NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	A Phase 4 Observational, Real-World Study of 20-valent Pneumococcal Conjugate Vaccine Effectiveness Against Vaccine-Type Invasive Pneumococcal Disease in Adults Aged 65 years and above
Protocol number	WI272461
Protocol version identifier	V1.1
Date	1 July 2024
EU Post Authorization Study (PAS) register number (EMA RWD Catalogues)	EUPAS1000000007
Active substance	Pneumococcal polysaccharide serotype 1[1,2] Pneumococcal polysaccharide serotype 3[1,2] Pneumococcal polysaccharide serotype 4[1,2] Pneumococcal polysaccharide serotype 5[1,2] Pneumococcal polysaccharide serotype 6A[1,2] Pneumococcal polysaccharide serotype 6B[1,2] Pneumococcal polysaccharide serotype 7F[1,2] Pneumococcal polysaccharide serotype 8[1,2] Pneumococcal polysaccharide serotype 9V[1,2] Pneumococcal polysaccharide serotype 10A[1,2] Pneumococcal polysaccharide serotype 11A[1,2] Pneumococcal polysaccharide serotype 12F[1,2] Pneumococcal polysaccharide serotype 14[1,2] Pneumococcal polysaccharide serotype 15B[1,2] Pneumococcal polysaccharide serotype 18C[1,2] Pneumococcal polysaccharide serotype 19A[1,2] Pneumococcal polysaccharide serotype 19F[1,2] Pneumococcal polysaccharide serotype 22F[1,2] Pneumococcal polysaccharide serotype 23F[1,2] Pneumococcal polysaccharide serotype 33F[1,2] [1]Conjugated to CRM197 carrier protein (approximately 51 µg per

	dose) [2]Adsorbed on aluminium phosphate ATC: J07AL02
Medicinal product	Pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed)
Research question and objectives	The primary objective is to estimate vaccine effectiveness (VE) of 20-valent pneumococcal conjugate vaccine (20vPnC) against invasive pneumococcal disease (IPD) due to any of the 20 serotypes that are included in the vaccine (20vPnC serotypes), in adults aged 65 years and above. The secondary objectives are (1) to estimate VE of 20vPnC against IPD due to any of the 13 serotypes that are included in 13vPnC (13vPnC serotypes), in adults aged 65 years and above and (2) to estimate VE of 20vPnC against IPD due to any of the 7 serotypes that are included in 20vPnC but not in 13vPnC (20non13vPnC serotypes), in adults aged 65 years and above.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
13vPnC	13-valent Pneumococcal Conjugate Vaccine
15vPnC	15-valent Pneumococcal Conjugate Vaccine
20vPnC	20-valent Pneumococcal Conjugate Vaccine
20non13vPnC	Serotypes included in 20vPnC but not in 13vPnC
CSF	Cerebrospinal Fluid
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
DAG	Directed Acyclic graph
DMP	Data Management Plan
ECDC	European Centre for Disease Prevention and Control
EDC	Electronic Data Capture
EEA	European Economic Area
EQA	External Quality Assessment
EMA	European Medicines Agency
EU	European Union
GDPR	General Data Protection Regulation
GEP	Good Epidemiological Practice
ICMJE	International Committee of Medical Journal editor
IEC	Independent Ethics Committees
IPD	Invasive Pneumococcal Disease

Abbreviation	Definition
IRB	Institutional Review Boards
NS-AEs	Non-serious Adverse Events
OPA	Opsonophagocytosis Assays
OR	Odds Ratio
PAS	Post-Authorisation Studies
PCV	Pneumococcal Conjugate Vaccine
PPV23	23-valent Pneumococcal Polysaccharide Vaccine
RDP	Remote Desktop Protocol
RMP	Risk Management Plans
RT-PCR	Reverse Transcription Polymerase Chain Reaction
RWD	Real World Data
SAP	Statistical Analysis Plan
sFTP	secure File Transfer Protocol
VE	Vaccine Effectiveness
VRT	Vaccine Related Serotype

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
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Eileen Dunne, PhD	Scientific Affairs and Epidemiology, Global Respiratory Vaccines	Pfizer	500 Arcola Road Collegeville, PA 19426 USA

Country Coordinating Investigators

See Annex 3- Country Coordinating Investigators will be listed upon contract completion.

4. ABSTRACT

- **Title:** A Phase 4 Observational, Real-World Study of 20-valent Pneumococcal Conjugate Vaccine Effectiveness Against Vaccine-Type Invasive Pneumococcal Disease in Adults Aged 65 years and above.

- **Rationale and background:** The 20-valent pneumococcal polysaccharide conjugate vaccine (20vPnC) was authorised for use in adults by the European Medicines Agency (EMA) (14 February 2022). This Phase 4 observational, real-world study is a post-approval evaluation of the effectiveness of 20vPnC against vaccine-type invasive pneumococcal disease (IPD) in adults aged 65 years and above in Europe, with inclusion of suitable non-European countries. International expansion will enable faster sample size achievement and provide earlier and more generalisable data to respond to EMA risk management plan (RMP).

- **Research question and objectives:** The primary objective is to estimate vaccine effectiveness (VE) of 20vPnC against IPD due to any of the 20 serotypes that are included in the vaccine (20vPnC serotypes), in adults aged 65 years and above. VE of 20vPnC against IPD due to serotypes included in the 13-valent pneumococcal conjugate vaccine (13vPnC) and serotypes included in 20vPnC but not in 13vPnC (20non13vPnC serotypes) will also be estimated.

- **Study design:** A multi-country observational study using the indirect cohort (Broome) method will be conducted, in which cases are IPD caused by vaccine serotypes and controls are IPD caused by non-20vPnC serotypes.

- **Population:** The study population for VE analysis is adults aged 65 years and above with IPD with an identified pneumococcal serotype who were reported to the study site reporting system and were eligible for 20vPnC vaccination, according to local vaccination policies. Study sites are national or regional surveillance systems, or hospital research networks, selected based on existing 20vPnC recommendation in adults, expected vaccine uptake, expected number of serotyped IPD cases, and availability of data on vaccination status. IPD data for all adults aged 18 years and above will be collected to monitor serotyping distribution. Participating sites will contribute up to four years of data.

- **Variables:** The primary outcome of interest will be IPD due to any of the 20vPnC serotypes; serotype will be the outcome variable collected. The exposure of interest is 20vPnC vaccination; vaccination status and time since vaccination will be collected. Patient-level information including study site, age, sex, and date of IPD diagnosis will also be collected.

- **Data sources:** Data sources per IPD patient, including serotyping, patient-level information and exposure ascertainment will differ across study sites and may include national/regional IPD surveillance system, patient medical records, and vaccination registries. Study sites will submit a de-identified dataset to the study sponsor.

- **Study size:** Assuming, in the base case, an estimated proportion of IPD due to 20vPnC serotypes of 64%, a 20vPnC VE of 65%, and 20vPnC uptake of 15%, a minimum of 338 evaluable IPD cases are required to address the primary objective.

- **Data analysis:** Descriptive statistics or every site and pooled for all sites will be performed. VE estimates will be adjusted for the major confounding factors (i.e., study site, year of IPD diagnosis, age). Previous pneumococcal vaccination will be considered in the analysis. For every objective, unadjusted and adjusted VE against vaccine serotype IPD will be estimated as VE = (1-odds ratio (OR)) x 100%, where OR denotes the odds ratio, comparing the odds of vaccination among vaccine serotype IPD to the odds of vaccination among non-vaccine serotype IPD. VE pooled estimates will be stratified by age group and time since 20vPnC vaccination (e.g., <2 years, 2-5 years after vaccination).

- **Milestones:**

Milestone	**Planned date**
Completion of feasibility assessment	31 March 2024
Start of data collection	01 September 2024*
End of data collection	31 August 2028*
Study progress report	31 October 2026
Interim report	31 March 2027
Registration in the HMA-EMA RWD Catalogues	25 March 2024
Final report of study results	31 December 2030

*Participating sites will contribute up to four years of data from the study start, plus eligible retrospective data from the time of 20vPnC availability.

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
1.1	01JUL2024	Administrative	Headers, Footers and page 2	Updated language per Pfizer protocol template, administrative changes and precisions to address the points raised in the assessment report of the EMA. Punctuation, typos and grammar updated/corrected as applicable.	Administrative change triggered by implementation of a new version of the protocol.
			Section 8: Research question and objectives and Section 9.8.2.3		Numbering of the objectives has been updated to be in agreement with table 1 and to avoid any confusion when referred to in the text. Inclusion of the regions of Spain with successful feasibility.
			Section 9.2:Settings		Revised numbering
			Inclusion/Exclusion criteria		Revised wording.
			Section 9.3.2: Exposure		Correction and update of table 2, Addition of serotype 3 data.
			Section 9.6: Study size		Precision added to headers of table 3, 4 and 6 to provide information regarding the

					population used for calculation.
1.0	19MAR2024	NA	Original	NA	NA

6. MILESTONES

Milestone	Planned Date
Completion of feasibility assessment	31 March 2024
Start of data collection	01 September 2024*
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Registration in the EU PAS register (HMA EMA RWD Catalogues)	25 March 2024
Final study report	31 December 2030

*Participating sites will contribute up to four years of data from the study start, plus eligible retrospective data from the time of 20vPnC availability.

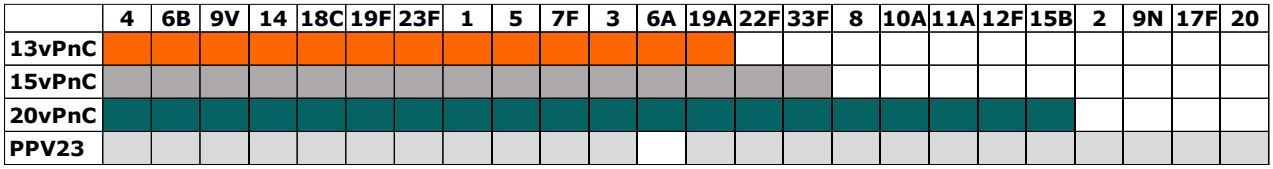
7. RATIONALE AND BACKGROUND

The 20-valent pneumococcal polysaccharide conjugate vaccine (20vPnC) was authorised for use in adults aged 18 years and above by the European Medicines Agency (EMA) on February 14, 2022 (1). The authorisation was based on safety and immunogenicity data, establishing an immunobridge to 13-valent pneumococcal conjugate vaccine (13vPnC), a licensed pneumococcal conjugate vaccine (PCV) with known efficacy. Although 20vPnC elicits robust responses to all vaccine serotypes in healthy adults that were non-inferior to the 13vPnC and 23-valent pneumococcal polysaccharide vaccine (PPV23) comparison group for 19 out of 20 serotypes, the opsonophagocytosis assays (OPA) responses of 11 of the 13 serotypes shared with 13vPnC were slightly lower than in the comparison group. Also, 20vPnC OPA response for serotype 8 did not meet pre-defined statistical noninferiority criteria (1). In its assessment report, the Committee for Medicinal Products for Human Use (CHMP) requested these uncertainties be addressed by conducting a number of 20vPnC real-world effectiveness studies. This protocol addresses the obligation to conduct a Phase 4 observational, real-world study to evaluate the effectiveness of 20vPnC against vaccine-type invasive pneumococcal disease (IPD) in adults in Europe.

Previous studies have shown that 13vPnC provides robust protection against 13vPnC serotypes in adults aged 65 years and above. Efficacy against 13vPnC types was estimated as 75% (95%CI 41–91) in one randomised controlled trial in the Netherlands (2), and effectiveness against 13vPnC types was estimated as 68% (95%CI 34–84), 59% (95%CI 11–81), and 47% (95%CI 4–71) in three observational studies conducted in the United States (3). 13vPnC also provides some level of cross-protection against a number of vaccine-related types (VRTs) in children, amounting to 64% (33-81) for all VRTs, 94% (68-99) for serotype 6C and 59% (14-81) for serotype 23B in a multi-country observational study (4). Cross-protection against VRT has not been assessed so far in adults according to a 2023 systematic review of pneumococcal vaccine efficacy and effectiveness (3). Infants vaccinated with 20vPnC during clinical trials demonstrated cross-reactive antibody responses to serotypes 6C and 15C (5). Cross-reactivity to 15C was also demonstrated in adults vaccinated with 20vPnC; 6C was not assessed in this study but cross-reactive antibody responses to 6C have been demonstrated in adults vaccinated with 13vPnC.

At the time of 20vPnC authorisation, 25 European Member States were offering PPV23 and/or 13vPnC for older adults and/or for adults in high-risk groups (e.g., persons with immunocompromising conditions) and risk groups (e.g., persons with certain chronic conditions) (6) (Figure 1). PPV23 offers moderate (~45%) (3), short-term protection of 2-5 years against vaccine-type IPD in older adults (7, 8); whereas 13vPnC showed 75% efficacy in preventing vaccine-type IPD (2) and a duration of protection of at least 5 years (9).

Figure 1 Serotypes included in each adult pneumococcal vaccine



Abbreviations: 13vPnC: 13-valent pneumococcal conjugate vaccine; 15vPnC: 15-valent pneumococcal conjugate vaccine; 20vPnC: 20-valent pneumococcal conjugate vaccine; PPV23: 23-valent pneumococcal polysaccharide vaccine.

The epidemiology of IPD in adults in the EU has changed with the introduction of PCVs in the childhood immunisation programs of most European countries. These vaccines led to a notable decline in IPD incidence in older adults, which has been attributed to an indirect effect of the childhood program up to 2014 due to a decline in vaccine-serotype infections (10). However, in some settings an increase in IPD incidence in 2015-2018 occurred, due to an increase in non-13vPnC serotypes (serotype replacement) (10, 11). In 2018, a study conducted in ten European Union (EU)/European Economic Area (EEA) countries, reported a total of 9,410 IPD cases in adults aged 65 years and above and a pooled incidence of 28.5 per 100,000 population (10). Notification rates vary widely across countries due to differences in surveillance systems, such as case definitions and laboratory methods (12). In 2018, the five most common serotypes causing IPD in adults aged 65 years and above in EU/EEA were serotypes 3 (14.7%), 8 (14.0%), 19A (7.6%), 22F (7.4%), and 9N (5.4%) (11, 13, 14). Among all IPD cases, 66% were caused by serotypes included in the 20vPnC in ten EU/EEA countries (15). As expected, the contribution of 20non13vPnC serotypes was higher in countries with the most pronounced reduction in 13vPnC serotypes (16). Of special concern in recent years is the increase observed in serotype 8 IPD, a highly invasive 20non13vPnC serotype (10, 16, 17).

In 2020-2021, IPD incidence rates declined again in EU and non-EU countries in all age groups, likely due to the non-pharmaceutical interventions adopted during the COVID-19 pandemic, and then increased again in 2022-2023 (13). Infants, adults aged 65 years and above, and immunocompromised individuals continue to be the most affected.

Since 20vPnC EMA authorisation (2022), adult pneumococcal vaccine recommendations have been updated in different EU countries, with large variations in terms of funding, target groups (age and risk groups), and schedule for those already vaccinated with PPV23 and/or 13vPnC. 20vPnC uptake is expected to vary across countries, as it was observed in a multi-centre EU study for PPV23 and 13vPnC conducted in 2022 (18). In countries that recommended its administration to all adults aged 65 years and above, PPV23 uptake was as low as 15% in Norway and as high as 71% in England (18) and the Madrid region in Spain

(19), and even higher in Israel (77-79%) (20). In countries where PPV23 was recommended for adults at risk of IPD, such as Finland and France, the uptake remained low in 2018 (2-7%) (18). After EMA licensed 13vPnC for adult IPD in 2011, it has primarily been targeted for adults at risk (e.g., Denmark, Finland, France) or at high risk (e.g., England, Scotland, Sweden), with large uptake variation across countries, ranging from 4% in France to 25-30% in Finland (18). Few countries/regions (e.g., Czechia, Madrid region) have recommended 13vPnC for all older adults and uptake in these areas has varied, exceeding 45% in Madrid (19).

To address the commitment to EMA of a post-authorisation VE study, a surveillance network will be set up to conduct a multi-centre 20vPnC VE study against vaccine-serotype IPD using the indirect cohort (Broome) method (21). This design estimates the effectiveness of pneumococcal vaccines by comparing the vaccination status of vaccine-serotype cases to that of non-vaccine serotype cases; this has been the main method used to measure the effectiveness of PCVs against IPD in recent years (7, 22, 23).

8. RESEARCH QUESTION AND OBJECTIVES

This post-authorisation descriptive study does not aim to test a hypothesis but rather to estimate the effectiveness of the 20vPnC vaccine against vaccine-type IPD.

8.1. Primary objective

1. The primary objective (objective 1) is to estimate vaccine effectiveness (VE) of 20-valent pneumococcal conjugate vaccine (20vPnC) against IPD due to any of the 20 serotypes that are included in the vaccine (20vPnC serotypes), in adults aged 65 years and above.

8.2. Secondary objectives

The secondary objectives are:

2. To estimate VE of 20vPnC against IPD due to any of the 13 serotypes that are included in 13vPnC (13vPnC serotypes), in adults aged 65 years and above
3. To estimate VE of 20vPnC against IPD due to any of the 7 serotypes that are included in 20vPnC but not in 13vPnC (20non13vPnC serotypes), in adults aged 65 years and above

Secondary objectives will be contingent on reaching sample size requirements.

8.3. Exploratory objectives

4. To estimate serotype-specific VE of 20vPnC against IPD due to each of the 20vPnC individual serotypes, in adults aged 65 years and above
5. To estimate VE of 20vPnC against IPD due to any of the 20vPnC serotypes with the exclusion of serotype 3, in adults aged 65 years and above

6. To estimate VE of 20vPnC against IPD due to any of the 13vPnC serotypes with the exclusion of serotype 3, in adults aged 65 years and above
7. To estimate the serotype-specific VE of 20vPnC against IPD due to VRT 6C, individually and in combination with 20vPnC serotypes, in adults aged 65 years and above
8. To estimate the serotype-specific VE of 20vPnC against IPD due to VRT 15C, individually and in combination with the 20vPnC serotypes, in adults aged 65 years and above
9. To estimate the serotype-specific VE of 20vPnC against IPD due to 20vPnC serotypes and VRT 6C and 15C, in adults aged 65 years and above
10. To estimate the VE of 20vPnC against IPD due to other 20vPnC VRT, i.e., serotypes with the same serogroup as the 20vPnC serotypes (see list in Table 1 footnote), in adults aged 65 years and above
11. To estimate VE of 20vPnC in combination with previous pneumococcal vaccines against IPD due to 20vPnC serotypes in adults aged 65 years and above who previously received a different pneumococcal vaccine.
12. To assess waning by estimating the VE of 20vPnC against IPD due to any of the 20vPnC serotypes by time since vaccination, in adults aged 65 years and above
13. To describe IPD serotype distribution in adults aged 18 years and above, overall and by age subgroup

Exploratory objectives will be evaluated if case sample size allows.

9. RESEARCH METHODS

9.1. Study Design

This is a multi-country observational study, where VE will be measured using the indirect cohort (Broome) method (21). This method is a variant of the case-control design but only IPD patients are included. Here, for the primary objective, cases are IPD caused by serotypes that are included in the 20vPnC vaccine (vaccine-serotype patients), and controls are patients with non-20vPnC serotype IPD. All VE estimates are calculated by comparing vaccination status between cases (vaccine-serotype) and controls (non-vaccine serotype). This method is based on secondary data collection, i.e., data from IPD surveillance already collected by national or regional surveillance systems. All serotyped IPD patients are considered. Vaccine serotype IPD patients (cases) and non-vaccine serotype IPD patients (controls) are assumed to be similar in terms of risk factors and use of health care, which minimises selection bias. Moreover, information bias is unlikely to be differential between cases and controls as they all enter in the IPD surveillance system before serotyping is known. A limitation of the Broome method is that it may underestimate VE against VRT due to cross-protection, and it

may overestimate VE if vaccination increases the risk of non-vaccine serotype disease in vaccinated individuals compared to those who are unvaccinated.

Because of potential cross-protection against VRT, IPD patients with disease caused by VRT showing evidence of some level of cross-protection will be excluded from the control group.

9.2. Setting

The study will be based on data from IPD surveillance systems (e.g., national, regional, hospital-based). These registries systematically gather data on IPD cases at a population level, frequently encompassing an entire region or country. As this will be a multi-country study, this approach will give the study its best chance at achieving generalisability of study results to Europe.

Study sites will be selected based on their health authorities' recommendation for 20vPnC in adults, expected vaccine uptake, expected number of serotyped IPD cases, quality of surveillance system including the ability to access information on vaccination history, and feasibility to collaborate. Because of these requirements, many European countries are not currently eligible to participate in this study. Feasibility has been successfully completed for the regions of Catalonia, Galicia and Madrid (Spain), Israel, and Czechia. Additional sites might be added.

9.2.1. Inclusion Criteria

The study population consists of adult patients with IPD who were recorded in the collaborating IPD surveillance system.

The European Centre for Disease Prevention and Control (ECDC) definition of IPD (2018) will be used, see Box 1.

Box 1. ECDC case definition of IPD

ECDC defines IPD based on at least one of the following laboratory criteria (2018) (24):
- Isolation of *Streptococcus pneumoniae* from a normally sterile site (e.g., blood, cerebrospinal fluid, and pleural fluid) - Detection of *S. pneumoniae* nucleic acid from a normally sterile site - Detection of *S. pneumoniae* antigen from a normally sterile site

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

9.2.1.1. Inclusion Criteria for VE analysis

- IPD patients are eligible if they are 65 years of age or above, are eligible for 20vPnC vaccination in the site, and do not fulfil any of the exclusion criteria.

9.2.1.2. Inclusion Criteria for serotype distribution objective

- IPD patients are eligible if they are 18 years of age or above, and do not fulfil any of the exclusion criteria.

9.2.2. Exclusion Criteria

- Patients meeting any of the following criteria will not be included in the study:

9.2.2.1. Exclusion Criteria for VE analysis

The following exclusion criteria will be applied to IPD patients for all VE study objectives (see additional details in Table 1):

1. Missing serotype information (i.e., not typed)*
2. Pneumococcal vaccination status unknown**
3. 20vPnC vaccination <14 days prior to IPD
4. Age unknown
5. No informed consent (if applicable)

*Note that non-typeable (non-encapsulated) pneumococci will be counted as non-20vPnC type.

**Note that IPD patients with unknown vaccine status will be used to compare baseline characteristics between IPD patients with known and unknown vaccination status.

9.2.2.2. Exclusion Criteria for serotype distribution objective

1. Missing serotype information (i.e., not typed*)
2. Age unknown
3. No informed consent (if applicable)

*Note that non-typeable (non-encapsulated) pneumococci will be counted as non-20vPnC type.

9.2.3. Study period

Participating sites will contribute up to four years of data from the study start, plus eligible retrospective data from the time of 20vPnC availability (if applicable), with a minimum of one year of data collection.

9.3. Variables

9.3.1. Outcomes

Table 1 summarises the definitions of outcome per study objective.

Cases will be defined as patients with vaccine serotype or VRTs IPD (Table 1).

Controls will be defined as patients with IPD with non-vaccine serotypes and excluding VRTs 6C, 15C and 23B IPD, i.e., any serotype other than the 20vPnC serotypes and these three VRT (Table 1). Controls will be the same for all objectives.

The outcome variable to be collected is:

- *S. pneumoniae* serotype

Serotyping will be done as part of routine surveillance activities, and isolates will be typed or serotypes confirmed at regional or national reference laboratories. All laboratories performing serotyping activities will undergo regular External Quality Assessment (EQA) as part of the present post-authorization study (25).

Table 1. Outcome definition per study objective related to VE

Objectives	Outcome	
	Cases	**Controls**
Primary objective		
Objective 1: 20vPnC VE against IPD due to any of the 20 serotypes included in 20vPnC	IPD due to any 20vPnC serotype: 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F	IPD due to any serotype other than the 20vPnC serotypes and other than VRTs[a] 6C, 15C, and 23B
Secondary objectives		
Objective 2: 20vPnC VE against IPD due to any of the 13 serotypes that are included in both 20vPnC and 13vPnC	IPD due to any of the 13vPnC serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F	IPD due to any serotype other than the 20vPnC serotypes and other than VRTs[a] 6C, 15C, and 23B
Objective 3: 20vPnC VE against IPD due to any of the 7 20non13vPnC serotypes	IPD due to any of the 20non13vPnC serotypes: 8, 10A, 11A, 12F, 15B, 22F and 33F	
Exploratory objectives		
Objective 4: 20vPnC VE against IPD due to each of the 20vPnC individual serotypes	IPD due to a 20vPnC-specific serotype	IPD due to any serotype other than the 20vPnC serotypes and other than VRTs[a] 6C, 15C, and 23B
Objective 5: 20vPnC VE against IPD due to any of the 20 serotypes included in the 20vPnC excluding serotype 3	IPD due to any of the 20vPnC serotypes except serotype 3: 1, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F	
Objective 6: 20vPnC VE against IPD due to any of the 13 serotypes included in 20vPnC/13vPnC excluding serotype 3	IPD due to any of the 13vPnC serotypes except serotype 3: 1, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F	
Objective 7: 20vPnC VE against IPD due to VRT 6C (A) and in combination with 20vPnC serotypes (B)	IPD due to serotype 6C (A) OR 20vPnC serotypes and 6C (B)	
Objective 8: 20vPnC VE against IPD due to VRT 15C (A) and combination with 20vPnC serotypes (B)	IPD due to serotype 15C (A) OR 20vPnC serotypes and 15C (B)	
Objective 9: 20vPnC VE against IPD due to 20vPnC serotypes and VRT 6C or 15C	IPD due to serotype 20vPnC serotypes, 6C, and 15C (B)	
Objective 10: 20vPnC VE against IPD due to other 20vPnC-related serotypes	IPD due to other 20vPnC VRTs[b] than 6C, 15C, and 23B	IPD due to any serotype other than the 20vPnC serotypes and all VRTs

Table 1. Outcome definition per study objective related to VE

Objectives	Outcome	
	Cases	**Controls**
Objective 11: 20vPnC VE in combination with previous pneumococcal vaccine against IPD due to any of the 20vPnC serotypes in adults who previously received a different pneumococcal vaccine[c]	IPD due to any 20vPnC serotype: 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F	IPD due to any serotype other than the 20vPnC serotypes and other VRTs[a,b] than 6C, 15C, and 23B
Objective 12: 20vPnC VE against IPD due to any of the 20 serotypes included in 20vPnC serotypes by time since vaccination	IPD due to any 20vPnC serotype: 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F	IPD due to any serotype other than the 20vPnC serotypes and other than VRTs[a] 6C, 15C, and 23B

a. VRT serotypes selected per evidence of some level of cross-protection, i.e., immune response to 20vPnC vaccination, or some level of effectiveness in observational studies (e.g., 6C, 15C, 23B); the final VRT will be defined in the Statistical Analysis Plan (SAP) and will be based on the evidence collected during the time that the study is ongoing.

b. 20vPnC VRTs include other serotypes than 6A and 6B from serogroup 6, other serotypes than 7F from serogroup 7, other serotypes than 9V from serogroup 9, other serotypes than 10A from serogroup 10 and serotype 39 (26, 27), other serotypes than 11A from serogroup 11, other serotypes than 12F from serogroup 12, other serotypes than 15B from serogroup 15, other serotypes than 18C from serogroup 18, other serotypes than 19A and 19F from serogroup 19, other serotypes than 22F from serogroup 22, other serotypes than 23F from serogroup 23, and other serotypes than 33F from serogroup 33.

c. This includes 13vPnC, 15vPnC, and PPV23 vaccines. This objective will be based on different exposure than other objectives, see below under 9.3.2. The outcome will also vary based on prior pneumococcal vaccine, for example for those previously received 13vPnC cases would include IPD due to serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F or 23F. Further details on exposure and outcomes will be provided for this objective in the SAP.

Abbreviations: 13vPnC: 13-valent pneumococcal conjugate vaccine; 20vPnC: 20-valent pneumococcal conjugate vaccine; 20non13vPnC: serotypes included in 20vPnC but not in 13vPnC; IPD: invasive pneumococcal disease; VE: vaccine effectiveness; VRTs: vaccine-related serotypes.

9.3.2. Exposures

The exposure of interest is 20vPnC vaccination prior to invasive pneumococcal disease.

Information on doses of any pneumococcal vaccine (20vPnC and other) will be collected, including vaccination status, vaccination date, number of doses and vaccine type/brand.

IPD patients with 20vPnC vaccination <14 days prior to IPD will be excluded for VE analysis (see 9.2.1). For all objectives except objective 11, exposed and non-exposed patients will be identified among those with no history of PPV23 vaccination in the past 5 years and no history of 13vPnC or 15vPnC (15-valent pneumococcal conjugate vaccine) vaccination. For objective 11 (VE in adults who previously received a different pneumococcal vaccine), exposed patients will be those with a history of 13vPnC or 15vPnC or PPV23 vaccination

and 20vPnC vaccination. Non-exposed patients will be defined as those never vaccinated with any pneumococcal vaccine.

The exposure variables to be collected are:

- 20vPnC vaccination status (vaccinated, unvaccinated)
- Date of 20vPnC vaccination (DD/MM/YYYY) (preferred). If not possible at site level due to privacy concerns, the site should provide as an alternative the variable "Receipt of 20vPnC vaccination <14 days prior to IPD diagnosis" (yes/no), and "Time since 20vPnC vaccination", defined as the number of months between date of IPD sterile specimen collection (or hospital admission, or IPD diagnosis, date of report to surveillance system) and date of 20vPnC vaccination".
- PPV23 vaccination status (vaccinated, unvaccinated)
- Date of PPV23 vaccination (DD/MM/YYYY) (preferred). If not possible, the site should provide as an alternative the variable "Receipt of PPV23 vaccination <5 years prior to IPD diagnosis" (yes/no) and "Time since PPV23 vaccination" as explained before.
- 13vPnC vaccination status (vaccinated, unvaccinated)
- Date of 13vPnC vaccination (DD/MM/YYYY) (preferred). If not possible, the site should provide as an alternative the variable "Receipt of 13vPnC vaccination <14 days prior to IPD diagnosis" (yes/no), and "Time since 13vPnC vaccination" as explained before.
- 15vPnC vaccination status (vaccinated, unvaccinated)
- Date of 15vPnC vaccination (DD/MM/YYYY) (preferred). If not possible, the site should provide as an alternative the variable "Receipt of 15vPnC vaccination <14 days prior to IPD diagnosis" (yes/no), and "Time since 15vPnC vaccination" as explained before.

A multimodal variable will be used as exposure variable in the models (28). Immunisation status will be coded with mutually exclusive categories according to pneumococcal vaccination status (e.g., 20vPnC vaccination, previous PPV23, 13vPnC or 15vPnC vaccination), with no immunisation as the reference in all models, and depending on the objective. Additional analyses, for example, that report VE for other exposure categories beyond 20vPnC vaccination alone, will be described in the SAP (Statistical Analysis Plan).

9.3.3. Other variables

The list of variables below will be collected as potential confounding factors and/or as effect modifiers of the association between the vaccination status and the outcome.

- Study site (Site 1, 2, 3...)
- Age (years)
- Sex (female, male)
- Date of IPD diagnosis defined as the date of sterile specimen collection (DD/MM/YYYY) (preferred), or if this date is not available, consider as an alternative the date of hospital admission, date of IPD diagnosis, or date of report to surveillance system

- Site of sample (e.g., cerebrospinal fluid, blood)
- Clinical manifestation (e.g., meningitis IPD, non-meningitis IPD)
- Serotyping method (e.g., RT-PCR (Reverse Transcription Polymerase Chain Reaction), culture)
- Underlying disease (e.g., diabetes mellitus, chronic heart diseases, immunodeficiency)*
- Receipt of influenza vaccine in the past 12 months prior to IPD date (yes/no)

**Information on underlying disease will not be a criterion for exclusion of an IPD case. Likewise, data on influenza vaccination will be only collected where available.*

Details on variables collected at each site will be recorded in the surveillance manual.

9.4. Data Sources

9.4.1. IPD patient and serotype identification

Data sources for IPD patient definition (vaccine-serotype and non-vaccine serotype IPD) including serotyping and patient-level information will differ across study sites and may include national/regional IPD surveillance systems and patient medical records (i.e., secondary data collection). Sites will be selected per their ability to obtain serotyping and patient-level information (e.g., age, sex, date of IPD diagnosis and vaccination status) and provide individual-level data. Site-specific details on IPD surveillance methodology including data sources and serotyping methods will be captured in the site-specific documents. As serogroup 15 might not be completely typed in some sites, we will undertake external laboratory typing of serogroup 15 when needed.

9.4.2. Exposure ascertainment

Data sources for exposure ascertainment will mostly come from vaccination registries. Other sources may include patient medical records. Patient recall will not be accepted as source of information for vaccination status. Sites will be selected per their ability to obtain vaccination history data. IPD patients with vaccination status or date of vaccination unknown will be excluded from the VE analysis. Site-specific details on how pneumococcal vaccination status was ascertained at patient level will be captured in the site-specific documents. Data quality control is described under section 9.9.

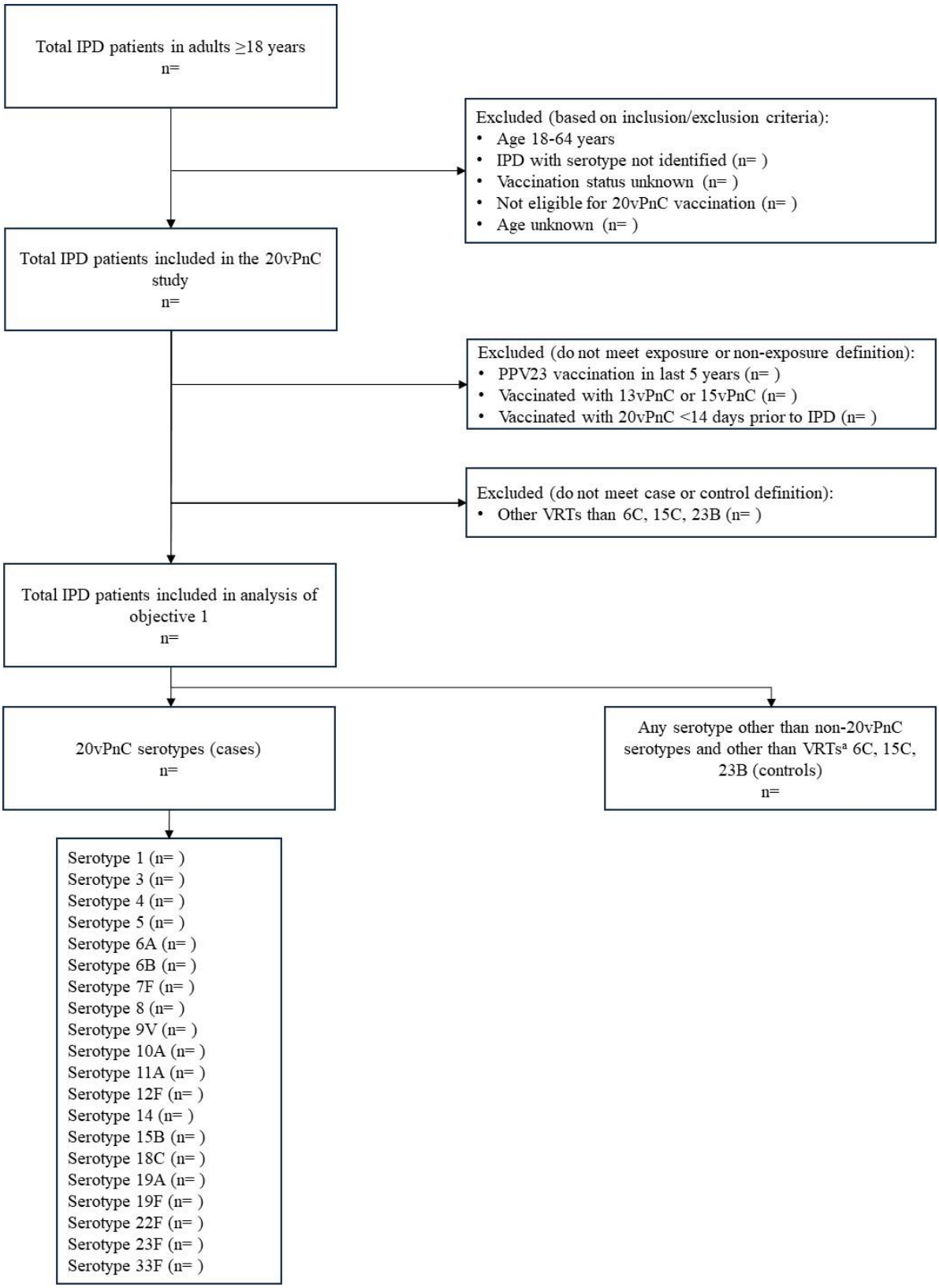
9.4.3. Identification of other variables

Data sources for identification of other variables will differ across study sites and may include, for example, patient hospital records or patient general practitioner records. Patient recall will not be accepted as a source of information for additional variables.

9.5. Attrition diagram

At a central level, and for every study site, an attrition diagram will be created per study objective (using Figure 2 as the pro forma). This diagram will describe the number of records excluded from the statistical analysis, by reason of exclusion. This diagram will be updated 1-2 times per year depending on the frequency of data uploading.

Figure 2. Pro forma attrition diagram (corresponding to objective 1)



a. VRTs excluded from controls will be selected per evidence of some level of cross-protection (see footnote in Table 1).
Abbreviations: 13vPnC: 13-valent pneumococcal conjugate vaccine; 15vPnC: 15-valent pneumococcal conjugate vaccine; 20vPnC: 20-valent pneumococcal conjugate vaccine; IPD: invasive pneumococcal disease; PPV23: 23-valent pneumococcal polysaccharide vaccine; VRTs: vaccine related serotypes.

9.6. Study Size

Sample size calculations are based on the primary objective (see Figure 2, box "Total IPD patients included in analysis of objective 1"). The number of patients that should be included in the analysis of the primary objective depends on the estimated VE, the ratio of cases to controls (depending on serotype distribution in the study population, see below), and the percentage of individuals vaccinated with 20vPnC. The total number of patients aged 65 years and above to be evaluated for study inclusion additionally depends on the proportion of patients that do not meet the inclusion/exclusion criteria, the exposed or non-exposed definition, the case or control definition or the degree of heterogeneity in the data (e.g., clustering). The sample size estimation provided below does not account for data clustering or adjustment for covariates.

Sample size calculations estimating the number of patients that should be included in the analysis were conducted for VE ranging from 55% to 75%, with a base case of 65%. The range of estimated VE was based on available data on 13vPnC efficacy and effectiveness against 13vPnC-type IPD. A randomised controlled trial in the Netherlands demonstrated 75% efficacy (95%CI 41–91) in adults aged 65 years and above (2). Three observational studies conducted in the United States reported 13vPnC effectiveness against 13vPnC serotype IPD in adults aged 65 years and above of 68% (95%CI 34–84), 59% (95%CI 11–81), and 47% (95%CI 4–71) (3).

For the estimated proportion of IPD due to 20vPnC, IPD surveillance data for adults aged 65 years and above in the EU/EEA reported to ECDC during 2018–2020 were used (Table 2). Serotypes included in 20vPnC caused 64% of IPD; however, after excluding VRTs 6C, 15C, and 23B from the total (7%), the proportion of IPD due to 20vPnC serotypes was 69%, which corresponds to a ratio of 1 case:0.45 controls. Although serotype distribution of IPD cases varies by country, the EU/EEA data serve as the estimated serotype distribution across the potential study sites that expressed interest in participating in this study (included in Table 2) for the purpose of sample size calculations.

Table 2 IPD serotype distribution for EU/EEA and selected countries.

Data are for adults aged 65 years and above from 2018–2020, except where noted.

Country	IPD cases (n)	20vPnC	13vPnC	20vPnC non-13vPnC	15C	23B	6C	6C+15C+23B	8	3
EU/EEA (29)	27835	63.9%	28.9%	35.0%	0.6%	2.7%	3.6 %	6.9%	14.9%	14.7%

Czechia (30)	606	68.8%	43.6%	25.2%	1.2%	2.0%	5.8 %	8.9%	9.4%	21.5%
Netherlands (29)	1012	72.3%	29.3%	43.0%	0.4%	2.5%	4.3 %	7.2%	22.4%	10.1%
Spain (29)	2903	63.1%	26.9%	36.2%	0.9%	2.6%	3.9 %	7.4%	16.7%	14.1%
Israel (20)[b]	170	48.8%	17.1%	31.8%	2.9%[c]	NA[d]	NA[d]	2.9%	12.4%	5.3%
Switzerland (31)[a]	2421	70.8%	31.4%	39.4%	0.4%	3.1%	1.6 %	5.0%	16.4%	17.8%

a. Data are for all ages; however, a large proportion of cases were from adults aged 65 years and above.

b. Data for Israel is for 2018-2019 only

c. This serotype was reported as 15B/C

d. These serotypes (23B and 6C) were not reported for Israel

For the percentage of individuals vaccinated with 20vPnC, sample size calculations were undertaken for a range of 10% to 40%. Uptake of 20vPnC will vary by country due to differences in vaccine recommendations, health care policies and utilisation, and will likely increase over time following vaccine introduction. For the base case, a conservative estimate of 15% was used, intended to reflect the average vaccine uptake across the study period.

As the objective of this study is to evaluate vaccine effectiveness, sample size estimates focus on the precision of the estimate, indicated by the width of the 95% confidence intervals (CI), rather than hypothesis-based testing, consistent with the approach used by ECDC for vaccine effectiveness study protocols evaluating COVID-19 and influenza vaccines (32). CI for the odds ratio (OR) are asymmetrical around the point estimate on the arithmetic scale, with the length shorter at the lower limit. As VE is calculated as (1-OR) x 100%, the length of the confidence interval will always be shorter at the upper limit of the VE point estimate. Therefore, the focus is on the precision of the lower limit (distance from the point estimate) of the 95% CI. Sample size estimates for the range of VE estimates (60-70%) and 20vPnC uptake percentage (10-20%) and assuming a 1:0.45 case:control ratio, with a precision of 40% and 30% (or 0.4 and 0.3) at the lower limit of 95% CI for VE are shown in Table 3. Sample size estimates for wider ranges for VE (55-75%) and 20vPnC uptake (10-40%), and precision of 20-40% (0.2-0.4) are shown in Annex 3 (Table 6).

Table 3. Sample size calculations for the primary objective VE against 20vPnC-type IPD, in adults ≥65 years of age.

Assumes case-control ratio of 1:0.45. Base case shown in bold. Sample size calculations for a wider range of VE, 20vPnC uptake, and 0.2 precision are provided in Annex 3.

Precision (distance to	20vPnC uptake (%)	Controls	Cases	Total evaluable	VE (%)	95% CI

lower bound of 95% CI)						
0.4	10	135	300	435	70	30-87
0.4	10	158	351	509	65	25-84
0.4	10	175	389	564	60	20-80
0.4	15	92	204	296	70	30-87
0.4	**15**	**105**	**233**	**338**	**65**	**25-84**
0.4	15	120	267	387	60	20-80
0.4	20	70	156	226	70	30-87
0.4	20	82	182	264	65	25-84
0.4	20	92	204	296	60	20-80
0.3	10	200	444	644	70	40-85
0.3	10	235	522	757	65	35-81
0.3	10	270	600	870	60	30-77
0.3	15	140	311	451	70	40-85
0.3	**15**	**158**	**351**	**509**	**65**	**35-81**
0.3	15	182	404	586	60	30-77
0.3	20	105	233	338	70	40-85
0.3	20	125	278	403	65	35-81
0.3	20	145	322	467	60	30-77

Abbreviations: 20vPnC: 20-valent pneumococcal conjugate vaccine; CI: confidence interval; IPD: invasive pneumococcal disease; VE: vaccine effectiveness. The sample size estimates above are for the crude analysis and an adjusted analysis would require a larger sample size.

For the primary objective under the base case assumption (64% of IPD due to 20vPnC serotypes, 65% VE, 15% 20vPnC uptake), 338 evaluable IPD cases are required for a precision of 0.4 (lower bound of the 95% CI equals 25) and 509 evaluable IPD cases are required for a precision of 0.3 (lower bound of the 95% CI equals 35). These numbers are considered the minimum target for evaluable cases; additional IPD cases will be required to account for exclusion of non-evaluable IPD cases such as patients ineligible for analysis because of prior pneumococcal vaccination, missing vaccination history or serotyping information, as well as the exclusion of IPD caused by VRTs. The proportion of non-evaluable IPD cases will likely vary by site; for a base case example (0.3 precision), if 25% of IPD cases are non-evaluable, a total of 679 IPD cases will be needed to obtain the target 509 evaluable cases. As this is a surveillance study, cases will be accrued continuously during the entire study period. A larger number of evaluable IPD cases will result in more precise VE estimates, with narrower 95%CI.

Sample sizes were also calculated for the secondary objectives and the exploratory objective of VE for individual 20vPnC serotypes (objective 4), with serotype 8 used as an example. Serotype distribution for the EU/EEA (Table 2) was used to calculate the ratio of case and control of each objective, using the case and control definitions in Table 1. The base case sample size calculations, assuming 65% VE, 15% 20vPnC uptake, and a precision (distance to the lower bound of the 95%CI) of 0.4 and 0.3 are shown in Table 4. It is important to note

that the total number of IPD cases needed for these secondary and exploratory analyses is driven by obtaining sufficient cases, according to the analytical case definition. For example, for VE against 13vPnC serotypes, if 29% of IPD is due to 13vPnC serotypes, 586 IPD cases are needed to obtain 170 evaluable 13vPnC-type cases. Additional IPD cases needed to account for exclusion of non-evaluable cases (due to prior pneumococcal vaccination except for objective 11, missing vaccination history or serotyping information, and exclusion of VRTs) are not included in Table 4.

Table 4 Base case (65% VE, 15% 20vPnC uptake) sample size calculations for secondary objectives and exploratory objective 4 (in adults ≥65 years of age).

(serotype 8 as an example)

Objective	Ratio of case : control	Precision (distance to lower bound of 95% CI)	Controls	Cases	Total evaluable	VE	95% CI
VE against 13vPnC serotypes (secondary)	1:1	0.4	170	170	340	65	25-84
		0.3	260	260	520	65	35-81
VE against 20non13vPnC serotypes (secondary)	1:0.82	0.4	150	183	333	65	25-84
		0.3	225	274	499	65	35-81
VE against serotype 8 (exploratory)	1:1.94	0.4	290	149	439	65	25-84
		0.3	430	222	652	65	35-81

Abbreviations: 13vPnC: 13-valent pneumococcal conjugate vaccine; 20non13vPnC: serotypes included in 20vPnC but not in 13vPnC; CI: confidence interval; VE: vaccine effectiveness. The sample size estimates above are for the crude analysis and an adjusted analysis would require a larger sample size.

During a feasibility assessment, data on the number of reported and serotyped IPD cases in adults aged 65 years and above in 2022 were collected from potential sites. For three sites planned to be included in the study, IPD serotyped case numbers in 2022 were as follows: Czechia n = 229, Israel n = 264, Madrid, Spain n = 200; total 693. Based on these case numbers, a total of 2722 serotyped IPD cases are estimated to be reported over a 4-year study duration. Only a portion of reported IPD cases will be evaluable, as cases with missing vaccination history, previous pneumococcal vaccination (except for objective 11) or other exclusion criteria as well as VRTs will need to be excluded from VE analysis. However, inclusion of a sufficient number of cases to meet the target sample size is expected. Additional sites are also being assessed for participation in the study, which may increase the total number of IPD cases.

9.7. Data Management

9.7.1. Data management at site level

Each site is responsible for the data collection, data entry, data validation, data cleaning, and data management of their patient-level study data. For every participating study site, the data flow and data management will be documented in detail in the Data Management Plan (DMP), including data collection, validation, data entry and data cleaning processes. All de-identified patient-level study data will be transformed to the study-specific dataset following the common codebook (this will be included in the SAP). The study site will perform quality checks and process any findings accordingly, with sufficient documentation to ensure transparency and reproducibility. When the performed data quality checks are satisfactory, the study site will upload the dataset to P95 systems. More detailed information on data management will be specified in the DMP.

Key data to monitor study progress in each site (at minimum: number of IPD patients per serotype group) will be uploaded 2-4 times per year. Data will undergo periodic checks to ensure its completeness (see section below). At the end of the study, the full dataset will be uploaded on P95 server.

9.7.2. Data management at central level

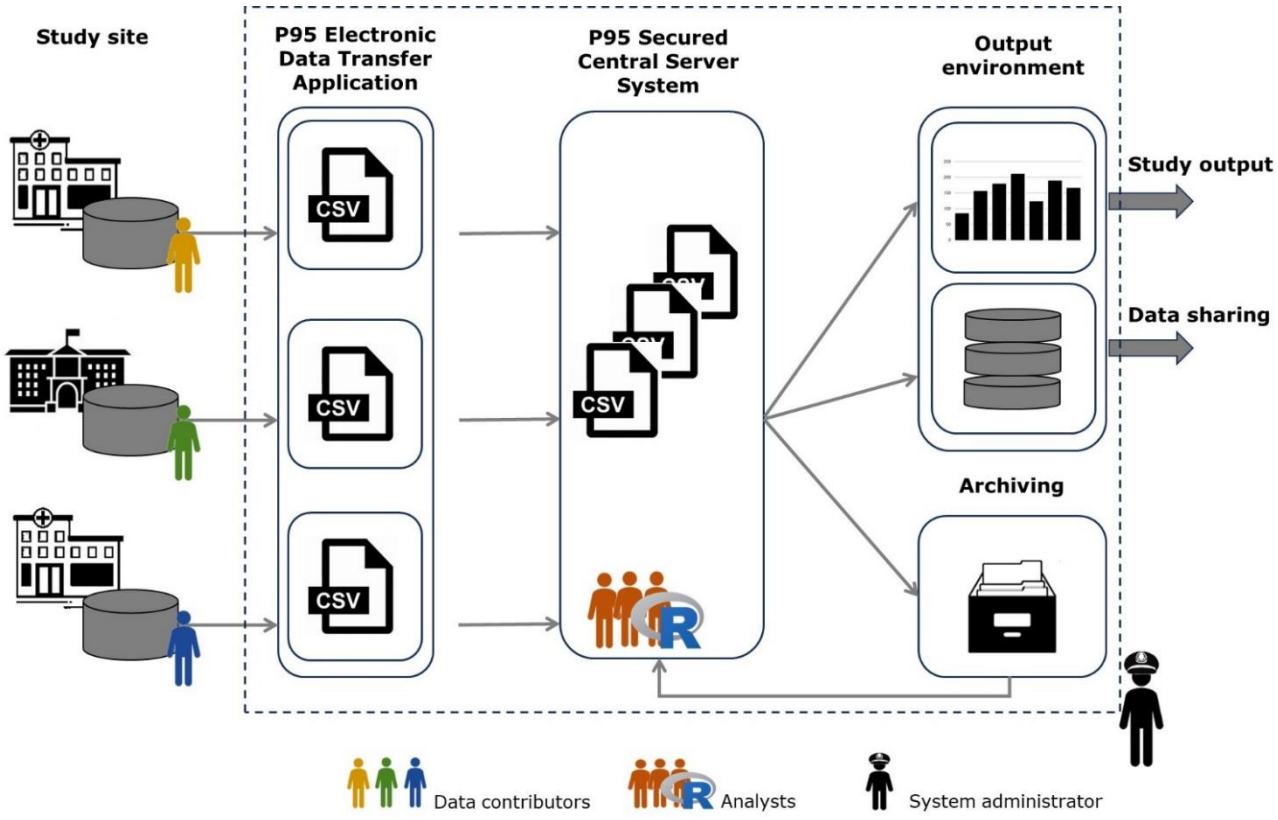
Study sites will submit to P95 a dataset with de-identified, patient-level IPD surveillance data for pooled analysis in a .csv file. The P95-secured central server will be an Azure data centre located in the EU. P95 will act as Data Processor according to the General Data Protection Regulation (GDPR) 2016/679. At the central level, a safe and robust electronic data capture (EDC) system, readily available for auditing and inspection, will be designated. The data flow from the study site to the central server and extraction of results from the central server is described in Figure 3.

1. Each site will upload the study-specific common dataset through the designated P95 EDC, a password-protected secure web application using a secure file transfer protocol (sFTP).
2. The data management team will perform data validations and quality checks as described in the DMP.
3. The P95 secure central server system administrator will check whether the data are compliant with the protocol, SAP, and privacy regulations.
    a. If the check is satisfactory, the system administrator will release the uploaded data to the study folder accessible to the data analysts (using remote desktop protocol (RDP)) and will perform a data lock (the data will be only readable by the data analysts and cannot be changed).
    b. If the check is not satisfactory, the system administrator will report this to the data and study managers and they will contact the study site responsible for the data. After that, data will be corrected and re-uploaded.
4. The data analysts will perform the required data transformations on the data released in the study folder as per the SAP.

5. When the data transformations are finalised, the data analysts will flag the resulting output files to the system administrator for extraction out of the secure central server. These output files will only contain aggregated summary data such as figures and tables with number of events, or estimates.
6. The system administrator will check the resulting output files flagged for extraction for compliance with the SAP.
    a. If the check is satisfactory, the resulting files will be extracted from the secure central server by the system administrator using sFTP.
    b. If the check is not satisfactory, the system administrator will report this to the data analysts and request changes to get the data into compliance with the SAP.
7. After the resulting files will be extracted from the secure central server, they can be used as the basis for reports, web applications and publications, per the SAP.

This data flow will be performed regularly (approximately 2-4 times per year) throughout the duration of the study.

Figure 3. Data flow from study sites to the P95 server and beyond



A DMP will be written detailing all steps of data management at the central level. The DMP will describe all functions, processes, responsibilities and specifications for data collection, data storage, and quality checking including internal and external audits, transfer, cleaning,

and validation. The DMP will be reviewed regularly and updated as appropriate in relation to lessons learnt within the study period.

9.8. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.8.1. Descriptive analysis

9.8.1.1. Descriptive analysis of missing data of variables

The completeness of information will be analysed for all the variables collected in the study. For each variable, the number and percentage of missing values will be described, by site and overall.

9.8.1.2. Description of participant characteristics

For every site and all sites together, the number of IPD patients (per objective – serotype group) will be described, along with their characteristics, including vaccination status and number of cases and controls.

The descriptive analysis will include at least the following participant characteristics:

- Serotype of IPD patients
- Sample site (e.g., blood, CSF(Cerebrospinal Fluid))
- Age group (to be defined depending on data availability)
- Sex (female, male)
- Year and month of IPD diagnosis (to be defined depending on data availability)
- Received 20vPnC (yes/no)
- Time since 20vPnC vaccination (e.g., <2 years, 2-5 years after vaccination)
- Prior pneumococcal vaccination (13vPnC, 15vPnC, PPV23 or any combination of these)
- Risk level defined based on underlying diseases
- Received influenza vaccine in the 12 months prior to diagnosis (yes, no)

A histogram showing the number of IPD cases and controls identified per month, stratified by serotype, serotype groups or main serotypes will be created.

Descriptive statistics will be used to identify outliers, inconsistencies, or implausible information at each study site.

9.8.1.3. Description of cases and controls

For each site and all sites together, the number of cases and controls (per objective – serotype group) will be described, along with the characteristics above described, including vaccination status and site. One-Way ANOVA, Wilcoxon, Chi-square, or other tests will be used to assess differences in baseline characteristics between cases and controls.

9.8.2. Statistical analyses for VE

9.8.2.1. Site-specific pneumococcal VE

For every study site and objective, the crude VE against vaccine serotype IPD will be estimated as VE = (1-OR) x 100%, with OR comparing the odds of vaccination among vaccine serotype IPD to the odds of vaccination among non-vaccine serotype IPD. The multimodal variable (see section 9.3.2) will be used as exposure variable. It accounts for 20vPnC exposure as well as for prior pneumococcal vaccination (e.g., PPV23 vaccination and 13vPnC vaccination) and is designed for each study objective according to Table 1.

A table per site showing the number of vaccinated and unvaccinated cases and controls and the crude VE per study site and objective will be built.

9.8.2.2. Pooled pneumococcal VE

Individual-level data will be pooled to assess the VE of 20vPnC against IPD. Crude analysis for pooled VE estimates will be performed. Confounder-adjusted pneumococcal VE estimates will be derived from multivariable logistic regression models (4, 7, 33). Models will be adjusted for potential confounding factors, including at least study site, year of IPD diagnosis, and age. Study site will be included as fixed effect in the models. Other variables (such as sex and influenza vaccination status) will be tested for potential confounding by using a directed acyclic graph (DAG), and included in final models if they are both significant and modify the vaccine effect by more than 10% (34, 35). Additionally, collinearity between independent variables will be assessed. Variables with high multicollinearity will be excluded from the model.

The sources of heterogeneity across sites (i.e., how much the effect size varies across sites) and their impact on VE estimates will be assessed (see SAP).

In accordance with the study objectives, we will build our main results tables. These tables will show the number of vaccinated and unvaccinated cases and controls and the crude and adjusted VE per study objective.

9.8.2.3. Stratified analysis

As part of objective 12 we will also stratify by time since 20vPnC vaccination (e.g., <2 years, 2-5 years after vaccination). Final stratifications will be defined in the SAP.

9.8.2.4. Assessment of bias

A limitation of the Broome method is that VE may be overestimated if vaccination increases the risk of non-vaccine serotype disease in vaccinated compared with unvaccinated individuals. To address this bias, we will evaluate its likelihood and, if appropriate, assess the magnitude of the bias based on published methods (36, 37). If appropriate, this bias will be assessed per each study objective separately.

9.8.2.5. Sensitivity analyses

To assess the robustness of our VE estimates, and depending on sample size, different sensitivity analyses will be considered:

- Adjustment for risk level as underlying diseases and immunocompromising conditions

may be confounding factors in the association between vaccination and IPD due to specific serotypes.
- Stratification for risk level, as this was a potential effect modifier in previous studies.
- Exclusion of all the VRTs (not only 6C, 15C, and 23B) from controls.

Other sensitivity analyses might be conducted when appropriate; all will be prespecified in the SAP.

9.8.3. Statistical analysis for serotype distribution

The number and proportion of total IPD due to individual serotypes will be reported for all adults aged 18 years and above and by age group (e.g., 18-64 years; 65 years and above). Sub-analyses, such as reporting serotype distribution by vaccine formulation by serotype, by site/country, and by year will be described in the SAP.

9.9. Quality Control

9.9.1. Data quality checks at site level

Each study site will describe the mechanisms and procedures to ensure data quality and integrity, including the accuracy of collected data and the extent of source data verification in the data quality plan.

9.9.2. Data quality checks at central level

Data quality checks will be performed at central level to assess compliance with the minimum data requirements, the presence of incomplete or duplicated records, variable formats, implausible values (e.g., dates of vaccination), inconsistencies between variables, and missing values. If data quality issues are identified, the site data manager will be contacted to clean the data prior to re-uploading. After this step, data will be re-uploaded, the study in/exclusion criteria will be applied, and an attrition diagram will be created (Figure 2).

An independent review of study results will be conducted by an external scientific expert committee, established by Pfizer and P95.

A data quality report will be produced for each site describing, at a minimum, the results of the quality checks performed and the attrition diagram. The report will be sent to the site for approval.

9.9.3. Qualifications

Each study site will provide certification and/or qualifications of any laboratories performing serotyping.

9.10. Limitations of the Research Methods

This study largely depends on the number of IPD serotyped cases and the availability of documented vaccination history. All sites will use serotyping methods with high specificity, thereby minimising the likelihood of outcome misclassification. Vaccination history will be

collected from all participants data and effort will be made to obtain documented vaccination records from national or regional vaccine registries if available, or electronic health records. Despite these planned approaches and after the data quality checks undertaken at central level (see section 9.9.2), it is likely that some proportion of patients will not have documented vaccination data available and so will be excluded from the VE analysis. We expect that data completeness will not affect the estimation of VE (under- or overestimation) since this will be non-differential between cases and controls.

The exclusion of previously 13vPnC-vaccinated IPD cases may limit sample size in settings with moderate to higher uptake and limit the representativeness of IPD patients if those at high risk are more likely to be 13vPnC vaccinated. The policies for revaccination of previously PPV23 vaccinated persons differ across countries and may also impact sample size. In sites in which the previously PPV23 vaccinated individuals represent a high proportion and are not being offered 20vPnC, this will limit sample size and impact the representativeness of the population as well. Also, remaining protection of PPV23 beyond 5 years cannot be ruled out, which will tend to underestimate 20vPnC VE (7, 8).

Although we will consider the most relevant potential confounders, residual confounding cannot be excluded from observational VE studies. Underlying diseases can potentially modify VE estimates, but only if immunocompromised individuals are more affected by non-20vPnC serotypes.

Another limitation of the study is that the Broome method assumes that 20vPnC vaccination does not change the risk of non-vaccine serotype disease in vaccinated compared to unvaccinated individuals. If the risk of non-vaccine serotype IPD is increased in vaccinated individuals, then VE could be overestimated. To estimate the effect of serotype replacement and potential overestimation of VE, we will provide an estimate of the potential bias (see 9.8.2.4). However, this bias has been found to have a small impact on VE estimates (2-5%) in previous studies in children (4, 36). To avoid the bias due to potential cross-protection against VRTs that would underestimate VE, we will exclude the selected VRTs 6C, 15C and 23B from the comparison group, and any other VRTs for which evidence has shown some level of cross protection (see 9.8.2.5).

Finally, our VE analysis will be limited to the IPD patients reported to the collaborating surveillance systems and with known vaccination status.

9.11. Archiving

To enable evaluations and/or audits from regulatory authorities or others, the site investigator(s) agree(s) to keep data relating to the study in an orderly manner in a secure study file, which will be available for audits/inspections, for a period of at least 10 years after the end of the study, or longer if required by local guidance/ legislation.

In the event that archiving of the file is no longer possible at the site, the site/investigator will be instructed to notify the study team. The investigator must contact the sponsor before destroying any study-related data. It is the responsibility of the sponsor to inform the study site of when these data no longer need to be retained. Retention, storage, and access rights will be predefined and described as appropriate.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

10.2. Patient Consent

This study will be based on IPD patients identified through routine surveillance at individual sites and conducted according to each local ethics regulations. Each site will be responsible for obtaining legal permission to process patient level confidential information. Due to the use of surveillance data, informed consent is typically not required. If informed consent is required, the feasibility of obtaining informed consent from patients (or their legal representative) will be assessed; if it is not considered feasible, the site will be excluded from the study. If required, informed consent will be obtained from the patient (or their legal representative).

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

This is an observational study involving secondary use of existing data. If at a site the study falls outside of the mandate of the Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) due to the use of surveillance data, a statement that no formal approval from the IRB/IEC is required is sufficient.

Sites for which ethics approval to share the data is required will submit the protocol to the relevant IRB/IEC for review, following local/national regulations and the Declaration of Helsinki. In this case, sites will not submit data to P95 until the study site has obtained written confirmation of a favourable opinion/approval from the relevant central or local IRB/IEC. The IRB/IEC will be asked to provide documentation of the date of the meeting at which the favourable opinion/approval was given that clearly identifies the study, the protocol version, and – if applicable - the informed consent form version reviewed. The investigator will share the approval with the study team.

Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IRB/IEC in a manner consistent with local regulations.

If applicable: there must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/ECs. All correspondence with the IRB/EC must be retained. Copies of IRB/EC approvals must be forwarded to Pfizer.

Should the study be terminated early for any unanticipated reason, the site investigator will be responsible for informing the IRB/IEC.

10.4. Ethical Conduct of the Study

To ensure the quality and integrity of research, this study will be conducted under the International Ethical Guidelines on Epidemiological Studies issued by the Council for

International Organizations of Medical Sciences (CIOMS, 2009), Good Epidemiological Practice (GEP), the ethical principles that have their origins in the Declaration of Helsinki and any applicable national laws, regulations, and guidelines.

This is an observational study without medical intervention or change in the clinical and diagnostic capacity. Therefore, there is no direct impact on participants. Nevertheless, there are important potential societal benefits derived from this VE study. Effective PCVs are key to reduce IPD incidence. Close monitoring of the effectiveness of PCVs is essential to guide decision-making regarding vaccine marketing approval, optimization of vaccination programmes and future pneumococcal vaccine development.

To support transparency requirements, that are outside the scope of Directive 2001/20/EC, and which are conducted pursuant to a condition of the marketing authorization or voluntarily, study information (including for studies conducted outside the EU) should be made available in the EU electronic register of post-authorization studies (EMA RWD Catalogues) maintained by the Agency. This recommendation is without prejudice to national transparency requirements.

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in section here above.

10.5. Patient confidentiality

Data will be de-identified at the site-level prior to data transfer to the P95 team.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant data. All parties will ensure protection of participants´ personal data and will not include participant names or other identifiable information on any study forms, reports, publications, or in any other disclosures, except where required by law. Every effort will be made to protect participant confidentiality according to Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons regarding the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC (GDPR).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a non-interventional epidemiological study for assessing the effectiveness of routine 20vPnC vaccination. The study sites should follow local requirements with respect to the submission of cases of suspected adverse events/reactions to the competent authority in the country where the event/reaction occurred.

This study involves a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event

(AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final report will be written containing all study results derived from the analyses prespecified in the study protocol and SAP, whether favourable or unfavourable. The final report will be submitted to the EMA by Pfizer to meet regulatory requirements. The final report will also be posted on the EMA RWD catalogue. In addition, study results will be dispersed to the scientific community through conference abstracts and publications in peer-reviewed journals. As this is a collaborative study, authors will include representatives from P95, Pfizer, and surveillance sites, according to ICMJE (International Committee of Medical Journal editor) criteria.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	1.1	TBC	Country Coordinating Investigators

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: A Phase 4 Observational, Real-World Study of 20-valent Pneumococcal Conjugate Vaccine Effectiveness Against Vaccine-Type Invasive Pneumococcal Disease in Adults ≥65 years

EU PAS Register® number: EUPAS1000000007
Study reference number (if applicable): NA

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	Yes	No	N/A	Section Number
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2, 9.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	8

Comments:

2.1.4. This post-authorisation descriptive study does not aim to test a hypothesis, but rather to estimate the effectiveness of the vaccine.

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1, 9.4.1, 10.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.8.3
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.8.2
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

3.3. Since this study describes the VE based on a case-control design, we do not measure disease occurrence. However, a study objective is to measure the serotype distribution of IPD cases.

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9.2

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2.2
4.2.2 Age and sex	☒	☐	☐	9.2.1
4.2.3 Country of origin	☒	☐	☐	PAES information, 9.2, 9.6
4.2.4 Disease/indication	☒	☐	☐	9.2.1
4.2.5 Duration of follow-up	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1

Comments:

4.2.5 This is a case-control study design with no follow-up of participants.

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.4.2, 9.9.2, 9.10
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.2
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.2
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.2
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.3.2

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.1 and Table 1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.1 and Table 1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.4.1

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

6.4 The outcomes included in this study are not related to Health Technology Assessment.

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.1, 9.8.2
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.1
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.1, 9.4

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.3.2, 9.3.3, 9.8.2.3

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4.2
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4.1
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.2
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.1
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3

Section 9: Data sources	Yes	No	N/A	Section Number
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

9.3.1 There is no precise ATC code for the 20vPnC vaccine, only for any pneumococcus polysaccharides antigen conjugated vaccine.

9.3.2 There is also no coding system described for the outcomes, which is pneumococcal serotypes, and IPD serotyping data is coming directly from the labs.

9.3.3 No coding system is defined for covariates in this master protocol. It is possible that underlying diseases would be reported by International Classification of Diseases (ICD) or International Classification of Primary Care (ICPC) codes at side level, but this will be described in the site-specific documents.

9.4 A linkage method between data sources is not described in this master protocol because this will vary per study site. It will be described in the site-specific documents.

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.8.2, 7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.6
10.3 Are descriptive analyses included?	☒	☐	☐	9.8.1
10.4 Are stratified analyses included?	☒	☐	☐	9.8.2.3
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.8.2.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.4.1
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.8.1.1, 9.9.2, 9.6
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.8.2.5

Comments:

10.7 Some approach is described in the protocol but methods for handling missing data will be further described in the Statistical analysis plan.

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.7.2
11.2 Are methods of quality assurance described?	☒	☐	☐	9.9

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.9.2

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.1
12.1.2 Information bias?	☒	☐	☐	9.1
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.8.2.4, 9.10
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.6 and 9.10

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.2
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.2
13.3 Have data protection requirements been described?	☒	☐	☐	10.4

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Germaine Hanquet

Date: dd/Month/year March 11, 2024

Signature: Germaine Hanquet

ANNEX 3. ADDITIONAL INFORMATION

Table 5. Country Coordinating Investigators

Name, Degree(s)	Job Title	Affiliation	Address

Table 6 Sample size calculations for the primary objective (in adults ≥65 years of age):

VE against 20vPnC-type IPD. Assumes case-control ratio of 1:0.45. Includes the following ranges: VE of 75-55%, 20vPnC uptake of 10-40%, precision (distance to lower bound of 95% CI) 0.4-0.2.

Precision (distance to lower bound of 95% CI)	20vPnC uptake (%)	Controls	Cases	Total evaluable	VE (%)	95% CI
0.4	10	120	267	387	75	35-90
0.4	10	135	300	435	70	30-87
0.4	10	158	351	509	65	25-84
0.4	10	175	389	564	60	20-80
0.4	10	200	444	644	55	15-76
0.4	15	80	178	258	75	35-90
0.4	15	92	204	296	70	30-87
0.4	15	105	233	338	65	25-84
0.4	15	120	267	387	60	20-80
0.4	15	135	300	435	55	15-76
0.4	20	60	133	193	75	35-90
0.4	20	70	156	226	70	30-87
0.4	20	82	182	264	65	25-84
0.4	20	92	204	296	60	20-80
0.4	20	105	233	338	55	15-76
0.4	25	49	109	158	75	35-90
0.4	25	58	129	187	70	30-87
0.4	25	68	151	219	65	25-84
0.4	25	76	169	245	60	20-80
0.4	25	88	196	284	55	15-76
0.4	30	42	93	135	75	35-90
0.4	30	50	111	161	70	30-87

Precision (distance to lower bound of 95% CI)	20vPnC uptake (%)	Controls	Cases	Total evaluable	VE (%)	95% CI
0.4	30	58	129	187	65	25-84
0.4	30	66	147	213	60	20-80
0.4	30	76	169	245	55	15-76
0.4	35	37	82	119	75	35-90
0.4	35	43	96	139	70	30-87
0.4	35	52	116	168	65	25-84
0.4	35	60	133	193	60	20-80
0.4	35	68	151	219	55	15-76
0.4	40	33	73	106	75	35-90
0.4	40	40	89	129	70	30-87
0.4	40	47	104	151	65	25-84
0.4	40	55	122	177	60	20-80
0.4	40	63	140	203	55	15-76
0.3	10	172	382	554	75	45-89
0.3	10	200	444	644	70	40-85
0.3	10	235	522	757	65	35-81
0.3	10	270	600	870	60	30-77
0.3	10	310	689	999	55	25-73
0.3	15	115	256	371	75	45-89
0.3	15	140	311	451	70	40-85
0.3	15	158	351	509	65	35-81
0.3	15	182	404	586	60	30-77
0.3	15	210	467	677	55	25-73
0.3	20	90	200	290	75	45-89
0.3	20	105	233	338	70	40-85
0.3	20	125	278	403	65	35-81
0.3	20	145	322	467	60	30-77
0.3	20	168	373	541	55	25-73
0.3	25	72	160	232	75	45-89
0.3	25	85	189	274	70	40-85
0.3	25	100	222	322	65	35-81
0.3	25	120	267	387	60	30-77
0.3	25	140	311	451	55	25-73
0.3	30	60	133	193	75	45-89
0.3	30	75	167	242	70	40-85
0.3	30	88	196	284	65	35-81

Precision (distance to lower bound of 95% CI)	20vPnC uptake (%)	Controls	Cases	Total evaluable	VE (%)	95% CI
0.3	30	102	227	329	60	30-77
0.3	30	118	262	380	55	25-73
0.3	35	55	122	177	75	45-89
0.3	35	66	147	213	70	40-85
0.3	35	77	171	248	65	35-81
0.3	35	90	200	290	60	30-77
0.3	35	105	233	338	55	25-73
0.3	40	48	107	155	75	45-89
0.3	40	60	133	193	70	40-85
0.3	40	72	160	232	65	35-81
0.3	40	86	191	277	60	30-77
0.3	40	100	222	322	55	25-73
0.2	10	310	689	999	75	55-86
0.2	10	370	822	1192	70	50-82
0.2	10	430	956	1386	65	45-78
0.2	10	500	1111	1611	60	40-74
0.2	10	580	1289	1869	55	35-69
0.2	15	210	467	677	75	55-86
0.2	15	250	556	806	70	50-82
0.2	15	310	689	999	65	45-78
0.2	15	365	811	1176	60	40-73
0.2	15	410	911	1321	55	35-69
0.2	20	160	356	516	75	55-86
0.2	20	200	444	644	70	50-82
0.2	20	240	533	773	65	45-78
0.2	20	280	622	902	60	40-73
0.2	20	320	711	1031	55	35-69
0.2	25	128	284	412	75	55-86
0.2	25	155	344	499	70	50-82
0.2	25	185	411	596	65	45-78
0.2	25	220	489	709	60	40-73
0.2	25	260	578	838	55	35-69
0.2	30	110	244	354	75	55-86
0.2	30	140	311	451	70	50-82
0.2	30	170	378	548	65	45-78
0.2	30	200	444	644	60	40-73

Precision (distance to lower bound of 95% CI)	20vPnC uptake (%)	Controls	Cases	Total evaluable	VE (%)	95% CI
0.2	30	230	511	741	55	35-69
0.2	35	95	211	306	75	55-86
0.2	35	120	267	387	70	50-82
0.2	35	145	322	467	65	45-78
0.2	35	170	378	548	60	40-73
0.2	35	200	444	644	55	35-69
0.2	40	85	189	274	75	55-86
0.2	40	105	233	338	70	50-82
0.2	40	130	289	419	65	45-78
0.2	40	155	344	499	60	40-74
0.2	40	185	411	596	55	35-69

Abbreviations: 20vPnC: 20-valent pneumococcal conjugate vaccine; CI: confidence interval; IPD: invasive pneumococcal disease; VE: vaccine effectiveness. The sample size estimates above are for the crude analysis and an adjusted analysis would require a larger sample size.