TECHNICAL DOCUMENT

Protocol for cluster investigations to measure influenza vaccine effectiveness in the EU/EEA

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

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This protocol is intended as a template for cluster investigations. If a study group decides to follow this protocol, the wording and format of this document can be reproduced, with study-specific information added in annexes.

Stockholm, December 2009

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Abbreviations

EEA	European Economic Area
EU	European Union
GP	General practitioner
ILI	Influenza-like illness
IVE	Influenza vaccine effectiveness
OR	Odds ratio
RR	Relative risk
VE	Vaccine effectiveness

☑ (Tick/check mark indicates specific action to be taken by Member States or additional information to be added in the format of annexes to current protocol.)

1 Background

With the recent emergence of the A(H1N1)v virus and its continued spread worldwide, at least four new vaccines against influenza A(H1N1)v have been developed and three have been already approved in the European Union (EU). Once available, it is crucial to rapidly estimate the vaccine effectiveness of the new vaccines against pandemic influenza. In addition, studies are needed to determine if the seasonal flu vaccination is protective against the new virus.

Having early influenza vaccine effectiveness (VE) estimates at European level as soon as possible after the pandemic vaccine is available and monitoring it along the course of the epidemic/pandemic is essential to:

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

In the current European context, only observational studies can be used to obtain real-time influenza VE estimates.

During the influenza 2008–09 season, the European Centre for Disease Prevention and Control (ECDC) funded five pilot case-control studies (Portugal, Spain, Denmark, Romania, Hungary) and two pilot cohort studies (Navarra (Spain) and UK) under the coordination of EpiConcept to measure seasonal influenza vaccine effectiveness (IVE) in the elderly (≥60 or ≥ 65 years old). The pilot studies were based on general practitioner (GP) surveillance networks and included a set of variables to adjust for positive and negative confounding.

These and additional case-control and cohort studies will continue to measure seasonal and pandemic IVE in the 2009–10 season, with ECDC funding and EpiConcept coordination. Screening method studies will also be included.

In addition to measuring IVE through these larger studies, IVE can also be estimated through investigation of clusters of influenza. Through analysis of influenza clusters, rapid IVE estimates potentially early in the season can be obtained. An advantage of cluster analysis is that in some settings (e.g. schools, care homes) vaccination records might be easily obtainable. Investigation can take place at the same time that control measures are being carried out.

We present here a core European protocol describing methods for investigation of clusters to measure IVE. The protocol will be updated as more information on pandemic vaccine and pandemic influenza become available. It is intended to be used by teams from national or local public health institutions that have to investigate a cluster of influenza. The specifics of each investigation will vary according to the context and can be detailed in annexes. Given the main study designs in cluster investigation situations, we have divided the methods section into two: cohort study and case-control study.

2 Objectives

2.1 Primary objective

To measure the effectiveness of pandemic vaccines against A(H1N1)v laboratory-confirmed influenza in EU/EEA countries.

2.2 Secondary objectives

If sample size allows, vaccine effectiveness can be obtained for the following strata:

- to provide VE estimates of seasonal vaccine against A(H1N1)v
- to estimate VE by age group;
- to estimate VE by risk group;
- to measure VE by vaccine brand;
- to estimate VE against other outcomes, such as hospitalisation, pneumonia, death.

☑ Other outcomes to be detailed in study-specific annexes.

☑ The specific secondary objectives of each investigation should be detailed in study-specific annexes.

3 Methods

3.1 Definition of cluster

A cluster is defined as a group of cases of pandemic influenza (H1N1) 2009 that are related in time and space. Examples include cases in residential care homes, schools, universities, out-of-home childcare settings, healthcare, workplace and household clusters, mass gathering events and outbreaks in cruise ships. Identification of a cluster suitable for measuring vaccine effectiveness – adapted from Orenstein et al[1]:

- absence of substantial prior influenza (H1N1) activity in the studied group;
- population containing both vaccinees and non-vaccinees;
- adequate population size in the group to be studied;
- high overall attack rate;
- good vaccination records available to differentiate non-vaccinees from vaccinees.

In addition, the cluster has to be identified early enough to obtain samples within a short delay between onset of symptoms and swabbing (to reduce misclassification of outcome), if laboratory-confirmed outcomes are used.

3.2 Preliminary steps

For all study designs, preliminary steps for the cluster investigation are the following:

- Confirm the cluster/outbreak.
- Verify the diagnosis of A(H1N1)v infection.
- Case identification: all persons with respiratory symptoms should be identified within the cluster (retrospectively and prospectively, if appropriate). Swabs should be taken as soon as possible. For information on case definitions and laboratory methods, see the respective study design chapters. In a well-defined cluster, the entire population can be surveyed.
- Establishing a case line listing with basic information on the cases or a line listing the total population, if the cluster is small.
- Cases should be described in terms of time, place and person.
- A study design approach for an analytical study should be decided upon (see next section).

3.3 Study design

Where the study population within a cluster is well defined (e.g. all residents of a nursing home, all pupils of a school, all passengers of a cruise ship), a cohort study could be the study design of choice. Otherwise, a case-control (traditional, case-cohort or density case-control study design) could be considered. The protocol contains a methods section for each of these study designs.

☑ The study design should be detailed in study-specific annexes and the irrelevant study design sections in 'Methods' can be deleted.

3.4 Cohort study design

☑ Delete section if not applicable

3.4.1 Study population

The study population is defined as the population at risk of A(H1N1)v infection within the population in which the cluster occurs.

3.4.2 Study participants

If the cluster has a manageable population size, the whole study population will be eligible for the VE study. If the population is very large and the attack rate is high, then a systematic or random sample of this population should be selected for the study.

☑ A sample size calculation should be detailed in study-specific annexes.

[1] Orenstein WA, Bernier RH, Dondero TJ, Hinman AR, Marks JS, Bart KJ, et al. Field evaluation of vaccine efficacy. Bull World Health Organ 1985;63(6):1055-68.

Exclusion criteria

Study participants are excluded if they are not eligible for vaccination with the pandemic/seasonal vaccine because of having a condition listed in the summary of products characteristics (e.g. anaphylactic hypersensitivity to eggs or its components), or if they refuse participation. People with laboratory-confirmed diagnosis of A(H1N1)v infection since the beginning of the pandemic (or other date according to the duration of the pandemic) and prior to the beginning of the outbreak/cluster of influenza are excluded as they are not at risk.

People who were not swabbed but had respiratory symptoms in the interval from the beginning of the pandemic (or other date according to the duration of the pandemic) and prior to the beginning of the outbreak/cluster will be documented and analyses carried out including and excluding them.

Reasons for exclusion must be documented.

3.4.3 Study period

The study period is the duration of the cluster or outbreak as defined by the study team.

☑ This should be detailed in study annexes.

Under certain circumstances the study period could be restricted to part of the duration of the cluster/outbreak if the influenza vaccination status changes substantially during this time period.

3.4.4 Exposure

Definition

For vaccinations requiring one dose (seasonal or pandemic vaccination)
An individual is considered vaccinated 14 days after vaccination is performed.

For children, for seasonal flu vaccination

- A child is considered fully vaccinated:
  - 14 days after he/she had the second of two influenza shots; or
  - 14 days after receipt of one influenza shot and was vaccinated in the previous influenza season.
- A child is considered partially vaccinated 14 days after receipt of one influenza shot in absence of vaccination the season before.

For pandemic vaccination requiring two doses:
If two doses of pandemic vaccine are required, the terms ‘fully’ and ‘partially’ vaccinated must be defined and applied.

Ascertainment

An individual should be considered as vaccinated against influenza if:

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

☑ The precise mode of vaccine ascertainment in each study should be specified in study annexes.

The exposures of interest in this study are vaccination with pandemic influenza vaccine and trivalent seasonal influenza vaccine. The history of vaccination will include date of administration, type of vaccine (seasonal or pandemic), number of doses and brand name.

The investigation team must identify brands used in the area and compile a list of possible brands used.

3.4.5 Outcome

The primary outcome of interest is laboratory-confirmed influenza A(H1N1)v infection.

Secondary outcomes of interest are:

- persons meeting the EU influenza-like illness (ILI) case definition;
- persons meeting the H1N1 clinical criteria (case definition EU);
- hospitalisations, pneumonia, deaths (or other, if relevant to the cluster).

3.4.6 Cases

Case identification

Information on signs and symptoms of respiratory illness will be collected from all study participants and include:

- cough;
- sore throat;
- shortness of breath;
- fever;
- myalgia;
- headache;
- malaise.

All persons presenting with any of those signs and symptoms since the beginning of the cluster should be swabbed.

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

EU ILI definition

A case of ILI is defined as an individual presenting:

- 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,
  - shortness of breath.

Clinical criteria – from EU novel influenza virus A(H1N1) case definition (30/4/2009)

Any person with one of the following three:

- fever > 38°C AND signs and symptoms of acute respiratory infection,
- pneumonia (severe respiratory illness),
- death from an unexplained acute respiratory illness.

Laboratory confirmation

Influenza laboratory confirmation should be done using RT-PCR and/or culture.

☑ RT-PCR characteristics for each study should be listed in study annexes.

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

☑ Selection of isolates for each study should be specified in study annexes.

If rapid diagnostic tests (RDTs) are to be used for laboratory confirmation, then their sensitivity and specificity needs to have been studied and documented in a similar situation (e.g. similar study population).

3.4.7 Risk groups

Pandemic vaccine

According to ECDC interim guidance[2], the risk groups to be considered for the pandemic vaccine are:

- people aged less than 65 years with chronic underlying conditions, namely:
  - chronic respiratory diseases;
  - chronic cardiovascular diseases;
  - chronic metabolic disorders (notably diabetes);
  - chronic renal and hepatic diseases;

[2] European Centre for Disease Prevention and Control (ECDC). Interim guidance: Use of specific pandemic influenza vaccines during the H1N1 2009 pandemic. Stockholm: ECDC; 2009. Available from: http://www.ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=388

  - persons with deficient immunity (congenital or acquired);
  - chronic neurological or neuromuscular conditions;
  - any other condition that impairs a person's immunity or prejudices their respiratory function;
- young children (especially under the age of two years);
- pregnant women.

Other target groups may include healthcare workers, essential service workers, caregivers of infants < 6 months old.

Seasonal vaccine

Individuals are considered to belong to a risk group if their patient record contains any of the ICD codes listed on Table 1 or if they report having one of the underlying conditions included in the same table..

3.4.8 Confounding factors and effect modifiers

To control for differences in vaccinated compared to non-vaccinated individuals, information on potential confounding factors is collected.

The minimum confounding factors to be considered include chronic diseases, indicators of the severity of chronic diseases, current vaccination with seasonal flu vaccination (if IVE of pandemic vaccine is calculated), current vaccination with pandemic flu vaccination (if IVE of seasonal vaccine is calculated), previous influenza vaccination, antiviral drug use, smoking and functional status (the latter if cluster is in elderly people).

Below is a list of confounding factors and effect modifiers. Not all information will be relevant or available, given the nature of the cluster.

The precise information collected in each study should be specified in annexes.

Chronic diseases

An individual will be classified as belonging to a high risk group if:

- medical records indicate presence of chronic disease (see Table 1);
- he/she reports having the following underlying conditions:
  - diabetes – if treated for insulin-dependent or non–insulin-dependent diabetes;
  - cardiovascular disease – if has had any of the following: myocardial infarction, angioplasty, coronary artery bypass surgery, stroke, transient ischaemic attacks, treated hypercholesterolaemia, treated hypertension;
  - chronic pulmonary disease;
  - immunodeficiency.

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

Chronic diseases	ICD Code	ICHPPC-2 code
Anaemia spleen	280–289 and 759.0	B82
Cirrhosis	571	D97
Diabetes and endocrine	250 and 251	T89 and 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, and 785.3	K71, K74-77, K81-K84, K86-K87 and K99
Haematologic cancer	200–208	B72 andB74
Immunodeficiency and organ transplant	042, 079, 279, V08, and V42	B99
Lung disease	011, 460, 462, 465, 466, 480–511, 512.8, 513–517, 518.3, 518.8, 519.9, and 714.81	A70, R83, R79, R95, R96 and R99
Non-haematologic cancer	140–198 and 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 and Y77-Y
Nutritional deficiencies	254, 255, 259.2, and 260–269	T05 and T99
Renal disease	274.1, 408, 580–591, 593.71–593.73, and 593.9	U99
Dementia, stroke	290–294, 331, 340, 341, 348, and 438	P70 and K90
Rheumatologic diseases	446, 710, 714.0–714.4, 714.8, 714.89, and 714.9	L88

☑ The precise codes used in each study should be specified in study annexes.

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

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

Former vaccination
Former vaccination includes:

- Vaccination against influenza in the previous two years (collecting information on vaccination for each of the seasons).

Functional status (where applicable)
Information on functional status will be collected in terms of needing assistance with bathing.

Antiviral administration
Use of antivirals will be documented: type, dose and date of administration.

Other confounding factors that should be considered if available or relevant include:
- Level of social interaction
  - Number of household members
  - Children: nursery vs. school-age children
- Indicators of socio-economic status
  - Education level
  - Profession
  - Others (e.g. deprivation score by area of residence)
- Any other available and relevant for the study population

3.4.9 Sample size

In a cluster investigation that is of manageable size, all persons in the study population should be surveyed. Therefore, the sample size is limited to the study population. Prior to the beginning of the study, calculations to determine the power of the study for detecting a given measure of effect with the set study population size can be useful. Elements needed to calculate the power are: ratio of unexposed to exposed, risk of illness in the unvaccinated, the number of vaccinated people and estimated measure of effect to detect. The table below shows some examples of power of a study with given parameters. Note that the power is lower than 80% with some of the parameters below.

Table 2: Examples of power of a study with given parameters

Power	Alpha	Ratio of unexposed / exposed	Attack rate among the non-exposed	Minimum risk ratio to detect	Number of exposed	Number of unexposed
0.25	0.05	1	10%	0.6	200	200
0.40	0.05	1	10%	0.5	200	200
0.53	0.05	1	20%	0.6	200	200
0.76	0.05	1	20%	0.5	200	200
0.92	0.05	1	20%	0.4	200	200
0.27	0.05	1	20%	0.6	100	100
0.43	0.05	1	20%	0.5	100	100
0.44	0.05	1	30%	0.6	100	100
0.66	0.05	1	30%	0.5	100	100
0.85	0.05	1	30%	0.4	100	100
0.63	0.05	1	40%	0.6	100	100

Power	Alpha	Ratio of unexposed / exposed	Attack rate among the non-exposed	Minimum risk ratio to detect	Number of exposed	Number of unexposed
0.84	0.05	1	40%	0.5	100	100
0.96	0.05	1	40%	0.4	100	100
0.32	0.05	1	40%	0.6	50	50
0.50	0.05	1	40%	0.5	50	50
0.45	0.05	1	50%	0.6	50	50
0.67	0.05	1	50%	0.5	50	50
0.85	0.05	1	50%	0.4	50	50

In a cluster situation where the study population is too large to survey everyone, the cohort study can be done with individuals included in the random or systematic sample. The minimum sample size should be estimated to have precise VE estimates.

☑ The sample size calculation for the study should be detailed in study annexes.

The following table illustrates the various possibilities regarding sample size needed in order to achieve an alpha error of 0.05, a power of 0.8 or 0.9, a detectable relative risk (RR) ranging from 0.3 to 0.7 and an attack rate among the non-exposed ranging from 10% to 30%.

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

Table 3: Sample size calculations

Power	Alpha	Ratio of unexposed / exposed	Attack rate among the non-exposed	Minimum risk ratio to detect	Number of exposed	Number of unexposed
0.90	0.05	1	10%	0.6	1014	1014
0.80	0.05	1	10%	0.6	771	771
0.90	0.05	1	10%	0.5	621	621
0.80	0.05	1	10%	0.5	474	474
0.90	0.05	1	10%	0.4	411	411
0.80	0.05	1	10%	0.4	316	316
0.90	0.05	1	10%	0.3	287	287
0.80	0.05	1	10%	0.3	222	222
0.90	0.05	1	20%	0.6	464	464
0.80	0.05	1	20%	0.6	354	354
0.90	0.05	1	20%	0.5	286	286
0.80	0.05	1	20%	0.5	219	219
0.90	0.05	1	20%	0.4	190	190
0.80	0.05	1	20%	0.4	147	147
0.90	0.05	1	20%	0.3	134	134
0.80	0.05	1	20%	0.3	104	104
0.90	0.05	1	30%	0.6	281	281
0.80	0.05	1	30%	0.6	214	214
0.90	0.05	1	30%	0.5	174	174
0.80	0.05	1	30%	0.5	134	134
0.90	0.05	1	30%	0.4	117	117
0.80	0.05	1	30%	0.4	90	90

Power	Alpha	Ratio of unexposed / exposed	Attack rate among the non-exposed	Minimum risk ratio to detect	Number of exposed	Number of unexposed
0.90	0.05	1	30%	0.3	82	82
0.80	0.05	1	30%	0.3	64	64
0.90	0.05	1	40%	0.6	189	189
0.80	0.05	1	40%	0.6	145	145
0.90	0.05	1	40%	0.5	119	119
0.80	0.05	1	40%	0.5	91	91
0.90	0.05	1	40%	0.4	80	80
0.80	0.05	1	40%	0.4	62	62
0.90	0.05	1	40%	0.3	57	57
0.80	0.05	1	40%	0.3	45	45

3.4.10 Data

Data collection

Data will be collected from all study participants using a standardised questionnaire. The procedures to collect data should be defined by each study coordinator (e.g. face-to-face, by telephone, postal questionnaire, web-based, etc.).

Double data entry is needed.

☑ Details on data collection methods, data entry and data transmission should be specified in study annexes.

Information collected

(see Annex)

- Study participant demographics
- Signs, symptoms
- Severity: hospitalisation, pneumonia, death
- Date of onset of symptoms
- Date of swabbing
- Laboratory results
- Selected underlying chronic conditions (including diabetes, heart disease, chronic obstructing pulmonary disorder and immunodeficiencies);
- Number of hospitalisations in the previous year (if relevant)
- Number of GP visits in the previous year (if relevant)
- Smoking history
- Current influenza vaccination(s) including date of vaccination, type (seasonal, pandemic), doses and brand (if possible)
- Former influenza vaccination
- Functional status (if relevant)
- Pregnant: yes/no (if relevant)
- Use of antivirals, type, dose and date of administration
- Information on respiratory symptoms or laboratory-confirmed A(H1N1) influenza since the beginning of the pandemic in their country (or other date according to the duration of the pandemic) and prior to the cluster/outbreak

Data validation

If data are collected using paper questionnaires, a sample of paper questionnaires should be checked against the study database to validate data entry.

☑ The specific validations procedures should be specified in study annexes.

Data cleaning

Summary and frequency tables and graphic displays of appropriate variables will be used to find illegal, implausible or missing values within the dataset. Checks for inconsistencies will be carried out (e.g. date of swabbing before date of onset of symptoms). These values will be checked against the questionnaires or queried

with the study participant. Any changes to the data will be documented and stored separately from the crude database. Any recoding of data (e.g. age from date of birth) will be documented.

3.4.11 Analysis

Analyses will be carried out separately for seasonal and pandemic IVE and for different vaccine brands.

Separate analyses will be carried out for the different primary and secondary outcomes.

Analyses will be carried out including and excluding persons with recent respiratory symptoms (prior to cluster) that were not lab-confirmed, where information is available.

An analysis will be carried out including only persons 'fully vaccinated' in the vaccinated group. A second analysis will include persons 'fully' and 'partially vaccinated' in the vaccinated group.

Descriptive and univariable analyses

Participation variables include:

- total number not eligible
- total number eligible
- total number included: vaccinated and unvaccinated; and
- total number of subjects that refused participation.

Study population baseline characteristics by influenza vaccination status

Baseline characteristics include:

- Age
- Gender
- Socio-economic status indicators
- Comorbidities
- Functional status (if relevant to cluster)
- Pregnancy status
- Previous vaccination (influenza)
- Antiviral use
- Smoking history

Baseline characteristics of vaccinated and unvaccinated participants will be described using proportions and mean/medians (depending on variable type). Missing data for each characteristic will be described, along with approaches on how the missing data were dealt with.

In order to test for differences between vaccinated and unvaccinated characteristics, Student's t test, Mann-Whitney test, chi-square test or Fisher's exact test will be used (depending on the nature and the sample size).

Table 4: Study population baseline characteristics by influenza vaccination status:
(to be completed/modified according to the variables collected)

Characteristics	Vaccinated (N =)	Unvaccinated (N =)
Demographic • Age • Sex • Socio-economic status		
Comorbidities		
Functional status (if relevant)		
Pregnancy status		
Previous flu vaccination		
Antiviral use		
Smoking history		

Crude VE estimates

The vaccine effectiveness will be computed as VE = (1 – RR) X 100; exact 95% CI are computed around the estimate for each outcome.

Stratified analysis

Analysis should be stratified according to:

- age groups;
- presence or absence of high risk conditions;
- effect modifiers are assessed one by one comparing the RR across the strata of the baseline characteristic;
- confounding is assessed by comparing crude and adjusted RR for each baseline characteristic.

Multivariable analysis

A multivariable analysis is conducted to control for negative and positive confounding. Variables will be tested for multicollinearity.

The type of multivariable analysis depends on the nature (high or low incidence) of the cluster and the type of denominator used (persons or person-time). Regression methods could include Cox, Poisson or logistic regression.

The multivariable analysis type and model building strategy should be specified in study annexes.

Sensitivity analysis

In order to assess effects of a potential confounding factor not included in the analysis on VE estimates, a sensitivity analysis could be conducted.

Any sensitivity analysis carried out should be specified in study annexes.

3.5 Case-control / case-cohort study design

☑ Delete section if not applicable

If, within a cluster, the study population is too large to survey the whole population, a cohort study design on a sample of the population could be carried out, or a case-control or case-cohort study could be undertaken. Also, if the study population of a cluster is not well defined – for example, if the study population is not closed – a case-control or case-cohort study might be carried out rather than a cohort study.

3.5.1 Study population

The study population is defined as the population in which cluster occurs.

3.5.2 Study period

The study period is the duration of the cluster or outbreak as defined by the study team.

☑ This should be detailed in study annexes.

Under certain circumstances the study period could be restricted to part of the duration of the cluster/outbreak if the vaccination status changes substantially during this time period.

3.5.3 Outcome

The primary outcome of interest is laboratory-confirmed pandemic influenza (H1N1) 2009.

Secondary outcomes of interest are:

- persons meeting the EU ILI case definition;
- persons meeting the H1N1 clinical criteria (case definition EU);
- hospitalisations, pneumonia, deaths (or other, if relevant to the cluster).

3.5.4 Cases

Case identification

Information on signs and symptoms of respiratory illness will be collected from all study participants and include:

- cough;
- sore throat;
- shortness of breath;
- fever;
- myalgia;
- headache;
- malaise.

All persons presenting with any of those signs and symptoms since the beginning of the cluster should be swabbed.

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

EU ILI definition

A case of ILI is defined as an individual presenting:

- 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,
  - shortness of breath.

Clinical criteria (from EU novel influenza virus A(H1N1) case definition (30/4/2009):

Any person with one of the following three:

- fever > 38°C AND signs and symptoms of acute respiratory infection,
- pneumonia (severe respiratory illness),
- death from an unexplained acute respiratory illness.

Laboratory confirmation

Influenza laboratory confirmation will be done using RT-PCR and/or culture.

☑ RT-PCR characteristics for each study should be listed in study annexes.

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

☑ Selection of isolates for each study should be specified in study annexes.

If rapid diagnostic tests (RDTs) are to be used for laboratory confirmation, then their sensitivity and specificity needs to have been studied and documented in a similar situation (e.g. similar study population).

Case inclusion criteria

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

☑ Oral or written informed consent according to country procedures should be specified in study annexes.

Case exclusion criteria

Cases are excluded if they are not eligible for influenza vaccination because of having a condition listed in the summary of products characteristics (e.g. anaphylactic hypersensitivity to eggs or its components) or if they refuse participation. Reasons for exclusion will be documented.

3.5.5 Controls

The selection of controls varies according to the nature of the cluster.

Controls must be representative of the source population from which the cases arise in respect to vaccination coverage. In a traditional case-control study, controls who are still disease free (i.e. who did not have A(H1N1)v infection or other outcome of interest) are chosen at the end of the cluster/outbreak. In a case-cohort study, controls are selected from persons who are disease-free at the beginning of the cluster/outbreak. Therefore, persons who got the outcome of interest during the cluster/outbreak can be included as controls. Control selection among people still free of the outcome of interest when a case arises forms a density case-control study.

Controls can be unmatched or matched to cases.

☑ Selection and characteristics of controls should be listed in study annexes.

Control inclusion criteria

Controls are eligible if they meet the above control definition and accept to participate.

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

Control exclusion criteria

Controls are excluded if they are not eligible for influenza vaccination because of having a condition listed in the summary of products characteristics (e.g. anaphylactic hypersensitivity to eggs or its components) or if they refuse participation. People with laboratory-confirmed diagnosis of A(H1N1)v infection since the beginning of the pandemic (or other date, according to the duration of the pandemic) and prior to the beginning of the outbreak/cluster of influenza are excluded, as they are not at risk.

People who were not swabbed but had respiratory symptoms in the interval from the beginning of the pandemic (or other date, according to the duration of the pandemic) and prior to the beginning of the outbreak/cluster will be documented and analyses carried out including and excluding them.

Reasons for exclusion must be documented.

3.5.6 Exposure (vaccination)

Definition

For vaccinations requiring one dose (seasonal or pandemic vaccination)
An individual is considered vaccinated 14 days after vaccination is performed.

For children, for seasonal flu vaccination

- A child is considered fully vaccinated:
  - 14 days after he/she had two influenza shots; or
  - 14 days after receipt of one influenza shot and was vaccinated in the previous year
- A child is considered partially vaccinated 14 days after receipt of one influenza shot in absence of vaccination the year before.

For pandemic vaccination requiring two doses:
If two doses of pandemic vaccine are required, the terms 'fully' and 'partially' vaccinated should be defined and applied.

Ascertainment

An individual will be considered as vaccinated against influenza if:

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

☑ The precise mode of vaccine ascertainment in each study should be specified in study annexes.

The exposures of interest in this study are vaccination with pandemic influenza vaccine and trivalent seasonal influenza vaccine. The history of vaccination will include date of administration, type of vaccine (seasonal or pandemic), number of doses and brand name.

The investigation team must identify brands used in the area and compile a list of possible brands used.

3.5.7 Risk groups

Pandemic vaccine

According to ECDC interim guidance[3], the risk groups to be considered for the pandemic vaccine are:

- people aged less than 65 years with chronic underlying conditions, namely:
  - chronic respiratory diseases;
  - chronic cardiovascular diseases;
  - chronic metabolic disorders (notably diabetes);
  - chronic renal and hepatic diseases;
  - persons with deficient immunity (congenital or acquired);
  - chronic neurological or neuromuscular conditions;
  - any other condition that impairs a person's immunity or prejudices their respiratory function;

[3] European Centre for Disease Prevention and Control (ECDC). Interim guidance: Use of specific pandemic influenza vaccines during the H1N1 2009 pandemic. Stockholm: ECDC; 2009. Available from: http://www.ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=388

- young children (especially under the age of two years);
- pregnant women.

Other target groups may include healthcare workers, essential service workers, caregivers of infants < 6 months old.

Seasonal vaccine

Individuals are considered to belong to a risk group if their patient record contains any of the ICD codes listed on Table 5 or if they report having one of the underlying conditions included in the same table.

3.5.8 Confounding factors/effect modifiers

To control for differences in vaccinated compared to non-vaccinated individuals, information on potential confounding factors is collected.

The minimum confounding factors to be considered include chronic diseases, indicators of the severity of chronic diseases, current vaccination with seasonal flu vaccination (if IVE of pandemic vaccine is calculated), current vaccination with pandemic flu vaccination (if IVE of seasonal vaccine is calculated), previous influenza vaccination, antiviral drug use, smoking and functional status (the latter if cluster is in elderly people).

Below is a list of confounding factors and effect modifiers. Not all information will be relevant or available given the nature of the cluster.

☑ The precise information collected in each study should be specified in the study annexes.

Chronic diseases

An individual will be classified as belonging to a high risk group if:

- medical records indicate presence of chronic disease (see Table 5)
- he/she reports having the following underlying conditions:
  - diabetes – if treated for insulin-dependent or non–insulin-dependent diabetes;
  - cardiovascular disease – if has had any of the following: myocardial infarction, angioplasty, coronary artery bypass surgery, stroke, transient ischaemic attacks, treated hypercholesterolaemia, treated hypertension;
  - chronic pulmonary disease;
  - immunodeficiency.

Table 5: ICD and ICHPPC-2 codes for chronic diseases

Chronic diseases	ICD Code	ICHPPC-2 code
Anaemia spleen	280–289 and 759.0	B82
Cirrhosis	571	D97
Diabetes and endocrine	250 and 251	T89 and 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, and 785.3	K71, K74-77, K81-K84, K86-K87 and K99
Haematologic cancer	200–208	B72 andB74
Immunodeficiency and organ transplant	042, 079, 279, V08, and V42	B99
Lung disease	011, 460, 462, 465, 466, 480–511, 512.8, 513–517, 518.3, 518.8, 519.9, and 714.81	A70, R83, R79, R95, R96 and R99
Non-haematologic cancer	140–198 and 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 and Y77-Y
Nutritional deficiencies	254, 255, 259.2, and 260–269	T05 and T99
Renal disease	274.1, 408, 580–591, 593.71–593.73, and 593.9	U99
Dementia, stroke	290–294, 331, 340, 341, 348, and 438	P70 and K90
Rheumatologic diseases	446, 710, 714.0–714.4, 714.8, 714.89, and 714.9	L88

☑ The precise codes used in each study should be specified in study annexes.

Severity

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

Smoking history

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

Former vaccination

Former vaccination includes:

- Vaccination against influenza in the previous two years (collecting information on vaccination for each of the seasons).

Functional status (where applicable)

Information on functional status will be collected in terms of needing assistance with bathing.

Antiviral administration

Use of antivirals will be documented: type, dose and date of administration.

Other confounding factors that should be considered if available or relevant include:

- Level of social interaction
  - Number of household members
  - Children: nursery vs. school-age children
- Indicators of socio-economic status
  - Education level
  - Profession
  - Others (e.g. deprivation score by area of residence)
- Any other available and relevant for the study population

3.5.8 Sample size

In a cluster investigation the number of cases available is often fixed, which limits the power of the study. Prior to the beginning of the study, calculations to determine the power of the study for detecting a given measure of effect with a set number of cases can be useful. This can also help determine if the control-to-case ratio needs to be increased to give more power.

Table 6 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%.

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

Table 6: 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	50%	0.6	345	345
0.80	0.05	1	50%	0.6	262	262
0.90	0.05	1	50%	0.5	194	194
0.80	0.05	1	50%	0.5	148	148
0.90	0.05	1	50%	0.4	116	116
0.80	0.05	1	50%	0.4	89	89
0.90	0.05	1	50%	0.3	72	72
0.80	0.05	1	50%	0.3	56	56
0.90	0.05	1	60%	0.6	341	341
0.80	0.05	1	60%	0.6	259	259

Power	Alpha	Controls/case	Vaccine coverage in source population/ controls	Detectable OR	Number of cases	Number of controls
0.90	0.05	1	60%	0.5	188	188
0.80	0.05	1	60%	0.5	144	144
0.90	0.05	1	60%	0.4	110	110
0.80	0.05	1	60%	0.4	85	85
0.90	0.05	1	60%	0.3	67	67
0.80	0.05	1	60%	0.3	52	52
0.90	0.05	1	70%	0.6	370	370
0.80	0.05	1	70%	0.6	281	281
0.90	0.05	1	70%	0.5	200	200
0.80	0.05	1	70%	0.5	153	153
0.90	0.05	1	70%	0.4	115	115
0.80	0.05	1	70%	0.4	89	89
0.90	0.05	1	70%	0.3	68	68
0.80	0.05	1	70%	0.3	53	53

3.5.10 Data

Data collection

Data will be collected from all study participants using a standardised questionnaire. The procedures to collect data should be defined by each study coordinator (e.g. face-to-face, by telephone, postal questionnaire, web-based, etc.).

Double data entry is needed.

☑ Details on data collection methods, data entry and data transmission should be specified in study annexes.

Information collected

(see Annex)

- Study participant demographics
- Signs, symptoms
- Severity: hospitalisation, pneumonia, death
- Date of onset of symptoms
- Date of swabbing
- Laboratory results
- Selected underlying chronic conditions
- Number of hospitalisations in the previous year (if relevant)
- Number of GP visits in the previous year (if relevant)
- Smoking history
- Current influenza vaccination(s) including date of vaccination, doses, type (seasonal, pandemic) and brand (if possible)
- Former influenza vaccination
- Functional status (if relevant)
- Pregnant: yes/no (if relevant)
- Use of antivirals, type, dose and date of administration
- Information on respiratory symptoms or laboratory-confirmed A(H1N1) influenza since the beginning of the pandemic in their country (or other date according to the duration of the pandemic) and prior to the cluster/outbreak

Data validation

If data are collected using paper questionnaires, a sample of paper questionnaires will be checked against the study database to validate data entry.

☑ The specific validations procedures should be specified in study annexes.

Data cleaning

Summary and frequency tables and graphic displays of appropriate variables will be used to find illegal, implausible or missing values within the dataset. Checks for inconsistencies will be carried out (e.g. date of swabbing before date of onset of symptoms). These values will be checked against the questionnaires or queried with the study participant. Any changes to the data will be documented and stored separately from the crude database. Any recoding of data (e.g. age from date of birth) will be documented.

3.5.11 Analysis

Analyses will be carried out separately for seasonal and pandemic vaccines and for different vaccine brands.

Separate analyses will be carried out for the different primary and secondary outcomes.

Analyses will be carried out including and excluding persons with recent respiratory symptoms (prior to cluster) that were not lab-confirmed, where information is available.

An analysis will be carried out including only persons 'fully vaccinated' in the vaccinated group. A second analysis will include persons 'fully' and 'partially vaccinated' in the vaccinated group.

Descriptive and univariable analyses

The proportion of eligible ILI cases and controls accepting 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, t-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, paired t-test, conditional logistic regression or the Wilcoxon signed-rank test (depending on the nature of the variable and the number of controls).

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

Measure of effect

The vaccine effectiveness will be computed as VE = 1 − OR. An exact 95% confidence interval is computed around the point estimate.

Stratified analysis

Analysis will be stratified according to:

- age groups;
- presence or absence of high risk conditions.

A sufficient sample size should be planned in order to ensure sufficient individuals in each stratum. Studies should aim to have at least 80 cases and 80 controls in each of the strata. Effect modification is assessed by 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 will be conducted to control for negative and positive confounding. Odds ratios and standard errors will be obtained. Preferably, the model will include: current influenza vaccination, former influenza vaccination, underlying chronic conditions, age, sex and smoking and functional status. Variables will be tested for multicollinearity. Interactions will be tested for using the Likelihood Ratio test (or Wald test) and included in the model if significant at 5% level. Factors other than statistical significance will also be used as criteria for inclusion of an interaction term.

4 Limitations

4.1 Sample size

An investigation of a cluster often has a fixed sample size that can be low. It is possible that the study will not have enough power to give a precise estimate of IVE in overall or stratified analysis.

4.2 Negative confounding

These are biases showing that high risk groups are more likely to be vaccinated, therefore reducing VE. Negative confounding will be minimised by taking into account the presence of chronic diseases in the adjustment and by stratifying by risk group, if sample size allows.

4.3 Positive confounding

These are biases reflecting a healthy vaccinee effect. People with a healthy behaviour and a good functional status are more likely to accept/request vaccination, therefore increasing the measured VE.

Positive and negative confounding are minimised through stratification and multivariable analysis, including presence of chronic diseases and variables collected to measure positive and negative confounding. We cannot rule out the presence in the study population of characteristics leading to positive or negative confounding for which information is not collected in the study questionnaire. Therefore, residual positive or negative confounding may be present. A sensitivity analysis will be conducted to assess the effect of a potential unmeasured confounding factor.

4.4 Misclassification bias

Notification of a cluster is often not prompt. This can lead to a delay between onset of illness and laboratory confirmation, which can result in misclassification of cases. If the swabbing delay is associated with vaccination status, then the IVE can be over- or underestimated. If this misclassification is irrespective of vaccination status, it can, under certain conditions, reduce test power lead bias study estimators to the null value.

4.5 Inclusion of persons with A(H1N1)v infection prior to the outbreak

While information on A(H1N1)v infection prior to outbreak is recommended to be collected, reliable information on this might not be available. Depending on the nature of the vaccine, including persons with previous illness could result in lowering the IVE estimates.

4.6 Overestimation of IVE

If the incidence of A(H1N1)v infections is high in the cluster/outbreak and a traditional case-control study design is used – or a cohort design using logistic regression to obtain ORs – then the IVE may be overestimated.

5 Consent

According to country-specific regulations, informed (oral or written) consent will be required from each participant into the study.

☑ The type of consent (oral/written) should be specified in study annexes.

6 Dissemination of results

Each study team will specify how the results will be disseminated.

☑ Dissemination of results should be specified in study annexes.

7 Logistical aspects

For each cluster investigation, a principal investigator needs to be appointed. For secondary attack rate in household analyses, a system of notification of index cases within households needs to be determined (e.g. sentinel network of GPs).

Computer support needs to be in place.

For each cluster investigation, the study group applies specific criteria to identify the relevant laboratories for RT-PCR, culture and sequencing. Key points to be taken care of include:

- sampling materials;
- transport;
- quality assurance; and
- funding of laboratory tests.

8 Budget

Key components include:

- study team;
- laboratory;
- IT support, programming.

☑ A detailed budget, specifying which part of the budget will be requested from ECDC, should be outlined in the study annexes.

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Annex: List of variables, definitions and coding

Variable name	Type	Values and coding	Definition
Participate	Numeric (binary)	0 = No 1 = Yes	Agrees to participate
Refuse	Text		Reasons to refuse to participate
Id	Numeric (continuous)	Unique integer	Unique number for each record
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	Date swabbing
Fever	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Fever
Malaise	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Malaise
Myalgia	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Myalgia
Cough	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Cough
Sorethroat	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Sore throat
Suddenonset	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Sudden onset
Headache	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Headache
shortness of breath	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Weakness
Hosp	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Was hospitalised for respiratory infection during current outbreak
Pneumo	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Was diagnosed with pneumonia during current outbreak
Death	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Died during current outbreak
lab_res	Numeric (categorical)	0 = Negative 1 = Positive 2 = Not done 8 = Don't know	Laboratory result (positive/negative/not done)
lab_virus	Text		Laboratory result: virus type
lab_subtype	Text		Laboratory result: virus subtype
Panvacc	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Received pandemic flu vaccination 2009–2010
Panvaccdate	Date	dd/mm/yyyy	Pandemic flu vaccination date
Panvacctype	Text		Type of pandemic flu vaccine (brand name)
Seasvacc	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Received seasonal flu vaccination 2009–2010
Seasvaccdate	Date	dd/mm/yyyy	Seasonal flu vaccination date

Seasvacctype	Text		Type of seasonal flu vaccine (brand name)
vacc_08	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Previous influenza vaccination 2008–9
vacc_07	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Previous influenza vaccination 2007–8
vacc_06	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Previous influenza vaccination 2006–7
vacc_05	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Previous influenza vaccination 2005–6
vacc_04	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Previous influenza vaccination 2004–5
Diabetes	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Diabetes and endocrine
heart_dis	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Heart disease
immune	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Immunodeficiency and organ transplant
Lungdis	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Lung disease
Severity	Numeric (count)	integer	Number of hospitalisations in the previous year for the chronic disease
fs_bath	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Requires assistance to bath
Pregnant	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Pregnancy status
Smoking		0 = Never 1 = Former 2 = Current 9 = Don't know	Never, former (stopped smoking at least one year before inclusion in the study), current smoker
Antivir	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Recent use of antivirals
Antivirdate	Date	dd/mm/yyyy	Date of antiviral administration
Antivirdose	Text		Doses of antiviral taken
Antivirbrand	Text		Type of antiviral taken (brand name)
ili_prior	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	ILI since beginning of pandemic, but prior to cluster
Ili_prior_lab	Numeric (categorical)	0 = Negative 1 = Positive 2 = Not done 8 = Don't know	Laboratory result (positive/negative)
ili_prior_virus	Text		Laboratory result: virus type and subtype of recent ILI
contra	Numeric (categorical)	0 = No 1 = Yes 8 = Don't know	Exclusion criteria: contraindication for influenza vaccination

This table represents a selection of covariates. Variables can be included or excluded as necessary.

Other annexes containing details of specific studies should be added to the current protocol.