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I-MOVE+

Generic Protocol for measuring influenza vaccine effectiveness among the elderly population using the screening method in the European Union and European Economic Area Member States

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Abbreviations

ARI	Acute respiratory infection
BMI	Body Mass Index
CI	Confidence interval
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
EU	European Union
EEA	European Economic Area
GP	General practitioner
ILI	influenza-like illness
MS	Member States
OR	Odds Ratio
PPV	Proportion of the population vaccinated
PCV	Proportion of cases vaccinated
VE	Vaccine effectiveness
☑	(Tick/check mark indicates the sections that study sites should adapt)

1. Background

Influenza viruses are the only vaccine preventable viruses that undergo frequent genetic and antigenic changes. Vaccine induced immunity is not known to last beyond 6-12 months, perhaps less. As a consequence, the influenza vaccine is reformulated each year and annual revaccination is recommended. Available seasonal influenza vaccines are only moderately effective and vaccine effectiveness (VE) may vary between vaccines types and brands. Observed VE varies from year to year, between population subgroups (age-groups, risk groups) and differs for the various influenza type and subtype outcomes measured.

In 2009 the European Council of Ministers recommended that all European Union Member States should reach an influenza vaccination coverage of 75% in all risk groups by the winter season 2014-15. Risk groups are defined as individuals 60 or 65 years and older, and people with a range of underlying medical conditions (1).

In Europe, influenza vaccination is universally recommended for the elderly population as this is a group at higher risk for severe influenza illness. The number of 65 years or older individuals targeted by vaccination was estimated to be 84 million in 2006 (2). It is therefore important to measure the effectiveness of the vaccine in this large target population.

Due to the reformulation of the influenza vaccines every year and to the changes in the virus circulating, influenza VE estimates from previous years cannot simply be carried over to subsequent years.

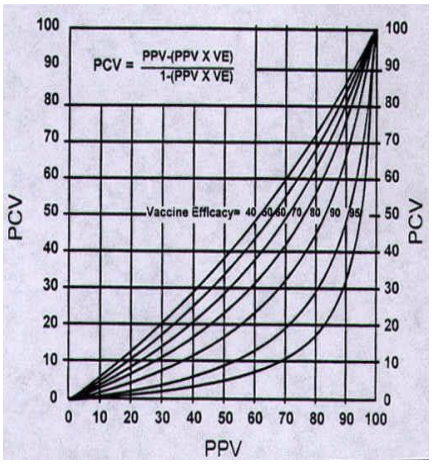
Conducting annual influenza VE estimates among the elderly population at the European level right at the beginning of a seasonal influenza epidemic/pandemic and monitoring VE along the course of the epidemic/pandemic is crucial in order to:

- decide on recommendations for the use of the vaccine and adapt communication strategies;
- target complementary or alternative public health measures (e.g. antivirals) for segments of the population where the vaccine is less effective or that constitute a high-risk group;
- allow more precise estimates of the impact of current vaccination strategies on the burden of disease to support vaccination campaigns;
- identify vaccines types that are more effective;
- 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
- provide elements for adequate risk management and cost-effectiveness analysis.

The screening method is an observational study design to measure VE. It is a type of case cohort design that compares the proportion of cases vaccinated (PCV) to the vaccination coverage of a reference group.

The figure below, represents the relationship between vaccine effectiveness PCV and proportion of population vaccinated (PPV).

Figure: Relationship between Vaccine Efficacy, Proportion of Population Vaccinated and Proportion of Cases Vaccinated, [Source: Orenstein 1985 (3)]



In the screening method, bias may be introduced in the VE estimations if the cases and the reference group are drawn from different populations. When vaccination coverage varies over time, the vaccine coverage in the reference group should be measured at the time of cases occurrence. One of the limitations of the screening method is that usually the variables collected in the reference group are limited and insufficient to adjust for selection bias and potential positive and negative confounding factors. If the methods are the same and bias is constant over time, the screening method would be able to identify changes in the influenza VE in different periods of the same season or along the seasons. Besides the methodological challenges, the screening method is easy to implement and can provide early and real-time influenza VE estimates using existing sentinel surveillance systems at primary care or hospital level.

In some European countries the screening method has been used in to measure seasonal and/or pandemic influenza VE against different outcomes, to provide real-time and early in the season VE estimates (4-12). Some of these authors suggest that the elderly is a more homogeneous population in which all individuals are targeted for influenza vaccination as compared to younger age-groups for which a targeted risk-group approach is implemented in most countries. Therefore, VE studies restricted to this age-group may be less subject to the presence of confounding factors making the screening method a simple study design to provide rapid VE estimates, comparable across seasons.

The I-MOVE+ network represents an opportunity to use the screening method and compare it with other study designs. Study sites conducting influenza VE (test-negative design, cohort studies) at hospital and primary care level will recruit influenza cases and document their vaccination status. If in those sites, the vaccination coverage in the population giving rise to the cases is easily available, the screening method will be a simple method to implement. In addition, the study sites having electronic registers may have the opportunity to link vaccine registries to the influenza surveillance database.

The purpose of this generic protocol on measuring influenza VE in the elderly using the screening method is to provide I-MOVE+ partners and other European study teams with a minimum set of requirements to conduct screening method studies. Depending on the setting and the data available, study teams can adapt this generic protocol to measure influenza VE against hospitalisation or against medically-attended influenza like illness.

2. Objectives

2.1 Primary objective

To measure in the elderly population (aged ≥60 or ≥65 years) at primary care level and/or hospital level, early and late in the season, the direct effect (effectiveness) of influenza vaccines against [outcome(s) defined by study site].

☑ *Each study to define the outcome to be measured and to precise the primary objective (e.g. which age-group, which setting - hospital/GP level).*

2.2 Secondary objectives

To estimate influenza VE:

- by type/subtype/lineage (if laboratory confirmed outcome used);
- weekly/monthly/intra-seasonally;
- every influenza season;
- by age group (e.g. <75 and >74 years);
- for the various types of vaccines (adjuvanted/non-adjuvanted; trivalent or quadrivalent), groups of vaccines (split virion, subunit, etc.), mode of injection (intradermal vs. intramuscular) and by vaccine brand.

☑ *Each study to define the secondary objectives and list them.*

Note: The feasibility to reach the proposed secondary objectives will depend on the information available on vaccine coverage for the reference group on the stratification variables (age group, time period, type of vaccine), on the information available on the influenza strain, and on the sample size.

3. Methods

3.1 Study design

Screening method (or case coverage or case cohort design).

3.2 Study population

The study population will be individuals aged ≥60 or ≥65 years and, depending on the sources used to identify cases:

- Identification of cases at Primary Care level:
  - residents of the catchment area of the GPs participating in the study;
  - individuals likely to consult the GPs participating in the study when developing ILI.
- Identification of cases at Hospital level:
  - residents of the catchment areas of the hospitals participating in the study;
  - individuals likely to be hospitalised in the hospitals participating in the study when developing a SARI.

☑ *Each study to define the study population based on the source to recruit cases, catchment area of the GPs/hospital, and case definition used.*

3.3 Study period

The study period will start when the influenza virus is circulating and the vaccine is available.

- Seasonal influenza vaccine:

  The study period will start at the beginning of the seasonal influenza period and >14 days after the beginning of the influenza vaccination campaign and finishes at the end of the influenza period.

  - Inclusion period: Cases will be included from the week of onset of the first influenza positive case included in the study until the end of the influenza period.

  ☑ *Each study site to define the beginning, the peak and the end of the influenza epidemic according to the information provided by the country influenza sentinel surveillance system.*

  ☑ *Each study to specify the starting date of their vaccination campaign.*

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

  ☑ *Each study site to define the beginning and end of the pandemic VE study period.*

3.4 Outcome(s)

Study sites can use different outcomes depending on the question to answer (VE to prevent what type of outcome) and the sources available to identify cases:

- Medically-attended-ILI
- Medically attended-ILI laboratory confirmed influenza
- Patient hospitalised with SARI
- Laboratory-confirmed influenza in patients hospitalised with a SARI
- Subtype-specific laboratory-confirmed influenza A
- Laboratory-confirmed influenza B overall and if available by lineage (B Victoria/B Yamagata)

☑ *Each study to define the outcome(s) used to measure the effectiveness of the influenza vaccine.*

3.5 Case definitions

3.5.1 ILI definition recommended

A case of ILI is defined as an individual who consults a participating GP, presenting the following symptoms (according to EC case definition):

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

☑ *Each study to define the ILI case definition used and, if different from the recommended one, how this can affect the VE results.*

For the pandemic vaccine, the ILI case definition may be revised during the course of the pandemic.

3.5.2 SARI definition

For cases identified in the existing SARI surveillance systems, the SARI definition used will be the one used in the surveillance system.

For SARI patients identified in the I-MOVE+ hospital network, the SARI definition will be the one agreed in the network.

The case definition used for I-MOVE+ is a hospitalised person with:

- at least one systemic symptom or sign (fever or feverishness, malaise, headache or myalgia) OR deterioration of general condition OR deterioration of functional status

  AND
- at least one respiratory symptom or sign (cough, sore throat or shortness of breath) at admission or within 48 hours after admission.

The symptoms onset should not have started (or clearly worsened, if chronic) more than 7 days before admission.

3.5.3 Influenza case

An influenza case is defined as an ILI or SARI case with a respiratory sample positive for influenza with at least type/subtype information.

☑ *Each study site to specify the case definition used.*

3.5.4 Laboratory confirmation (for laboratory confirmed outcomes)

Specimens will be collected from ILI or SARI cases <8 days of symptom onset, according to the requirements of the specific study or the influenza surveillance system.
Influenza laboratory confirmation will be done using RT-PCR and/or culture.

☑ *Each study site to specify the maximum delay between symptom onset and swabbing recommended.*
☑ *Each study site to specify the mode of specimen collection, storage and transport.*
☑ *Each study to list the RT-PCR characteristics in the protocol annexes.*

3.6 Case identification

Cases will be identified among patients presenting to a participating GP with ILI or hospitalised with SARI or reported within the national (regional) disease surveillance system.
If laboratory confirmed influenza is the outcome used in the study, following the procedures outlined in each study, or the surveillance system, if possible, all elderly with ILI/SARI will be selected and asked to provide a respiratory specimen for influenza testing. Influenza-positive ILI or ARI cases will be considered influenza cases.

☑ *Each study site to describe:*

- GPs or hospitals participating in the case identification (number, distribution, catchment population);
- At hospital level, procedures to identify SARI cases (e.g. use of ICD codes, systematic screening of patients with respiratory symptoms, etc);
- The national disease surveillance system;
- Procedures to select ILI/SARI cases for specimen collection;

3.7 Case exclusion criteria

Cases will be excluded if they:

- refuse to participate in the study;
- are not eligible for influenza vaccination due to a condition listed in the summary of product characteristics (if the information is available);
- are institutionalised;
- are unable to give informed consent or follow an interview in their native language because of aphasia, reduced consciousness, or other reasons;
- are swabbed >7 days after ILI/SARI symptom onset (for laboratory confirmed outcomes);
- had his/her SARI onset ≥ 48 hours after admission at the hospital;
- tested positive to any influenza virus in the current season before the onset of symptoms.

Reasons for exclusion will be documented.

☑ *Each study site to define exclusion criteria (depending on data available).*

3.8 Exposure (vaccination)

3.8.1 Vaccination status definition for cases

Current seasonal vaccine:

- an individual is considered as vaccinated against influenza if the vaccination occurred more than 14 days before disease onset.
- an individual is considered as unvaccinated if they did not receive influenza vaccine or if they were vaccinated <15 days before symptom onset.

Pandemic vaccine:
the definition of vaccinated, partially vaccinated and unvaccinated will be defined when it is known how many doses of vaccine are recommended. Once this is known the protocols will be updated.

☑ *Each study site to specify the definition of vaccinated and unvaccinated.*

3.8.2 Ascertainment of vaccination in cases

The exposure of interest in this study will be a vaccination history with trivalent/quadrivalent influenza vaccine (for seasonal vaccine) and vaccination history with the pandemic vaccine (in case of a pandemic). The vaccination history will include date of administration and brand names (if brand or vaccine type-specific VE will be measured).

An individual is considered as vaccinated against influenza if:

- he or she reports having received an influenza vaccination during the current season;

  or

- he or she is registered as vaccinated in a vaccination registry;

  or

- he or she is reported within the disease surveillance system (e.g. by local public health office staff) as being vaccinated against influenza during the current season;

  or

- his or her insurance company can show evidence of pharmacy delivery or re-imbursement of influenza vaccine/vaccination during the current influenza season.

  or

- has influenza vaccination recorded this season in his/her vaccination card/vaccination booklet.
- Pandemic vaccine: if more than one dose is recommended, the number of doses is documented.

☑ *Each study site to document:*

- the seasonal and pandemic vaccines used;
- the precise mode of vaccine ascertainment for each study is specified in the study annexes.

3.8.3 Vaccine coverage in the reference group

In European Member States, several sources of data are used to estimate influenza vaccine coverage (13).
Vaccine coverage can be measured using different population sub-groups (from now on called reference groups). The best reference group will be the one representing the vaccination coverage in the population giving rise to the cases.
The size of the reference group should be large (> 1000 individuals).

Examples of sources for vaccination coverage include:

- For GPs with computerised medical records, vaccination coverage can be extracted from the GP's database;
- For GPs without computerised medical records, a sample of patients in a defined time period may be selected and influenza vaccination status documented;
- For GPs without computerised medical records, a sample of the population in the catchment area can be selected and interviewed on their influenza vaccination status (telephone, face to face):
  - Vaccination registries;
  - Health insurance claims data;
  - National surveys;
  - Vaccines distributed, vaccines sales in pharmacies.

☑ *Each study site to specify and describe the reference group selected: source, accessibility, variables available, data validation, time of data extraction (if available). In case of national surveys, the methods used for the survey should be described.*

3.8.4 Exposure ascertainment by reference group

- Vaccine delivery and vaccine registration might be country specific. Each study team should identify the best method to ascertain vaccination coverage in the reference group.
- The definition of vaccinated will depend on the data source used and on the availability of date of vaccination. If possible and if the date of vaccination is available, an individual of the reference group will be considered vaccinated if he/she has been vaccinated more than 14 days before his/her vaccination status is documented.
- An individual will be considered as unvaccinated if he/she did not receive influenza vaccine or if they were vaccinated <15 days before vaccination status documentation.

☑ *Each study to specify the definition of vaccinated in the reference group.*

3.9 Sample size

The sample size for cases should be calculated taking into account (14):

- Expected true vaccine effectiveness;
- The precision around the VE estimate (e.g. 40-60%);
- PPV: Vaccination coverage expected in the reference group;
- Alpha error.

Number of vaccine eligible cases to achieve a 95% confidence interval width of 5% (either site of the VE estimate) for various vaccine effectiveness and PPV

PPV		**VE (%)**				
%	40	50	60	70	80	90
40	2841	2153	1558	1052	628	279
50	2510	1846	1292	840	480	203
60	2047	1706	1150	715	387	154
70	2060	1717	1107	652	330	120
80	2360	1967	1205	664	307	98
90	3627	3022	1742	882	361	94

Number of vaccine eligible cases to achieve a 95% confidence interval width of 10% (either site of the VE estimate) for various vaccine effectiveness and PPV (Farrington)

PPV		**VE (%)**				
%	40	50	60	70	80	90
40	744	565	410	277	166	410
50	666	492	346	226	130	55
60	646	462	314	197	108	43
70	685	474	309	185	95	35
80	832	555	346	195	93	31
90	1365	874	516	271	117	33

If the vaccination coverage is homogeneous between population subgroups in which stratified analysis is planned, the sample size needed for each sub-group will be similar (e.g. age groups (<75 and >74 years), time period (early, peak, late influenza season or weekly/monthly estimates)).

3.10 Data collected

Data on cases will be collected at GP or hospital level depending on the setting. The data collection on the vaccination coverage in the reference group, will depend on the reference group used (GP interviews, GP reports, interviews, health surveys, vaccine registry, etc.).

☑ *Each study should include details on data collection methods, data entry and data transmission.*

Information collected for cases:

- Study identification: country, study site
- Case demographics (age)
- Date of onset of ILI / SARI
- Date of specimen collection (for laboratory confirmed outcomes)
- Laboratory results (for laboratory confirmed outcomes including type/subtype if available)
- Influenza vaccination including date of vaccination (or other way to ascertain protection)
- Brand of vaccine (if this information is available in the reference group)
- Information on comorbidities (if this information is available in the reference group)

Information collected for the reference group will depend on the population and data collection method.

☑ *Each study site to detail the information collected and the data sources for cases and in the reference group.*

3.11 Analysis

3.11.1 Descriptive analysis

The proportion of eligible cases who accepted to participate in the study will be calculated (response rate). The reasons for non-participation or exclusion will be described.
Cases will be described by baseline characteristics and vaccination status.
The vaccination coverage in the reference population will be described by baseline characteristics (e.g. age-group, vaccine type).

3.11.2 Measure of effect

When looking within populations where the coverage represents the same population as the cases, the VE against each of the outcomes selected (e.g ILI, SARI, type/subtype laboratory confirmed influenza) can be calculated as 1 – odds of vaccination in cases / odds of vaccination in the population, or:

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

in which PPV is the proportion of the reference group vaccinated (vaccine coverage in the reference group), and PCV the proportion of influenza cases vaccinated.
Ninety five percent confidence intervals will be computed using the Farrington method (14).

3.11.3 Stratified analysis

Analysis will be stratified according to the availability of vaccination coverage in the reference group:

- age groups (<75 and >74 years);
- time: early influenza season/peak/late influenza season or weekly/monthly estimates;
- chronic conditions

These analyses could only be performed if appropriate sample size in each stratum could be reached.

☑ *Each study site to detail the stratifications to be performed.*

3.11.4 Adjusted analysis, Farrington method

Each case is matched to the coverage from the population that best matches that case according to key confounding variables such as age, chronic conditions and time period. The analysis is then performed as a logistic regression with an offset as the logit of the matched coverage (14).

These variables are included in the model to look at the interaction and define if there is effect modification. If effect modification is identified, then a stratified analysis will be conducted. The analysis can be done only if PCV and PPV are available by the effect modifiers strata:

$$\text{Logit}[PCV] = \text{logit}[PPV] + a + b_x X_x + \ldots b_k X_k$$

An adjusted VE and its 95% CI will be obtained.

3.11.5 Sensitivity analyses

Sensitivity analyses can be conducted by varying the vaccination coverage of the reference group (increasing/decreasing the estimated coverage by some percentage points), using a different definition of vaccination status of cases (e.g. excluding cases vaccinated < 15 days before onset of symptoms or defining them as vaccinated); restricting the case definition (e.g. those swabbed < 5 days after symptom onset if laboratory confirmed outcome used), etc..

☑ *Each study site to detail the sensitivity analyses to be conducted.*

3.12 Data management

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

4. Limitations

Information from the reference group is generally minimal and the possibility to control for confounding factors is limited. Therefore, several biases have to be anticipated.

4.1 Negative confounding

These are biases reflecting that high risk groups are more likely to be vaccinated therefore reducing VE. Negative confounding will be minimised by stratifying by age group, or time period.

4.2 Positive confounding

These are biases reflecting a healthy vaccine effect. People with healthy behaviour and a good functional status are more likely to accept / request vaccination, therefore increasing the measured VE. Positive confounding is also present if very frail people are not offered vaccination. Without the variables used to evaluate healthy behaviour or frailty, it is not possible to control for positive confounding.

4.3 Representativity of the reference group in which vaccine coverage is measured

The main limitation of the screening method is that it is difficult to have a reference group representing the vaccination coverage of the source population giving rise to the cases. The potential difference between the reference group and the source population should be described.
For instance cases recruited at GP level may represent a group of individuals seeking health care more often and thus having a better vaccination coverage than the rest of the population. Using the vaccine coverage of a reference group not recruited at GP practices (e.g. in the general population, health survey), may underestimate the VE.

If the vaccine coverage in the reference group is estimated through a survey, the representativity of the sample population in which the vaccine coverage is measured should be assessed to understand how this could affect the estimates.
If the vaccine coverage in the reference group is estimated at a specific point in time (e.g. early in the season), and the vaccine coverage increases during the season, VE may be underestimated.

4.4 Vaccine status ascertainment

Depending on the reference group, vaccine ascertainment may be different between the cases and the reference group. This may overestimate or underestimate the VE.

4.5 Limitations related to the setting, case definition used, data sources, etc

Each study setting will have specific limitations related to the study population, variables documentation, specificity of the outcome used, etc.

☑ *Each study site should evaluate the potential biases present in their study and how they will affect the results.*

5. Dissemination of results

First VE estimates (intra-seasonal) will be disseminated early during the influenza season and final estimates at the end of the season. The results will be shared with the I-MOVE+ Steering-Scientific Committee.

Each study coordinator will decide in which journals the results of the study will be published and in which Scientific Conferences the results can be presented.

6. Training

Participating study teams (GPs, study nurses, etc) will be trained on the study protocol before the start of the study. They will receive the protocol, questionnaires and laboratory swabbing procedures.

7. Consent

According to country specific regulations informed (oral or written) consent will be required from each participant who has a specimen collected. For patients unable to provide an informed consent, their relatives will be approached (if ethical committee allows). National ethical committees will specify if oral consent or written consent are needed. Study teams should identify the procedures to get ethical clearance to conduct the study.

☑ *Each study will give details on the consent procedures and the ethical approval needed.*

8. Additional studies

Additional studies potentially include:

- Comparing results obtained in the same population with the screening method and other methods such as cohort or case control studies
- Validating vaccine coverage in the reference group

Any other study that study teams would think could contribute to better interpretation of the study results.

☑ *Additional studies should be outlined in the protocol annexes.*

9. References

Reference List

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(13) European Centre for Disease Prevention and Control (ECDC). Seasonal influenza vaccination in Europe- Overview of vaccination recommendations and coverage rates in the EU Member States for the 2012-13 influenza season. Stockholm: ECDC; 2015 Jan.

(14) Farrington CP. Estimation of vaccine effectiveness using the screening method. Int J Epidemiol 1993 Aug;22(4):742-6.

Annexes

Study-specific annexes:

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

- Description of the GPs/hospitals participating in the study (number, distribution, catchment population, mode of recruitment).
- Vaccine products used in the elderly
- Definition of beginning, peak, end of influenza season
- ILI/SARI cases: case identification,
- Laboratory confirmation: mode of selection of individuals for whom a specimen is collected
- Vaccine ascertainment method used for cases
- Sample size calculation for cases
- Detailed data collection methods, data entry and data transmission
- Data validation procedures
- Vaccination coverage in the reference group: size of the reference group, data sources, VC by age group (<75 and >74 years), time
- Laboratory methods:
  - specimen collection, storage, transport
  - Tests used (PCR, culture, strain characterisation)
- Consent, study ethical procedures
  - Oral / written consent if applicable
  - Submission to ethical committee if applicable
- Human resources needed
- Additional studies if applicable