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I-MOVE+

Deliverable n°2.2:
Generic Protocol for measuring the impact of influenza vaccination programmes among the elderly population in the European Union and European Economic Area Member States

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Abbreviations

EEA	European Economic Area
EU	European Union
ILI	Influenza-like illness
MS	Member States
NAE	Number of averted events
PF	Prevented fraction
VC	Vaccination coverage
VE	Vaccine effectiveness
☑	(Tick/check mark indicates the sections that study sites should adapt and detail in their study annexes.)

1 Background

Influenza infection can cause serious complications in the elderly including hospitalisations and death. In 2009 the European Council of Ministers recommended that all European Union (EU) Member states (MS) 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, seasonal influenza vaccination coverage (VC) in the elderly varies by season and in most MS does not reach the target set by EC (2). To increase the acceptability of the vaccine, it is important to quantify the benefits of vaccinating the elderly. Influenza vaccine effectiveness studies are conducted in Europe every season and suggest that the effect of the vaccine is moderate in the elderly population. However, there is limited data on the influenza-associated outcomes prevented each season by influenza vaccination in this population.

2 Definition of vaccination effects

In epidemiology, effect is the amount of change in a population's disease frequency caused by a specific factor. Effects in vaccinology measure various absolute or relative changes in incidences observed between populations exposed and not exposed to an intervention (vaccination).

In this protocol we propose the following definitions on Halloran (3) description of vaccination effects (Figure 1).

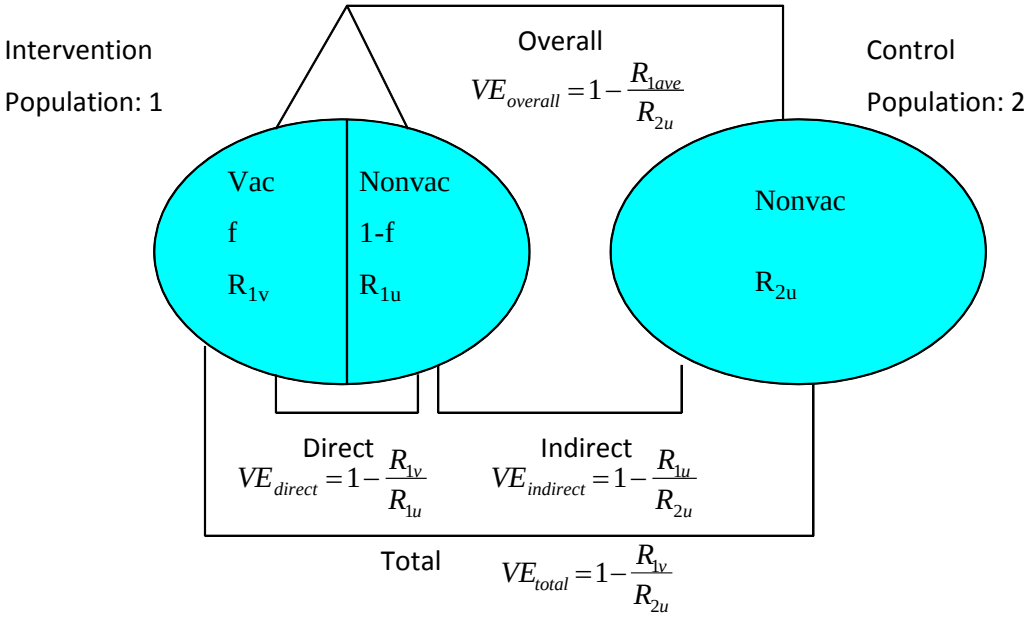

Figure 1: Diagram on vaccination effect adapted from Halloran *et al* [*ibid*. 6]:

R=rate or risk in vaccinated (*v*) or unvaccinated (*u*)

Direct effect

The direct effect is the effect of the vaccine in inducing protective immunity in a person who is vaccinated. It is measured by comparing the incidence of disease (or other outcome) of vaccinated and unvaccinated persons belonging to the same population and exposed to the same vaccination programme.

Overall effect

The overall effect is the effect of the vaccination programme in the entire population, including vaccinated and unvaccinated. To measure the overall effect, the overall (average) incidence of disease (or other outcome) of the population in which there is a vaccination programme is compared to the incidence of disease (or other outcome) in a completely unvaccinated population (Figure 1). It represents the weighted average of indirect effect on the individuals not receiving the intervention and the total effect on the individuals receiving the intervention.

Indirect effect

The indirect effect is the population-level effect on the unvaccinated portion within a population with a vaccination programme. This type of effect is usually estimated by comparing the incidence of disease (or other outcomes) in the unvaccinated portion of a population in which some individuals have been vaccinated, with the incidence of disease (or other outcomes) in a completely unvaccinated population (Figure 1). The indirect effect can be measured by comparing the incidence rates of disease (outcome) in a group never targeted for vaccination before and after the introduction of the vaccination programme.

Total effect

The total effect of a vaccination programme measures the population-level effect of vaccination on the vaccinated portion of a population. This can be estimated by comparing the incidence of disease (or other outcome) in the vaccinated portion of a population in which some individuals have been vaccinated, with the incidence of disease (or other outcomes) in a completely unvaccinated population (Figure 1).

In this protocol, the term “impact” refers to overall, indirect and total effect of vaccination while the term “effectiveness” refers only to the direct effect of vaccination under field conditions.
When a new vaccine is introduced in a population, the most straightforward method to measure the impact of the vaccination programme is to conduct “before/after studies”. Before/after studies compare the occurrence of the vaccine preventable disease before the introduction of the vaccine to its occurrence once the vaccine is used.

In the European Union and European Economic Area, influenza vaccination in the elderly has been recommended for many years. Most European countries do not have data of the pre-vaccination period and consequently cannot conduct “before/after studies” to measure influenza vaccination impact.

Another approach to measure the impact of the influenza vaccination programme is to estimate, in a population with a vaccination programme, the number of influenza related outcomes averted. This can be done by comparing the outcomes that would have occurred without the vaccination programme to the observed number. In this protocol we propose to use this method: based on the number of influenza related outcome(s) observed in the elderly population we will estimate the number of outcomes that would have occurred in the same population without the vaccine. This will enable computing the number of averted influenza related outcomes. The number of outcomes in the population without a vaccination programme will be estimated based on the vaccination coverage, vaccine effectiveness and outcomes observed in the population with a vaccination programme (4). This method assumes that there is no indirect effect: the number of outcomes in the unvaccinated fraction of the population with a vaccination programme is the same as the number of outcomes in the population without a vaccination programme.

In Europe, influenza vaccination coverage in the non-elderly population is low (5). We therefore assume that the indirect effect in the elderly population of the vaccination of non-elderly is minimal. However, the VC in elderly is above 50% in many countries and there might be an indirect protective effect in the elderly. If this is the case, our impact estimates will underestimate the number of influenza-associated outcomes averted.

I-MOVE+ will provide VE every season against various outcomes. Taking into account that most of the participating countries measure VC every season, with the method proposed, participating countries would be able to estimate every year the number of influenza related outcomes. They would also be able to estimate the number of averted cases at different levels of VC.

☑*Each study site to provide recent estimates of VC in the elderly and non-elderly population.*

3 Objective

The primary objective is to estimate the effect of the influenza vaccination programme in the elderly by measuring the reduction in the number of influenza-associated outcomes.
The secondary objectives are to measure:

- the number of vaccines needed to avoid one influenza-associated outcome
- the prevented fraction

☑*Each study site to define the objective by specifying the site, the outcomes used, the study period.*
E.g. To measure the effect of the influenza vaccination programme in the elderly in country X by measuring the reduction in the number of outcomes Y over X influenza seasons.

4 Methods

Retrospective study using information from existing data sources on:

- Number of influenza-associated outcomes occurred during the seasonal epidemic period;
- Seasonal influenza vaccine effectiveness;
- Seasonal influenza vaccination coverage.

The averted outcomes will be estimated using the formula:

$$NAE = N - n = \frac{n}{1 - (VC * VE)} - n = n * (\frac{VC * VE}{1 - (VC * VE)})$$

In which

- NAE is the number of influenza-associated averted events
- N the number of influenza-associated outcomes in the elderly population without influenza vaccination programme
- n the number of influenza-associated outcomes observed in the elderly population with influenza vaccination programme
- VC: the influenza vaccination coverage in the elderly population
- VE: the vaccine effectiveness in the elderly against the outcome measured

4.1 Outcomes and potential data sources

To measure the number of influenza associated outcomes averted in elderly, we can use different outcomes depending on which component of the burden of disease we want to address.
We list below some of them, their potential data sources and some references using these outcomes.

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Group of outcomes	Outcome	Potential source(s)	☑ Issues to be defined in each study site protocol
Mortality	All cause deaths	Deaths registry Mortality Surveillance system	
	Influenza attributable deaths (6)(7)	Deaths registry Mortality Surveillance system Influenza surveillance system	How is influenza death defined? What is the method to estimate influenza attributable deaths? (e.g. difference-in-differences (7,8) Are there delays in death codification?
Hospitalisations	Influenza related hospitalisations Respiratory hospitalisations (4)	Hospital discharge records (ICD codes)	Are ICD codes used? If yes, which are the selected codes? What is the method to attribute a certain proportion of hospitalisations to influenza?
	Severe Acute Respiratory Infections (SARI)	SARI surveillance	If sentinel surveillance system, what is the method used to estimate all cases? What is the method to attribute a certain proportion to influenza?
Medically-attended consultations	Influenza-like Illness; Acute Respiratory Infections Rates of ARI/ILI (9)	Influenza surveillance systems	If sentinel surveillance system, what is the method used to estimate all cases? What is the method to attribute a certain proportion to influenza?
Laboratory confirmed outcomes	Hospitalisations with laboratory-confirmed influenza	Hospital surveillance	What is the proportion of patients with specimens collected? Is the sampling fraction available? Which are the criteria to test a patient?
	ILI/ARI laboratory confirmed	GP sentinel surveillance	If sentinel surveillance system, what is the method used to estimate all cases? Which are the criteria used to test a patient?

☑ Each study site to define and describe the outcomes selected, data sources.

4.2 Vaccination coverage and potential data sources

The influenza vaccination coverage in the elderly population during the study period should be available. Potential sources include immunisation registries, surveys, administrative data, etc.

☑ Each study site to describe the methods to estimate vaccination coverage in elderly, the data sources and the potential limitations.

4.3 Vaccine effectiveness and potential data sources

The vaccine effectiveness (direct effect) against the selected outcome should be available for the elderly population during the study period.
Potential data sources include influenza VE estimates:

- from the study site (preferable)
- from other sites: I-MOVE+ study sites, non I-MOVE+ study sites
- from previous influenza seasons
- against other outcomes

☑ Each study site to describe the source of VE, the methods used to estimate it, the potential limitations and assumptions to use it.

4.4 Study period

The number of influenza seasons covered by a retrospective study will depend on the number of influenza seasons for which data are available. The study can also be conducted for a single influenza season.

We assume that the influenza vaccine will only prevent influenza-associated outcomes during the period in which influenza is circulating. Therefore, the study period includes only the weeks in which influenza is circulating. The start and end of influenza circulation will be defined based on the data from the national/regional surveillance systems.

☑ Each study site to define the study period and the methods to define the start/end of the influenza period

4.5 Analysis

4.5.1 Estimation of number of outcomes

The first step in the analysis is to estimate the number of influenza-associated outcomes that occurred during the study period.

Depending on the outcome selected, the number of events can be directly extracted from existing data sources (e.g. number of deaths from mortality registry) or should be estimated using information from different data sources (e.g. some laboratory-confirmed outcomes)

- e.g. number of hospitalisations for influenza- associated respiratory infections
  = number of hospitalisations with respiratory ICD code * (number of influenza positive/number of patients with respiratory ICD code tested for influenza).
- e.g. number of influenza-associated deaths in several seasons:
  - the average number of deaths that occurred in a week when the week is included in the influenza epidemic period is compared with the average number of deaths per week when the same week lies outside the epidemic period. The difference in the number of deaths is assumed to be due to influenza (7,8).
  - influenza-associated excess deaths estimated using times series analysis (10).
- e.g. number of influenza associated outcomes (hospitalisation, deaths, etc) using a Poisson regression to take into account the effect of other factors like air-temperature (FluMOMO model: http://www.euromomo.eu/methods/pdf/pooled_analyses_winter_2013_14.pdf).
- e.g. number of influenza-laboratory confirmed outcomes: if laboratory specimens are available from only a fraction of patients, the sampling fraction should be taken into account to estimate the total number of influenza patients laboratory confirmed.

☑ Study sites to define methods used to estimate the number of outcomes

4.5.2 Estimation of vaccination coverage

The vaccination coverage is the proportion of elderly vaccinated with the seasonal vaccination during the study period.

☑ Study sites to define methods used to estimate the VC and the period in which VC is measured (weekly estimates? after seasonal campaign? at the end of the season?)

4.5.3 Estimation of vaccine effectiveness

Study sites will use the study site overall adjusted VE and sub-type specific VE (when available) against the influenza-associated outcome for the study. If VE is based on other studies, other age groups the methods to estimate it should be defined (e.g. any correction applied to derive VE against a clinical outcome from VE against laboratory-confirmed outcome?)

☑ Study sites using VE from other studies, to define methods used to correct for potential differences.

4.5.4 Outcomes averted during the study period

If the study period is one season, the influenza-associated outcomes averted are computed with the formula below using the season estimates for observed influenza-associated outcomes, VC and VE.

Number Averted Events = n*[(VC*VE)/((1-(VC*VE))]

If the period covers more than one season, the seasonal average of the influenza-associated outcomes can be computed or a pooled estimate of the seasons included in the study.

4.5.5 Number of vaccinations required to avoid one influenza-associated outcome

The number of influenza-associated outcomes without influenza vaccination programme would be the sum of the observed outcomes and the outcomes averted.

N = NAE+ n

In which

- N is the number of influenza-associated outcomes in the elderly population without influenza vaccination programme
- NAE is the number of influenza-associated averted outcomes
- n is the number of observed influenza-associated outcomes

The number of vaccinations needed to avoid one influenza-associated outcome can be estimated using the formula:
NVN = 1/(VE*N/pop)

In which

- NVN is the number of vaccines needed to avoid one influenza-associated outcome
- N the number of influenza-associated outcomes in the elderly population without influenza vaccination programme
- VE: the vaccine effectiveness in the elderly against the outcome measured
- Pop: elderly population

4.5.6 Prevented fraction

The prevented fraction in the elderly population is the proportion of averted influenza-associated outcomes in a population with a vaccination programme out of the number of influenza-associated outcomes in the population without influenza vaccination programme;
PF = NAE/N

In which

- PF is the prevented fraction
- NAE is the number of influenza-associated outcomes averted in a population with a vaccination programme
- N the number of influenza-associated outcomes in the elderly population without influenza vaccination programme

5 Limitations

5.1 Limitations related to the outcome used and outcome data source

- Sensitivity/specificity of the outcome. The number of influenza associated-outcomes averted may be overestimated when using sensitive outcomes.
- The validity of the study will depend on the validity of the data sources used for measuring the occurrence of the outcome (e.g. completeness of the surveillance system, validity of the ICD codes used, etc).
- If the total number of outcomes occurred in the vaccinated population has been derived from sentinel surveillance systems, depending on the method used, the number of outcomes may have been over or underestimated. The sensitivity of the surveillance system may not be optimal.
- Laboratory confirmed outcomes: in most surveillance systems, not all patients presenting with influenza infections have a laboratory test. Potential underreporting should be discussed.

☑ Study sites to identify and discuss the potential limitations related to the outcome chosen and method to estimate the number of outcomes occurred.

5.2 Limitations related to the study period used

- If estimations are done over various seasons, potential changes in the various parameters (including case identification, case ascertainment, changes in rates of hospitalisations, changes in severity of the influenza season, etc) may underestimate or overestimate the number of cases averted. The number of outcomes averted can be measured for each season to identify how the changes in the different parameters affect the estimates.

☑ Study sites to identify and discuss the potential limitations related to the study period used.

5.3 Limitations related to the vaccination coverage, vaccine effectiveness estimates, number of outcomes observed

The potential limitations in the VC and VE estimates will affect the estimation of the number of influenza-associated outcome (e.g. limitation of self-report vaccination status, limitations of estimations of VE against non-specific outcomes such as deaths).
If VC and VE estimates are derived from other population(s) (e.g. other countries, regions, other seasons) this may not represent the VC and VE of the study population.

The parameters used to estimate the number of outcomes averted (n, VC and VE) will have an associated random error. To take into account the span of the confidence interval, Monte Carlo simulations can be used (11).

☑ Study sites to identify and discuss the potential limitations related to the VC, VE, number of outcomes averted used.

5.4 Limitations related to assumptions

- The indirect effect due to the vaccination is not taken into account. This may result in the underestimation of the number of influenza-associated outcomes averted.
- Previous immunity: outcomes observed in one season may depend on previous vaccination and/or previous infections.

☑ Study sites to identify and discuss the potential limitations related to the assumptions inherent to the method used to estimate averted influenza-associated outcomes.

6 Ethical aspects

The proposed method is based on existing databases. No patient identification is needed.
Each study will comply with national ethics committee requirements.

☑ Each study site to specify if ethical clearance is needed for the study. If yes, ethical clearance should be obtained from the corresponding national or regional committee.

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