European Union

I-MOVE+

Protocol for joint report on measuring the impact of influenza vaccination programmes among the elderly population in Spain, Navarra, the Netherlands and Portugal

WP nr:	2
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Abbreviations

EEA	European Economic Area
EC	European Commission
ES	Spain
EU	European Union
ILI	Influenza-like illness
IVE	Influenza vaccine effectiveness
MS	Member States
NA	Navarra
NAE	Number of averted events
PF	Prevented fraction
RSV	Respiratory syncytial virus
SARI	Severe acute respiratory infection
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 of 75% set by the European Commission (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 (3–5). 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 incidence observed between populations exposed and not exposed to an intervention (vaccination).
In this protocol we propose the following definitions on Halloran (6) description of vaccination effects (Figure 1).

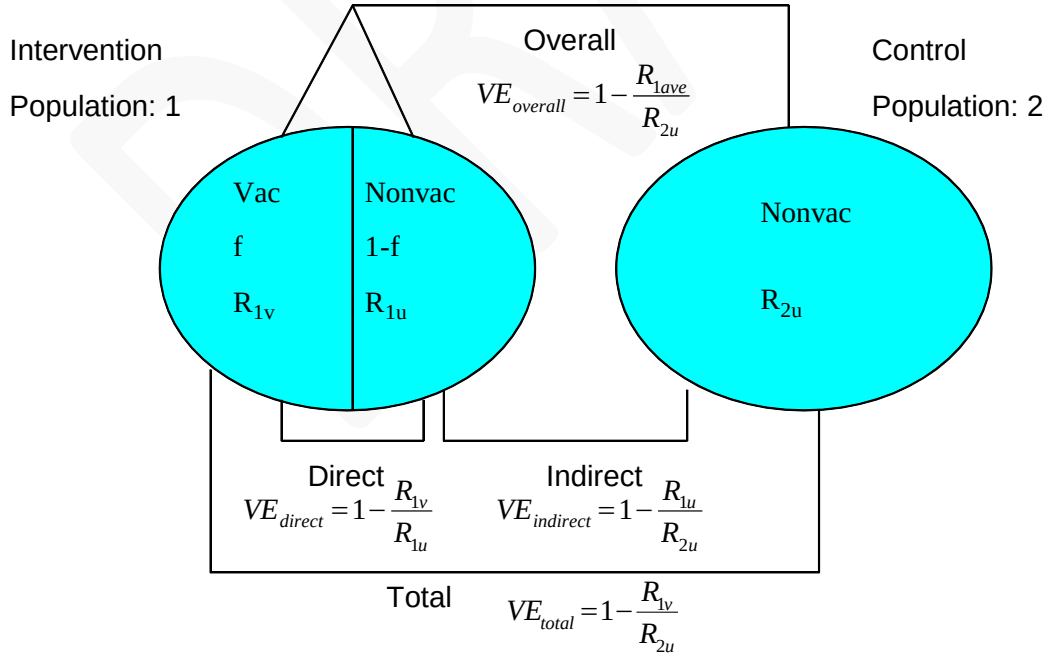

Figure 1: Diagram on vaccination effect adapted from Halloran *et al* [*ibid*. 6]:

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 (Figure 1).

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 (7).

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 (8). 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, ranging from 29% and 80% among clinical risk groups, according to a VENICE survey (9). 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.

3. Introduction to this protocol

Deliverable D2.19, as part of the EU's Horizon 2020 research and innovation programme (grant agreement No 634446), is a joint study site final influenza vaccine impact report. Four study sites participate in the impact part of WP2 in terms of actively providing results: Spain, Navarra, the Netherlands and Portugal.

In order to prepare this report with harmonised results between sites, the study sites with EpiConcept as the coordination team held a technical meeting in Lisbon, Portugal, on the 21 and 22nd of February 2018. During this meeting the study sites agreed on feasible approaches for all. This protocol reflects these approaches agreed during this meeting.

4. Objective

The primary objective is to estimate the effect of the influenza vaccination programme in those aged 65 years and older in Spain, Navarra, the Netherlands and Portugal by measuring the reduction in the number of the following influenza-associated outcomes: ILI laboratory-confirmed as influenza, hospitalized severe acute respiratory infection (SARI) attributable to influenza, mortality attributed to influenza. Estimates will be study-site specific for the influenza seasons covered by I-MOVE+: 2015-16, 2016-17 and 2017-18 (where available), as well as an average across seasons.

The secondary objectives are to measure:

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

5. 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

5.1. Outcomes and potential data sources

To measure the number of influenza associated outcomes averted in elderly, we will use different outcomes depending on which component of the burden of disease we want to address.

Mortality attributable to influenza

Mortality attributable to influenza will be calculated with the FluMOMO model (http://www.euromomo.eu/methods/flumomo.html). All study sites participate in FluMOMO. To obtain the mortality attributable to influenza study sites will need

- Weekly number of all-cause deaths in the 65 year and older age group
- Weekly influenza activity in the 65 year and older age group. The Goldstein Indicator is the preferred measure of influenza activity (number of ILI * percent positive for influenza)
- Weekly deviation from the expected temperature, which can be downloaded from the FluMOMO website

In some study sites, other outcomes more specific to influenza may be available, but for the purposes of this joint report, mortality attributable to influenza will be used since it is available in all study sites.

SARI attributable to influenza

For the hospitalised outcome, study sites will use a measure similar to the mortality above. Using the diagnosis codes (for primary diagnosis) from the I-MOVE+ hospital based IVE study protocol, that are used to screen patients for onset of SARI symptoms, study sites will calculate SARI attributable to

influenza. This will be done using the FluMOMO regression model (http://www.euromomo.eu/methods/flumomo.html). All study sites participate in FluMOMO. To obtain the SARI attributable to influenza study sites will need

- Weekly number of SARI in the 65 year and older age group from the 2011-12 season onwards (starting at ISO week 40), as estimated using the primary diagnosis discharge data with codes in table 1. NB: the data from either 2010-11 or 2011-12 up to 2014-15 will be used as historical data (study sites to specify the length of historical data).
    - The weekly data will be the total of patients with primary diagnosis discharges in the table.
- Weekly influenza activity in the 65 year and older age group. The Goldstein Indicator is the preferred measure of influenza activity (number of ILI * percent positive for influenza)
- Weekly deviation from the expected temperature, which can be downloaded from the FluMOMO website.
- Where available, RSV can be included in the model as a covariate.

Influenza-related hospitalization discharge data codes, using ICD codes ICD 9 and 10, are listed in the I-MOVE+ hospital protocol (http://www.i-moveplus.eu/wp2) and in table 1 below:

Table 1: List of diagnosis codes for which patients could be screened for onset of SARI symptom that started within the past seven days, IMOVE+ hospital based IVE studies

Category	Morbidity	ICD-9	ICD-10
Influenza like illness	Cough	786.2	R05
	Difficulty breathing	786.05	R06
	Sore throat	784.1	R07.0
	Dysphagia	787.20	R13
	Fever	780.6	R50.9
	Headache	784.0	R51
	Myalgia	729.1	M79.1
	Fatigue/malaise	780.79	R53.1, R53.81, R53.83
Cardiovascular diagnosis	Acute myocardial infarction or acute coronary syndrome	410-411, 413-414	I20-23, I24-25
	Heart failure	428 to 429.0	I50, I51
Respiratory diagnosis	Emphysema	492	J43.9
	Chronic obstructive pulmonary disease	496	J44.9
	Asthma	493	J45
	Myalgia	729.1	M79.1
	Dyspnoea/respiratory abnormality	786.0	R06.0
	Respiratory abnormality	786.00	R06.9
	Shortness of breath	786.05	R06.02
	Other respiratory abnormalities	786.09	R06.00, R06.09, R06.3, R06.89
Infections	Pneumonia and influenza	480-488.1	J09-J18
	Other acute lower respiratory infections	466, 519.8	J20-J22
	Viral infection, unspecified	790.8	B34.9
	Bacterial infection, unspecified	041.9	A49.9

Category	Morbidity	ICD-9	ICD-10
	Bronchitis	490, 491	J40, 41
Inflammation	SIRS non infectious without acute organ dysfunction	995.93	R65.10
	SIRS non infectious with acute organ dysfunction	995.94	R65.11
Diagnoses related to deterioration of general condition or functional status	General physical deterioration, lethargy, tiredness	780.79	R53.1, R53.81, R53.83
	Anorexia	783.0	R63.0
	Feeding difficulties	783.3	R63.3
	Abnormal weight loss	783.21	R63.4
	Other symptoms and signs concerning food and fluid intake	783.9	R63.8
	Desorientation/Altered mental status	780.97	R41.0
	Dizziness and giddiness	780.4	R42
	Infective delirium	293.0, 293.1	F05
	Coma	780.01	R40.2
	Transient alteration of awareness	780.02	R40.4
	Other alteration of consciousness (Somnolence, stupor)	780.09	R40.0, R40.1
	Febrile convulsions (simple), unspecified	780.31	R56.00
	Complex febrile convulsions	780.32	R56.01

**SIRS: Systemic inflammatory response syndrome*

Patients with these discharge codes represent SARI-related hospitalisations rather than influenza-related hospitalisations. Navarra has data on the proportion of SARI attributable to influenza, as well as Spain in two hospitals (in the 2015-16, 2016-17 season, with the 2017-18 season pending). In a sensitivity analysis, Navarra and Spain data using SARI discharge data and SARI attributable to influenza will be compared.

☑ *Each study site to specify the length of historical data to be used.*

Medically-attended ILI laboratory-confirmed as influenza

Weekly ILI rates among those aged 65 and over are obtained through country-/region-specific systems (sentinel physician data extrapolated to the population or from GP databases) and weekly proportions of ILI positivity are extrapolated to the ILI rates.

☑ *Each study site will provide ILI case definitions used, which will be compared in the joint report. Each study site to specify any restrictions regarding the delay between onset of symptoms and swabbing for samples used.*

5.2. Vaccination coverage and potential data sources

The influenza vaccination coverage in the elderly population during the study period is available for each study site. Potential sources include immunisation registries, surveys, administrative data, etc. Where vaccination coverage is based on a sample, confidence intervals around the estimates will be made available.

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

5.3. Vaccine effectiveness and potential data sources

VE against mortality

As VE against mortality is not available by study site, all study sites will use the vaccine effectiveness against all-cause mortality from the Navarra study combining seasons 2011-12 to 2012-13: **16% (95% CI: 7-24%)** (Castilla J , Guevara M , Martínez-Baz I et al. Enhanced estimates of the influenza vaccination effect in preventing mortality: a prospective cohort study. Medicine (Baltimore) 2015; 94:e1240).

The outcome is deaths attributable to influenza, so the VE against mortality is not the same. This will be discussed in the limitation section of the report/paper.

VE against hospitalised outcome

The VE to be applied to the hospital outcome is the pooled European IVE, as study site-specific VE against hospitalized outcome is likely to have low precision. For certain influenza type/subtypes even pooled-country VE estimates may not be very precise. Therefore pooled-country multicenter estimates by type/subtype will be pooled across the three seasons included in the I-MOVE+ impact report (2015-16 to 2017-18).

Preliminary pooled VE results from the multicenter hospital study are in the table below. They include 2015-16 and 2016-17 end-of-season but only interim 2017-18 results. They will be updated later this year with end-of-season 2017-18 results.

Years included	Type/subtype	VE (95% CI)
2015-16/2017-18	A(H1N1)pdm09	43.8 (95%CI: 24.7;58.1)
2016-17/2017-18	A(H3N2)	13.5 (95%CI: -2.8;27.1)
2015-16/2017-18	B	37.1 (95%CI: 18.7;51.4)

Study sites can weight the pooled type/subtype VE by the study site-specific influenza type/subtype distribution among those aged 65 and older. For example if in 2015-16 a study site has a circulation of 30% influenza A(H1N1) and 70% influenza B, then the formula will be adapted as follows:

$$NAE = N - n = \frac{n}{1-(VC*(0.3*VE_{A(H1N1)}+0.7*VE_B))} - n = (\frac{VC*(0.3*VE_{A(H1N1)}+0.7*VE_B)}{1-(VC*(0.3*VE_{A(H1N1)}+0.7*VE_B))}$$

In order to obtain the weighted 95% confidence intervals, the log standard error (SE) needs to be weighted. Study sites can use the metan command in Stata to easily compute the weighted 95% CI. An example is in Annex 1.

The outcome is SARI attributable to influenza. The outcome used to compute the VE (hospitalisation lab-confirmed as influenza) is not the same. This will be discussed in the limitation section of the report/paper.

VE against primary care-attended lab-confirmed influenza

Multicentre pooled VE results will be pooled across the seasons included in the I-MOVE as well to make the results more precise.
Preliminary pooled VE results from the multicenter primary care based study are in the table below. They include 2015-16 and 2016-17 end-of-season but only interim 2017-18 results. They will be updated later this year with end-of-season 2017-18 results.

Years included	Type/subtype	VE (95% CI)
2015-16/2017-18	A(H1N1)pdm09	28.9 (-10.7-54.4)
2016-17/2017-18	A(H3N2)	10.7 (-12.7-29.2)
2015-16/2017-18	B	27.3 (-3.9-49.2)

Study sites can weigh the pooled type/subtype VE by the study site-specific influenza type/subtype distribution among those aged 65 and older. For example if in 2015-16 a study site has a circulation of 30% influenza A(H1N1) and 70% influenza B, then the formula will be adapted as follows:

$$NAE = N - n = \frac{n}{1-(VC*(0.3*VE_{A(H1N1)}+0.7*VE_B))} - n = (\frac{VC*(0.3*VE_{A(H1N1)^*}+0.7*VE_B)}{1-(VC*(0.3*VE_{A(H1N1)}+0.7*VE_B))}$$

In order to obtain the weighted 95% confidence intervals, the log standard error (SE) needs to be weighted. Study sites can use the *metan* command in Stata to easily compute the weighted 95% CI. An example is in Annex 1.

For validation, ES and NA will use study site-specific VE and pooled season multicenter VE. The results of these two approaches will be compared and included as a sensitivity analysis in the report.

5.4. Study period

The seasons within the study period will include the I-MOVE+ years: 2015-16, 2016-17 and 2017-18, where data are available. Previous years may be used as historical data to establish baselines for the outcomes attributable to influenza analysis.

Study sites will carry out the analyses for each season and will also provide a pooled average across the three I-MOVE+ seasons.

Within a season, the study periods will be defined using study-site specific definitions.

☑ Each study site to describe the methods to determine the study period and dates of the study period in each study site will be documented in the report/paper.

5.5. Analysis

5.5.1. 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. If study-site specific VE estimates are used, then the VE in the formula below is from the study-site specific VE estimate against "any influenza".

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

If pooled-season multicentre VE estimates are used (in study sites where study-site specific VE may have low precision,) the type/subtype specific VE will be weighted by the proportion of influenza A(H1N1)pdm09 [x], A(H3N2) [z] and B [y] circulating in the study site during the study period. x, y, and z are a number between 0 and 1 and have 1 as a cumulative sum.

$$NAE = N - n = \frac{n}{1-(VC*(x*VE_{A(H1N1)} + y*VE_B + z*VE_{A(H3N2)})} - n = n(\frac{VC*(x*VE_{A(H1N1)} + y*VE_B + z*VE_{A(H3N2)})}{1-(VC*(x*VE_{A(H1N1)} + y*VE_B + z*VE_{A(H3N2)})}$$

The average NAE across the three seasons will be the sum of NAE in seasons 2015-16, 2016-17 and 2017-18 divided by three or analogous if fewer seasons available.

NAE will also be presented per 100 000 population, to enable comparison of NAE between countries.

5.5.2. 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

As above if pooled-season multicentre VE estimates are used (in study sites where study-site specific VE may have low precision, the type/subtype specific VE will be weighted by the proportion of influenza A(H1N1)pdm09 [x], A(H3N2) [z] and B [y] circulating in the study site during the study period. x, y, and z are a number between 0 and 1 and have 1 as a cumulative sum.

$$NVN = 1/((x * VE_{A(H1N1)} + y * VE_{B} + z * VE_{A(H3N2)}) * N/pop)$$

The average Number of Vaccines Needed to avert an event across the three seasons will be the sum of NVN in seasons 2015-16, 2016-17 and 2017-18 divided by three or analogous if fewer season available.

5.5.3. *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

The average prevented fraction across the three seasons will be the average NAE divided by the average N.

5.5.4. *Uncertainty*

For most of the elements in the analysis (VC (when measured from a sample of the population), VE and number of events) there is a level of uncertainty. An exception is for some countries where vaccine coverage is measured using an exhaustive vaccine registry or similar. Where an estimate is not exhaustive, then a measure of uncertainty should be used in the calculations. All sites agreed in using a probabilistic Monte Carlo approach similar to Foppa et al 2015[1].

[1] https://www.sciencedirect.com/science/article/pii/S0264410X15002315

A do-file, developed by Irina Kislaya from INSA Portugal, is in Annex 1 that calculated NAE taking uncertainty in VE and VC into account. The do-file needs to be slightly modified if no uncertainty is used around the VC or if added uncertainty is added around the number of observed events. The do-file in Annex 1 is an example for ILI – for outcomes attributable to influenza (such as hospitalisations and mortality attributable to influenza using the FluMOMO model), the uncertainty for the number of events should be the result of the FluMOMO model estimation.

5.5.5. List of sensitivity analyses

Several sensitivity analyses were proposed in the above sections, they are listed here and their results will be compared with results from the main analyses in the report:

1) Navarra and Spain (from 2 hospitals) will compare NAE for the hospitalized outcome using SARI attributable to influenza (using the FluMOMO approach) and lab-confirmed SARI.
2) Navarra and Spain will compare for the primary care specific lab-confirmed influenza outcome NAE from calculations using study-site specific VE and using pooled season multicenter VE (weighted by the proportion of type/subtype circulating in the study site).

6. Limitations

6.1. 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 non-specific 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.

Limitations will be discussed in the report/paper.

6.2. 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.

Limitations will be discussed in the report/paper.

6.3. 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.

6.4. 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 by vaccination programmes.

- Previous immunity: outcomes observed in one season may depend on previous vaccination and/or previous infections.

Limitations will be discussed in the report/paper.

7. Ethical aspects

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

8. Communication

The results from these analyses will form Deliverable D2.19, as part of the EU's Horizon 2020 research and innovation programme (grant agreement No 634446): a joint study site final influenza vaccine impact report. The report is due to be finalised in September.

Study sites agreed that they would attempt to write an article resulting from the report.

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10. Annex 1: Example on how to use Stata to calculate weighted 95% confidence intervals

The table below shows how the data could be organised. This should be the database in Stata.

type	weight	VE	95%lower	95%upper	or	orlower	orupper
A(H3)	0.013	0.23	0.032	0.387	0.77	0.968	0.613
A(H1)pdm09	0.904	0.545	0.38	0.64	0.455	0.62	0.36
B	0.085	0.457	0.242	0.611	0.543	0.758	0.389

You can then use the metan command using user-defined weights :

metan or orlower orupper, wgt(weight)

Study	ES	[95% Conf.	Interval]	% Weight
1	0.770	0.613	0.968	1.30
2	0.455	0.360	0.620	90.22
3	0.543	0.389	0.758	8.48
* pooled ES	0.467	0.348	0.585	100.00

The pooled ES is the OR that you change into VE and use in the calculations.

Annex 2: Stata script to take uncertainty around estimates into account, developed by Irina Kislaya from INSA Portugal

The script below can be pasted into a Stata do-file and run. Please note that the highlighted section needs to be adapted for hospitalisation and mortality analysis.

```
* Monte Carlo simulation (CI 95% for adverted events)
capture program drop mcsim
program define mcsim, rclass
  drop _all

  *define number of observed events (GP consultations, Hospitalizations etc)
    local f = 1207

  * define Vaccine Effectiveness and respective confidence intervals limits
  local ve=0.601
  *lower limit
  local velb=-1.305
  *upper limit
  local veub=0.931

  * define Vaccine coverage and respective confidence intervals limits
  local vc = 0.501
   *lower limit
  local vclb = 0.421
  *upper limit
  local vcub = 0.581

  * transform VE and VC according to Foppa et all and calculate SE
  local vet =log(1-`ve')
  local vese = (log(1-`velb')-log(1-`veub'))/(1.96*2)

  local vct=log(`vc'/(1-`vc'))
  local vcse = (log(`vcub'/(1-`vcub'))-log(`vclb'/(1-`vclb')))/(1.96*2)

  *determine number of observations use in simulation
  set obs 10000

  *generate parameters from assumed distributions
       * needs to be adapted for mortality and hospitalisation
gen a = rpoisson(`f')
gen b = rnormal(`vet', `vese')
gen c = rnormal(`vct', `vcse')

* re-transform back
gen effectivness =1-exp(b)
gen coverage=exp(c)/(1+exp(c))

*calculate adverted events
gen adverted=a*effectivness*coverage/(1-(effectivness*coverage))

* calculate CI for adverted events, VC and VE
centile   adverted coverage effectivness, centile(2.5 50  97.5)

end

set seed 446655
mcsim
hist adverted
```