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Generic protocol for studies on vaccine effectiveness against Invasive Pneumococcal Disease and/or Pneumococcal Community Acquired Pneumonia using the indirect cohort method in the European Union/European Economic Area

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Version history:

Version number	Date	Type document	Comments
V1.0	31 Jul 2015	Original document	Document submitted for partners' comments and to EC as part of deliverable D3.1.
V2.0	30 Oct 2015	Original document	Document including partners' comments and decisions of the First technical meeting (Copenhagen, Sep 2015). This version was used as basis for site specific protocols and submitted as part of deliverable D3.2.
V2.1	15 Dec 2016	Amendment	Version amended with the decisions of the second technical meeting (Paris, September 2016) on definitions of underlying conditions based on ICD codes, IPD clinical manifestations categories.
V2.2	15 Dec 2017	Amendment	Version amended with further clarifications on minimum set of underlying conditions to be collected for effectiveness studies (decision of the Utrecht technical meeting, 2-3 Oct 2017)

Contents

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)
PPSV23	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
EUCAST	European Committee on Antimicrobial Susceptibility Testing, European standards for antimicrobial susceptibility testing (http://www.srga.org/Eucastwt/eucastdefinitions.htm)
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 the effects of a specific vaccination programme in a specific population, which include indirect, total and overall 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 site
MIC	Minimum inhibitory concentration, a method for antimicrobial susceptibility testing
PCV7	7-valent pneumococcal conjugate vaccine
PCV10	10-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PPSV23	23-valent pneumococcal polysaccharide vaccine
Sentinel surveillance system	A surveillance system that involves collecting data from a sample of reporting sites
Surveillance/study site (country)	Surveillance system (in a country) that participating to the EU/EEA project. The term “surveillance site” with no other mention refers to a country involved in this ECDC project
Surveillance/study site	Regional surveillance system in a country that are participating to the EU/EEA project and are included in the respective country surveillance site.
Surveillance unit	Hospital/laboratory reporting cases to a surveillance site included in the 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)

Term	Definition
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

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, more than ninety serotypes *of Streptococcus pneumoniae* have been identified. These serotypes differ not only in prevalence by area and over time, but also in pathogenicity, clinical presentation 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, represent 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. The pneumococcal carriage is lower in adults without children (estimated 5-10% in the US), but can be higher in the institutionalised individuals[1] Few European studies presented a low carriage rate in the elderly (2.3% in Portugal[2], 5.3% in Finland, 6% in Dutch elderly with ILI, being dependent on the detection method and type of the sample[3]).

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)[4]. Pneumococcal conjugate vaccines[5] (PCV7, PCV10 and PCV13) covering the 7, 10 and 13 serotypes most frequently causing IPD in developed countries during pre-vaccine era (Table 1), 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

[1] Centers for Disease Control and Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. Hamborsky J, Kroger A, Wolfe S, eds. 13th ed. Washington D.C. Public Health Foundation, 2015

[2] Almeida ST, Nunes S, Santos Paulo AC, Valadares I, Martins S2 Breia F, Brito-Avô A, Morais A, de Lencastre H, Sá-Leão R. Low prevalence of pneumococcal carriage and high serotype and genotype diversity among adults over 60 years of age living in Portugal. PLoS One. 2014 Mar 6;9(3):e90974. doi: 10.1371/journal.pone.0090974. eCollection 2014.

[3] Palmu AA, Kaijalainen T, Saukkoriipi A, Leinonen M, Kilpi TM Scand J Infect Dis. Nasopharyngeal carriage of Streptococcus pneumoniae and pneumococcal urine antigen test in healthy elderly subjects. 2012 Jun;44(6):433-8. doi: 10.3109/00365548.2011.652162. Epub 2012 Jan 21.

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

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

of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in adults ≥18 years of age and the elderly[6].

PCV10 and PCV13 were approved on the basis of immunogenicity data. Most EU countries have introduced PCV vaccines in children, 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 in children). The introduction of the PCV13 vaccination in the elderly is still under evaluation in many EU/European Economic Area (EEA) countries.

Table 1: *Streptococcus pneumoniae* serotypes included in different vaccines

Vaccine	Serotypes
PCV7	4, 6B, 9V, 14, 18C, 19F, 23F
PCV10	PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) and 1, 5, 7F
PCV13	PCV10 serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F) and 3, 6A, 19A
PPSV23	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F

1.1 Rationale

A total of 1.6 million deaths due to pneumococcal disease among all ages occur annually worldwide[7]. After the decrease in IPD incidence in children due to PCV introduction, the burden of pneumococcal disease lays now in the elderly.

PCV13 is likely to provide better protection against IPD and pneumococcal pneumonia presenting different immunogenic properties[8] than PPSV23. CAPITA study was a randomised, double-blind clinical trial including 84,496 elderly ≥65 years in the Netherlands[9]. CAPITA compared PCV13 to placebo for the prevention of a first episode of vaccine-type (VT) Sp CAP (primary objective), first episode of nonbacteriemic/noninvasive VT Sp CAP and a first episode of VT-IPD[10]. The PCV13 efficacy for the first episode VT-Sp CAP was 45.56% (95%CI: 21.82%-62.49%, p=0.0006), 45.00% (95%CI: 14.21%-65.31%, p=0.0067) for nonbacteriemic/noninvasive VT SpCAP and 75.00% (95%CI 41.43%-90.78%, p=0.0005) for the first episode of VT-IPD. No efficacy for all cause CAP (5.1%; 95%CI:−5.1 - 14.2) or confirmed deaths

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

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

[8] Bonten, M., Bolkenbaas, M., Huijts, S., Webber, C., Gault, S., Gruber, W., and Grobbee,D., 12-3-2014. Community acquired pneumonia immunisation trial in adults (CAPiTA). Pneumonia, volume 3: ISPPD special issue. Page 95.

[9] Bonten MJ, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, van Werkhoven CH, van Deursen AM, Sanders EA, Verheij TJ, Patton M, McDonough A, Moradoghli-Haftvani A, Smith H, Mellelieu T, Pride MW, Crowther G, Schmoele-Thoma B, Scott DA, Jansen KU, Lobatto R, Oosterman B, Visser N, Caspers E, Smorenburg A, Emini EA, Gruber WC, Grobbee DE. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015 Mar 19;372(12):1114-25. doi: 10.1056/NEJMoa1408544.

[10] Pfizer Press Relase March 12, 2014. Available on http://www.pfizer.com/news/press-release/press-release-detail/pfizer_presents_detailed_results_from_landmark_community_acquired_pneumonia_immunization_trial_in_adults_capita_evaluating_efficacy_of_prevenar_13

due to neither VT SpCAP / VT IPD nor confirmed all type SpCAP/All type IPD were reported. However, CAPITA study was not powered to measure neither serotype specific VE nor VE for other outcomes.

Many aspects of PCV13 vaccination in adults still need to be answered:

- No efficacy shown for all cause CAP
  - 5% decline in all cause pneumonia consistent but not significant
- No efficacy shown for mortality
- Efficacy unknown for high risk patients
  - Immunocompromised
  - Institutionalized
  - Very old
- Duration of protection at least about 4 years
  - Need for revaccination?
- Real world effectiveness?
  - How can we distinguish direct PCV13 effects from indirect effects?

PPVS23 is still used in many European countries in the elderly, even though its efficacy against IPD and non-invasive pneumonia is controversial. A meta-analysis on PPSV23 efficacy reported a VE of 74% (OR 0.26, 95% CI: 0.15-0.46, I^2 = 0%) against IPD, 46% (OR 0.54, 95% CI 0.43 to 0.67, I^2 = 19%) against all-cause pneumonia in low-income countries and 29% (OR 0.71, 95% CI 0.45 to 1.12, I^2 = 93%) in high-income countries[11]. The latest literature overview that estimated PPSV23 effectiveness for preventing vaccine-type IPD in the 65+ years, suggested an average VE of 60% (range 40%-70%)[12]. The PPSV23 effectiveness varied according to immune-competency and decreased after 3-5 years.[13,14]

Pneumo2[15] survey was conducted under SpIDnet project between July-November 2013 among 30 EU/EAA countries to gather information on IPD surveillance, laboratory capacity and vaccination programmes. None of the 22 countries that filled in a PCV13 questionnaire had introduced the vaccination in adults at that time; however the latest data from ECDC show that seven countries recommend PCV13 in adults[16]. Among the 24 countries that filled in a PPSV23 questionnaire in 2013 survey, 10 stated PPSV23 was included in the national immunisation plan and three in the regional immunisation plan. In 12 countries it was recommended by professional associations and in 20 countries the vaccine was on the market. The target population for the PPSV23 vaccination were high risk groups for invasive pneumococcal infection (15 countries), elderly ≥65 years of age (six countries) or ≥60 years of age (one country).

[11] Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013 Jan 31;1:CD000422. doi: 10.1002/14651858.CD000422.pub3.

[12] Steens A, Vestrheim DF, Freiesleben de Blasio B. Pneumococcal vaccination in older adults in the era of childhood vaccination: Public health insights from a Norwegian statistical prediction study. Epidemics 2015: 11, 24–31

[13] Shapiro, E.D., et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. N. Engl. J. Med. 1991 : 325, 1453–1460

[14] Andrews, N., et al. Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. Vaccine 2012: 30, 6802–6808

[15] ECDC. Pneumo 2 survey report. A survey for identifying potential study sites for active IPD surveillance in the EU/EAA under SpIDnet project. Available from ECDC.

[16] ECDC VPD programme http://vaccine-schedule.ecdc.europa.eu/pages/scheduler.aspx

1.2 Study design

This protocol presents a generic approach for conducting vaccine effectiveness studies using the indirect cohort method (also called case only or Broome method) in the elderly. This method was first proposed by Broome et al[17] in early '80s to measure the effectiveness of PPSV vaccines. The design compares the vaccination coverage in IPD/ SpCAP cases due to vaccine serotypes to that of IPD/ SpCAP cases due to non-vaccine serotypes. Therefore, this design may be conducted only with data collected through the IPD/ SpCAP surveillance systems and provides a reliable estimate of vaccine effectiveness. However, this design is not appropriate to measure the VE against all type IPD/SpCAP or all cause CAP, and different designs need to be foreseen to answer questions related to these outcomes.

The design is based on the assumption that the vaccination coverage among the IPD cases due to non-vaccine serotypes is similar to the vaccination coverage in the source population giving rise to the IPD cases due to vaccine serotypes. This may be challenged if the vaccination is associated with a higher or a lower risk of getting non-vaccine serotypes. Two studies in the US[18] and UK[19], evaluated the potential bias introduced by the violation of this assumption when measuring the PCV7 vaccine effectiveness using data from US CDC ABCs and UK IPD surveillance systems in children. The results suggested that the bias that has been attributed to the violation of this assumption is low in the context of observational studies.

Other designs were discussed and proposed in a WHO manual[20] published in 2012 to help countries in their efforts to measure the impact of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b conjugate vaccination in children. A prospective matched density case-control study design was proposed as standard. In this study design, cases are identified through the IPD surveillance system and controls are selected among the hospitalised (or outpatient/community) children free of disease at the moment of the case hospitalisation (matching by hospital, age and date of admission). The design was successfully used in the US for measuring PCV7 effectiveness using CDC's ABCs data[21], and compared with the indirect cohort and screening methods.

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Member states are invited to adapt this Generic protocol for PPSV23/PCV13 effectiveness using the indirect cohort method to the local needs and capacities by developing site-specific protocols with the ultimate goal to improve the knowledge on the performance of available vaccines against invasive or non-invasive *Streptococcus pneumoniae* diseases in the elderly.

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[17] Broome CV, Facklam RR, Fraser DW. Pneumococcal disease after pneumococcal vaccination. An alternative method to estimate the efficacy of pneumococcal vaccine. N Engl J Med 1980; 303:549:-52

[18] De Serres G, Pilishvili T, Link-Gelles R, Reingold A, Gershman K, Petit S, Farley MM, et al. Use of Surveillance Data to Estimate the Effectiveness of the 7-valent Conjugate Pneumococcal Vaccine in Children Less Than 5 Years of Age over a 9 Year Period. Vaccine 30, no. 27 (June 8, 2012): 4067–4072

[19] Andrews N, Waight PA, Borrow R, Ladhani S, George RC, Slack MPE, Miller E. Using the Indirect Cohort Design to Estimate the Effectiveness of the Seven Valent Pneumococcal Conjugate Vaccine in England and Wales. *PloS One* 6, no. 12 (2011): e28435.

[20] WHO, Measuring impact of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b conjugate vaccination, WHO/IVB/12.08, September 2012

[21] Whitney CG, Pilishvili T, Farley MM, Schaffner W, Craig AS, Lynfield R, Nyquist AC, et al. Effectiveness of Seven-valent Pneumococcal Conjugate Vaccine against Invasive Pneumococcal Disease: a matched case-control study. *Lancet* 368, no. 9546 (October 28, 2006): 1495–1502.

2. Background of the protocol

The I-MOVE+ programme is a response to the 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+ consortium are to identify, pilot test, use, and disseminate in and beyond the EU the best study designs to measure the effectiveness and impact of vaccines used in the elderly population to prevent influenza and pneumococcal infections.

As part of I-MOVE+, we will measure the effectiveness of the available (PPSV23) and if it is the case, of the newly introduced vaccine (PCV13) in the elderly population in order to:

- estimate the level of individual protection and its duration against specific and non-specific pneumococcal disease outcomes;
- determine the best data sources to provide evidence for informing public health actions at regional, national and supranational levels.

The following information for the specific study settings should be described in the protocol:

- date of introduction of the vaccine(s): PPSV23 and/or PCV13 in the high risk groups, childhood and all ages vaccinations;
- type(s) of vaccine used and changes over time in the targeted age population;
- vaccination calendar in the elderly;
- target groups for vaccination and potential changes over time;
- estimated PCV and/or PPSV23 vaccination coverage by age group/risks group;
- IPD surveillance system as primary source of IPD related outcomes (i.e. laboratory surveillance, hospital surveillance, primary care surveillance), including serotyping; or hospital discharge data sets as a source for either IPD or pneumonia outcomes.
- sources to document vaccination status;
- sources to document potential confounding factors;
- ethical/ consent requirements.

► *Each study site to provide a brief description of the specific background for the study site: introduction of vaccine(s), calendar, vaccination coverage, etc.*

3. Objectives

3.1 General objective

To measure PPSV23 and/or PCV13 effectiveness against IPD or SpCAP due to vaccine serotypes in the elderly ≥65 years eligible for vaccination in the study site.

3.2 Secondary objectives

To measure the effectiveness of the PPSV23/PCV13:

- By age group among the elderly population, i.e. 65-74, 75–84 and ≥85 years
- By vaccine received: PCV13 or PPSV23 (if PCV13 recommended in the elderly population);
- Against specific vaccine serotypes, including vaccine related serotypes;
- Against different IPD clinical manifestations and SpCAP;
- Against different levels of IPD severity (ICU admission and/or length of hospital stay >14 days and/or presence of septic shock and/or intra-hospital death);
- Against antimicrobial non-susceptibility (by antibiotic tested);
- By time since vaccination.

► *Each surveillance site to adapt the above objectives to the data sources available in the country/region.*

4. Methods

4.1 Study design

Indirect cohort also called case only or Broome method.

4.2 Study setting

The study is embedded in the IPD surveillance system, using the same data sources and database.

► *Each study site to define the study setting according to the data sources: IPD surveillance system or hospital discharge databases;*

► *Description of the surveillance units used to recruit cases: hospitals, laboratories;*

► *Number of participating units, proportion out of the total number of existing institutions (e.g. participating hospitals/ total number of hospitals);*

► *Representativeness of the surveillance units reporting IPD or SpCAP cases in the elderly age groups.*

4.3 Study population

The study population comprises the elderly ≥65years eligible for vaccination and living in the catchment area of the laboratory/ hospitals participating in the already set up surveillance system, for whom information is collected for surveillance purposes.

► *Each study site to define the study population according to the date of PPSV23/PCV13 introduction (if the case), recommendations for vaccination according to age / high risk groups.*

4.4 Study period

The study period depends on the date when the PPSV23/PCV13 started to be available for the elderly population in the country/ region or the IPD surveillance system including the targeted age group was set up.

► *Each study site to describe the study period: start and end.*

4.5 Outcomes

The primary outcome consists of hospitalised IPD due to any of 13 vaccine serotypes included in the PCV13 or 23 vaccine serotypes included in PPSV23.

Secondary outcomes include:

- Hospitalised IPD cases due to both specific vaccine serotype and vaccine-related serotypes;
- Hospitalised [clinical manifestation] due to vaccine serotypes. In this context, clinical manifestation can be: pneumococcal meningitis, bacteraemic/non-bacteraemic pneumococcal pneumonia (includes empyema), pneumococcal bacteraemia and others clinical presentations;
- Hospitalised IPD cases of vaccine serotype non-susceptible to antimicrobials;
- Hospitalised severe IPD cases of vaccine serotype.

4.5.1 Case definitions

For the primary outcome, a case is a hospitalised person eligible for PPSV23 and/or PCV13 vaccination confirmed with an IPD according the ECDC case definition (below), in whom serotyping identified a vaccine serotype (PCV13 or PPSV23 IPD/SpCAP cases). The EC 2008 case definition should be used to recruit IPD cases[22] :

PNEUMOCOCCAL INVASIVE DISEASE(S) (*Streptococcus pneumoniae*)

Clinical criteria

Not relevant for surveillance purposes

Laboratory criteria

At least one of the following three:

- Isolation of Streptococcus pneumoniae from a normally sterile site
- Detection of Streptococcus pneumoniae nucleic acid from a normally sterile site
- Detection of Streptococcus pneumoniae antigen from a normally sterile site

Epidemiological criteria

NA

Case classification

A. Possible case
NA

B. Probable case
NA

C. Confirmed case
Any person meeting the laboratory criteria

For secondary outcomes, the case is defined as above for the primary outcome, and in addition:

- A specific vaccine serotype is identified (this can be a vaccine serotype or vaccine related serotype);
- A clinical manifestation is identified as: meningitis, pneumonia, bacteraemia and others;
- Severity is assessed according to: ICU admission and/or length of hospital stay >14 days and/or death within 30 days.

[22] European Commission, Commission Decision 2008/426/EC of 28 April 2008 amending Decision 2002/253/EC laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Council *(notified under document number C(2008) 1589)*

► *Each study site to state the case definitions for each primary and secondary outcome according to data collected.*

4.5.2 Reference group

The primary reference group comprises all persons ≥65 years eligible for vaccination, hospitalised for an IPD/SpCAP laboratory confirmed with a serotype identified as non-vaccine serotype (NVT, mainly nonPPSV23 controls) and excluding vaccine related serotypes. Cases with IPD/SpCAP due to vaccine related serotypes will be excluded from the analysis (i.e. serotypes from the same serogroups as the vaccine serotypes for which cross-protection was demonstrated or assumed).

For the secondary outcomes, the reference groups are the following:

- Specific vaccine serotype/ vaccine–related serotypes: NVT-IPD controls, same as for the primary outcome (see above);
- A [clinical manifestation]: NVT controls of the respective [clinical manifestation];
- Antimicrobial susceptibility: NVT controls in which antimicrobial susceptibility is investigated, and MIC provided (EUCAST thresholds will be taken into account for classification);
- Severe IPD cases: NVT-IPD controls admitted in the ICU / a length of hospital stay >14 days.

Matching

Matching can be an option when clustering by age, time or location is observed or the number of VT-IPD cases overpass NVT-IPD cases. For example, when the vaccine serotype IPD cases are clustered in certain age/location/time and NVT in other ages/locations/time, then matching/group matching by age/location/time would be required. Matching by region (or hospital if possible), age and time of hospitalisation (month/years) can be used[23].

► *Each study site to describe the selection of the control group (all NVT controls) and matching by different variables (if it is the case) taking into account the outcome used.*

4.5.3 Cases and controls identification

Depending on the data source used: IPD surveillance (laboratory based or hospital based), or hospital discharge data bases, the identification includes:

- Admission for compatible clinical syndromes or discharge with a compatible diagnostics code (Table 2, ICD codes)
- Link with or data provided by laboratories (including serotypes)

► *Each surveillance site to describe how the case identification is done according to data sources. In any case, the individual data collection will require a link between the clinical, laboratory and vaccination data.*

4.5.4 Cases and controls inclusion and exclusion criteria

IPD/SpCAP cases and controls will be included if individuals are eligible for PCV13 or PPSV23 vaccination, were hospitalised for an IPD or SpCAP, and have had the serotype identified.

IPD cases and controls will be **excluded** if:

[23] Andrews, N., et al. Impact and effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in the elderly in England and Wales. Vaccine 2012: 30, 6802–6808

- Individuals are not eligible for vaccination due to conditions that contra-indicate vaccination;
- Testing of non-sterile body fluid was used for diagnosis;
- Recurrent invasive disease is diagnosed (only the first episode will be included in the analysis). Recurrent invasive disease is defined as IPD episodes in the same individual with the diagnosis/admission date at 30 days apart or identification of the same serotype.
- Serotyping could not be performed.

SpCAP cases and controls will be excluded if:

- Individuals are not eligible for vaccination due to conditions that contra-indicate vaccination;
- Recurrent disease is diagnosed (only the first episode will be included in the analysis). Recurrent disease is defined as SpCAP episodes in the same individual with the diagnosis/admission date at 30 days apart or identification of the same serotype.
- Serotyping could not be performed.

4.5.5 Laboratory methods

To comply with the IPD case definition, laboratory confirmation through culture, PCR or antigen detection could be used for diagnosis in order to allow serotyping. Serotyping is of paramount importance as it is required for IPD cases inclusion and it makes the differentiation between cases and controls.

- Isolation and identification/ PCR could be done at the hospital laboratory or at the reference laboratory
- Serotyping of isolates is usually done at the reference laboratory using capsular reaction testing (Quellung test), PCR or gel diffusion with type-specific antisera
- Antimicrobial susceptibility testing should be done for all isolates for at least the following antimicrobials: penicillin, macrolide, and cephalosporin. MIC will be reported and EUCAST clinical breakpoints used will be used for classification

Specimen collection, transportation and tests used are well defined in case an IPD surveillance system is in place.

For non-invasive SpCAP, the diagnosis can be made using similar tests from non-sterile fluids (sputum, tracheobronchial aspirates, urine, etc.) or the urine antigen testing which allows serotyping.

► *Each study site to describe how specimens are collected, transported and types of the tests performed for confirmation and serotyping. When confirmation and serotyping was done by PCR, the method and the algorithms used should be described. The sensitivity and specificity of all tests should be provided.*

4.6 Exposure

4.6.1 Definition of vaccination status

- Unvaccinated: absence of records of vaccination with PCV13 or PPSV23 in the vaccination registry or medical records, or if the vaccine dose was given less than 14 days prior to onset of symptoms;
- Vaccinated with PCV13: individuals that have received at least one dose PCV13 at least 14 days before onset of symptoms;
- Vaccinated with PPSV23: individuals who have received at least one dose of PPSV23 at least 14 days before onset of symptoms regardless the age and time since vaccination;

- Vaccinated with both PCV13 and PPSV23: individuals who have received both vaccines, the last one received at least 14 days before onset of symptoms, regardless the age and time since vaccination with the first provided vaccine;
- Repeated vaccination with PPV23: individuals who received more than one dose of PPV23, the last one at least 14 days before onset of symptoms regardless the age and time since vaccination;
- Uncertain vaccination history: individuals with no vaccination information available (no written medical records or no registry available, brand name not mentioned, date of administration unknown) or vaccinated during a clinical trial.

4.6.2 Vaccination status ascertainment

The exposure of interest in this study is the history of vaccination with any of PPSV23 or PCV13 vaccines. The vaccination history includes number of doses, date of administration of each dose and brand of each vaccine.

Vaccination status is extracted from available data sources: vaccination registry, hospital or family physicians medical records, or vaccination cards. Efforts should be made to validate the vaccination status. Information on individuals with no information on vaccination status is collected and considered for the sensitivity analysis.

► *Each study site to describe the quality and source of the vaccination data and whether they plan to validate the vaccination ascertainment using other sources or studies (vaccination survey, etc.).*

4.7 Confounding factors and effect modifiers

Individual data collection is required for all IPD cases for surveillance purposes. A minimum set of variables to be collected in the enhanced surveillance systems are included in the table 3. Efforts should be made to harmonise the data collected by all sites.

To control for differences in the characteristics of VT-IPD cases and NVT-IPD controls, information on potential confounding factors should be collected. Those factors will include:

- Age;
- Gender;
- Time of diagnosis (year or month);
- Underlying conditions and other risk factors included in the recommendation for pneumococcal vaccination as defined Table 3 (end of the document). A minimum set of data on high risk conditions will be collected. The sites can include additional data if available;
- Functional status (Barthel index or other criteria available in the site);
- Influenza vaccination in the current season.

Other confounding factors can be included in addition to those already collected for IPD surveillance: number of children in the family, indicators of socio-economic status, smoking history etc.

► *Each study site to define the variables used to identify potential confounding factors or effect modifiers and source of identification if different than data collected for surveillance purposes.*

4.8 Power and sample size and calculation

a) Power calculation

According to the number of cases and controls (i.e. VT-IPD cases and NVT-IPD controls, respectively) collected in the IPD surveillance system, we can calculate the power to detect a given vaccine effectiveness (i.e. 1-odds ratio for vaccination). In order to calculate the power, the following parameters should be taken into account:

- the vaccination coverage in the site;
- number of cases, i.e. VT-IPD;
- number of controls, i.e. NVT-IPD;
- predicted vaccine effectiveness depending on the outcome and exposure;
- a significance level of 5%.

For example, in case of o sample size of 100 VT-IPD cases and 300 NVT-IPD controls, the power will vary according to the vaccination coverage and predicted vaccination effectiveness (Figure 1)

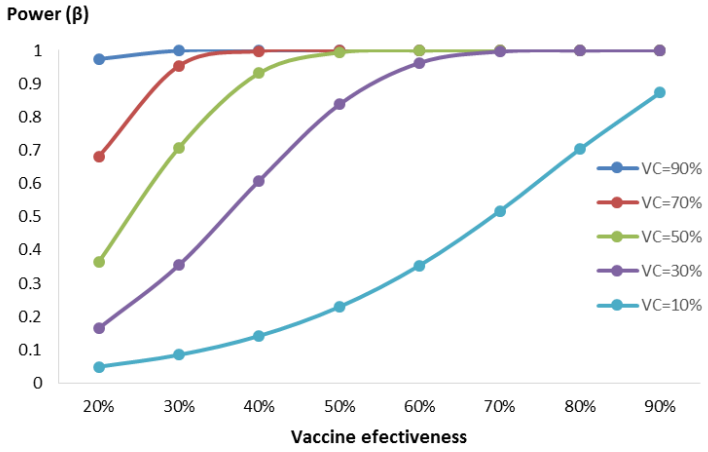

Figure 1. Power calculation for different vaccination coverage (VC), vaccine effectiveness, for a sample size of 100 VT-IPD and 300 NVT-IPD

b) Sample size calculation

In case not sufficient number of IPD cases are collected by the surveillance system in a given period of time, the sample size should be calculated in order to reach the desired power and precision of VE estimate. To calculate the sample size, the following parameters should be taken into account:

- a significance level of 5%;
- a power of 80%;
- a precision of 20% around the point VE estimate;
- the vaccination coverage available in the site;
- a vaccine effectiveness of 20%-90% depending on the outcome and exposure;
- a proportion of PPV23-IPD among the all IPD cases of 0.60 (based on SpIDnet1 data in >64 years 2012-2014).

The calculation should be done according to each outcome considered: primary outcome (IPD of vaccine serotypes) and secondary outcomes (specific vaccine serotypes/vaccine related serotypes, clinical manifestation, IPD antimicrobial non-susceptibility and severe IPD of vaccine serotypes).

Table 4 presents the sample size needed to reach the chosen precision around point estimate.

Table 4. Sample size needed for the for different vaccine coverages and vaccine effectiveness.

Precision	Alpha	Power	Proportion of vaccine type/ all cases	Vaccine coverage in the source population	Detectable VE(1-OR)	Number of cases	Number of controls	Total IPD patients included
0.2	0.05	0.8	0.6	0.1	0.9	346	231	576
0.2	0.05	0.8	0.6	0.1	0.8	509	339	849
0.2	0.05	0.8	0.6	0.1	0.7	717	478	1195
0.2	0.05	0.8	0.6	0.1	0.6	963	642	1605
0.2	0.05	0.8	0.6	0.1	0.5	1246	831	2077
0.2	0.05	0.8	0.6	0.1	0.4	1566	1044	2610
0.2	0.05	0.8	0.6	0.1	0.3	1922	1281	3203
0.2	0.05	0.8	0.6	0.1	0.2	2315	1543	3858
0.2	0.05	0.8	0.6	0.3	0.9	104	69	173
0.2	0.05	0.8	0.6	0.3	0.8	167	111	278
0.2	0.05	0.8	0.6	0.3	0.7	251	167	418
0.2	0.05	0.8	0.6	0.3	0.6	354	236	590
0.2	0.05	0.8	0.6	0.3	0.5	476	317	793
0.2	0.05	0.8	0.6	0.3	0.4	617	411	1028
0.2	0.05	0.8	0.6	0.3	0.3	777	518	1295
0.2	0.05	0.8	0.6	0.3	0.2	957	638	1595
0.2	0.05	0.8	0.6	0.5	0.9	58	38	96
0.2	0.05	0.8	0.6	0.5	0.8	106	70	176
0.2	0.05	0.8	0.6	0.5	0.7	171	114	285
0.2	0.05	0.8	0.6	0.5	0.6	255	170	424
0.2	0.05	0.8	0.6	0.5	0.5	356	238	594
0.2	0.05	0.8	0.6	0.5	0.4	477	318	794
0.2	0.05	0.8	0.6	0.5	0.3	616	411	1027
0.2	0.05	0.8	0.6	0.5	0.2	891	594	1484
0.2	0.05	0.8	0.6	0.7	0.9	43	29	72
0.2	0.05	0.8	0.6	0.7	0.8	94	63	157
0.2	0.05	0.8	0.6	0.7	0.7	166	111	277
0.2	0.05	0.8	0.6	0.7	0.6	260	174	434
0.2	0.05	0.8	0.6	0.7	0.5	379	253	631
0.2	0.05	0.8	0.6	0.7	0.4	523	348	871
0.2	0.05	0.8	0.6	0.7	0.3	693	462	1154
0.2	0.05	0.8	0.6	0.7	0.2	891	594	1484

► *Each study site to estimate the power and/or calculate the sample size according to the available parameters.*

4.9 Data collection

Data for IPD cases is extracted from existing surveillance database or from hospital discharge databases. In countries or regions with a unique identifier, investigators can link various databases. For each variable, the database source and its characteristics should be defined. A table like Table 3 presented at the end of the document can be adapted and completed to summarise the sources for each of the variables to be extracted and included in the analysis.

► *Each study site to specify the list of variables to be extracted.*

4.10 Data management

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

- Who extracts data?
- Who validates data?
- How, by whom and when are data stored?
- Who links databases?
- How are data extracted?
- Who analyses data?
- Softwares used?
- How and who do the anonymization of the database to be used in the analyses?

5. Analysis

5.1 Data checking

As much as possible, data should be completed or validated against the data source. Data will be checked to find outliers, implausible or missing information. The inclusion and exclusion criteria will be checked for the studies using IPD surveillance. If the following variables are missing, cases will be excluded:

- Date of birth/ age;
- Date of onset /hospital admission /diagnosis;
- Serotype.

Baseline characteristics of records with missing serotype will be compared to records without missing serotype in order to assess the bias due to differential serotyping by vaccination status.

For all the other variables, baseline characteristics of records with missing data will be compared to records without missing data. If there is no evidence of bias in the missing data, the distribution of IPD/SpCAP cases with known data will be applied to the cases with missing results. If a high proportion of data are missing and/or there is no evidence of bias in the missing data, and variables that are considered good predictors of the missing data are available, multiple imputation using chained equations can be used to replace missing values.

► *Each study site to describe the data cleaning process and the management of missing data*

► *Each study site to specify the percentage of missing by variable collected and assess differences between serotyped and non-serotyped IPD/SpCAP cases.*

5.2 Descriptive analysis

VT cases and NVT controls will be described by baseline characteristics (age, gender, clinical presentations, length of hospital stay, underlying conditions, vaccination). Baseline characteristics are compared in unmatched studies 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). In matched studies, characteristics of cases and controls are compared using McNemar's chi-square test, paired t-test, conditional logistic regression, or the Wilcoxon signed-rank test (depending on the nature of the variable and the number of controls).

In addition, the association between vaccination status and baseline characteristics will be also measured for cases due to vaccine serotypes and due to non-vaccine serotypes.

► *Each study site to specify the descriptive analysis planned*

5.3 Measure of association

Vaccine effectiveness will be computed as 100% X (1 – the odds of vaccination in VT cases / odds of vaccination in NVT controls). An exact 95% confidence interval will be computed around the point estimate. The crude and adjusted estimates of vaccine effectiveness will be provided.

The VE will be computed for all exposures mentioned above.

5.4 Stratified analysis

Analysis will be stratified according to age group, year of diagnosis and any other variable relevant for the study setting depending on the sample size (e.g. gender, underlying diseases, influenza vaccination, etc.).

Effect modifiers should be assessed one by one, comparing the OR across the strata of baseline characteristics.

Confounding factors will be identified by comparing crude and adjusted OR for each baseline characteristic.

► *Each study site to specify the stratified analysis planned*

5.5 Multivariable analysis

A multivariable (conditional if matched) logistic regression analysis will be conducted to control for identified confounding factors (such as age, gender, year of notification, underlying chronic conditions, etc.). Odds ratios and standard errors will be obtained. Variables will be tested for multicollinearity. Interactions will be tested using the likelihood ratio test or Wald's test and will be included in the model if significant at the 5% level. Factors other than statistical significance will also be used as criteria for inclusion of an interaction term.

► *Each study site to describe the type of multivariable analysis planned.*

5.6 Further analyses

5.6.1 Sensitivity analyses

Different sensitivity analyses can be planned to take into account:

1. the effect of vaccine related serotypes (that gives cross-protection or not) by including these serotypes in the control group.
2. excluding the vaccinated <14 days.
3. vaccinated with PPSV23 more than x years ago (e.g. 10 years) considered unvaccinated.
4. missing vaccination status by considering individuals with missing vaccination status:
   - unvaccinated;
   - vaccinated;
   - imputed according the available predictors.

   Taking into account uncertain vaccination status: to help determine if no record of vaccination mean unvaccinated, some sites might obtain the date of registration with the general practice. This will allow to run a sensitivity analysis including those registered with the general practice in the last x years (to be determined).

► *Each study site to describe the sensitivity analyses planned.*

5.6.2 Time since vaccination

Where sample size allows, further analyses will be carried out to explore the duration of protection. VE by time since vaccination will be computed. Time since vaccination can be calculated by subtracting the date of vaccination from the date of onset/diagnosis/notification and it can then be modelled as a continuous variable. Otherwise the analysis can be done, if sample size permit by several categories: vaccination within <2 years, 2-4 years, ≥5years.

6. Limitations

6.1 Assessment of bias due to replacement in the indirect cohort method

Andrews et al examined the bias introduced by the complete replacement when using the indirect cohort method when the true PCV effectiveness (VE) is 70% and 90%, for different levels of VE against carriage (VEc) and proportion of carriage of vaccine serotypes in the unvaccinated (Pu). The formula relating these parameters is:

$VE_{Broome} = 1 – (1-VE)/ (1 + VEc\ Pu / (1-Pu))$

where: VE= true vaccine effectiveness, VEc = vaccine effectiveness against acquisition of the vaccine serotype in the nasopharynx, Pu=proportion of carriage of vaccine serotypes in unvaccinated.

Bias increases as VEc increases and with increasing Pu (Figure 2). Data on acquisition of vaccine serotype in nasopharynx is not available and difficult to be obtained, therefore data available on carriage prevalence was used by Andrews et al to calculate the VEc. Considering an average Pu=40% and a VEc=50%, the calculated VE_{Broome} will be 92.5% when the true VE is 90%. For a true VE of 70%, and a VEc

of 30%, the VE_{Broome}= 75%. The authors concluded that a realistic range of bias using UK data is around 2-5%. However this assumption should be investigated for the specific site situations.

In a study using CDC's ABCs data, De Serres et al simulated the VE estimates when changing the ratio of an increase in NVT among vaccinated and unvaccinated children (Figure 3). The authors concluded that the VE results are not biased if the change in NVT affects equally (proportional increase) vaccinated and unvaccinated children. The most likely scenario presented for USA was the increase in incidence of NVT of 150% greater in vaccinated than unvaccinated children, as the vaccination coverage was ≥90% for PCV7. In this scenario, the absolute overestimation was judged minimal (2%) for a true VE of 95% and reasonable (10%) for a true VE of 70%. However, the authors stated that in a setting where vaccine is provided only to high-risk children who are at increased risk for NVT disease compared to healthy children, VE estimates using the indirect cohort method will be less reliable and is not recommended.

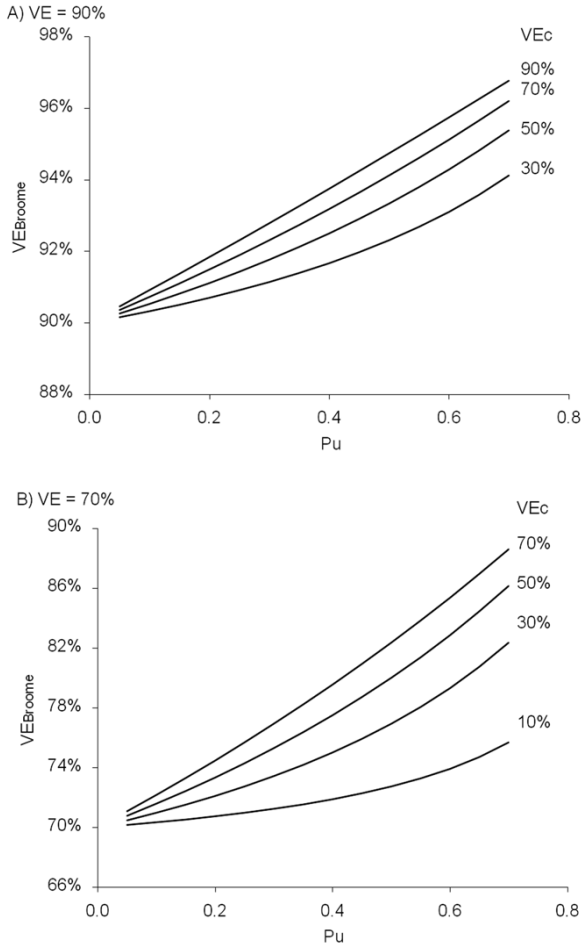

Figure 2: Assessment of bias with the indirect cohort method when assuming complete serotype replacement (from Andrews et al 2012).

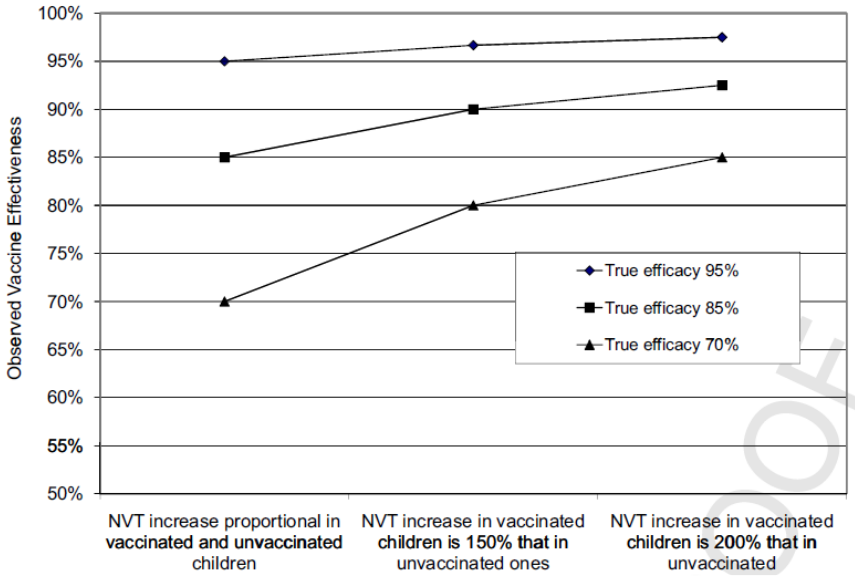

Figure 3: Assessment bias with the indirect cohort method using different scenarios (from De Serres et al 2011).

6.2 Limitations related to different aspects of the study

6.2.1 Study population

► *Each study site to describe the limitations related to the representativeness of the study population and thus the generalisability of the results.*

6.2.2 Database(s) quality, validity

► *Each study site to describe the data quality in the surveillance database or other sources used for vaccine effectiveness analysis. If variables in the database used has not been validated, the possibility of validating the information using other data sources should be addressed.*

6.2.3 Exposure, vaccination status

► *Each study site to describe any potential bias related to ascertainment of vaccination status, ways to minimise the bias and how bias can affect the estimates.*

6.2.4 Outcome

► *Each study site to describe any potential bias related to the outcome used and the way the outcome is ascertained.*

6.2.5 Control group

► *Each study site to describe the limitations related to the use of the IPD/SpCAP cases due to non-vaccine serotypes as reference group (i.e. do reference group represent the vaccination coverage of the population giving rise to the IPD/SpCAP cases due to vaccine serotypes?).*

6.2.6 Selection bias

► *Each study site to describe any selection bias that may occur in the selection of individuals to be tested for an IPD or SpCAP. Testing is frequently related to the clinical presentation and the severity of the disease, therefore the results will mainly reflect the effectiveness against these more severe diseases. Also, a*

selection bias may occur if testing is done differentially according to the vaccination status. In addition, increasing blood culturing and PCR testing over time should be also taken into account in the interpretation of the results.

6.2.7 Confounding

► *Each study site to describe how they will minimise the effect of potential confounding factors and how residual confounding may affect the VE estimates.*

6.2.8 Indirect effect of childhood vaccination

► *It can be argued that the indirect effect of childhood vaccination will influence the effectiveness of the pneumococcal vaccines in the elderly, through the herd effect. However, if the random mixing of the population can be assumed, the herd effect affects equally the vaccinated and unvaccinated elderly, not biasing the effectiveness estimates. Study sites are invited to discuss how the indirect effect may influence the VE estimates in their settings if not random mixing can be assumed.*

7. Ethical approval

► *Each study site to describe the procedures to obtain the approval of the national / ethics committee.*

8. Dissemination of results

Each study coordinator will decide where the results of the individual studies will be published and which scientific conferences will be attended in order to present the results. An article presenting the results of the pooled analysis and estimates for the EU/EEA will be submitted to a peer-reviewed journal. The list of authors will respect the recommendations of authorship stated by the International Committee of Medical Journal Editors http://www.icmje.org/ethical_1author.html. The actual authorship for the pooled article will be discussed and agreed with the study teams at the beginning of the study.

► *Each study site to describe the plans to disseminate the results: preliminary reports, final report, publications.*

9. 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*

Tables

Table 3: List of variables, coding, definitions and data sources, as collected in the IPD surveillance systems (harmonised under the SpIDnet/I-MOVE+project)

Variable name	Name of the variable in the site specific database	Variable label	Type	Values and coding	Definition	Comments
siteid		Site identification	Unique ID	AAA	Surveillance site identification	
recordid		Record identification code	Unique ID	string	Surveillance unit identification and record identification code	
datenotif		Date of notification	Date	dd/mm/yyyy	Date when the case is notified the first time to the site level	
residence		Residence in the catchment area	Numeric	0-no 1-yes 9-unknown	Residence in the catchment area of the surveillance unit reporting to the system	
ageyears		Age of the case in years	Numeric	###	Age of patient in years as reported at the site level in years at time of hospital admission	

Variable name	Name of the variable in the site specific database	Variable label	Type	Values and coding	Definition	Comments
sex		Gender	Code	0-female 1-male 9-unknown	Gender of the reported case	
dateadm		Date of the admission in the hospital	Date	dd/mm/yyyy	Date when the case was admitted to the hospital	
datedis		Date of the discharge from the hospital	Date	dd/mm/yyyy	Date when the case was discharged from the hospital	
outcome		Outcome	Code	0-alive 1-deceased 9-unknown	Information on survival at the end of hospitalisation: alive, deceased, unknown	
datedeath		Date of death	Date	dd/mm/yyyy	Date of death of the admitted patient (if outcome==1)	
clinic		Clinical entity	Multiple choice	0-unknown 1-meningitis 2-pneumonia 3- 4-bacteremia 5- 6- 9-other, specify	Clinical manifestation of the IPD case	This multiple-choice variable can be collected as such or each clinical entity can be entered separately using variables 12-20. If clinic =9, variable 20 (otherclin) specifies other

Variable name	Name of the variable in the site specific database	Variable label	Type	Values and coding	Definition	Comments
						clinical entities of IPD not listed
meningitis		Pneumococcal meningitis	Code	0-no 1-yes 9-unknown	A case presenting with lab confirmed pneumococcal meningitis	
pneumonia		invasive pneumococcal pneumonia	Code	0-no 1-yes 9-unknown	A case presenting with lab confirmed pneumococcal pneumonia	
bacteremia		Bacteremia without known focus of infection	Code	0-no 1-yes 9-unknown	A case presenting with lab confirmed bacteremia (blood stream infection) without known focus of infection	
otherclin		Other clinical entities	Text	String20	Other clinical entities of the IPD case	Please specify other clinical entity for the IPD cases
icuadm		Admission in the ICU	Code	0-no 1-yes 9-unknown	A lab confirmed case who needed admission in the ICU during the pneumococcal episode	
datediag		Date of diagnosis	Date	dd/mm/yyyy	Date when the diagnosis was made, should be the same with	

Variable name	Name of the variable in the site specific database	Variable label	Type	Values and coding	Definition	Comments
					the identification/confirmation of the	
serotype		Serotype identified	Text	String3 PEN – pending NTP – non-typeable UKN - unknown	Serotype identified	
micpeni		MIC to penicillin	Numeric	##.###	MIC to penicillin in µg/ml	If not tested, the variable will be left blank
mic[macrolid]		MIC to macrolide	Numeric	##.##	MIC to macrolide in µg/ml [please specify the antimicrobial used: Erythromycin, Azithromycin, Clarithromycin, etc.]	If not tested, the variable will be left blank
mic[cepha]		MIC to cephalosporin	Numeric	##.##	MIC to cephalosporin in µg/ml [please specify the antimicrobial used: Cefotaxime, Ceftriaxone, etc]	If not tested, the variable will be left blank
mic[antimicrobial]		MIC to antimicrobial	Numeric	##.##	MIC to different other antimicrobial tested	Please specify the antimicrobial using specific variables

Variable name	Name of the variable in the site specific database	Variable label	Type	Values and coding	Definition	Comments
nbdosepcv13		Number doses PCV13	Numeric	#	Number doses PCV13	
dosepcv13		PCV13 vaccination	Code	0-no 1-yes 9-unknown	Vaccination with PCV13	
datepcv13		Date of vaccination with first dose PCV	date	dd/mm/yyyy	Date of latest dose PCV	
nbdoseppv		Number doses PPSV23	Numeric	#	Number doses PPSV23	
doseppv		PPSV23 vaccination	Code	0-no 1-yes 9-unknown	Vaccination with PPSV23	
dateppv		Date vaccination with PPSV23	date	dd/mm/yyyy	Date of vaccination with PPSV23 for the latest and previous dose if available	
underdis		Underlying diseases	Code	0-no 1-yes 9-unknown	Presence of at least one underlying disease which represents high risk groups for getting IPD	This variable can be collected as such or by specifying conditions 52-59
underdistype		Underlying diseases by immune status	Code	0-no	Underlying diseases by immune status	For definitions please refer to table 4

Variable name	Name of the variable in the site specific database	Variable label	Type	Values and coding	Definition	Comments
				1-immunocompetent 2-immunocompromissed 9-unknown		
cardiovasc		Cardiovascular diseases	Code	0-no 1-yes 9-unknown	Patient was diagnosed with a chronic cardiovascular disease: see table 4 for ICD codes	
respdis		Respiratory diseases	Code	0-no 1-yes 9-unknown	Patient was diagnosed with a chronic respiratory disease or asthma: see table 4 for ICD codes	
rendis		Renal diseases	Code	0-no 1-yes 9-unknown	Patient was diagnosed with a chronic renal disease including nephrotic syndrome	
immunodef		Immunodeficiency	Code	0-no 1-yes 9-unknown	Patient was diagnosed with an acquired or congenital immunodeficiency	

Variable name	Name of the variable in the site specific database	Variable label	Type	Values and coding	Definition	Comments
hiv		Human immunodeficiency virus (HIV) disease	Code	0-no 1-yes 9-unknown	See table 4	
leukemia		Lymphoid and myeloid leukaemia; multiple myeloma	Code	0-no 1-yes 9-unknown	See table 4	
lymphoma		Hodgkin lymphoma, Follicular lymphoma, Non-follicular lymphoma, MatureT/NK-cell lymphoma, Other and unspecified types of non-Hodgkin lymphoma	Code	0-no 1-yes 9-unknown	See table 4	
transplant		Solid organ transplat	Code	0-no 1-yes 9-unknown	See table 4	
malignancy		Generalized malignancy	Code	0-no 1-yes 9-unknown	See table 4	

Variable name	Name of the variable in the site specific database	Variable label	Type	Values and coding	Definition	Comments
immunomed		Immunosuppressing medication	Code	0-no 1-yes 9-unknown	See table 4	
diabetes		Diabetes mellitus	Code	0-no 1-yes 9-unknown	Patient was diagnosed with diabetes mellitus type 1 or 2	
asplenia		Asplenia or splenectomised	Code	0-no 1-yes 9-unknown	Patient with functional or anatomical asplenia / splenectomy in the clinical history	
sicklemia		Sickle cell disease	Code	0-no 1-yes 9-unknown	Patient with sickle cell disease in the clinical history Also include: Thalassemia, Other haemoglobinopathies	
csfleak		Cerebrospinal fluid (CSF) leak	Code	0-no 1-yes 9-unknown	See table 4	
cohlear		Cochlear implant	Code	0-no 1-yes 9-unknown	See table 4	

Variable name	Name of the variable in the site specific database	Variable label	Type	Values and coding	Definition	Comments
alcoholism		Alcoholism	Code	0-no 1-yes 9-unknown	See table 4	
liverdis		Liver chronic disease including cirrhosis	Code	0-no 1-yes 9-unknown	See table 4	
smoking		Cigarette smoking	Code	0-no 1-yes 9-unknown	See table 4	
institutionalised		Institutionalized persons	Code	0-no 1-yes 9-unknown	See table 4	
otherdis		Other underlying disease	Text	string20	Specify other underlying conditions included in the recommendation for PCV/PPV vaccination.	
Fluvac		Influenza vaccination	Code	0-no 1-yes 9-unknown	Influenza vaccination for the current season	

Variable name	Name of the variable in the site specific database	Variable label	Type	Values and coding	Definition	Comments
Other variables						Please include all other variables collected in the site specific surveillance system

Table 2: ICD codes for case identification

Clinical IPD

ICD-9 Code	ICD-10 Code	Diagnosis in Text
038 003.1 995.91	A40, A41	Streptococcal sepsis; other sepsis
041	A49	Bacterial infection of unspecified site
320	G00	Bacterial meningitis, not elsewhere classified
711	M00	Pyogenic arthritis
420	I30.1	Infective pericarditis
041.09	B95.3	*S. pneumoniae* as the cause of diseases classified to other chapters
041.09	B95.4	Other *Streptococcus* as the cause of diseases classified to other chapters
041.00	B95.5	Unspecified *Streptococcus* as the cause of diseases classified to other chapters
995.91 and 790.7		Sepsis with bacteremia ??

SpCAP		
Pneumococcal pneumonia	481	J13

Table 4: ICD codes for the underlying conditions by immune status

Risk conditions	Description	ICD-9 Code	ICD-10 Code
Immunocompromised persons			
Congenital/acquired immunodeficiency		135, 279	D80-D89
Human immunodeficiency virus (HIV) disease		042	B20-B24
Chronic kidney disease		585	N18
Nephrotic syndrome		581	N04
Leukemia	Lymphoid and myeloid leukaemia; multiple myeloma	203 – 205	C91-C92, C90
Lymphoma	Hodgkin lymphoma, Follicular lymphoma, Non-follicular lymphoma, MatureT/NK-cell lymphoma, Other and unspecified types of non-Hodgkin lymphoma	200 – 202	C81, C82, C83, C84, C85
Generalized malignancy			*No specific ICD-10 codes*
Immunosuppressing medication			*No specific ICD-10 codes*
Solid Organ Transplant	Transplanted organ and tissue status	V42	Z94
Functional or anatomical asplenia			
Thalassemia, Sickle cell disorders, Other haemoglobinopathies, Diseases of the spleen (including anatomical asplenia)		282, 289.4-5	D56, D57, D58.2, D73
Immunocompetent persons			

Cerebrospinal fluid (CSF) leak		349.81, 388.61	G96.0
Cochlear implant		431	Z96.1
Chronic heart disease	Chronic ischemic heart disease, Cardiomyopathy, Heart failure	412 – 414, 425, 428	I25, I42, I50
Chronic lung disease	Emphysema, Other COPD, Asthma	492, 493	J43, J44, J45
Diabetes mellitus	Type 1 Diabetes, Type 2 Diabetes, Malnutrition-related diabetes, Other specified diabetes, Unspecified diabetes	250	E10, E11, E12, E13, E14
Alcoholism	Mental and behavioral disorders due to use of alcohol, Degeneration of nervous system due to alcohol, Alcoholic polyneuropathy, Alcoholic myopathy, Alcoholic cardiomyopathy, Alcoholic gastritis, Alcoholic liver disease, Alcohol-induced acute pancreatitis, Alcohol-induced chronic pancreatitis, Maternal care for (suspected) damage to fetus from alcohol,	305, 281, 357.5, 425.5, 535.30-31, 571, 655	F10, G31.2*, G62.1, G72.1*, I42.6, K29.2, K70, K85.2*, K86.0*, O35.4
Chronic liver disease, cirrhosis	Hepatic failure, NES, Chronic hepatitis, NES, Fibrosis and cirrhosis, Other diseases of liver, Malignancy of liver	155, 470 – 474	K72, K73, K74, K76, K76.9, C22

Cigarette smoking	Tobacco use, Mental disorders due to tobacco	300.51 292.89	Z72.0*, F17.2, F17.3*
Institutionalized persons	Nursing homes and long-term facilities		*No specific ICD-10 codes*
Other ICD codes	Site specific conditions included in the high-risk groups for pneumococcal infection		

Appendix 1: Validation of "non-vaccine serotypes" as control group using other control groups

The use of the indirect cohort method implies that the serotyping results are available for all or a systematic sample of IPD or SpCAP cases. This assumption should be validated by comparing the VE results with those of other controls groups using the same data sources.

Below we present advantages and disadvantages of each additional groups and specific features for analyses.

Using a unique identifier allows linkage of various datasets:

- hospital discharge register – diagnosis codes;
- laboratory data;
- vaccination data.

This constitutes the unique opportunity to measure effectiveness using different control groups and evaluate which one better represents the vaccination coverage of the population that gives rise to IPD/SpCAP caused by vaccine serotypes.

These additional control groups could be:

1. Hospitalised elderly according to other disease codes:
    a. hospitalised elderly≥65 years for other ICD codes than pneumococcal related codes as presented in Table 4.
    b. hospitalised elderly ≥65 years for condition that do not include those considered high risk for IPD/SpCAP (i.e. ICD9CM 800-999 or ICD10CM: S00-T98: Injury and poisoning).

Advantages:

- Feasibility (access to the data)
- Same type of data available
- Can compute VE against all type IPD/SpCAP

Disadvantages:

- Susceptible to selection bias: the control group might not represent in terms of exposure the population given rise to the pneumococcal cases
- Need for adjustment for different confounders: severity of disease, access to care (information not always available)

2. Controls from community
    a. Screening method using the vaccination coverage of the elderly by age and risk groups

Advantages:

- Quick analysis when incidence rates are not available
- Could be done only with data readily available for surveillance or available surveys
- Can be used for other outcomes such as all type IPD/SpCAP
- Adjustment difficult but possible for some factors (age groups, high risk groups) if vaccination coverage is available by group

Disadvantages:

- VC in the population might not represent the one of the source population of pneumococcal hospitalised cases
- VE estimates are highly dependent on time period during which it is used and the choice of outcome (VT versus all type IPD/SpCAP)

Vaccine coverage in the reference group

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.

Analysis

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 IPD, SpCAP or pneumococcus serotype outcome) 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[24].

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

Stratified analysis

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

- age groups (<75 and >74 years);
- underlying conditions

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

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[25].

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.

► *Each study site to describe additional studies used to validate the indirect cohort method.*

[25] Idem 24

Version number	Date published	Text in original document	Changes included in the amended version	Comments
V2.1	15 Dec 2016	Page 14 (secondary outcomes) Page 14 (Case definitions for secondary outcomes) Table 3 "Clinical presentation (meningitis, pneumonia, sepsis)"	Modified by "Clinical presentation (meningitis, bacteraemic pneumonia, bacteraemia, other clinical presentations)"	Note that bacteraemia covers all bacteremia and not only bacteremia without focus (because in Denmark no difference between pneumonia and bacteremic pneumonia can be made) Decision during the technical meeting (Paris, September 2016) because the definition of sepsis is not homogenous over the sites.
		Page 15 (Case definitions for secondary outcomes and reference group) "Severity is assessed according to: ICU admission and/or length of hospital stay >14 days and/or presence of septic shock and/or intra-hospital death"	Modified as: "Severity is assessed according to: ICU admission and/or length of hospital stay >14 days and/or death within 30 days"	Decision during the technical meeting (Paris, September 2016
		Page 17: Definition of vaccination status	Included a definition for repeated vaccination	Decision during the technical meeting (Paris, September 2016)
		Page 17-18: confounders and effect modifiers Table 4: text replaced by the ICD codes for risk conditions	Modified to include the ICD codes for the underlying conditions	Decision during the technical meeting (Paris, September 2016)

		Table 4 ICD codes for IPD and SpCAP	Table 4 becomes table 2 and includes ICD codes for clinical IPD and SpCAP	Decision during the technical meeting (Paris, September 2016)
		Table 4: ICD codes for the underlying conditions by immune status	The new table 4 includes ICD 9 and 10 codes for underlying conditions	Decision during the technical meeting (Paris, September 2016)
v2.2	15 Dec 2017	Table 3 List of variables, coding, definitions and data sources, as collected in the IPD surveillance systems (harmonised under the SpIDnet/I-MOVE+ project)	Table 3 amended to include additional variables on the minimum set of high risk conditions collected	Decision during the technical meeting (Utrecht, October 2017)