TECHNICAL DOCUMENT

Protocol for cohort database studies to measure influenza vaccine effectiveness in the European Union and European Economic Area Member States

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Protocol for cohort database studies to measure pandemic and seasonal influenza vaccine effectiveness in the European Union and European Economic Area Member States

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

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Revised edition

Stockholm, November 2009

First published Stockholm, July 2009

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Abbreviations

ECDC	European Centre for Disease Prevention and Control
HCWs	Healthcare workers
GP	General practitioner
ILI	influenza-like illness
MAARI	medically attended respiratory infection
MS	Member States
RR	Relative risk
VE	Vaccine effectiveness

þ (Tick/check mark indicates specific action to be taken by Member States.)

1 Background

Influenza viruses constantly evolve, vaccines are reformulated every year. Therefore, vaccine effectiveness (VE) estimates from previous years cannot simply be used to estimate effectiveness in 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 exact 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. Strain-specific vaccines become available four to six months after the start of vaccine development. Consequently, when the vaccines are administered, the virus is already circulating and VE results are needed as soon as possible. In addition, vaccine availability is likely to increase over time, depending on vaccine production output and the licensing of additional vaccines, which means that IVE measurements need to be repeated over time during the pandemic. VE studies may help determining if the seasonal influenza vaccination is (partially) effective or interacts with pandemic vaccine 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 provide early estimates of 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 the 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 two pilot cohort studies (Spain, Navarre region, and Scotland and England) to measure influenza vaccine effectiveness. The two pilot studies were based on computerised GP databases.

The following generic protocol summarises the methodological issues related to conducting database cohort studies in order to measure vaccine effectiveness. The methods selected reflect the results of expert meetings held in Paris (23 to 25 April 2008) and Stockholm (17 June 2008). A meeting held on 13 May 2009 discussed preliminary results, methodology and further steps regarding the current cohort studies.

The 2008-09 results and the adaptation of the current protocols for the current A(H1N1)v situation were discussed in a workshop entitled ‘Monitoring vaccine effectiveness during seasonal and pandemic influenza in EU’ (Lisbon, 15 to 17 June 2009). 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. The expert group recommended that the number of individuals swabbed for the laboratory-confirmed subsample analysis should be increased. In the context of the pandemic, the experts underlined the importance of having timely results of VE against severe outcomes.

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

- Cohort studies for seasonal vaccines will start in September. The preparation phase will already start in summer: informing the GPs, training, reinforcing swabbing, etc.
- As information on the pandemic vaccination strategy becomes available in each of the participating countries, the investigation team will adapt the protocol to ensure that the target groups for the pandemic vaccine are included and the necessary information for estimating pandemic VE is available. The country study group will decide if the protocol needs to be simplified.
- During the whole process, the I-MOVE network will exchange information and coordinate activities.

This is a generic outline protocol that needs to be adapted to country-specific priorities and needs. The generic protocol includes the minimum requirements to be included in the cohort study protocols for seasonal and pandemic influenza. It represents the state of knowledge about the pandemic in August 2009. This protocol will be updated in accordance with these factors:

- the final vaccination strategy (target groups, vaccine delivery, number of doses) in each of the participating Member States;
- the point in time when the vaccine will become available;
- the extent of the virus circulation;
- the identification of new groups at risk; and
- the potential clinical evolution of the A (H1N1)v infection.

The studies will be conducted in accordance with Good Epidemiological Practice guidelines (http://www.dundee.ac.uk/iea/GEP07.htm).

Note: Teams willing to conduct a nested case-control should specify the methods for the case control (see: generic case-control protocol).

2 Objectives

2.1 Aim

To measure influenza vaccine effectiveness (seasonal and pandemic) among the study population (defined in each study) at various points of time in several EU/EEA Member States.

þ Member States will define the study population to be included, for example:

- individuals registered in the list of participating GPs;
- individuals of all ages recommended for influenza vaccination;
- elderly (> 64 years) residents of county (to be specified);
- elderly (> 64 years) from the health insurance scheme;
- children; or an
- ad hoc cohort (e.g. healthcare workers, members of the military).

2.2 General objective

To estimate the relative risk (RR) of defined outcome(s) in vaccinated versus unvaccinated individuals of a defined study group.

þ Member States will define the outcome(s) to be measured.

2.3 Secondary objectives

- To estimate VE for seasonal and pandemic vaccine:
  - by age group targeted for vaccination;
  - in (high) risk groups;
  - for different vaccines (if different vaccines used in the study area); and
  - according to time since vaccination.

- For seasonal vaccine:
  - to estimate VE by influenza subtype;
  - to provide intra-seasonal VE estimates; and
  - to monitor VE over seasons.

- For pandemic vaccine:
  - to provide early VE estimates;
  - to estimate VE by vaccine brand; and
  - to estimate VE for one and two doses.

3 Methods

3.1 Study design

Prospective cohort study (with person-time data).

3.2 Study population and data source

Definition of study population: The study population will be composed of the individuals of the study age group/specific group (with no contraindication for influenza vaccination) included in the database (GP, population, or health insurance) who have at least one year of recorded database history prior to the start of the study. This criterion will permit capturing information on potentially confounding variables and allow for adjustment.

Exclusion criteria: Study participants will be excluded if they are not eligible for influenza vaccination, e.g. if they suffer from a condition listed in the summary of product characteristics such as anaphylactic hypersensitivity to eggs or its components, or if they refuse to participate (in Member States where consent is mandatory).

þ Member States should define additional inclusion/exclusion criteria (e.g. institutionalised elderly). How are individuals identified that are not eligible for influenza vaccination?

To recruit the cohorts, several data sources can be used, depending on the Member States' preferences:

- GP computerised databases: vaccinated and unvaccinated cohorts will be identified through extraction from the computerised database.
- Population registries (including occupational registries like HCW): the vaccinated cohort will be selected using a vaccination registry. The unvaccinated cohort will be selected from the population register.

þ Member States should indicate which option they will use.

- Health insurance schemes: vaccinated and unvaccinated cohorts will be selected from health insurance databases.

3.3 Study setting

þ Member States will describe:

- total number of practices for GP databases;
- total number of patients registered at GP, or in GP catchment area, or in health insurance scheme;
- representativeness (proportion of population age, sex, geographical distribution, vaccine coverage);
- completeness of database; and
- structure of the database.

3.4 Study period

Data will be collected throughout the year from … to … (to be determined by each study). The study period will be subdivided into several periods according to influenza activity. Influenza activity will be determined by using data from the national or regional influenza surveillance systems (incidence of ILI, circulating virus).

þ Member States should define the study period for each year, e.g. '1 September to 31 August ', or 'week 40 to week 39 of the following year'. Member States should specify the surveillance data to be used for defining the various periods (see below).

Definition of periods

Seasonal vaccine

- Pre-influenza, e.g. from September to start of influenza season.
- Influenza season, e.g. time period with 70 % of cases, first to last positive isolate, pre-defined threshold, etc.
- Peak influenza, e.g. five weeks, spanning the two weeks before/after the week of peak viral circulation. Alternatively, modal week for positive influenza isolates plus the week before and after, including 80 % of isolates for the season.

- Peri-influenza, e.g. winter weeks during the influenza period.
- Post-influenza, e.g. end of seasonal influenza season until 31 May.
- Summer, e.g. 1 June to 31 August.

Data from the pilot phase will be used to determine which periods are suited best for the various analyses. The minimum analysis will include estimates for the onset of the pre-influenza period, the influenza period and the post-influenza period.

Pandemic vaccine

- Pandemic vaccine: the study period will be defined depending on the gradual availability of vaccines and the pandemic incidence.

þ Each study will define the beginning and end of the pandemic VE study period.

3.5 Exposure

Seasonal vaccine:

An individual will be considered vaccinated against influenza 14 days after vaccination is performed.

- Children are considered fully vaccinated:
  - 14 days after he/she has received two doses of the vaccine; or
  - 14 days after he/she has received one dose of the vaccine in absence of a second dose and was vaccinated against influenza the previous year.
- Children are considered partially vaccinated 14 days after receipt of a first dose of vaccine (in absence of a second dose) and were not vaccinated against influenza the previous year.

Pandemic vaccine:

An individual will be considered:

- fully vaccinated 14 days after he/she has received two doses of the vaccine
- partially vaccinated:
  - 14 days after he/she has received one dose of the vaccine in absence of a second dose; or
  - within 14 days after receipt of a second dose.
- *unvaccinated* if he/she has not received any dose or within 14 days of receipt of a first dose.

The definition of the vaccination status may be revised and should be taken into account in the analysis if preliminary clinical data indicate that one dose is sufficient to confer protection, or that the immunisation delay is different from the currently assumed 14 days.

Ascertainment: Vaccination status will be extracted from the study databases (vaccination register or GP database). Individuals with no information on vaccination status will be considered non-vaccinated. Two separate analyses will be carried out: one including all individuals, one excluding individuals with missing information on vaccination status. The vaccination history will include date of administration and brand names. Documenting the flu batch codes will allow identifying the vaccine brand, the vaccine content (seasonal, pandemic) and the dose.

If special registries are used for the pandemic vaccine, ascertainment should be employed using these registries.

þ Member States should provide details if they plan to use additional sources to ascertain/verify vaccination status.

3.6 Outcome(s)

þ Member States should provide a concise case definition for the different outcomes they use and how these outcomes are identified in the databases (codes included):

- medically attended respiratory infection (MAARI);
- medically attended ILI;
- total deaths;
- respiratory deaths;
- hospitalisations for pneumonia and influenza;
- hospitalisations for all respiratory conditions; and
- laboratory-confirmed cases of MAARI/hospitalised pneumonia and influenza, etc.

Some outcomes will be available in real time, others will not become available before the end of the season. Therefore, VE for different outcomes will be calculated at different time periods. It is recommended to include laboratory-confirmed influenza outcomes in all studies.

þ Member States to define timeliness of VE for each of the selected outcomes.

3.7 Sub-groups

Study subjects will be categorised according to age groups and risk categories (high risk, low risk).

Seasonal vaccine:

- Definition of high risk groups, e.g. presence of certain codes in the patient's record. See Table 1.
- Procedures to identify high risk groups (precise data extraction and codes should be included). See Table 1.

Pandemic vaccine:

According to ECDC interim guidance (http://www.ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=388) (25 August 2009) 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;
- young children (especially under the age of 2 years);
- pregnant women.

The risk groups may differ between countries. Other risk groups may be included during the pandemic.

þ Member States should define and identify risk groups:

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

3.8 Confounding factors and effect modifiers

In order to control for differences in health status and health seeking behaviour in vaccinated compared with non-vaccinated individuals, information on potentially confounding factors will be collected.

The minimum confounding factors to be considered will include chronic diseases, indicators of the severity of chronic diseases, previous vaccination, antiviral drug use, and healthcare utilisation.

Presence of chronic diseases

The list of underlying conditions in the questionnaire should include at least those for which the vaccine is recommended in the study country and may include:

Seasonal vaccine:

Major chronic diseases:

- 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: asthma, chronic bronchitis, bronchopulmonary dysplasia, cystic fibrosis;
- chronic renal diseases: chronic renal failure;
- immunodeficiency: conditions that suppress the immune function due to underlying disease and/or therapy, e.g. people receiving chemotherapy, HIV infection; and
- anaemia.

Minor chronic diseases: non-treated hypertension, depression, osteoarthritis, rheumatoid arthritis.

Pandemic vaccine:

The list of underlying conditions extracted should include all diseases used to define the risk groups in each of the study countries.

Previous vaccinations

- Influenza vaccination in any of the previous two seasons.
- For severe outcomes (e.g. hospitalisation for pneumonia), pneumococcal vaccination: ever administered and if so, year of (last) vaccination.

Indicators of severity of chronic diseases

At least one variable should be included for assessing underlying ill health. Examples include:

- number of hospitalisations for chronic diseases during the 12 months; and the
- number of repeat prescriptions related to chronic diseases during the previous 12 months.

Use of antiviral drugs

Antiviral drug use should be included as a confounding factor/effect modifier. Type used and date of administration should be collected.

Indicators of healthcare utilisation

At least one variable should be included for assessing indicators of healthcare utilisation, for example:

- number of GP visits for respiratory diseases during the previous 12 months, or
- total number of GP visits during the previous 12 months.

3.9 Miscellaneous confounding factors

Other confounding factors that should be considered include social interaction, functional status, smoking history, and socio-economic status.

Level of social interaction

- Number of household members.
- Children: nursery or school-age children.

Functional status

þ Member States should define variables that can be extracted from the database in order to assess functional status (e.g. Barthel's index).

Smoking history

- Can be coded as: never-smoker, former smoker (stopped smoking at least one year before inclusion in the study), current smoker.

Indicators of socio-economic status

- Education level.
- Profession.
- Other (e.g. deprivation score by area of residence).

Further confounding factors

þ Member States should define included confounding factors and describe how they are identified (e.g. by including codes: ICD codes, International Classification of Primary Codes).

Relevant ICD codes:

- enlarged spleen, anaemia (280–289, 759.0);
- cirrhosis (571);
- diabetes and endocrine diseases (250, 251);
- 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);
- hematologic cancer (200–208);
- immunodeficiency and organ transplant (042, 079, 279, V08, and V42);
- lung disease (011, 460, 462, 465, 466, 480–511, 512.8, 513–517, 518.3, 518.8, 519.9, and 714.81);
- nonhematologic cancer (140–198 and 199.1);
- nutritional deficiencies (254, 255, 259.2, and 260–269);
- renal disease (274.1, 408, 580–591, 593.71–593.73, and 593.9);
- dementia, stroke (290–294, 331, 340, 341, 348, and 438); and
- rheumatologic diseases (446, 710, 714.0–714.4, 714.8, 714.89, and 714.9).

3.10 Data collection

þ Member States should adapt and define the information below.

For GP-based studies, data are collected by the GPs in their practices. Data are extracted from databases.

Depending on the study outcome, Member States with unique identifiers could link various databases (see Table 2) such as:

- hospital discharge databases;
- vaccination registries;
- death registries;
- census data; and
- GP databases.

Table 2: Data sources for each collected variable

þ Member States should complete/modify this table.

Group of variables	Variables	Data source	Timeliness of extraction
Demographic characteristics	Date of birth (if not available: age)		
	Gender		
	Location		
Exposure	Seasonal influenza vaccination		
	Date of vaccination		
	Type of vaccine		
	Batch		
	Pandemic influenza vaccination		
	Dates of vaccination		
	Number of doses		
	Type of vaccine		
	Batch		
Outcomes (include date of onset of symptoms, clinical symptoms)	MAARI		
	Hospitalisations		
	Death		
	Laboratory-confirmed cases		
Confounding factors			
	List of chronic diseases		
	Indicator functional status (e.g. living on his/her own)		
	Indicator severity (e.g. prescriptions/hospitalisations during the previous 12 months)		
	Indicator healthy vaccine effect (e.g. education level)		
	Previous vaccinations (pneumococcal, influenza previous season)		

If any of the above characteristics are missing in a database, missing values will be coded 'absent', as it is assumed that the characteristic under study is not present.

Covariate values are updated on a date that will be defined for each study and for every study year, based on information recorded in the study database.

þ Member States should define the dates for updating the covariates (e.g. 1 September).

Procedures for database management

þ Member States should describe all procedures:

- Who enters data?
- Who validates data?
- Who links databases?
- How are data extracted?
- Who extracts data?
- Who centralises data?
- Who analyses data?
- Software used?

Sample size

þ Each Member State should estimate the power of the study by taking into account:

- the estimated sample size of their study population;
- an alpha error of 0.05;
- the expected vaccination coverage;
- the expected rate of the selected outcome; and
- the minimum sample size for using stratified sampling/stratification.

The validation subset should include a minimum of 500 laboratory-confirmed cases.

The power of the study should be computed for each of the population subgroups for which a sub-analysis is planned. For stratified analysis, at least three factors have to be included:

For seasonal vaccine:

- age group (at least two age groups for the elderly);
- high/low risk group; and
- influenza period (at least pre-influenza, influenza, post-influenza).

For pandemic vaccine:

- age group; and
- target groups.

Subsample validation analysis

To determine VE of influenza vaccine against laboratory-confirmed influenza, specimens are taken in a sample of participants with clinical outcome.

þ Member States should explain how patients are selected for testing. Selection should be systematic or random. Procedures should be described, e.g. 'first patient presenting with ILI at GP level every week', or 'all patients in a specific age group', etc.

Laboratory methods

Specimen collection:

- þ Member States should describe how specimens are collected:
  - GP collects nasopharyngeal swabs (date).

Transport:

- þ Member States will describe transport (how, when).
- þ Member States will describe where samples are sent: national reference laboratory; regional laboratory.

Tests used:

Influenza laboratory confirmation will be provided by using RT-PCR and cultures. Isolates will undergo a molecular analysis for circulating influenza A viruses, influenza B and respiratory syncytial virus.

þ Member States should describe sensitivity/specificity of tests used: number, period and selection of sequenced isolates.

Analysis

Seasonal vaccine: Analysis will be restricted to the groups for which seasonal vaccine is recommended in each of the participating countries.

Pandemic vaccine: Analysis will be restricted to the groups for which the pandemic vaccine is recommended in each of the participating countries.

Analyses are carried out:

- separately for seasonal and pandemic vaccines and for different vaccine brands;
- separately for different outcomes;
- separately for different time periods.

Analyses will be conducted for all individuals and excluding individuals with missing information on vaccination status.

Analyses for laboratory-confirmed outcomes will be conducted:

- on all data — and separately on data with an interval of < 4 days between date of onset of symptoms and swab taken;
- for overall VE and strain-specific VE, sample size permitting.

Descriptive and univariable analyses

Participation variables will include:

- 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 will include:

- age group;
- gender;
- socio-economic status indicators;
- comorbidities;
- utilisation of medical services;
- functional status;
- previous vaccination (influenza, pneumococcal vaccine);
- smoking history; and
- level of social interaction.

Baseline characteristics of vaccinated and unvaccinated participants should be described using proportions and mean/median (depending on variable type). Missing data for each characteristic should be described, and an account should be given on how missing data were handled in the analysis.

In order to test for differences between vaccinated and unvaccinated characteristics, the following tests will be used: 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).

Table 3: Study population baseline characteristics by influenza vaccination status

Characteristics	Vaccinated (n =)	Unvaccinated (n =)
Demographics • gender • age groups • socio-economic status		
Comorbidities		
Functional status		
Indicators of medical services utilisation • number of hospitalisations during previous 12 months • number of GP contacts during previous 12 months		
Pneumococcal vaccination		
Smoking history		
Level of social interaction		

Note: Table is to be completed/modified according to collected variables.

3.11 Crude VE estimates

VE = (1 – RR) x 100; the exact 95 % CIs will be calculated around the estimate for each outcome.

3.12 Stratified analysis

Analysis will be stratified according to:

Seasonal vaccine:

- Age groups (including < 75 years and > 74 years).
- Presence or absence of high-risk conditions.
- Time (early influenza season, peak, late influenza season).
- Virus strain.

Pandemic vaccine:

- vaccine brand.
- time: different periods defined by pandemic vaccine availability.
- target groups.

Effect modifiers will be assessed one by one, comparing the relative risk (RR) across the strata of baseline characteristics.

Confounding factors will be assessed by comparing crude and adjusted RR for each baseline characteristic.

Multivariable analysis

This is a person-time analysis and vaccination status should be used as a time-varying variable. Most other variables will be set to a specified date (for example their status as of 1 October).

A multivariable analysis will be conducted to control for negative and positive confounding.

Adjusted VE estimates will be calculated for each outcome and by risk/target group and influenza periods.

- A priori confounders and level of significance for inclusion of other covariates in adjusted analysis should be outlined and clinical relevance noted, if necessary.
- Presence of effect modification/interaction terms should be explored.

þ Member States should describe the planned type of multivariable analysis (Poisson, Cox). Also described should be the methods how VE estimates for laboratory-confirmed influenza will be obtained from a validation sample of lab-confirmed cases (e.g. mean score method [4, 13]).

Propensity scores

The propensity score is the conditional probability of being vaccinated, given the observed covariates. It can be derived from a multivariable logistic regression analysis that includes all variables that are associated with vaccination in a statistically significant way.

þ Member States that have the capability to develop propensity scores should describe how these scores are defined and used.

- Subclassification of subjects on different levels of propensity score?
- Introducing propensity score in multivariable analysis as a variable?

Sensitivity analysis

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

þ Member States should describe how the sensitivity analysis will be conducted.

4 Limitations

4.1 Study population

þ Member States should describe limitations relating to the representativeness of the study population and thus the generalisability of results.

4.2 Exposure, vaccination status

If individuals vaccinated outside GP practices are not considered vaccinated, VE will be underestimated. In a pandemic situation, vaccine may be administered outside of GP offices (e.g. in vaccine centres). Other sources of information than the GP database might be needed to ascertain vaccination status.

þ Member States should specify if individuals vaccinated outside GP practices can be identified. If not, the proportion of persons not vaccinated by GPs should be estimated, so this factor can be taken into account. Any potential bias related to the ascertainment of vaccination status through external sources should be discussed.

4.3 Outcome

VE depends on the specificity of the selected outcome. For less specific outcomes, VE is underestimated. A laboratory-confirmed outcome should be preferred.

4.4 Sample size for sub-analysis

A small sample size for the subgroup analysis may not allow precise estimates.

4.5 Negative confounding

Negative confounding may occur as high risk groups are more likely to be vaccinated than individuals that are at low risk, thus leading to a reduced measured VE.

þ Member States should try to minimise negative confounding through stratification, logistic regression, propensity score, and sensitivity analysis.

4.6 Positive confounding

Positive confounding may occur as result of 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.

þ Member States should specify how bias can be minimised, depending on the chosen approach: stratification, logistic regression, and propensity score — before, during, and after the study.

Comparing VE estimates of periods of different influenza activity helps to answer one essential question: Are the observed differences in the occurrence of selected outcomes in vaccinated and unvaccinated subjects due to the effect of the vaccine or do they reflect baseline differences between the two groups?

VE between outcomes of different specificity and age groups will be compared in order to assess potential bias (e.g. VE for less specific outcomes should be lower).

The severity of the outbreak and the match between vaccine strains and circulating strains for the season should be taken into account when interpreting the results [14].

5 Dissemination of results

- First VE estimates (intra-seasonal) will be disseminated early during the influenza season (at week 8 of the seasonal vaccine, as soon as a sufficient sample size has been reached for the pandemic vaccine). Those preliminary results include … (þ Member States need to specify what should be included.)
- One essential goal of the project is to obtain a robust VE estimate, adjusted for the early influenza season.

- As soon as a sample size of 90 laboratory-confirmed cases has been attained, a nested test-negative case-control study can be carried out, giving crude and adjusted estimates.
- A mid-season adjusted estimate for each outcome (where possible) should be calculated for the cohort design, provided that a minimum required sample size has been reached.
- A more robust VE estimate will be disseminated at the end of the season.
  þ Member States need to specify the planned adjustments for confounding factors, e.g. if VE against other outcomes are planned, etc.

6 Ethical approval

The study protocol will be submitted to the national ethics committee, following country-specific regulations.

- Linkage of databases?
- Consent (oral, written)?
- Selection procedures for subjects selected for swab sampling?

7 Logistical aspects

Study leader: In each participating country, a principal investigator needs to be appointed for the pilot test.

Human resources needed: A part-time investigator needs to be named.

Supervision: Site visits will be organised by EpiConcept/consortium in order to carry out an appraisal of the ongoing studies in various countries. The appraisal team will be composed of two persons from the various project partners.

Computer support needs to be in place.

Laboratory: In each country, the study group will apply 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 will include:

- study team;
- training needs: GP network;
- laboratory;
- IT support, programming;
- access to databases;
- validation studies; and
- supervision visits.

þ Member States need to provide a detailed budget that specifies which part of the budget will be requested from ECDC.

9 Additional studies

During the pilot phase, complementary studies will be conducted to validate, improve, and adapt the methods.

As a minimum, validation studies should ensure:

- the completeness of vaccination records;
- the accuracy of medical codes;
- the completeness of information on confounding factors; and
- the completeness of GP databases in terms of reported cases.

þ Member States should describe how they plan to conduct the validation studies.

Further potential studies could focus on:

- differences between vaccinated and unvaccinated individuals in terms of confounding factors;
- validation subsets to identify potential confounding factors: select subset of participants and collect additional detailed information on confounding factors;
- sensitivity analysis, e.g. quantifying the effect of hypothetical confounding factors in the VE estimates (variation of the prevalence of the potential confounding factors and assessment of the VE variation).

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