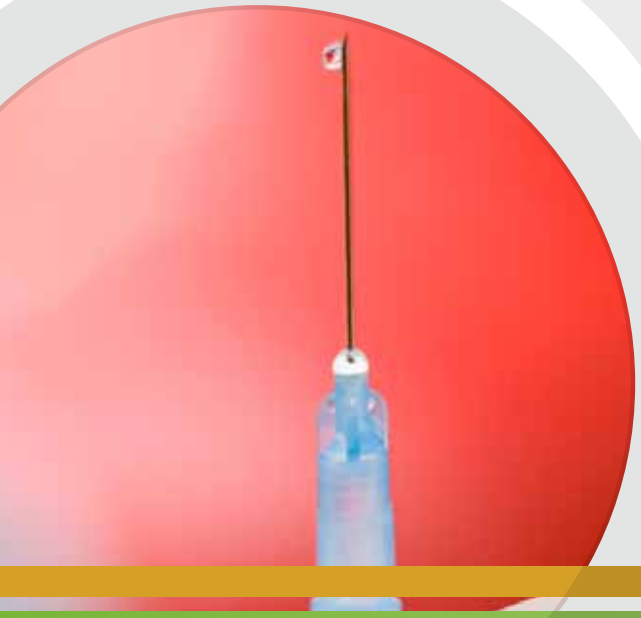

TECHNICAL DOCUMENT

Protocol for case-control studies to measure influenza vaccine effectiveness in the European Union and European Economic Area Member States

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ECDC TECHNICAL DOCUMENT

Protocol for case-control studies to measure influenza vaccine effectiveness in the European Union and European Economic Area Member States

This document was commissioned by the European Centre for Disease Prevention and Control, coordinated by Bruno Ciancio (ECDC), and produced by

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Stockholm, July 2009

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Abbreviations

ECDC	European Centre for Disease Prevention and Control
GP	General practitioner
ILI	influenza-like illness
MS	Member States
OR	Odds ratio
VE	Vaccine effectiveness
☑	(Tick/check mark indicates the sections that Member States should adapt and detail in their study annexes.)

1 Background

Influenza viruses constantly evolve, vaccines are reformulated every year. Therefore, vaccine effectiveness (VE) estimates from previous years cannot simply be carried over to subsequent years.

Conducting annual influenza VE estimates at the European level right at the beginning of a seasonal influenza epidemic/pandemic and monitoring VE along the course of the epidemic/pandemic is crucial in order to:

- decide on recommendations for the use of the vaccine;
- target complementary or alternative public health measures (e.g. antivirals) for segments of the population where the vaccine is less effective;
- allow more precise estimates of the impact of current vaccination strategies on the burden of disease to support vaccination campaigns;
- trigger further investigations on seasonal and pandemic vaccines (improve composition, use of adjuvants, need for booster doses);
- better manage and respond to expected reports of vaccine failures (especially during a pandemic); and
- counterbalance the reports of adverse events following immunisation by providing elements for adequate risk management and cost-effectiveness analysis.

The recent occurrence of the new A(H1N1)v virus augments the importance of obtaining reliable and early vaccine effectiveness estimates for the pandemic vaccine. VE studies are needed to determine the effectiveness of the new vaccine once it is made available. In addition, VE studies may help determining if the seasonal influenza vaccination is effective in protecting against the A(H1N1)v virus.

Currently, only observational studies can be used to provide real-time estimates of influenza VE in Europe.

In order to estimate real-time influenza VE, it is necessary to define which methods can be adopted in the European Union and the European Economic Area (EU/EEA) Member States. These methods have to take into account the specific situation of each Member State in terms of resources and available data. It is assumed that expertise developed during seasonal influenza season can be applied when measuring influenza VE during a pandemic.

During the 2008-09 influenza season, the European Centre for Disease Prevention and Control (ECDC) funded five pilot cohort studies (Portugal, Spain, Denmark, Romania, Hungary) to measure influenza vaccine effectiveness in the elderly (>= 60 or >= 65 years old). The five pilot studies were based on GP surveillance networks. Four of them used the influenza-like illness (ILI) EU case definition. All of them included a common set of variables to adjust for positive and negative confounding.

The five case-control study teams met in Madrid in March 2009 to discuss the preliminary results of the pilot studies. One of the main limitations identified was the limited sample size in each of the studies. The expert group recommended that the possibility of conducting a pooled analysis should be studied, using individual data from the pilot studies conducted in the 2008-09 season. In addition, it was suggested that a common core protocol for the 2009-10 season should be developed, including a pooled analysis to facilitate more precise VE estimates at the European level. The core protocol would determine the study design and the standard methods to be used in each of the studies (case definitions, exposure, outcome, minimum covariates to be collected, and their definition and coding).

This publication presents the core European protocol, outlining the agreed methods for measuring VE for each of the individual studies. The protocol includes a proposed plan for pooled analysis. For groups interested in adhering to the core protocol, the specificities of each study are detailed in the study annexes. The collected variables, their definition and the plan of analysis were revised based on the results of the pilot studies 2008-09 and the recommendations of a workshop entitled ‘Monitoring vaccine effectiveness during seasonal and pandemic influenza in EU’ (Lisbon, 15 to 17 June 2009). During the workshop, experts discussed how to adapt the protocol in order to measure VE for the pandemic vaccine in 2009-10. The participating experts concluded that adaptation depended on the vaccination strategy (target groups, vaccine delivery, number of doses), the vaccine availability (time), and the extent of the virus circulation. It was recommended that the protocol should be adapted to include all target groups (and all age groups, if appropriate). If this posed an undue burden on GPs, the protocol should be simplified by dropping some of the proposed control groups.

For 2009-10, the experts agreed to have a phased approach in order to adapt to the evolving situation:

- Case-control studies for seasonal vaccines will start in October. The preparation phase will already start in summer: informing the GPs, training, etc.

- As soon as the information on the pandemic vaccination strategy becomes available in each of the participating countries, the investigation team adapts the protocol to ensure that the target groups for the pandemic vaccines are included. The country study group decides if the protocol needs to be simplified and if only one control group is used for the study. The questionnaire is then revised to collect information specific to the pandemic vaccine (e.g. the number of doses). Also, the selection procedures for subjects selected for swab sampling may change, i.e. countries swabbing all eligible ILI cases for seasonal influenza may switch to systematically selecting only a sample.
- During the whole process, the I-MOVE network provides exchange information and coordinates activities.

2 Objectives

2.1 Primary objectives

The primary objectives are to:

- measure seasonal influenza vaccine effectiveness among people aged 65 years and above in EU/EEA countries; and
- measure pandemic influenza vaccine effectiveness in the target groups.

2.2 Secondary objectives (for pandemic and seasonal influenza)

The secondary objectives are to:

- estimate VE in each of the participating countries;
- provide intra-seasonal VE estimates;
- estimate VE by risk group;
- estimate VE by influenza subtype;
- monitor VE estimates every year; and
- to estimate VE for one and two doses (for pandemic vaccines only, if two doses are administered).

3 Methods

3.1 Study design

- Case-control study in each participating country, with various sets of controls.
- Multicentre case-control study in several countries, with various sets of controls.

3.2 Study population

For the seasonal vaccine, the study population is community-dwelling individuals aged 65 years and above with no contra-indication for influenza.

For the pandemic vaccines, the study population is the population targeted by the vaccine.

3.3 Study period

The prospective study period starts at the beginning of the influenza period and finishes at the end of the influenza period. Each study defines the beginning, the peak and the end of the study period according to the information provided by the country influenza sentinel surveillance system (☑ details available in the study annexes).

For the pandemic vaccines, the study period is defined depending on the gradual availability of vaccines.

3.4 Outcome

The outcome of interest is laboratory-confirmed influenza.

3.5 Cases

ILI definition: A case of ILI is defined as an individual aged 65 years or above who consults a participating GP, presenting a sudden onset of symptoms AND at least one of the following four systemic symptoms:

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

AND at least one of the following three respiratory symptoms:

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

For the pandemic vaccine, if applicable, the case definition is revised according to the influenza (H1N1)v case definition.

3.6 Influenza case

An influenza case is defined as an ILI case with a respiratory sample positive for influenza during the influenza season. The beginning and end of the influenza season varies from country to country.

☑ Indicators to define cases are specified in the study annexes.

3.7 Laboratory confirmation

Specimens are collected from ILI cases who consult their GP within seven days of symptoms onset.

☑ Mode of specimen collection, storage and transport for each study are listed in the study annexes.

Influenza laboratory confirmation is provided by using RT-PCR and/or cultures.

☑ RT-PCR characteristics for each study are listed in the study annexes.

Isolates undergo a molecular analysis for currently circulating influenza A viruses (subtypes H3 and H1) and influenza B. A systematic subset undergoes gene sequencing.

☑ Selection of isolates for each study are specified in the study annexes.

3.8 Case finding

Case identification

For seasonal vaccine, cases are identified among patients aged 65 years and above presenting to a participating GP with ILI. For the pandemic vaccine, the age group to be recruited depends on the target group. Following the procedures outlined by each study, all ILI cases (or a systematic sample of them) are selected and asked to provide a nasal/throat swab specimen for influenza testing. Influenza-positive ILI cases are considered as influenza cases.

☑ Description of the GPs participating in each of the studies (number, distribution, catchment population) is available in the study annexes.

Case inclusion criteria

Cases are eligible if they meet the above case definition and accept to participate.

☑ Oral informed consent or written informed consent according to country procedures, as specified in the study annexes.

Case exclusion criteria

Cases are excluded if they:

- refuse to participate in the study;
- are not eligible for influenza vaccination due to a condition listed in the summary of product characteristics;
- are institutionalised;
- are unable to give informed consent or follow an interview in their native language because of aphasia, reduced consciousness, or other reasons.

Reasons for exclusion are documented.

3.9 Controls

For the seasonal vaccine, various control groups are included in the study. For the pandemic vaccine, some of the control groups are dropped. All studies (seasonal and pandemic influenza) include at least control group 1 (ILI influenza negative) as defined below. When the studies are adapted in order to measure the pandemic vaccine effectiveness, countries evaluate if other control groups could be used in addition to control group 1 (control group selection depends on feasibility).

☑ The various control groups selected by each study are detailed in the study annexes.

- Control group 1, ILI flu negative:
  - ILI cases that tested negative for influenza are included in control group 1.
- Control group 2, non-ILI GP clients (density case-control design):
  - Controls are selected among GP clients seen at the GP office and selected concurrently to cases (+/− one week from the date of consultation of the corresponding case). Controls are selected by simple or systematic random sampling among clients who did not yet develop ILI during the influenza season.
    ☑ Procedures for selection in each of the studies are detailed in the study annexes.
    If feasible, controls should be matched by age group (< 75 years; >= 75 years).
- Control group 3, GP clients (case-cohort design):
  - Controls are selected randomly from a list of GP patients.
    ☑ Procedures for selection in each of the studies are detailed in the study annexes.
- Control group 4, community controls (density case-control design):
  - Controls are individuals living in the same geographical area (defined by postcode or other geographical/administrative division) as the corresponding case. Control individuals have not

suffered from ILI during the current influenza season until after the corresponding case became ill.
☑ Procedures for selection are detailed in the study annexes.
☑ If feasible, controls should be matched by age group (< 75 years; >= 75 years). The feasibility of matching was discussed during a workshop in June 2009, based on results of the 2008-09 pilot studies.

- Control group 5, community controls (case cohort):
  - Controls are individuals living in the same geographical area of the corresponding case.
    ☑ Procedures for selection are detailed in the study annexes.
    If feasible, controls may be matched by age group (< 75 years; >= 75 years).
    ☑ The feasibility of matching was discussed during a workshop in June 2009, based on the results of the 2008-09 pilot studies.
- Control group 6, community controls (screening method):
  - Vaccine coverage of cases is compared to the vaccine coverage of the elderly population in the GP catchment area.
    ☑ Procedures for estimating VC are detailed in the study annexes.

3.10 Exposure (vaccination)

Definition

An individual is considered as vaccinated against influenza if the vaccination occurred more than 14 days before disease onset or more than 14 days before being selected as a control.

Ascertainment

An individual is considered as vaccinated against influenza if:

- he or she reports having received an influenza vaccination during the current season;
  or
- he or she is registered as vaccinated in a vaccination registry;
  or
- his or her insurance company can show evidence of pharmacy delivery or re-imbursement of influenza vaccine/vaccination during the current influenza season.

For the pandemic vaccine, if two doses are needed, the number of doses is documented. Individuals are defined as partially vaccinated if they received one dose, and as fully vaccinated if they received two doses.

☑ The precise mode of vaccine ascertainment for each study is specified in the study annexes.

The exposure of interest in this study is a vaccination history with trivalent influenza vaccine (for seasonal vaccine) and vaccination history with the pandemic vaccine (once the vaccine becomes available). The vaccination history includes date of administration and brand names.

3.11 Risk groups

Definition and identification

Individuals are considered to belong to a risk group if their patients' records contain any of the ICD codes listed below or if they report suffering from one of the underlying conditions included in the interview questionnaire (see below).

3.12 Confounding factors and effect modifiers

Chronic diseases

If GPs that recruit cases and controls use electronic medical records, the list of ICD codes or classification of Health Problems in Primary Care (ICHPPC-2) codes can be used to document a study participant's chronic diseases (see Table 1):

Table 1: ICD and ICHPPC-2 codes for chronic diseases

Chronic diseases	ICD code	ICHPPC-2 code
Enlarged spleen, anaemia	280–289, 759.0	B82
Cirrhosis	571	D97
Diabetes and endocrine disease	250, 251	T89, T90
Heart disease	093, 112.81, 130.3, 391, 393–398, 402, 404, 410–429, 745, 746, 747.1, 747.49, 759.82, 785.2, 785.3	K71, K74-77, K81-K84, K86-K87, K99
Hematologic cancer	200–208	B72, B74
Immunodeficiency and organ transplant	042, 079, 279, V08, V42	B99
Lung disease	011, 460, 462, 465, 466, 480–511, 512.8, 513–517, 518.3, 518.8, 519.9, 714.81	A70, R83, R79, R95, R96, R99
Nonhematologic cancer	140–198, 199.1	A79, D74-D78, F74, H75, K72, L71, N74, N76, R84, R85, S77, S79, T71, T73, U75-U77, U79, W72-W73, X75-X77, X81, Y77-Y
Nutritional deficiencies	254, 255, 259.2, 260–269	T05, T99
Renal disease	274.1, 408, 580–591, 593.71–593.73, 593.9	U99
Dementia, stroke	290–294, 331, 340, 341, 348, 438	P70, K90
Rheumatologic diseases	446, 710, 714.0–714.4, 714.8, 714.89, 714.9	L88

☑ The exact codes used in each study are specified in the study annexes.

Each patient is evaluated for the presence of any of the diseases/codes and is classified as ‘high risk’ if any of them are present.

If ICD or ICHPPC codes are not available, a shortened list of underlying conditions is prepared by using a short questionnaire. The list of underlying conditions should include at least:

- diabetes, if treated for insulin-dependent or non-insulin-dependent diabetes;
- cardiovascular disease: myocardial infarction, angioplasty, coronary artery bypass surgery, stroke, transient ischemic attacks, treated hypercholesterolemia, treated hypertension;
- chronic pulmonary disease;
- immunodeficiency.

Severity

The severity of the underlying conditions is measured by the number of hospital admissions due to the underlying conditions in the year prior to inclusion in the study.

Smoking history

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

Previous vaccinations

Vaccination against influenza in the last two years (recording vaccination information for each influenza season).

Functional status

Criteria for documenting a subject’s functional status are agreed upon after analysing the results of 2008-09 season. For studies conducted during the 2008-09 season, low functional status was defined as needing help to bathe or to walk.

Number of GP consultations in the previous year

In order to document, and control for, access to care in the various control groups, the number of GP visits in the year before inclusion in the study is recorded.

Antivirals administration

Use of antivirals is documented: type, date of administration.

Source of information

Data is collected using a standardised questionnaire. For cases and controls selected at GP practices, data are collected face-to-face. For community controls, the procedures for data collection are defined by each study coordinator.

☑ The precise modes of data collection for community controls are specified in the study annexes.

If GPs use electronic medical records, information on collected variables can be extracted from these records to validate the information collected through the standardised questionnaire.

3.13 Sample size

A minimum of 30 GPs are required for each of the studies.

Providing VE estimates for each separate study is one of the objectives of this project. Therefore, the minimum sample size should be estimated for each study in order to obtain precise VE estimates. The pooled analyses should not prevent study teams to include a big enough sample size to obtain exact estimates for each separate study.

☑ The sample size calculation for each study is detailed in the study annexes.

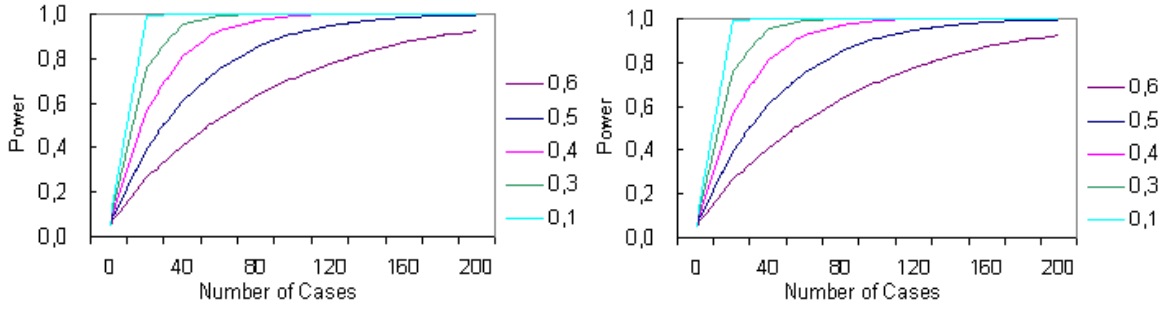
Table 2 illustrates the various sample sizes that would ensure an alpha error of 0.05, a power of 0.8 or 0.9, a detectable odds ratio ranging from 0.3 to 0.6, and a vaccine coverage among the source population (or among controls) ranging from 50 to 70 %.

Table 2: Sample size calculations

Power	Alpha	Controls/ case	Vaccine coverage in source population/controls	Detectable OR	Number of cases	Number of controls
0.90	0.05	1	0.5	0.6	345	345
0.80	0.05	1	0.5	0.6	262	262
0.90	0.05	1	0.5	0.5	194	194
0.80	0.05	1	0.5	0.5	148	148
0.90	0.05	1	0.5	0.4	116	116
0.80	0.05	1	0.5	0.4	89	89
0.90	0.05	1	0.5	0.3	72	72
0.80	0.05	1	0.5	0.3	56	56
0.90	0.05	1	0.6	0.6	341	341
0.80	0.05	1	0.6	0.6	259	259
0.90	0.05	1	0.6	0.5	188	188
0.80	0.05	1	0.6	0.5	144	144
0.90	0.05	1	0.6	0.4	110	110
0.80	0.05	1	0.6	0.4	85	85
0.90	0.05	1	0.6	0.3	67	67
0.80	0.05	1	0.6	0.3	52	52
0.90	0.05	1	0.7	0.6	370	370
0.80	0.05	1	0.7	0.6	281	281
0.90	0.05	1	0.7	0.5	200	200
0.80	0.05	1	0.7	0.5	153	153
0.90	0.05	1	0.7	0.4	115	115
0.80	0.05	1	0.7	0.4	88	88
0.90	0.05	1	0.7	0.3	67	67
0.80	0.05	1	0.7	0.3	52	52

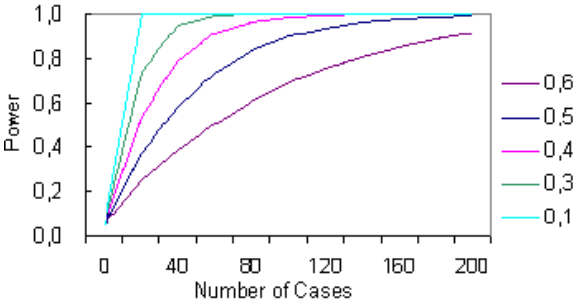
The sample size calculations presented in Figures 1-3 do not include a continuity correction and their results should be regarded as minimum sample sizes.

Figure 1: Case-control power, vaccinated controls = 70 %

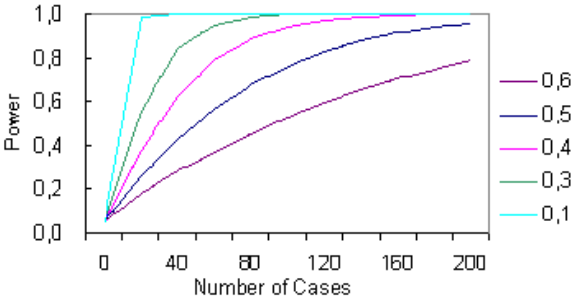


Four controls per case OR

Three controls per case OR

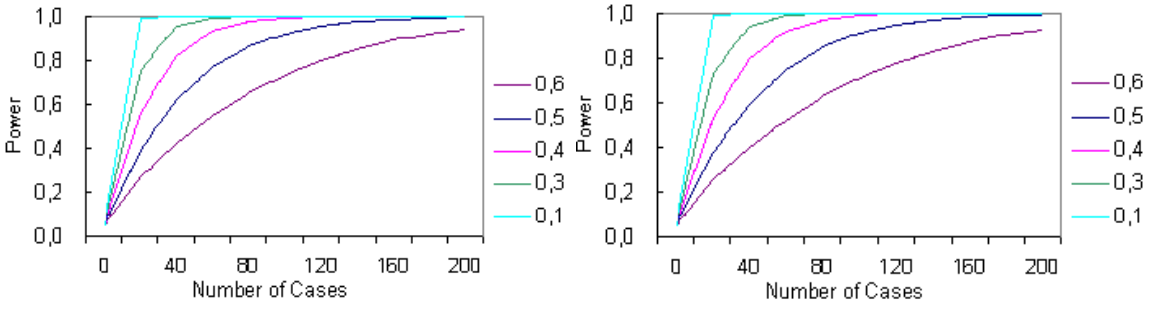


Two controls per case OR



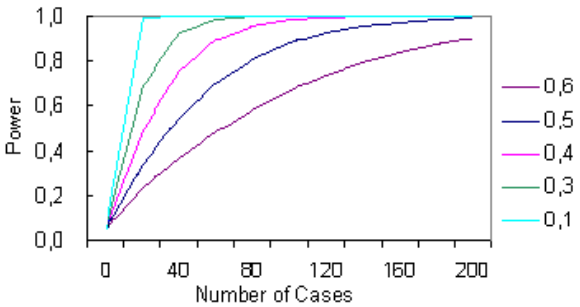
One control per case OR

Figure 2: Case-control power, vaccinated controls = 60 %

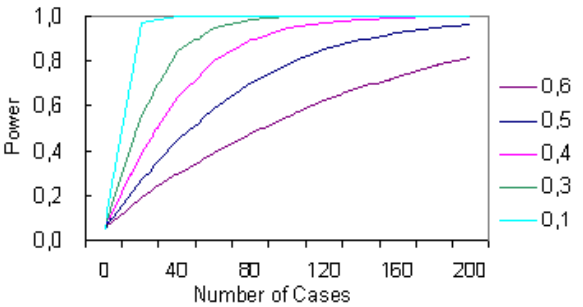


Four controls per case OR

Three controls per case OR

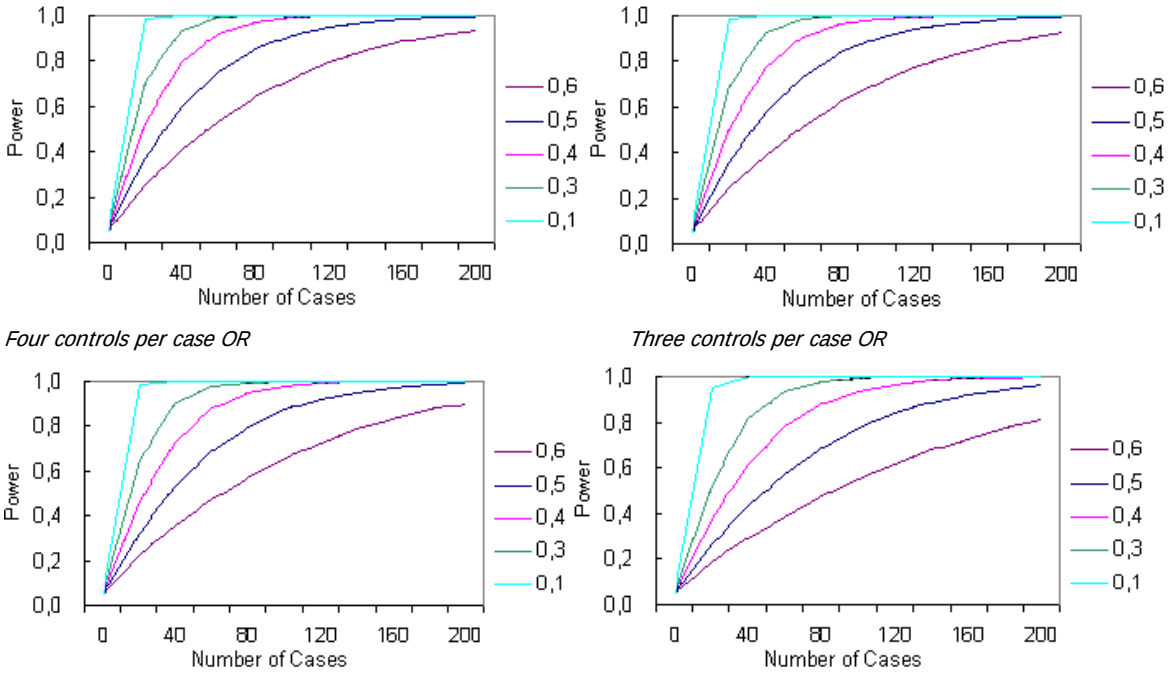


Two controls per case OR



One control per case OR

Figure 3: Case-control power, vaccinated controls = 50 %



Four controls per case OR

Three controls per case OR

Two controls per case OR

One control per case OR

The sample size should be respected for each population subgroup for which a sub (stratified) analysis (e.g. effect modification) is planned.

3.14 Data

Data on cases and GP controls are collected at GP office level. GPs interview the patients using a standardised questionnaire. GPs having electronic medical records can extract some of the variables from these records (e.g. vaccination status, chronic diseases).

☑ Data collection methods for the community controls are detailed in the study annexes.

EpiConcept develops an electronic questionnaire and a web-based questionnaire for participating GPs. Double data entry is needed unless electronic records are used.

☑ Details on data collection methods, data entry and data transmission are available in the study annexes.

Collected information

Collected information includes (see also Annex 1: List of variables, definition and coding):

- study identification: country and GP;
- case/control demographics;
- signs, symptoms;
- date of onset of ILI;
- date of swabbing;
- laboratory results;
- selected underlying chronic conditions;
- number of hospitalisations in the previous year;
- number of GP visits in the previous year;
- smoking history;
- current season influenza vaccination including date;
- pandemic vaccination including number of doses, date, brand;
- influenza vaccination in the previous two years;
- functional status; and
- antivirals administration.

Data validation

A sample of paper questionnaires is be checked against the study database to validate data entry.

For GPs with electronic medical records, a sample of questionnaires are checked against the medical records and against the study database.

The agreement between patient vaccine records/vaccination status reported by study participant/vaccine registries is validated.

☑ The specific validation procedures are specified in the study annexes.

3.15 Analysis

Analyses are carried out first for each individual study. In a second step, a pooled analysis is conducted.

All analyses are done separately for seasonal and pandemic vaccine.

Analyses are conducted for:

- all data — and restricted to cases/controls from whom swabs were taken < 4 days since the date of onset of symptoms;
- overall VE and strain-specific VE, sample size permitting; and
- the pooled analysis, separately for studies with different control groups (using an unmatched or a matched analysis as appropriate).

Individual study analysis

Descriptive and univariable analysis

The proportion of eligible ILI cases and controls who accepted to participate in the study is calculated (response rate).

Study participants are described by baseline characteristics. Baseline characteristics of cases and controls in unmatched studies are compared using the chi-square test, Fisher's exact test, or the Mann-Whitney test (depending on the nature of the variable and the sample size). In matched case-control studies, characteristics of cases and controls are compared using McNemar's chi-square test or the Kruskal-Wallis test.

The association between vaccination status and baseline characteristics is assessed for both case and control groups.

Measure of effect

Vaccine effectiveness is computed as VE = 1 – OR. An exact 95 % confidence interval is computed around the point estimate.

For studies using the screening method, VE is estimated by comparing the proportion of cases vaccinated to the proportion of the source population that is vaccinated (vaccine coverage in the source population) using the following formula:

$$VE = \frac{PPV - PCV}{PPV\,(1 - PCV)}$$

— in which PPV is the proportion of population vaccinated (vaccine coverage in the population), and PCV the proportion of cases vaccinated.

Stratified analysis

Analysis is stratified according to:

- age groups (< 75 years and > 74 years);
- presence or absence of high-risk conditions;
- time (early influenza season, peak, late influenza season); and
- virus strain.

A sufficient sample size should be planned in order to ensure sufficient individuals in each stratum. Studies should aim to have at least 80 individuals in each of the strata. Effect modification is assessed comparing the OR across the strata of the baseline characteristics. Confounding is assessed by comparing crude and adjusted OR for each baseline characteristic.

Multivariable analysis

A multivariable (conditional if matched) logistic regression analysis is conducted to control for negative and positive confounding. Odds ratios and standard errors are obtained. Preferably, the model includes: current influenza vaccination, former influenza vaccination, pneumococcal vaccination, underlying chronic conditions, age, gender, smoking, and functional status. Variables are tested for multicollinearity. Interactions are tested using the likelihood ratio test or Wald's test and included in the model if significant at the 5 % level.

Pooled analysis

A pooled analysis with all studies using the same control groups is conducted. The main characteristics of each study are summarised including:

- number of GPs participating and catchment population;
- beginning of the pilot study;
- beginning, peak, end of influenza period;
- proportion of ILI flu positive among all ILI cases; and
- sample size.

Study-specific adjusted ORs and their CIs are plotted in a forest plot. Heterogeneity between studies is tested using the DerSimonian and Laird Q-statistic. Study design and study quality characteristics are also used to take a qualitative decision if one or more studies differ substantially from the others, which should lead to the exclusion of the questionable study/studies from the pooled analysis.

Data are analysed using a two-stage model. Study-specific adjusted ORs and standard errors for the effect of current influenza vaccination obtained from of the individual studies are combined in a model that incorporates random effects of the studies in order to account for heterogeneity of unmeasured environmental and study factors that differ between studies.

The study-specific exposure-disease effects are then weighted by the inverse of their marginal variances. The marginal variance is the sum of the individual study-specific variances and the variance of the random study effects. This calculation provides the pooled odds ratio and standard error.

The study-specific ORs and their CIs, along with the pooled odds ratio, is presented graphically in a forest plot.

If, despite the common protocol, covariates in the different studies are not uniformly collected, a sensitivity analysis is conducted excluding certain studies and comparing the results with those obtained by including all studies. In a different scenario, analyses can also be conducted that exclude certain study participants for whom variables were collected differently.

Strain-specific analysis is carried out with the specific strains as outcomes (as opposed to all influenza positives).

3.16 Data management

Individual analysis

EpiConcept provides the option of web-based data collection methods, if so desired by the countries. These methods can also be combined with paper-based methods.

If the EpiConcept web-based data collection methods are not used, data are coded as outlined in Annex 2. Alternatively, after adding labels to variables and values, EpiConcept provides a codebook that includes the variable names, variable descriptions, and the coding of variable values.

Data cleaning

Summary and frequency tables as well as visual representations of appropriate variables are used to find illegal, implausible or missing values within the dataset. Checks for inconsistencies are carried out (e.g. date of swabbing before date of onset of symptoms). These values are checked against the questionnaires or queried with the GP. Any changes to the data are documented and stored separately from the crude database. Any recoding of data (e.g. age) is documented. A guide and/or an example Stata do-file for data cleaning is provided if so desired.

Pooled analysis

EpiConcept conducts the pooled analysis. Each individual study is sent to EpiConcept's study database. All personal identifier information such as names, addresses, and medical registration codes are deleted before data transmission to EpiConcept, where all individual data are pooled. A country (or study) identifier is included in each record (e.g. ESP for Spain, UK for the United Kingdom), a GP code is included (e.g. a unique number), and each record is given a unique number. This number is also included in the study database, so that records can be traced back if there are any further queries during pooling. Study databases can be sent to EpiConcept in any format. EpiConcept performs all necessary data cleaning. EpiConcept documents and shares any further data cleaning and analysis with all study coordinators to ensure it can be reproduced.

Missing data

Missing data are imputed at individual study level.

3.17 Potential biases

Negative confounding

Negative confounding refers to biases that reflect the fact that high risk groups are more likely to be vaccinated and therefore reduce VE.

Positive confounding

Positive confounding refers to biases that reflect a 'healthy vaccine effect'. People with good functional status or healthy lifestyle are more likely to accept/request vaccination, thus leading to an increase of measured VE.

Positive and negative confounding is minimised through stratification and multivariable analysis (including presence of chronic diseases) and variables collected in order to measure positive and negative confounding. It is not possible to rule out the presence of characteristics in the study population for which no information is collected in the study questionnaire and that therefore could lead to positive or negative confounding. Therefore, residual positive or negative confounding may be present. A sensitivity analysis is conducted to assess the effect of a potential and unmeasured confounding factor.

Pooled estimate and its bias

Any bias in the individual studies influences the pooled estimate. The power of the test for the presence of heterogeneity between individual studies is low. Therefore, the test may not be able to detect heterogeneity between studies although heterogeneity is present. It is important that heterogeneity is assessed using qualitative knowledge about differences between studies. Depending on the nature of the bias, the inclusion of biased studies in the pooled estimate could lead to over- or underestimation of the true vaccine effectiveness.

3.18 Consent

According to country-specific regulations, an informed (oral or written) consent is required from each study participant. ☑ Details are available in the study annexes.

3.19 Dissemination of results

The enrolment of cases/controls is regularly updated by each study coordinator on the 'I-MOVE in Europe' web page (http://sites.google.com/site/epiflu). First VE estimates (intra-seasonal) are disseminated early during the influenza season; final estimates follow at the end of the season.

Publications, scientific communication

Each study coordinator decides where the results of the individual studies are published and which scientific conferences are attended in order to present the results. An article presenting the results of the pooled analysis and estimates for the EU/EEA is submitted to a peer-reviewed journal. The list of authors includes one representative for each of the studies. Co-workers and contributors are acknowledged. The actual authorship is discussed with the study teams at the beginning of the study.

3.20 Training

Participating GPs are trained on the study protocol before the start of the study. They receive the protocol, questionnaires and laboratory swabbing procedures.

4 Logistical aspects

4.1 Study leader

In each country, a principal investigator coordinates the study at the country level and acts as focal point for the European study. EpiConcept is in charge of the pooled analysis.

4.2 Human resources

In each country, a part-time investigator is in charge of monitoring data collection at the GP office level. GPs collect information among cases and controls. GPs could be offered a payment or compensation for their participation in the study.
☑ The specific human resources needed in each country are detailed in the study annexes. EpiConcept ensures the overall coordination of the various studies.

4.3 Supervision

Site visits and joint workshops are organised by EpiConcept/Member States consortium in order to carry out an appraisal of the ongoing studies in the various countries involved. The appraisal team is composed of two persons from the various project partners.

4.4 Questionnaires

Standardised questionnaires are developed for the study. The variables used at the European level are collected in the same way for each of the studies (see Annex 1: List of variables, definition and coding).

4.5 Computer support

Data collection and entry is conducted at the country level. EpiConcept provides a structured data entry form. For countries willing to submit data electronically, EpiConcept provides an online questionnaire.

4.6 Consent

Each study complies with national ethics committee requirements. Informed consent is required from all participants. The national ethics committees specify whether oral or written consent is required.

4.7 Further studies

Further potential studies could focus on:

- comparing results obtained from all six control groups (ILI flu negative cases; random or systematic sample of GP patients seen at GP office; random sample of people from the catchment area of GP-selected cases);
- comparing results obtained from various swabbing deadlines, e.g. 2, 3, or 4 days after onset of ILI;
- comparing vaccine status and severity of influenza cases selected through systematic or GP ad hoc selection of ILI cases;
- comparing acceptability and feasibility of various sizes of questionnaires to assess negative confounding;
- test questions to measure positive confounding;
- acceptability of the study among GPs;
- comparing GP accessibility for different groups within the local population;
- any other topic that study teams consider helpful in interpreting the study results.

☑ Further potential studies are detailed in the study annexes.

5 Budget

Funding can be used for:

- payment of study supervisor;
- payment of GPs;
- training of GPs; and
- support to laboratory tests.

☑ Each study group provides a detailed budget in the study annexes.

6 References

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Annexes

Annex 1: List of variables, definitions and coding

Variable name	Type	Values and coding	Definition
idcountry	Numeric	Coded according to international country codes	Identifier uniquely identifying the country
participate	Numeric (binary)	0 = No 1 = Yes	Agrees to participate
refuse	Text		Reasons for refusal to participate
id	Numeric (continuous)	Unique integer	Unique number for each record
case	Numeric (binary)	0 = control 1 = case	Identifies cases and controls
gpcode	Numeric (continuous)	Unique integer	Unique number for each GP (preventing identification of GP)
casenr	Numeric (continuous)	Integer	Identifies which controls are connected to which case
dob	Date	dd/mm/yyyy	Date of birth of study participant
age	Numeric (continuous)	Integer	Age of each participant in years
sex	Numeric (binary)	0 = female 1 = male	Sex of study participant
onsetdate	Date	dd/mm/yyyy	Date of onset of symptoms
swabdate	Date	dd/mm/yyyy	Swabbing date
fever	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Fever
malaise	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Malaise
myalgia	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Myalgia
cough	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Cough
sorethroat	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Sore throat
suddenonset	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Sudden onset
headache	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Headache
shortness of breath	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Weakness
lab_res	Numeric (categorical)	0 = Negative 1 = Positive 8 = Do not know	Laboratory result (positive/negative)
lab_virus	Text		Laboratory result: virus type
lab_subtype	Text		Laboratory result: virus subtype
Seas_vacc	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Received flu vaccination 2009-10

Variable name	Type	Values and coding	Definition
Seas_vaccdate	Date	dd/mm/yyyy	Vaccination date
Seas_vacctype	Text		Type of vaccine (brand name)
Pan_vacc	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Received flu vaccination 2009-10
Pan_vaccdate1	Date	dd/mm/yyyy	Vaccination date first doses
Pan_vaccdate1	Date	dd/mm/yyyy	Vaccination date first doses
Pan_vacctype	Text		Type of vaccine (brand name)
Pan_vaccdose	Numeric	0, 1, 2	Number of doses received
vacc_08	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Previous influenza vaccination 2008-09
vacc_07	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Previous influenza vaccination 2007-08
anemia_spleen	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Enlarged spleen, anaemia
cirrhosis	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Cirrhosis
diabetes	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Diabetes and endocrine
heart_dis	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Heart disease
hema_cancer	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Hematologic cancer
immuno	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Immunodeficiency and organ transplant
lungdis	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Lung disease
nonhem_cancer	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Nonhematologic cancer
nut_def	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Nutritional deficiencies
ren_disease	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Renal disease
dem_stroke	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Dementia, stroke
rheumat	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Rheumatologic diseases
severity	Numeric (count)	integer	Number of hospitalisations previous year for the chronic disease
Consultations (inclusion of variable to be discussed during June meeting)	Numeric (count)	integer	Number of GP consultations previous year
fs_bath	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Requires assistance to bathe

Variable name	Type	Values and coding	Definition
fs_walk	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Requires assistance to walk
smoking		0 = Never 1 = Former 2 = Current 9 = Do not know	Never, former (stopped smoking at least 1 year before inclusion in the study), current smoker
antivir	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Administration of antivirals
antivirdate	Date	dd/mm/yyyy	Date administration antiviral
antivirtype	Text		Type of antiviral (brand name)
res_home	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Exclusion criteria: living in a residential home
contra	Numeric (categorical)	0 = No 1 = Yes 8 = Do not know	Exclusion criteria: contraindication for influenza vaccination
dens_cc	Numeric (categorical)	0 = No 1 = Yes	Exclusion criteria for density case-control: ILI symptoms in the season

Annex 2: Guidelines for coding (to be developed)

Study-specific annexes

Study specifications for each country are summarised in the annexes. Each study annex should include:

- description of the GPs participating in the study (number, distribution, catchment population, mode of recruitment);
- definition of beginning, peak, end of influenza season;
- ILI cases: specify if all ILI cases are recruited or a simple random or systematic sample is taken;
- criteria for selection of control groups and definition of control groups to be used; specifics for control groups that will be dropped when adapting the protocol to the pandemic vaccine;
- vaccine ascertainment method;
- information on application of ICD or ICHPPC-2 codes;
- sample size calculation;
- details on methods for data collection, data entry and data transmission;
- data validation procedures;
- laboratory issues (laboratory performing tests; tests used: PCR, culture, strain characterisation; methods for specimen collection, storage, transport; selection procedures for vaccine strain characterisation);
- consent, ethical procedures (oral/written consent; submission to ethics committee, if applicable);
- human resources needed;
- provisions to train GPs;
- detailed budget;
- estimate of GPs acceptance of EpiConcept's web-based questionnaire; and
- outline of additional studies (if applicable).