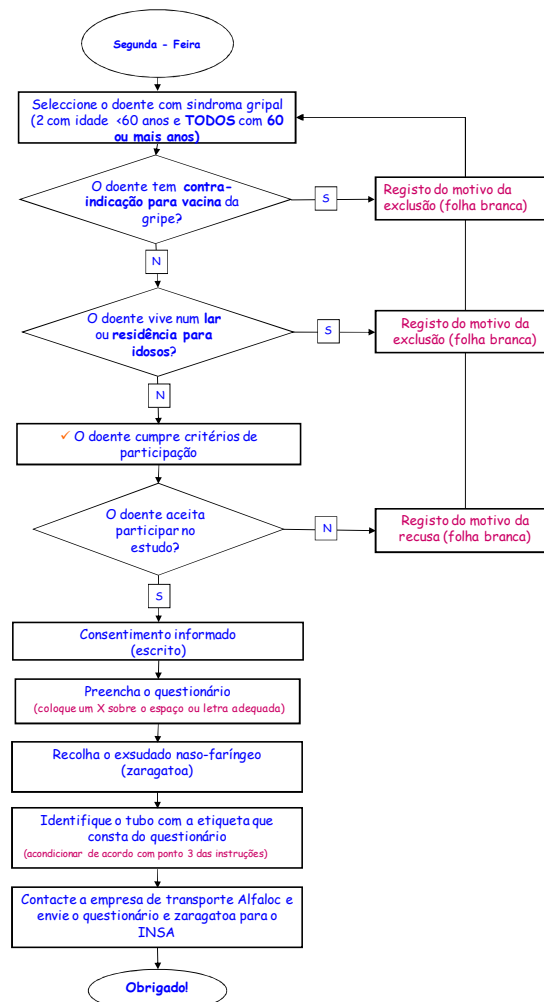


um serviço de transporte específico para este Programa) identificando a [conta do INSA número 6226](#) e o seu [código de Médico \(na primeira página destas instruções\)](#) seguido da localidade da recolha.

- **Por e-mail:** enviar o pedido de recolha para [www.alfaloc.pt](http://www.alfaloc.pt) indicando a [conta do INSA número 6226](#) e o seu [código de Médico \(na primeira página destas instruções\)](#) seguido da localidade da recolha. O responsável da Alfaloc pelo registo das recolhas acusará a recepção deste e-mail no prazo máximo de 15 minutos; se o requerente não receber a confirmação da recepção do pedido de recolha neste prazo, deverá contactar o serviço de clientes pela linha **707 212 707**.

Serão disponibilizadas, nos locais de recolha, guias de transporte pré-impresas com informação do nome e morada do expeditor e do destinatário (o INSA).

Para qualquer informação adicional, por favor contactar o Laboratório Nacional de Referência para o Vírus da Gripe do Instituto Nacional de Saúde Dr. Ricardo Jorge, Av. Padre Cruz, 1649-016 Lisboa, Tel: 217526455 ou 217519216.



# Annex D- Project Newsletter

**Número 1**

dezembro de 2011

**Em Destaque**

A gripe ainda não chegou a Portugal. Não houve atividade gripal até a semana 47 de 2011.

A atividade gripal na Europa continua abaixo dos níveis basais. Tem sido detetados esporadicamente vírus Influenza A (H3N2), B e A(H1N1)2009.

Conte com a sua colaboração! Qualquer dúvida ou sugestão contacte-nos por:

Tel: +351 217 525 400

baltazar.junior@insa.mn-saude.pt

avacencia.machado@insa.mn-saude.pt

ines.balata@insa.mn-saude.pt

**Notícias EuroEVA 2011-2012**

Boletim de Informação do Projeto EuroEVA- Efetividade da Vacina Antigripal em Portugal

**O Projeto EuroEVA 2011-2012**

O Projeto EuroEVA começou a 21 de Novembro de 2011 e já conta com 7 casos de síndrome gripal (SG) identificados, tendo todos sido negativos para o vírus da gripe.

Nesta época participam no estudo 57 médicos de medicina geral e familiar (MGF), dos quais 21 pela primeira vez. Na Figura 1 observa-se a distribuição dos MGF participantes pelo país, e como podemos ver ainda temos 4 distritos por cobrir.

Nesta época o número de MGF aumentou em relação ao ano passado mas está aquém dos 80 planeados. Como tal, ainda estamos a recrutar médicos que queiram participar neste estudo. Assim, se conhecer algum colega que esteja interessado em participar, por favor dê-nos o seu contacto!

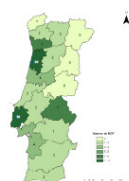


Figura 1. Distribuição dos MGF participantes no Projeto EuroEVA

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**I-MOVE: a situação do estudo nos restantes países**

O estudo multicêntrico I-MOVE (no qual se integra o EuroEVA) com delineamento caso-controlo, para medir a efetividade da vacina antigripal, envolve 9 países esta época (Figura 2).

No âmbito deste projeto, na época anterior, 2010-2011 foram publicados 2 artigos e feita uma apresentação com os resultados nacionais:

Kissling E, Valenciano M, Garhen JM, Ortol R, Barret AS, Ruiz C, Skellern P, Nunes B, Pflanz D, Larraz A, Davalos I, Honoth JK, O'Donnell S, Snyler T, Parashovska-Stankovska A, Pedreira F, Venkatesh AJ, Jimenez-Jorge S, Sanchez C, Garcia BC, Moreno A. I-MOVE Multi-Centre Case-Control Study 2010-11: Overall and Stratified Estimates of Influenza Vaccine Effectiveness in Europe. *PLoS One* 2011;16(11):e27822.

Kissling E, Valenciano M. Item I-MOVE. Early estimates of seasonal influenza vaccine effectiveness in Europe, 2010-11. I-MOVE, a multicentre case-control study. *Euro Surveill* 2011;16(11).

Machado A, Nunes B, Pedreira F, Gonçalves F, Conde P, Guanan R, Falcão J. Influenza vaccine effectiveness 2010-11 in Portugal obtained by two methods: results from the EuroEVA study. *European Scientific Conference on Applied Medicine Disease Epidemiology (ESCADE)*, Sevilha, 4-6th November 2011.




Figura 2. Países participantes no projeto I-MOVE 2011-2

**Mais informações e contactos**

Projeto I-MOVE: <http://files.google.com/infopdf/home>  
 A gripe em Portugal: <http://www.insa.pt/ins/Pages/Documentos/Gripe2.pdf>  
 A gripe na Europa: [http://ecdc.europa.eu/en/healthtopics/influenza/epidemiological\\_data/Pages/Weekly\\_influenza\\_surveillance\\_Overview.aspx](http://ecdc.europa.eu/en/healthtopics/influenza/epidemiological_data/Pages/Weekly_influenza_surveillance_Overview.aspx)

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**Notícias EuroEVA 2011-2012**

Boletim de Informação do Projeto EuroEVA- Efetividade da Vacina Antigripal em Portugal Nº 2 / Janeiro 2012

**Em destaque**

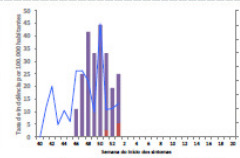
Em Portugal a atividade gripal, na semana 1 de 2012, foi esporádica e de baixa intensidade, tendo alguns países reportado atividade local ou foram detetados casos esporádicos de Infecção esporádica. Tem sido detetados esporadicamente o vírus da gripe A(H3N2), B e A(H1N1)2009.

**O Projeto EuroEVA 2011-2012**

Até à semana 1 de 2012 foram selecionados 84 casos de síndrome gripal no âmbito do projeto EuroEVA.

De entre estes, apenas 3 foram positivos para o vírus da gripe do tipo A(H3).

Dos casos de síndrome gripal selecionados 12 tinham menos de 25 anos (13%) e 23 casos (25%) pertenciam ao grupo etário 60 ou mais anos de idade.



Distribuição semanal do número de casos de síndrome gripal enviados no contexto do projeto EuroEVA e respetivo resultado laboratorial.

**I-MOVE: a situação do estudo nos restantes países**

País	Data início da campanha de vacinação	Data do primeiro caso de gripe confirmado	Nº Casos síndrome gripal (SG)	Nº Casos SG positivos	Nº Casos SG negativos	Resposta percentual
Hungria	02/11/2011	12/12/2011	57	2	55	
Frância	26/09/2011	02/01/2012	85	7	78	
Holanda	17-10-2011	17-11-2011	33	4	27	2
Portugal	01-10-2011	20-12-2011	84	3	81	0
România						
Polónia	12-09-2011		5	0	4	1
Itália	15-10-2011		63	0	25	38
Espanha	15-08-2011	28-12-2011	41	21	16	4

**Mais informações e contactos**

Projeto I-MOVE: <http://files.google.com/infopdf/home>  
 A gripe em Portugal: <http://www.insa.pt/ins/Pages/Documentos/Gripe2.pdf>  
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**Notícias EuroEVA 2011-2012**

Boletim de Informação do Projeto EuroEVA- Efetividade da Vacina Antigripal em Portugal Nº 3 / Fevereiro 2012

**Em destaque**

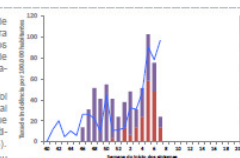
Em Portugal a atividade gripal na semana 7 foi moderada com tendência crescente. Dos 13 casos positivos para o vírus Influenza, 12 pertenciam ao subtipo A(H3) e um ao B/Yamagata.

Na Europa a atividade gripal foi moderada a alta em 18 países, com tendência crescente em 19. Dos casos positivos para gripe, 95,1% pertenciam ao tipo A e 3,3% ao tipo B.

**O Projeto EuroEVA 2011-2012**

Até à semana 7 foram recrutados 183 casos de SG, dos quais 71% (130) foram negativos para o vírus Influenza e 29% (53) foram positivos para o vírus do tipo A(H3). A distribuição de casos e controlos ao longo do tempo encontra-se na Figura 1.

Com os dados recolhidos até ao momento foi possível estimar a cobertura da vacina sazonal nos casos (12%) e nos controlos (21%), o que corresponde a uma estimativa bruta da efetividade da vacina de 70% (IC95%: 14% - 91%). Esta estimativa é ainda preliminar e não sofreu qualquer ajuste para variáveis como sexo, idade, doenças crónicas, vacinações antigripal anteriores etc.



Distribuição semanal do número de casos de síndrome gripal recebido no projeto EuroEVA e respetivo resultado laboratorial.

**I-MOVE: a situação do estudo nos restantes países**

País	Data início da campanha de vacinação	Data do primeiro caso de gripe confirmado	Nº Casos síndrome gripal (SG)	Nº Casos SG positivos	Nº Casos SG negativos	Resposta percentual
Hungria	02/11/2011	12/12/2011	319	18	279	27
Frância	26/09/2011	02/01/2012	783	240	543	0
Holanda	17-10-2011	17-11-2011	81	25	43	13
Portugal	01-10-2011	20-12-2011	183	53	130	0
România	08-11-2011	27-12-2011	98	19	79	0
Polónia	12-09-2011	10-01-2012	67	3	64	0
Itália	15-10-2011	02-01-2012	142	55	72	15
Espanha	15-08-2011	28-12-2011	935	601	307	27

**Mais informações e contactos**

Projeto I-MOVE: <http://files.google.com/infopdf/home>  
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 A gripe na Europa: [http://ecdc.europa.eu/en/healthtopics/influenza/epidemiological\\_data/Pages/Weekly\\_influenza\\_surveillance\\_Overview.aspx](http://ecdc.europa.eu/en/healthtopics/influenza/epidemiological_data/Pages/Weekly_influenza_surveillance_Overview.aspx)

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**Notícias EuroEVA 2011-2012**

Boletim de Informação do Projeto EuroEVA- Efetividade da Vacina Antigripal em Portugal Nº 4 / Março 2012

**Em destaque**

Em Portugal, na semana 13/2012 a atividade gripal era baixa com tendência decrescente, com predominância do vírus Influenza do tipo A(H3).

Na Europa a atividade gripal apresentou uma tendência decrescente em 19 países. Dos casos de síndrome gripal positivos para Influenza 78% eram do tipo A e 22% do tipo B.

**O Projeto EuroEVA 2011-2012**

Até à semana 13/2012 foram recrutados 344 casos de SG. Restringindo a análise à semana 11/2012, 138 dos casos SG selecionados eram positivos para o vírus da gripe (96% do tipo A(H3) e 4% do tipo B) e 153 eram negativos. Na população geral a percentagem de vacinados era de 13,2% e 28,7%, respetivamente para casos e controlos; no grupo alvo da vacina antigripal, a cobertura era de 25,0% nos casos e 46,0% nos controlos (em ambas as situações as diferenças eram estatisticamente significativas).

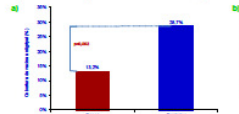


Fig. 1 Cobertura da vacina antigripal estimada no contexto do projeto EuroEVA (semana 11/2012) a) na população geral, b) no grupo alvo da vacinação

**I-MOVE: a situação do estudo nos restantes países**

A Figura 2, descreve o ponto de situação, na semana 12/2012, do recrutamento de casos de SG para o estudo multicêntrico I-MOVE.




Fig. 2 Recrutamento de casos de SG no estudo multicêntrico I-MOVE.

**Mais informações e contactos**

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 A gripe em Portugal: <http://www.insa.pt/ins/Pages/Documentos/Gripe2.pdf>  
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