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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Abbreviations

ECDC	European Centre for Disease Prevention and Control
GP	General practitioner
MS	Member States
RR	Relative risk
VE	Vaccine effectiveness
☑	(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. 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 (partially) 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 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 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 the 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 be providing 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.

Note: For teams willing to conduct a nested case control, please specify the methods for the case control (see: generic case-contol 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.

☑ Member States 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.

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

Minimum requirement: a subset of individuals should have a laboratory confirmation.

- Cases identified at GP level:
  - ILI? MAARI?
  - Laboratory confirmed
- Cases identified at hospital level: exact outcome?
- Death? (Specific causes?)

2.3 Secondary objectives

- To estimate VE for seasonal and pandemic vaccine:
  - by age group;
  - in (high) risk groups;
  - for different vaccines (if different vaccines used in the study area);
  - according to time since vaccination; and
  - by virus strain.
- To provide intra-seasonal VE estimates.
- To monitor VE over seasons.

3 Methods

3.1 Study design

Prospective cohort study.

3.2 Study population and data source

Study population — definition: The study population is 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 permits capturing information on potentially confounding variables and allows for adjustment.

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

☑ 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 are identified through extraction from the computerised database.
- Population registries (including occupational registries like HCW): the vaccinated cohort is selected using a vaccination registry. The unvaccinated cohort is selected from the population register.

☑ Member States should indicate which option they will use.

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

3.3 Study setting

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

☑ 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

- 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 is used to determine which periods are best suited for the various analyses. The minimum analysis includes estimates for the onset of the pre-influenza period, the influenza period and the post-influenza period.

3.5 Exposure

Definition: An individual is considered vaccinated 14 days after vaccination is performed.

For children:

- Children are considered fully vaccinated if they:
  - had two influenza shots, completed at least 14 days before inclusion in the study; or
  - were vaccinated the previous year and had one influenza shot at least 14 days before inclusion in the study.
- Children are considered partially vaccinated if they only received one influenza shot 14 days before inclusion in the study and were not vaccinated the previous year.

Pandemic vaccine: If two doses of the pandemic vaccine are received, the terms 'fully' and 'partially vaccinated' will be defined and applied.

Seasonal vaccine: Individuals are considered as vaccinated early if they have received the vaccine before the end of December. For the pandemic vaccine, vaccinated early will be defined according to the availability of the vaccine.

Ascertainment: Vaccination status is extracted from the study databases (vaccination register or GP database). Individuals with no information on vaccination status are considered non-vaccinated.

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

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

3.6 Outcome(s)

☑ 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);
- total deaths;
- respiratory deaths;
- hospitalisations for pneumonia and influenza;
- hospitalisations for all respiratory conditions;
- laboratory confirmed cases of MAARI/hospitalised pneumonia and influenza, etc.

Some outcomes will be available in real time, but others will not become available before the end of the season. Therefore, VE for different outcomes is calculated at different time periods.

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

3.7 Sub-groups

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

☑ Member States should define and identify risk groups:

- 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.

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

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

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

Presence of chronic diseases

Major chronic diseases: heart disease, lung disease, diabetes mellitus, chronic renal disease, rheumatological disease, dementia, stroke, immunosuppression.

Minor chronic diseases: hypertension, depression, osteoarthritis, rheumatoid arthritis.

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 previous year; and the
- number of repeat prescriptions during the previous year.

Use of antiviral drugs

Antiviral drug use should be included as a confounding factor/effect modifier.

Indicators of healthcare utilisation

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

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

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

☑ Member States should define variables that can be extracted from the database in order to assess functional status.

Smoking history

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

Indicators of socio-economic status

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

Further confounding factors

☑ 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

☑ 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

☑ 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 year)		
	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 are coded 'absent', as it is assumed that the characteristic under study is not present.

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

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

Procedures for database management

☑ 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

☑ 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:

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

Subsample validation analysis

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

☑ 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:

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

Transport:

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

Tests used:

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

☑ Member States should describe sensitivity/specificity of tests used. Number, period and selection of sequenced isolates.

Analysis

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 for laboratory-confirmed outcomes are 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 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 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 how missing data were handled in the analysis.

In order to test for differences between vaccinated and unvaccinated characteristics, Student's t-test for continuous variables and chi-square tests (or Fisher's exact test for small samples) for categorical variables are used.

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 year • number of GP contacts during previous year		
Pneumococcal vaccination		
Smoking history		
Level of social interaction		

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

3.11 Crude VE estimates

(1 – RR) x 100; the 'exact 95% CI' is calculated around the estimate for each outcome.

3.12 Stratified analysis

Analysis is stratified according to:

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

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

Confounding factors are 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.

VE estimates are adjusted for risk group, influenza period, and outcome.

- Analysis: for included variables, what is the level of significance; is there clinical relevance?
- Presence of effect modification/interaction terms should be explored.

☑ Member States should describe the planned type of multivariable analysis (Poisson, Cox) and the methods to obtain VE estimates for laboratory-confirmed influenza 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.

☑ 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 is conducted.

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

4 Limitations

4.1 Study population

Representativeness? Generalisability? (Depends on the database and should be described.)

4.2 Exposure, vaccination status

If individuals vaccinated outside GP practices are not considered vaccinated, VE would be underestimated.

☑ Member States should specify if individuals vaccinated outside GP practices can be identified. If not, the proportion not vaccinated by GPs should be estimated, so this issue can be taken into account.

4.3 Outcome

Depends on specificity of the selected outcome. For less specific outcomes, VE is underestimated.

4.4 Sample size for sub-analysis

Does the sample size allow precise estimates for the subgroup analysis?

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.

☑ 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.

☑ 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 are compared 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) are disseminated early during the influenza season (at week 8 of the seasonal vaccine, as soon as a sufficient sample size is reached for the pandemic vaccine). Those preliminary results include … (☑ Member States need to specify what should be included.)
- A more robust VE estimate is disseminated at the end of the season.
  ☑ Member States need to specify the planned adjustments for confounding factors, e.g. if VE against other outcomes are planned, etc.
- One essential goal of the project is to obtain a robust VE estimate, adjusted for the early influenza season.

6 Ethical approval

The study protocol is 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 are organised by EpiConcept/consortium in order to carry out an appraisal of the ongoing studies in various countries. The appraisal team is composed of two persons from the various project partners.

Computer support needs to be in place.

Laboratory: In each country, 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;
- training needs: GP network;
- laboratory;
- IT support, programming;
- access to databases;
- validation studies; and
- supervision visits.

☑ 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.

☑ 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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