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Population-level impact of Pneumococcal Conjugate Vaccines in older adults

Generic protocol for impact analysis on pneumonia

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Document prepared by I-MOVE+ partners involved in pneumococcal vaccines studies from WP3 and WP4, coordinated by THL and EpiConcept.

Adapted in parts from the I-Move+ Generic Protocol to measure PCV impact on pneumonia in adult population using pre-post comparison.

Version history:

Version number	Date	Type document	Comments
V1.0	6 Oct 2017	Original document	
V2.0	14 Dec 2017	Updated document	Updated to cover before-after analysis with and without trend adjustment. Unspecified pneumonia was added to outcomes. Control conditions were complemented with other conditions (e.g. urinary tract infections).

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List of abbreviations

Ag	Antigen, referring to the laboratory method to detect *Streptococcus pneumoniae* antigen
AMS(NS)	Antimicrobial susceptibility or non-susceptibility according to context
CAP	Community acquired pneumonia
CSF	Cerebrospinal fluid
EARS-net	European Antimicrobial Resistance Surveillance Network
EC	European Commission
ECDC	European Centre for Disease Prevention and Control, Stockholm, Sweden
EU/EEA	European Union/European Economic Area
ICU	Intensive care unit
IPD	Invasive Pneumococcal Disease
MS	Member States
OR	Odds Ratio
NIP	National Immunisation Plan
NRC	National Reference Centre for Pneumococci in a country
PCR	Polymerase Chain Reaction
PCV	Pneumococcal conjugate vaccine (according to the number of serotypes covered: PCV7, PCV10, PCV13)
PPV23	Pneumococcal polysaccharide vaccine 23-valent
SAGE	WHO Strategic Advisory Group of Experts
Sp	Streptococcus pneumoniae
VE	Vaccine Effectiveness
VI	Vaccination Programme Impact
WHO	World Health Organization

Glossary

Term	Definition
Antimicrobial susceptibility	In this context, used as the capacity of antibiotic/antimicrobial treatment to successfully inhibit the bacterial growing, according to clinical breakpoints of the standards used
Antimicrobial non-susceptibility	Intermediate susceptibility or resistance to an antimicrobial as defined by the standards used
CAP	Community Acquired Pneumonia
CLSI	Clinical and Laboratory Standards Institute, international standards that describe the methods and clinical breakpoints for antimicrobial susceptibility testing
Completeness of the surveillance system	The proportion of all cases with no missing variable or information
Comprehensive surveillance system	A population-based surveillance system implying notifications from all possible reporting sites
Coverage of the surveillance system	The proportion of the population effectively under surveillance compared to the total population of the country
EUCAST	European Committee on Antimicrobial Susceptibility Testing, European standards for antimicrobial susceptibility testing (http://www.srga.org/Eucastwt/eucastdefinitions.htm)
Herd immunity	The proportion of subjects with immunity in a given population where a vaccine is offered [John, Eur J Epidemiol 2000]
Herd effect	The reduction of infection or disease in the unimmunised segment as a result of immunising a proportion of the population[1]
ICD	International Statistical Classification of Diseases and Related Health Problems, used as discharge diagnostic codes or for coding causes of death. The 9th or 10th revision are currently used in most countries
Impact of a vaccination programme	The measure of effects of a specific vaccination programme in a specific population, which include overall, indirect and total effect against the target disease
IPD	Invasive pneumococcal disease, defined as isolation of *Streptococcus pneumoniae* or the detection of *Streptococcus pneumoniae* nucleic acid or antigen from a normally sterile side
MIC	Minimum inhibitory concentration, a method for antimicrobial susceptibility testing

Term	Definition
MLST	Multilocus sequence typing
Sentinel surveillance system	A surveillance system that involves collecting data from a sample of reporting sites
Sensitivity (of the surveillance system)	The proportion of cases reported by the surveillance system out of the total number of cases meeting the same case definition in the entire population. Also called the degree of ascertainment or the exhaustiveness of the surveillance system
Surveillance site	Surveillance system (in a country) participating in the I-MOVE+ project.
Surveillance unit	Hospital/laboratory reporting cases to a surveillance site included in the I-MOVE+ project
Vaccination coverage	The proportion of the eligible population which is effectively vaccinated. Vaccine coverage should be defined by schedule (number of doses or complete schedule)
Vaccination registry	Electronic database where vaccination data are recorded. It usually includes patient unique identifier; age; sex; vaccine type; vaccination date; vaccine brand/ manufacturer; vaccine lot number
VE	Vaccine effectiveness, defined as the measure of the direct effect of vaccination against target disease when used under field conditions

1 Introduction

1.1 *Streptococcus pneumoniae* and pneumococcal vaccines

Streptococcus pneumoniae is a Gram-positive diplococcus bacterium causing a wide spectrum of illness either by invading the bloodstream or by mucosal contiguity. Based on capsule polysaccharide composition, almost 100 serotypes of *Streptococcus pneumoniae* have been identified. These serotypes differ not only in prevalence by area and over time but also in pathogenicity and age distribution.

Invasive pneumococcal disease (IPD), defined as the isolation of *Streptococcus pneumoniae* or the detection of nucleic acid or antigen of *Streptococcus pneumoniae* from a normally sterile fluid, may present different clinical conditions such as meningitis, bacteraemic pneumonia, bacteraemia without focus, septic shock, and other less frequent conditions such as arthritis, peritonitis, etc. Transmitted by contiguity to middle ear, sinuses or other locations of the respiratory tract, *Streptococcus pneumoniae* can also cause non-invasive diseases such as acute otitis media, sinusitis or pneumonia. *Streptococcus pneumoniae* nasopharyngeal colonization, particularly in young children, represents the main reservoir of pneumococci and the primary means of transmission to susceptible individuals. As recent acquisition of *Streptococcus pneumoniae* in nasopharynx is thought to precede episodes of pneumococcal disease, carriage plays a key role in the epidemiology of pneumococcus.

Two major groups of vaccines are currently available to protect against *Streptococcus pneumoniae*: polysaccharide vaccine (23-valent vaccine - PPSV23) and more recently pneumococcal conjugate vaccines (PCVs). PPSV23, licensed in 1983, is generally recommended for use in the elderly as well as adults and children ≥2 years with underlying medical conditions (risk groups) [WHO position paper 2012]. Pneumococcal conjugate vaccines [WHO PPV23 vaccine position paper 2008] (PCV7, PCV10 and PCV13) covering the 7, 10 and 13 serotypes most frequently causing IPD in developed countries during pre-vaccine era, were licensed in the European Union (EU) in 2001 (PCV7), and in 2009 (PCV10 and PCV13) for the use in children under five years old, with PCV10 and PCV13 replacing PCV7. PCV13 was approved for use in adults in 2011, and in children up to 17 years in November 2012. Currently, PCV13 is licensed for prevention of invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* in infants, children and adolescents from 6 weeks to 17 years of age, as well as for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in adults ≥18 years of age and the elderly [EMA Prevnar 13]. Most EU countries have introduced PCV vaccines for routine infant vaccination, but vaccination policies widely vary across member states in terms of vaccine (PCV 10/13), dose schedule (2+1 or 3+1 doses) and target groups (risk groups only or universal vaccination) [ECDC survey report 2013, ECDC&Venice II 2012].

1.2 Definition of vaccination effects

In epidemiology, effect is the amount of change in a population's disease frequency caused by a specific factor. Absolute effects are differences in incidences rates, incidence proportions, prevalence, or incidence time. Relative effects involve ratios of these measures [Rothman 2002]. Effects in vaccinology measure various absolute or relative changes in incidences observed between populations exposed and not exposed to an intervention (vaccination).

For the purpose of this document, the following terms will be used, based on Halloran [Halloran et al. 2010] description of vaccination effects (Figure 1).

1.2.1 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).

1.2.2 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. For age-group-specific estimates, the age-groups of interest can vary according to time since introduction of vaccination. For example, unless a catch up campaign is conducted, two years after vaccination, the indirect effect can be measured by comparing outcome rates in those older than two years before and after the introduction of the vaccination programme. Three years after vaccination, the comparison can be made among those aged more than three years; and so on.

1.2.3 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).

For the purpose of this document, the term "impact" refers to overall, indirect and total effect of vaccination as the term "effectiveness" refers only to the direct effect of vaccination under field conditions [Hanquet et al. 2013].

1.3 Rationale

A total of 1.6 million deaths due to pneumococcal disease occur annually worldwide among all ages [WHO the global burden of disease 2004 update]. Despite the herd effects from routine infant PCV introduction, substantial burden of pneumococcal disease remains in older adults.

This protocol presents a generic approach for conducting PCV impact studies on pneumonia among older adult population by using the before and after design with hospital discharge data bases in Europe.

2 Background of the protocol

I-MOVE+ project is part of the EC work programme PHC 17 – 2014: “Personalising health and care”, “Comparing the effectiveness of existing healthcare interventions in the elderly”.

The objectives of the I-MOVE+ network are to identify, pilot test, use, and disseminate in and beyond the EU the best study designs to measure, in near real time the effectiveness and impact of vaccines used in the elderly population to prevent influenza and pneumococcal infections.

As part of I-MOVE+, we measure the impact of available pneumococcal vaccines against IPD and CAP in the elderly population in order to determine the best study designs and data sources to provide evidence for informing public health actions at regional, national and supranational levels.

This generic protocol will be adapted to the specific context of each partner site.

The following information for the specific study setting should be reviewed and provided:

- date of introduction of the vaccine(s) in routine infant vaccination programmes and among the elderly (PPSV23 and/or PCV13);
- vaccination schedules for children and/or adults;
- target groups for vaccination (universal/ risk group);
- estimated vaccination coverage;
- data sources for pneumococcal disease outcomes (i.e. hospital discharge registries);
- sources to document different factors that may influence the results interpretation;
- ethical/ consent requirements;

► *Each study site will provide a description of the specific background for the country/region: introduction of vaccine(s), calendar, vaccination coverage, organisation of the hospital discharge register (reporting flow, data collected, reports on evaluations, possible changes in register maintaining, diagnose practices etc., any references of published articles, etc.).*

3 Objectives

3.1 Overall objective

To estimate the population-level impact of pneumococcal conjugate vaccination programmes on community acquired pneumonia (CAP) burden among adults 65 years of age and older. This will be accomplished by comparing population-based rates of all-cause pneumonia and SpCAP before and after conjugate vaccine introduction (pre-PCV7 or PCV7 periods vs. PCV10/13 period) for comparing the estimated and expected pneumonia rates during PCV10/13 period at each study site.

- *Each study site to specify the effect measure to be used. According to the recommendation and uptake of PCV13 in older adults at each study site, the overall and/or indirect effect of vaccination programmes will be measured.*

3.2 Specific objectives

Estimate the reduction in the incidence among older adults ≥65 years of age by comorbidity groups.

4 Methods

4.1 Study design

Population-based before and after study, comparing pneumonia rates during the PCV10/13 period with pre-PCV/PCV7 periods, with or without pre-PCV/PCV7 trend adjustment. The periods before introduction of the PCV10/13 vaccination (pre-PCV and PCV7 periods) will be considered for reference periods.

The trend adjustment will be performed by using interrupted time-series design, where the estimated PCV10/13 trend is compared to the expected trend predicted using pneumonia incidence during the pre-PCV/PCV7 period.

4.2 Study setting

The available hospital discharge data sources and databases as well as population registries will be used.

- *Each study site to define the study setting according to the data sources or the organisation of the reporting system for pneumonia;*
- *Description of the hospital discharge registry: number of participating units, proportion out of the total number of existing institutions (e.g. participating hospitals/ total number of hospitals); representativeness of the reporting of pneumonia cases in the 65 years and older population.*

4.3 Study population

The study population comprises all (community dwelling) individuals ≥65 years of age who are residents of the catchment area of the hospitals.

► *Each study site to state the study population (65 years of age and older).*

4.4 Study period

The study period depends on the date when PCV was introduced in the country or when the hospital discharge register was set up. Efforts should be made to extract data for sufficiently long reference (baseline) periods to account for changes in medical and diagnostic practices.

4.4.1 Definitions of periods before and after the PCV introduction

Pre-PCV period: XX (calendar) years (at least two) before introduction of the PCV vaccine in the country or beginning of universal infant PCV vaccination programme (the number of years will depend on the data available). Note that a longer pre-PCV baseline period allows a better assessment of secular trends.

PCV7 period (where applicable): XX years before introduction of infant PCV10/13 vaccination programme in countries in which PCV7 vaccination was available (the number of years will depend on the data available).

Post-PCV10/13 period: years starting from infant PCV10/13 introduction in the country.

Transitional periods: In countries where the PCV vaccine was introduced progressively, the first year(s) in which the vaccine was available but low vaccination coverage (i.e. <40%) was achieved may be considered as "transitional period" between periods with no vaccine available and periods with high vaccine coverage (i.e. years with vaccine available prior to universal introduction).

► *Each study site to describe the study periods: pre-PCV, PCV7, transition, post-PCV10/13 periods. The most years included in the pre-PCV period, the better the secular trends could be taken into account in the interpretation of the results.*

4.5 Outcomes

The primary outcomes of interest are all-cause pneumonia, SpCAP and non-specific pneumonia according to the ICD codes (Annex 1).

Secondary outcomes may include:

1. Primary outcome cases by comorbidity high risk group (high risk immunocompromised, high risk immunocompetent, no high risk conditions, other chronic illness conditions – site specific)

4.5.1 Case definitions

Clinical criteria

Described in Annex 1

Laboratory criteria

Not relevant

Epidemiological criteria

NA

Case classification

A. Possible case

NA

B. Probable case

NA

C. Confirmed case

Not relevant

4.5.2 Episode definition

In hospital discharge data, multiple records within a short time period are often related to same episode and should therefore be combined. With regard to pneumonia, a 90 day period is often used.

► *Each study site to state the case and episode definitions for primary and secondary outcomes according to data available.*

4.6 Data source and collection

4.6.1 Cases (numerator)

Data will be extracted from hospital discharge register according to ICD codes. Outcomes are defined in Annex 1. Monthly (or yearly) number of cases will be extracted and aggregated by age-group.

4.6.2 Denominator

Population data can be extracted from population statistics or birth registers in hospital catchment areas or available census results. Changes in population of the catchment area should be recorded.

Data collected for denominators includes population by age group and calendar year. If the study population is considered to be stable during a year, the annual census could provide the denominator.

4.7 Additional information to be collected for results interpretation

4.7.1 Vaccination coverage

Estimates of vaccination uptake can be obtained from vaccine sales or distribution, vaccination registries, or specific coverage surveys in the surveillance catchment areas. Vaccination coverage over time should be recorded in the target age group for PPSV23 and PCV13 (if recommended) as well as for childhood vaccination programmes (if possible annual coverage).

4.7.2 Other information

Interviews with experts can be conducted to gain information on medical practices (case management protocols, diagnosing practices) or site-specific particularities (e.g. outbreaks, vaccine trials) etc. These data may not be directly analysed, but will help in the interpretation of results by explaining possible variations in trend.

► *Each study site to specify data to be extracted and the source for numerator, denominator, vaccination coverage and additional information gathered.*

4.8 Data management

► *Each study site to describe all procedures for data management:*

- Who extracts data?
- Who validates data and how?
- How, by whom and when are data stored?
- Who links databases?
- How are data extracted?
- Who analyses data?
- Softwares used?

4.9 Sample size

The studies will require sufficient power to detect the impact of PCV vaccination. The achievable power of each study should be calculated taking into account the following parameters (Figure 3):

- the observed rate of the selected outcome in the reference period (pre-PCV/PCV7)
- the expected effect to be detected
- an alpha error of 0.05
- a power of 80% or 90%

If the achievable sample size is too low to assure representativeness of the data and meaningful results, the study should be reconsidered.

On the next page, power calculations are presented for more specific pneumococcal disease outcomes such as pneumococcal pneumonia or invasive pneumococcal disease (10-110/100,000 person-years). Incidence of all cause pneumonia is much higher, which means that the studies estimating vaccine impact on all cause pneumonia are usually powered to correctly reject the null hypothesis of no impact, with available population sizes.

However, impact studies using non-specific outcomes such as all cause pneumonia rarely can identify an effect when it is small. There is a dilution of the effect; any change can be due to a change in non-pneumococcal pneumonia.

► *Each study site to estimate the power of the study, if relevant with respect to outcomes used.*

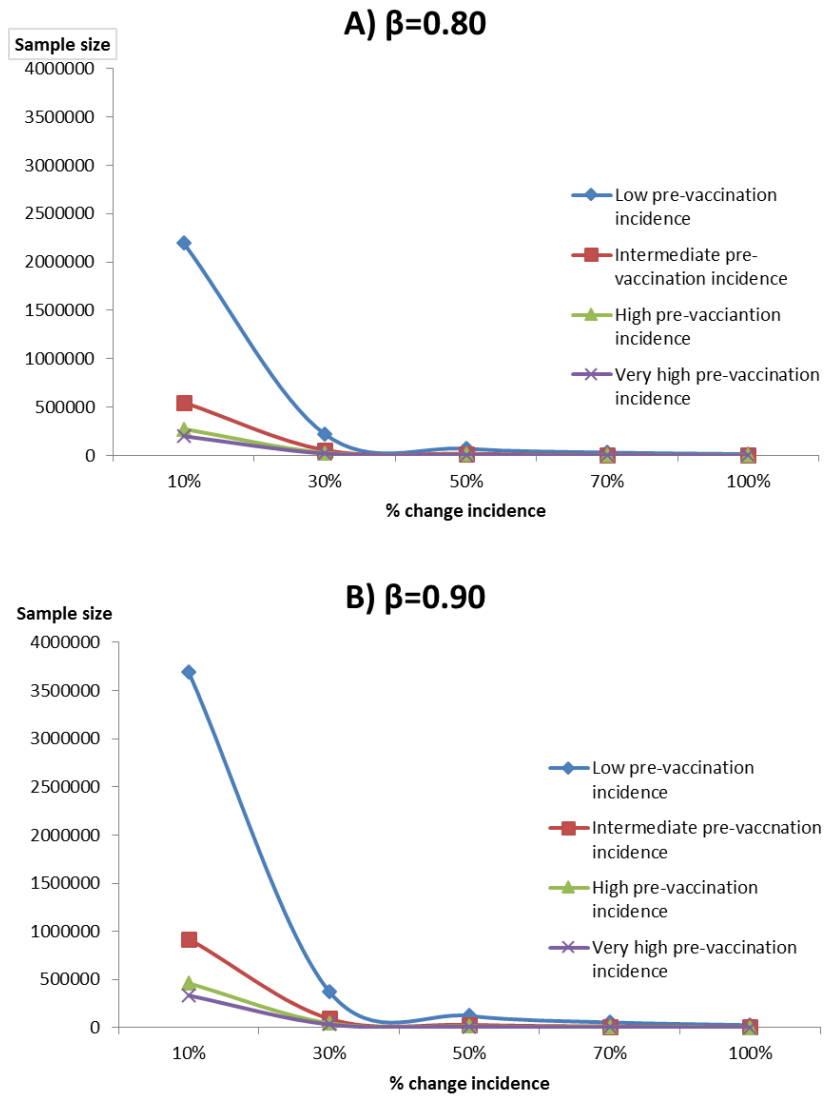

Figure 3: Sample size calculation taken into account the pre-PCV incidence of invasive pneumococcal disease (low=10/100,000, moderate=40/100,000, high=80/100,000, very high=110/100,000), percentage change to be reached with different power scenarios (A)β=0.8 and B)β=0.9)

5 Analysis

5.1 Data checking

Data will be collected on reported pneumonia cases. Data will be checked to find outliers, implausible or missing information. As much as possible, data should be completed or validated against the data source.

► *Each study site to describe data checking.*

5.2 Descriptive analysis

Pneumonia cases will be described by time period and age group. Baseline characteristics by periods will be compared using the chi-square test, Fisher's exact test, t-test or the Mann-Whitney test (depending on the nature of the variable and the sample size) if individual data provided.

Incidence by period will be calculated according to the data available from data base:

- Numerator = pneumonia cases by month/calendar year, age group
- Denominator = population in the study catchment area by year, age group
- Graph presentation of yearly number of cases or incidence is recommended. If a long time period is available, smoothing procedures using 52 weeks moving average to describe long term trends may be used.

► *Each study site to present the descriptive analysis plan.*

5.3 Measure of impact

The methods used for comparing IPD rates between reference periods and post-PCV10/13 years depend on available data and should be specified for each study site. The impact (see also Hanquet et al. 2013) may be reported as:

- the reduction in the cumulative incidence or rate in the post-PCV10/13 period compared with the reference periods, expressed as rate/risk difference with the corresponding 95% CI;
- the relative reduction in the incidence proportion or rate in the post-PCV10/13 period compared to the reference periods, expressed as a percentage change in incidence or an incidence rate/risk ratio with the corresponding 95% CI.
- the reduction in the mean number of cases in the post-PCV10/13 period compared with the reference periods, expressed as absolute numbers or percentage change in the number of cases with corresponding 95% CI;

With interrupted time series method, the impact of PCV10/PCV13 may be reported as:

- the change in the cumulative incidence or rate in the post-PCV10/13 period compared with the expected cumulative incidence or rate during the same time period, had the vaccine not been introduced in the programme, expressed as rate difference with the corresponding 95% CI;
- the relative change in the incidence or rate in the post-PCV10/13 period compared to the expected incidence or rate during the same time period, had the vaccine not been introduced

in the programme, expressed as a percentage change in incidence or an incidence rate ratio with the corresponding 95% CI.

On the basis of estimates of pneumococcal vaccination uptake among individuals 65 years of age and older, we can describe:

- an overall effect: the measure of impact in the age group ≥65 years of age in a population where a proportion of people in this age group and in the paediatric age group is vaccinated with PCV10/13 compared with the expected cumulative incidence or rate during the same time period, had the vaccine not been introduced in the programme;
- indirect effect: the measure of impact of infant conjugate vaccination programme among persons ≥65 years of age in the absence of direct PCV13 vaccination programme in older adults, compared with the expected cumulative incidence or rate during the same time period, had the vaccine not been introduced in the programme.

► *Each study site to describe the measure of impact that will be reported.*

5.4 Interrupted time-series method

Monthly or yearly incidence rate of pneumonia will be modelled with a Poisson regression model with an offset term representing the population size of each time point. To take into account the possible over-dispersion between observations, a negative binomial model can be also used. In the model, there are terms for baseline rate in the beginning of the study, pre- and post-vaccine trends, and possibly for the change in trend level.

As pneumonia incidence fluctuates from season to season being high during winter months and low during summer, this variation can be modelled. For example, a categorical term representing a calendar month, or a Fourier term, can be included.

In time series data, consecutive observations tend to be more similar to one another than those that are further apart. Autocorrelation will largely be explained by other variables (seasonality, trend), but it should be assessed with plot of residuals and the partial autocorrelation function.

After fitting the full model, the expected rate (counterfactual) in post-vaccination period, had the vaccine not been introduced, will be estimated using the data from pre-vaccination period. The vaccine impact will be the ratio (IRR, incidence rate ratio) or difference (IRD, incidence rate difference) of the expected and estimated rates during the post-vaccination period.

Confidence intervals around incidence rate ratio or incidence rate difference should be estimated taking into account the possible covariance between estimated and expected rates; for example bootstrapping or delta method can be used [Feikin PlosMed 2013, Zhang 2009].

► *Each study site to specify the methods used for calculation of the impact and confidence intervals.*

5.5 Pooled analysis

Monthly aggregated data will be shared for conducting a pooled analysis, using the Table 1 format. If feasible, and dependent on data quality, these data may be analysed to compute pooled impact measures.

► *Each study site to prepare the data for submission according tables 2 and 3.*

6 Limitations

6.1 Study design and related

In studies comparing pre and post intervention, the main limitation is that the effect measured can be due to other factors not related to vaccination. Therefore, different factors should be considered, such as:

- secular trends
- changes in medical practices and in health seeking behaviour
- other factors that may influence pneumonia incidence

Efforts to collect information on all the potential factors that can explain the changes should be described.

► *Each study site to describe changes in the reporting, medical practice that may have occurred in the study period. If possible, pre-vaccination trends should be identified and taken into account in the interpretation of measures of impact.*

6.2 Sample size

If achieved sample size does not meet the planned one, large confidence intervals will limit the possible interpretation of results. In this case, several years need to be aggregated in order to reach a sufficient number of cases for precise results.

► *Each study site to describe the limitations related to the sample size.*

6.3 Pre-existing vaccination

PCV vaccination may have begun earlier in some regions or a country, and certain coverage may have been achieved before the vaccine's universal introduction in a country. It is the case in the countries where the vaccine was first introduced for risk groups or recommended by professional associations or large clinical trials were conducted. Therefore these years should be included in the transition periods, analysed separately and taken into account in the result interpretation. Not taking into account the pre-existing vaccine use in the target population could lead to an underestimation of the impact of the vaccine.

► *Each study site to describe the limitations related to the pre-existing vaccination in the study area.*

7 Ethical approval

► *Each study site to describe the procedures to obtain the approval of the national / ethics committee if such approval is required according to national law.*

8 Human resources

The roles and responsibilities of the members of the investigation team should be described: principal investigator, assistant, data manager, etc.

► *Each study site to describe the team members' roles and responsibilities.*

9 References

John TJ, Samuel R. Herd immunity and herd effect: new insights and definitions. Eur. J. Epidemiol. 2000: 16 (7): 601–6. doi:10.1023/A:1007626510002. PMID 11078115

WHO, Pneumococcal vaccines – WHO position paper -2012, WER 2012; 14; 87:, 129–144

WHO, 23-valent pneumococcal polysaccharide vaccine WHO position paper – 2008, WER 2008; 83: 373–384

European Medicines Agency. Prevenar 13: EPAR – Product information. Annex I - Summary of product characteristics. 12/05/2015.

ECDC, Report of Survey for identifying potential study sites for active IPD surveillance in the EU/EAA, 2013.

ECDC and Venice II, Impact of childhood pneumococcal vaccination programmes and activities for pneumococcal vaccines in the EU and EEA \EFTA countries. Available from http://venice.cineca.org/VENICE_Survey_PNC_1_2012-02-24.pdf

Rothman KJ, Epidemiology – An introduction; Oxford University Press, 2002

Halloran ME, Longini Jr IM, Struchiner CJ. Design and Analysis of Vaccine Studies. Series: Statistics for Biology and Health 2010, XVIII, 389 p. Hardcover, ISBN 978-0-387-40313-7

Hanquet G, Valenciano M, Simondon F, Moren A. Vaccine effects and impact of vaccination programmes in post-licensure studies. Vaccine 2013; doi:10.1016/j.vaccine.2013.07.006

WHO. The global burden of disease: 2004 update. Geneva: World Health Organization; 2008.

Feikin DR et al. Serotype-Specific Changes in Invasive Pneumococcal Disease after Pneumococcal Conjugate Vaccine Introduction: A Pooled Analysis of Multiple Surveillance Sites. PLoS Med 2013

F Zhang et al. Methods for estimating confidence intervals in interrupted time series analyses of health interventions. J Clin Epidemiol, 2009

Palmu AA et al. Pneumococcal Conjugate Vaccine and Clinically Suspected Invasive Pneumococcal Disease. Pediatrics 2015: 136(1), pp. e22 -e27. doi: 10.1542/peds.2015-0458 http://pediatrics.aappublications.org/content/136/1/e22.long

Table 1: Data to be collected for pooled analysis

Site: _____ **Age group**: ☐ ≥65 years ☐ 65-69; ☐ 70-74; ☐ 75-79 years; ☐ 80-84 years; ☐ ≥85 years

Coverage and population data can be provided annually. Case numbers can be provided monthly (preferably) or annually.

Variable	Years*	**Pre-vaccination** (please add additional years if needed)						**Post-vaccination PCV7** (please add additional years if needed)			**Post-vaccination PCV10/13** (please add additional years if needed)		
		Year 6 Jan	Year 6 Feb	…	Year 1 Jan	Year 1 Feb	Year 1 Dec	Year 1 Jan	Year 1 Feb	Year … Dec	Year 1 Jan	Year 1 Feb	Year… etc
Year													
PCV Vaccine	PCV7, PCV10 or PCV13	NA	NA	NA	NA	NA	NA						
PCV coverage	Percentage vaccination	NA	NA	NA	NA	NA	NA						
PPV23 vaccine	PPV23 recommendation Yes/No; if yes, high risk, all elderly												
PPV23 coverage	Percentage vaccination												

Population	Number of inhabitants in the age group												
All-cause pneumonia	Number of cases												
Pneumococcal pneumonia	Number of cases												
Unspecified pneumonia	Number of cases												
All-cause hospitalizations (comparison group)	Number of cases												
Other control conditions (e.g. urinary tract infections)	Number of cases												

Annex 1: Impact analysis of pneumococcal vaccines using register-based data

Overview

For impact analyses, data from hospital discharge registries can be used to measure changes in register-based pneumonia. Cases will be extracted using the following case definitions.

Outcomes

Three outcomes (depending on feasibility) will be used**:**

1. Pneumococcal pneumonia
2. All cause pneumonia (only primary discharge diagnoses)
3. Unspecified pneumonia

All-cause hospitalizations and other control conditions (e.g. urinary tract infections) will serve as a comparison groups according to feasibility.

Episode definition

If possible, an episode definition of 90 days will be used for pneumonia outcomes. An episode starts from index notification with pneumonia-related ICD-9/10 code and all care notifications within 90 days are combined into one episode; the next pneumonia episode of the person can start only 90 days after the first index notification. If an ICD-9/10 code related to pneumococcal pneumonia appears somewhere during an episode, the episode will be labelled as pneumococcal pneumonia. Otherwise, it will be considered as all cause or unspecified pneumonia.

Table 1.1. Pneumococcal pneumonia

ICD-9 Code	ICD-10 Code	Diagnosis in Text
481	J13	Pneumonia due to *S. pneumoniae*

Table 1.2. All-cause pneumonia

ICD-9 Code	ICD-10 Code	Diagnosis in Text
487.0, 480	J10.0, J11.0, J12.0-12.3, J12.8-12.9, J17.1	Viral pneumonia
481, 482 (except for 482.89), 483.1	J13, J14, J15.0-15.8, J16.0, J17.0	Bacterial pneumonia (specified)

483.2, 484.7, 484.8	J16.8, J17.2, J17.3, J17.8	Pneumonia due to fungal, parasitic, or other infectious disease
482.9	J15.9	Bacterial pneumonia, unspecified
485	J18.0-18.2	Bronchopneumonia, unspecified; lobar pneumonia, unspecified; , hypostatic pneumonia, unspecified
486	J18.8-J18.9	Other pneumonia, organism unspecified; pneumonia, unspecified
510	J86	Pyothorax (Incl. Empyema)

Table 1.3. Unspecified pneumonia

ICD-9 Code	ICD-10 Code	Diagnosis in Text
486	J18.8-J18.9	Other pneumonia, organism unspecified; pneumonia, unspecified

► *Each study site to describe the ICD codes and episode definitions used for outcome conditions. All sites should provide for each code percentage of all diagnoses in reference cohorts as described in Palmu et al 2015.*