PREVENAR 20 (PNEUMOCOCCAL POLYSACCHARIDE CONJUGATE VACCINE [20-VALENT, ADSORBED])

RISK MANAGEMENT PLAN

RMP version to be assessed as part of this application:

RMP Version number: 6.0

Data lock points for this RMP:

Clinical trial data	09 September 2022 (paediatric dataset) 04 June 2020 (adult dataset)
Postmarketing data	07 December 2023

Date of final sign off: 18 April 2024

Rationale for submitting an updated RMP: This RMP is being updated to consolidate the EU RMP v. 4.1 with the latest approved EU RMP for adults (v. 5.0 dated 05 December 2023, which received a positive CHMP opinion on 11 April 2024).

Summary of significant changes in this RMP:

RMP Part/Module	Major Change (s)
PART I. PRODUCT(S) OVERVIEW	Minor update to reflect the paediatric indication as 'current' and clarify current posology for paediatric and adult subjects.
PART II. SAFETY SPECIFICATION	
Module SI. Epidemiology of the Indication(s) and Target Populations	Minor update to reflect the paediatric indication as currently approved.
Module SII. Non-Clinical Part of the Safety Specification	None.
Module SIII. Clinical Trial Exposure	Minor update to reflect the paediatric study B7471012 has completed.
Module SIV. Populations Not Studied in Clinical Trials	None.
Module SV. Post-Authorisation Experience	Updated to align the postauthorisation exposure to that of the latest Periodic Safety Update Report with data-lock point 07 December 2023.
Module SVI. Additional EU Requirements for the Safety Specification	None.
Module SVII. Identified and Potential Risks	None.
Module SVIII. Summary of the Safety Concerns	No updates made.
PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)	None.

RMP Part/Module	Major Change (s)
PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES	Updated to align with the latest approved EU RMP v. 5.0, where the feasibility assessment and SAP submission milestones were removed from the EU/Israel portion of Study B7471015 and reference to the inclusion of final protocol in Annex 5 is made. Additionally, protocol submission milestones of the IPD study has been removed.
PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)	No updates made.
PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN	Updated to reflect updates made in the other Parts of the RMP v. 6.0.
PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN	Annex 5 has been updated to include final Protocol for Study B7471015. Annex 8 has been updated to reflect changes made in EU RMP v. 6.0.

Other RMP versions under evaluation:

None.

Details of the currently approved RMP:

RMP Version number	Date of approval (Opinion date):	Procedure number:
v. 4.1	25 January 2024	EMEA/H/C/005451/II/0012
v. 5.0	11 April 2024	EMEA/H/C/005451/II/0023

QPPV name: Barbara De Bernardi

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

LIST OF ABBREVIATIONS

Abbreviation	Term
7vPnC	7-valent pneumococcal conjugate vaccine
13vPnC	13-valent pneumococcal conjugate vaccine
15vPnC	15-valent pneumococcal conjugate vaccine
20vPnC	20-valent pneumococcal conjugate vaccine
ABCs	Active Bacterial Core surveillance
ACIP	Advisory Committee on Immunization Practices
AE	adverse event
AIDS	acquired immunodeficiency syndrome
AOM	acute otitis media
ATC	anatomic classification
CAP	community-acquired pneumonia
CDC	Centers for Disease Control and Prevention
CSF	cerebrospinal fluid
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
COVID-19	Coronavirus Disease of 2019
CRM_{197}	cross-reactive material 197
CRP	C-reactive protein
CSR	clinical study report
cTnI	cardiac troponin I
DLP	data-lock point
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EEIG	European Economic Interest Grouping
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EPAR	European Public Assessment Report
EU	European Union
Excl.	excluding
FIB	fibrinogen
FUM	follow-up measure
GLP	Good Laboratory Practice
Hib	*Haemophilus influenzae* vaccine
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
H1N1	Pandemic influenza A 2009 virus strain
HSCT	haematopoietic stem cell transplant
ICU	intensive care unit
IgG	immunoglobulin G
IM	intramuscular
INN	international nonproprietary name
IPD	invasive pneumococcal disease

Abbreviation	Term
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MEA	measure
mRNA	messenger ribonucleic acid
NA	not applicable
NaCl	sodium chloride
NDTI	National Disease and Therapeutic Index
NMTA	National Medical and Treatment Audit
NR	Not reported
NZW	New Zealand white
OM	otitis media
OPA	opsonophagocytic activity
PAES	postauthorisation efficacy studies
PAS	post authorization study
PASS	postauthorisation safety study
pH	potential of hydrogen
PL	package leaflet
PK	pharmacokinetic
PnC	pneumococcal conjugate
PPSV23	pneumococcal polysaccharide 23-valent
PR	Puerto Rico
PSUR	periodic safety update report
PV	pharmacovigilance
PVA	pharmacovigilance activity
QIV	quadrivalent inactivated (vaccine)
QPPV	Qualified Person for Pharmacovigilance
RMM	risk-minimisation measure
RMP	Risk Management Plan
RWD	real world data
SAP	statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCD	sickle cell disease
SmPC	Summary of Product Characteristics
SIIV	seasonal inactivated influenza vaccine
UAD	urinary antigen detection
UK	United Kingdom
US	United States
USA	United States of America
VE	vaccine efficacy
VT	vaccine type
WHO	World Health Organisation

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PART I. PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed)
Pharmacotherapeutic group(s) (ATC Code)	Pneumococcal vaccines, ATC code: J07AL02
Marketing Authorisation Applicant	Pfizer Europe MA EEIG (Belgium)
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Prevenar 20
Marketing authorisation procedure	Centralised
Brief description of the product:	*Chemical class* Pneumococcal polysaccharide conjugate vaccine
	Summary of mode of action Pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed) (hereafter referred to as 20vPnC) contains 20 pneumococcal capsular polysaccharides, each conjugated to a CRM_{197} carrier protein, which modifies the immune response to the polysaccharide from a T-cell independent response to a T-cell dependent response. The T-cell dependent response leads to both an enhanced antibody response and generation of memory B-cells, allowing for an anamnestic (booster) response on re-exposure to the bacteria. Vaccination with 20vPnC induces serum antibody production and immunologic memory against the vaccine serotypes. Antibodies to some polysaccharides may cross react with related types and provide some protection against additional serotypes.
	Important information about its composition 20vPnC is a sterile liquid suspension for intramuscular (IM) administration of capsular polysaccharide antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F, each individually conjugated to the nontoxic variant of diphtheria toxin $CRM_{197,}$ as a carrier protein. Each prefilled syringe of 20vPnC is designed to deliver 2.2 µg of each serotype-specific polysaccharide conjugate, except for 6B, which is 4.4 µg/dose. The vaccine is formulated in 5 mM succinate buffer containing 0.88% sodium chloride (NaCl), 0.02% polysorbate 80 (PS 80), at pH 5.8, and aluminum phosphate at 0. 25 mg/mL aluminum as an adjuvant.
Hyperlink to the Product Information:	Module 1.3.1
Indication(s) in the EEA	Proposed: N/A
	Current: • Active immunisation for the prevention of invasive disease, pneumonia, and acute otitis media caused by *Streptococcus pneumoniae* in infants, children, and adolescents from 6 weeks to less than 18 years of age • Active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in individuals ≥18 years of age.

Dosage in the EEA	Proposed N/A.
	Current: *Paediatric:* See Section 4.2 *Posology and method of administration* of the SmPC for detailed information. The recommended immunisation series for 20vPnC given as part of a routine infant immunisation programme, consists of four doses, each of 0.5 mL. The primary infant series consists of three doses, with the first dose usually given at 2 months of age and with an interval of at least 4 weeks between doses. The first dose may be given as early as 6 weeks of age. The fourth (booster) dose is recommended between 11 and 15 months of age.[1] *Adult:* Single dose (0.5 mL) suspension for injection in prefilled syringe, to be given intramuscularly.
Pharmaceutical form(s) and strengths	Current: Single dose (0.5 mL) suspension for injection in prefilled syringe to deliver 2.2 µg of each serotype-specific polysaccharide, except for 6B, which is 4.4 µg/dose. The vaccine is formulated in 5 mM succinate buffer containing 0.88% NaCl, 0.02% polysorbate 80, at pH 5.8, and 0.25 mg/mL aluminium as an adjuvant.
Is/will the product be subject to additional monitoring in the EU?	Yes

[1] A Phase 3 randomised active-controlled trial, B7471011, conducted in healthy infants in the USA/Puerto Rico, provides immunogenicity data to support this dosing schedule.

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population(s)

Indication

The currently approved indications for 20vPnC in the European Union in paediatric and adult subjects are:

- Active immunisation for the prevention of invasive disease, pneumonia, and acute otitis media caused by *Streptococcus pneumoniae* in infants, children, and adolescents from 6 weeks to less than 18 years of age.

- Active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in individuals ≥18 years of age.

Incidence:

The incidence of pneumococcal disease is age specific, with the highest incidence among children <5 years of age (particularly among <2 years of age) and older adults.[1-3] Mucosal disease represents the majority of pneumococcal disease in all age groups. While IPD is less frequent, some clinical syndromes, such as meningitis and sepsis, are associated with a high case fatality ratio and risk of long-term sequelae. *Streptococcus pneumoniae* was included as 1 of the 12 WHO global priority pathogens in 2017 because of its high burden of disease and increasing rates of antibiotic resistance in many countries.[4]

Impact of 7vPnC and 13vPnC on Pneumococcal Disease Burden in Children

The introduction of 7vPnC and 13vPnC in national paediatric immunisation programs globally has led to substantial reductions in cases and deaths due to pneumococcal disease through direct and indirect effects. 13vPnC alone was estimated to have prevented ~175 million cases of pneumococcal infections and ~625,000 deaths among children <5 years of age globally between 2010 and 2019.[5]

Following the introduction of 7vPnC and 13vPnC in infant vaccination programs, a rapid, significant, and sustained reduction in all-cause and VT IPD was observed in children in many European countries compared with both the pre-7vPnC and pre-13vPnC periods.[6-12] In Denmark, overall IPD in children <2 years of age decreased by 65%–82% from 55 cases per 100,000 in 2000–2007 (pre-7vPnC period) to 10 and 19 cases per 100,000 in 2018 and 2019, respectively (13vPnC period).[13] In England and Wales, following introduction of 7vPnC and 13vPnC, overall IPD declined by 72% (95% CI: 65%–77%) and 74% (95% CI: 64%–81%) compared with the pre-7vPnC period among children <2 years and 2 to <5 years of age, respectively.[6]

The incidence of 13vPnC-type IPD declined by 88% in both the <2-year-old and 2 to 4-year-old age groups in 2016–2017, compared with the 7vPnC period (2008–2010), highlighting the incremental impact of 13vPnC over 7vPnC.[6] The reductions seen after 13vPnC was introduced into existing 7vPnC programs provide evidence that 13vPnC reduced IPD caused by the 6 additional serotypes as a group and maintained reductions in cases due to the

original 7vPnC serotypes.[6,14-16] In addition, the serotype 6A component of 13vPnC provided cross protection against carriage acquisition and invasive disease caused by serotype 6C.[6,17,18]

The introduction of 7vPnC and 13vPnC also resulted in large declines in the incidence of paediatric pneumococcal mucosal disease in Europe and globally.[19-33]. Declines in the incidence of all-cause CAP were observed in Europe after the introduction of 7vPnC and 13vPnC.[11,22,29] In France, the incidence of paediatric CAP emergency department visits decreased by 44% (95% CI: 32–56%) from 6.3 to 3.5 cases per 1000 visits in children ≤15 years of age within 3 years of 13vPnC introduction.[29] Vaccine impact against OM and mastoiditis have also been demonstrated after 13vPnC introduction.[33-35] While there are no VE studies against OM from Europe, a longstanding surveillance site in Israel demonstrated 13vPnC VE was 77.4% (95% CI: 53.3–92.1) against VT complicated OM including 89.0% [95% CI: 23.9–98.4] effectiveness against complicated OM caused by serotype 3.[36,37] In the UK, all-cause OM incidence in children <10 years of age declined by 51.3% between 2002 and 2012, from 135.8 episodes per 1000 person-years (95% CI: 134.4–137.3) to 66.1 episodes per 1000 person-years (95% CI: 64.9-67.4).[25]

Both 7vPnC and 13vPnC also provided indirect protection of vaccinated and unvaccinated persons by reducing nasopharyngeal carriage and transmission of vaccine serotypes from vaccinated populations. Indirect protection is an important component of pneumococcal conjugate vaccination programs and has led to substantial declines among children too young to be vaccinated (<6 weeks of age), older children, and adults.[21,38-41] In England and Wales, compared with the 7vPnC periods, the incidence of 7vPnC-type and 13vPnC-type IPD declined in all ages by 84% (95% CI: 80%–88%) and 64% (95% CI: 60%–68%), respectively, including 86% and 63% reductions among adults 45 through 64 years, respectively, and 84% and 47% reductions among ≥65 years of age, respectively.[6]

Despite reductions in disease due to 7vPnC and 13vPnC, a significant burden of paediatric pneumococcal disease remains, with a substantial proportion caused by the 20vPnC serotypes – mainly the 7 additional 20vPnC serotypes. By 2015, although paediatric pneumococcal deaths had declined by an estimated 51% since 2000, *S pneumoniae* still accounted for 3.7 million cases of severe pneumococcal disease and 294,000 deaths in children <5 years of age globally.[42]

Pneumococcal Disease in Older Children

Although the incidence of pneumococcal disease is lower in older children and adolescents than in younger children, healthy older children and adolescents still have some risk of pneumococcal disease. Incidence, severity, and case fatality rates are significantly elevated among older children with risk factors for pneumococcal disease, such as chronic medical conditions, cochlear implants, asthma, and sickle cell disease, and particularly among children with immunosuppression or immunodeficencies.[15,43-45] Risk of 13vPnC-type IPD was 27, 122, and 822 times higher among US children 6 through 18 years of age with SCD, HIV/AIDS, and hematologic malignancies, respectively, than among those without these conditions.[45]

Invasive Pneumococcal Disease in Adults

IPD incidence rates in adults for surveillance years between 2013 and 2019 have been reported for several European countries. The annual incidence per 100,000 population in adults ≥65 years of age was between 22.2 and 51.0[6,46-50] and 30-day case fatality rates for IPD varied between 11% and 30% for adults ≥65 years of age.[51-54]

The Active Bacterial Core surveillance (ABCs) system of the US Centers for Disease Control and Prevention (CDC) reported an incidence of 9.5 cases of IPD per 100,000 population in 2017.[55] An estimated 93% of 31,000 total US cases of IPD and 96% of 3590 associated deaths occurred in adults ≥18 years of age. The incidence (per 100,000 population of each age group) was highest among older adults (≥85 years: 41.8; 75–84 years: 29.3; 65–74 years: 20.8; 50–64 years: 16.6). There was a significant IPD case fatality rate of 13%, 11%, and 23% in persons 65 through 74, 75 through 84, and ≥85 years of age, respectively.

S. pneumoniae also remains the leading cause of acute bacterial meningitis in adults, with reported incidence rates between 0.51 and 1.5 per 100,000 in adults ≥65 years of age in Finland and France, respectively.[56,57] Similar incidence has been reported in the US.[58-60] Approximately one third of pneumococcal meningitis survivors develop neurologic sequelae, including hearing loss, followed by cranial nerve palsies, paresis, seizures, and hydrocephalus. The pooled prevalence of specific sequelae includes 21% with hearing loss, 12% with cranial nerve palsies, 9% with spasticity/paresis, 7% with seizures, 7% with hydrocephalus, and 2% with visual impairment.[61]

Burden of IPD in Adults ≥65 Years of Age Due to 13vPnC and 20vPnC Serotypes

The introduction of paediatric vaccination programs with 7vPnC and 13vPnC have led to substantial reductions in IPD and pneumococcal pneumonia in the paediatric population and older adults. However, despite the indirect effects from 13vPnC paediatric vaccination programs, the 13vPnC serotypes continue to circulate in the adult population and contributed between 19% and 48% of IPD cases in adults ≥65 years of age in the EEA in 2018[62] and to 27% of IPD cases in adults in this age group in the US in 2017.[63]

Also, the reduction of 13vPnC-type IPD cases in the adult population have been partially offset in some countries by increases in non-13vPnC serotypes (Table 1), which have disproportionately affected older adults and those with underlying comorbidities. Of note, increases in disease due to serotypes not covered by 13vPnC (including those covered by PPSV23 only) have also been observed in countries that have adult PPSV23 immunisation programs with high vaccine uptake in the target population. The increased burden of disease due to non-13vPnC serotypes, and the inability of PPSV23 to provide long-term protection at the population level, has created an unmet need for an expanded valency pneumococcal conjugate vaccine to protect older adults.

Table 1 Distribution of IPD Cases by Pneumococcal Conjugate Vaccine Serotype in Adults ≥65 Years of Age in Europe,[a] 2010–2018

STs	Surveillance Year								
	2010	2011	2012	2013	2014	2015	2016	2017	2018
7vPnC	17.7%	13.3%	11.5%	9.3%	8.3%	7.3%	6.9%	7.1%	5.3%
Additional 6 serotypes of 13vPnC									
All 6	36.4%	36.4%	32.0%	28.5%	25.3%	24.2%	22.9%	24.2%	24.0%
1	4.6%	3.8%	3.4%	2.7%	1.7%	0.9%	0.5%	0.3%	0.2%
5	0.6%	0.5%	0.3%	0.2%	0.1%	0.1%	0.0%	0.1%	0.0%
7F	7.5%	7.9%	6.3%	5.0%	4.3%	2.7%	2.0%	1.1%	0.9%
3	11.5%	11.2%	11.7%	12.5%	11.9%	12.6%	13.3%	14.7%	14.7%
19A	9.7%	10.4%	9.1%	7.0%	6.3%	7.0%	6.5%	7.3%	7.6%
6A	2.6%	2.5%	1.3%	1.1%	0.9%	0.9%	0.6%	0.7%	0.6%
Additional 7 serotypes of 20vPnC									
All 7	17.5%	21.5%	24.0%	25.5%	28.6%	32.1%	35.8%	34.9%	34.3%
22F	5.6%	7.4%	8.0%	7.6%	8.1%	7.9%	8.2%	8.0%	7.4%
33F	1.6%	2.3%	2.5%	2.5%	3.0%	3.1%	3.0%	2.5%	2.5%
8	3.8%	4.5%	5.2%	6.7%	7.7%	10.2%	12.7%	12.0%	14.0%
10A	1.7%	1.4%	1.7%	1.6%	2.3%	2.6%	2.3%	2.9%	2.3%
11A	2.1%	2.3%	2.7%	3.1%	2.7%	2.8%	2.6%	3.5%	2.8%
12F	1.9%	2.7%	2.6%	2.7%	3.8%	4.9%	6.0%	5.0%	4.0%
15B	0.8%	0.9%	1.2%	1.2%	0.9%	0.6%	1.0%	1.1%	1.3%
Non-20vPnC	28.4%	28.9%	32.6%	36.6%	37.8%	36.4%	34.4%	33.9%	36.4%

a. Includes Austria, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Romania, Slovakia, Slovenia, Spain, Sweden, and UK.
Source: ECDC Surveillance Atlas.[62]

The 7 additional serotypes covered by 20vPnC but not 13vPnC (8, 10A, 11A, 12F, 15B, 22F, and 33F) are responsible for a substantial proportion of the remaining IPD disease burden. In the EU, serotype 8 is of particular concern, causing 14% of all IPD cases in older adults in 2018, followed by 22F (7.4%), 12F (4.0%), 11A (2.8%), 33F (2.5%), 10A (2.3%) (Table 1). Overall, the serotypes included in 20vPnC represent 7 of the 10 most prevalent IPD serotypes in adults ≥65 years.

In addition, these serotypes have characteristics that make them medically important, including antibiotic resistance (11A, 15B), association with outbreaks (8, 12F), and a tendency to cause more severe disease (eg, association with meningitis and/or increased mortality rate) (10A, 11A, 22F).[64-71]

The percent of IPD in US adults ≥65 years of age in 2017 was determined using US CDC ABCs data.[63] The 7 additional serotypes covered by 20vPnC but not 13vPnC accounted for approximately one-quarter of the remaining IPD burden. Serotypes 22F, 11A, 33F, 8, and 15B were the 5 most prevalent. Together they accounted for 23.2% and individually they accounted for 9.4%, 4.4%, 3.8%, 3.3%, and 2.3%, respectively, of IPD. Of the 11 most common serotypes (3, 22F, 35B, 23A, 15A, 11A, 9N, 33F, 16F, 6C and 8, listed in descending order), 5 are 20vPnC serotypes (3, 22F, 11A, 33F and 8) and 6 are PPSV23

serotypes (3, 22F, 11A, 9N, 33F and 8), which has achieved population vaccination coverage between 60% to 70% over the past 10 years in this age group.[72]

The capsular polysaccharide of serotype 15B is highly related to 15C and has potential to induce cross-protective antibody to 15C. Serotype 15C has been shown to contribute 0.5% (in the EU) and 1.5% (in the US) of IPD in adults ≥65 years of age.[62,63]

Pneumococcal CAP in Adults

S. pneumoniae accounts for a significant amount of the global burden of lower respiratory tract infection cases. Studies from Europe have reported a high proportion of community-acquired pneumonia (CAP) due to *S. pneumoniae* in hospitalised adults. In a recent population-based cohort study from the UK, 36.6% of CAP cases in adults ≥16 years of age were caused by *S. pneumoniae*.[73] Similar proportions were also found in the Netherlands, Germany, Spain, and Sweden, and by a meta-analysis of 35 pneumonia studies in adults predominantly conducted in developed countries.[74-78]

Based on surveillance conducted by the US CDC from January 2010 to June 2012 of adults with all-cause CAP requiring hospitalisation, *S. pneumoniae* was the most common cause of bacterial pneumonia in adults ≥18 years of age, accounting for 9.7% of all-cause CAP.[79] *S. pneumoniae* was detected more frequently in patients requiring intensive care unit (ICU) support than in patients not requiring ICU support (8% vs 4%) and was associated with higher severity scores.[80]

Nonbacteraemic pneumococcal pneumonia is much more common than bacteraemic pneumococcal pneumonia. The specific etiology of nonbacteraemic pneumonia is difficult to determine due to a decrease in microbiological testing and routine use of empiric antibiotic treatment prior to testing. Therefore, the burden of pneumonia in the literature attributed to pneumococci may even be underestimated.[78] Use of diagnostic tests that do not rely on culturing a viable organism (eg, BinaxNOW and serotype-specific urinary antigen detection [UAD] assays) have identified a notable increase in proportion of pneumonia due to *S. pneumoniae* compared with culture alone (16.7% vs 4.6%).[81]

A study of pneumococcal disease of adults ≥50 years of age seen at inpatient and outpatient US Veterans' Affairs facilities between 2002 and 2011 found that nonbacteraemic pneumococcal pneumonia (diagnosed by respiratory culture and corresponding clinical diagnosis) was 6-fold more prevalent than bacteraemic pneumococcal pneumonia.[82] Similarly, 89.7% and 82.3% of adult cases of pneumococcal CAP large pneumonia surveillance studies in the UK (2013–2018) and Spain (2011–2014) were noninvasive.[73,76]

Regardless of the presence of bacteraemia, pneumococcal pneumonia is associated with complications and long-term sequelae in all age groups, including respiratory failure requiring hospitalisation, empyema, and necrotising pneumonia, exacerbations of chronic medical conditions,[83] declines in quality of life,[84] and with a significant increased risk of death within 30 days (acute) and 1 year (long-term) after the event.[85] In recent studies of older adults hospitalised with pneumococcal pneumonia in the US, 7.6% experienced a cardiovascular event after hospitalization, 58% continued to experience cognitive impairment

6 months after hospitalization, and quality of life remained lower at 6 months post-hospitalisation compared with before hospitalisation.[83,84,86] The surveillance conducted in veterans found inpatient mortality rates of 9.5% and 29.1% associated with nonbacteraemic and bacteraemic pneumococcal pneumonia, respectively.[82] Thirty-day mortality of adults ≥18 years of age with pneumococcal CAP in Spain was 8% (10% for those with invasive CAP and 6% for those with noninvasive CAP), and in the Netherlands was 13% for those with invasive CAP and 9% for those with noninvasive CAP.[87,88]

Moreover, *S pneumoniae* has been identified as one of the most common pathogens in influenza-related secondary bacterial pneumonia.[89] Coinfection with influenza and *S pneumoniae* may cause more severe disease than infection with either alone.[90-92] Both pneumococcal pneumonia and IPD have been associated with severe and fatal cases of influenza during influenza pandemics, including the 2009 H1N1 pandemic.[93-96]

Additionally, bacterial coinfection or secondary infection, including with *S pneumoniae*, has been reported with COVID-19 infections, and may be associated with more severe disease, although estimates of frequency vary and may be lower than with previous influenza pandemics.[97-103] Moreover, emerging data suggest that *S pneumoniae* may contribute to the pathogenesis of lower respiratory tract infections associated with respiratory viruses among adults.[104-107]

Burden of Pneumococcal CAP Due to 13vPnC and 20vPnC Serotypes in Adults

There exists a substantial burden of disease due to the 13vPnC and 20vPnC serotypes in adult CAP. The Pfizer UAD assay is a robust tool for clinical and epidemiological evaluation of both invasive and noninvasive pneumococcal disease in adults and provides an alternative to traditional serotyping methods from culture. The original UAD1 assay detects *S. pneumoniae* serotypes covered by 13vPnC. In addition, the UAD2 assay has been developed to detect 11 additional serotypes (2, 8, 9N, 10A, 11A, 12F, 15B/C, 17F, 20, 22F and 33F), including those in 20vPnC. UAD1 demonstrated 97% sensitivity and 100% specificity, and UAD2, 92.2% sensitivity and 95.9% specificity, both against a gold standard of bacteraemic CAP.[108,109]

In a prospective, observational study of 518 adults ≥18 years of age hospitalised with radiologically-confirmed CAP in Malmö, Sweden, 13vPnC or 20vPnC serotypes were detected in 10.0% and 15.2% in adults ≥65 years of age (Table 2). CAP in individuals ≥65 years of age with high-risk conditions was also associated with a high proportion of 13vPnC or 20vPnC-type pneumococcal disease (11.3% and 17.0%, respectively, Table 2).

Table 2. Proportion of CAP Due to 13vPnC and 20vPnC Serotypes in Adults in Sweden, 2016–2018

Risk Group	n	13vPnC	20vPnC
18-64 Years			
All	169	21 (12.4%)	35 (20.7%)
High risk	39	9 (23.1%)	10 (25.6%)
At-risk	52	5 (9.6%)	13 (25.0%)
≥65 Years			

Table 2. Proportion of CAP Due to 13vPnC and 20vPnC Serotypes in Adults in Sweden, 2016–2018

Risk Group	n	13vPnC	20vPnC
All	349	35 (10.0%)	53 (15.2%)
High risk	141	16 (11.3%)	24 (17.0%)
At-risk	169	15 (8.9%)	24 (14.2%)
≥18 years of age			
All	518	56 (10.8%)	88 (17.0%)
High risk	180	25 (13.9%)	34 (18.9%)
At-risk	221	20 (9.0%)	37 (16.7%)

Note: Vaccine serotypes were detected by UAD or blood culture.
Source: Theilacker et al, 2020.[77]

In a study in US adults ≥18 years of age that enrolled patients with radiologically confirmed CAP across 10 US cities between October 2013 and September 2016. The percent of CAP attributed to 13vPnC or 20vPnC serotypes was assessed by culture and serotyping of *S. pneumoniae* isolates from standard-of-care specimens (including blood, sputum, and pleural fluid) and by UAD1 and UAD2 testing on urine samples.[110] The number and percent of CAP patients positive for a 13vPnC or 20vPnC serotype is presented by age group in Table 3.

Table 3. Proportion of CAP Due to 13vPnC and 20vPnC Serotypes in Adults in the USA, 2013–2016

Vaccine Serotypes	18-64 Years n=5708	≥65 Years n=6347	≥18 Years n=12055
13vPnC	290 (5.1%)	269 (4.2%)	559 (4.6%)
20vPnC	497 (8.7%)	441 (7.0%)	938 (7.8%)

Source: Grant et al, 2020.[111]

In this regard it should be noted, that relying on only radiologically confirmed or etiologically confirmed outcomes likely substantially underestimate the public health benefits of pneumococcal conjugate vaccines. A recent systematic literature review for Phase 3/4 efficacy trials concluded that vaccine-preventable disease incidences (control group minus intervention group incidences) were 2.2- to 2.9-fold higher for clinically defined pneumonia compared with etiologically confirmed pneumococcal or vaccine serotype CAP in adults.[112,113]

In addition, the epidemiologic burden of pneumococcal disease attributable to the 20vPnC serotypes was recently estimated in US adults, using published and unpublished data on incidence rates, serotype coverage, and mortality for IPD and pneumonia (Table 4).[114] ABCs data from 2017 was used for IPD data. Data was extrapolated to the total US adult population, stratified by age and risk group.

This analysis showed that an additional 9900 cases of IPD, 44,000 cases of inpatient pneumonia, 52,000 cases of outpatient pneumonia, and 4300 deaths are estimated to be caused by the 7 additional 20vPnC serotypes.

Table 4. Estimated Annual Burden Due to the 13vPnC and 20vPnC Serotypes for Adults in the USA

Burden	STs	Estimate	Age Groups				
			18–49 Years		50–64 Years		65+ Years
			All	At-Risk[a]	All	At-Risk[a]	All
Disease Cases	13vPnC[b]	Bacteraemia	1560	805	2857	1538	3786
		Meningitis	127	65	232	125	307
		Inpatient CAP	9216	6156	16069	9997	39763
		Outpatient CAP	23034	14334	18204	11785	33324
		Total	33937	21360	37362	23445	77180
	20vPnC[c]	Bacteraemia	3556	1835	5927	3191	7842
		Meningitis	288	149	481	259	636
		Inpatient CAP	15990	10253	27564	16649	65585
		Outpatient CAP	40644	23872	31460	19627	54809
		Total	60478	36109	65432	39726	128872
Deaths	13vPnC[b]	Bacteraemia	93	49	315	170	564
		Meningitis	8	4	26	14	46
		CAP	127	87	820	498	3749
		Total	228	139	1161	682	4359
	20vPnC[c]	Bacteraemia	212	111	653	352	1168
		Meningitis	17	9	53	29	95
		CAP	220	144	1402	830	6201
		Total	449	264	2108	1210	7464

a. At-risk was defined including those who were immunocompetent with ≥1 chronic medical condition.
b. Serotypes included 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. Serotype 6C was also included given cross-reactivity with 6B.
c. Serotypes included 13vPnC serotypes, 6C, 8, 10A, 11A, 12F, 15B, 22F, 33F, and 15C. The capsular polysaccharide of serotype 15B is highly related to 15C, with a high potential to induce cross-protective antibody to 15C.
Source: Perdrizet et al, 2020.[114]

Prevalence:

Given the acute nature of the IPD onset, the prevalence estimates are not clinically meaningful and hence are not discussed.

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Use in children at high risk of pneumococcal disease:

Children with functional or anatomic asplenia, particularly those with sickle cell disease, and children with immunocompromising conditions are at very high risk for invasive disease, with rates in some studies more than 50 times higher than those among children of the same age without these conditions (i.e., incidence rates of 5,000 to 9,000 per 100,000 population).

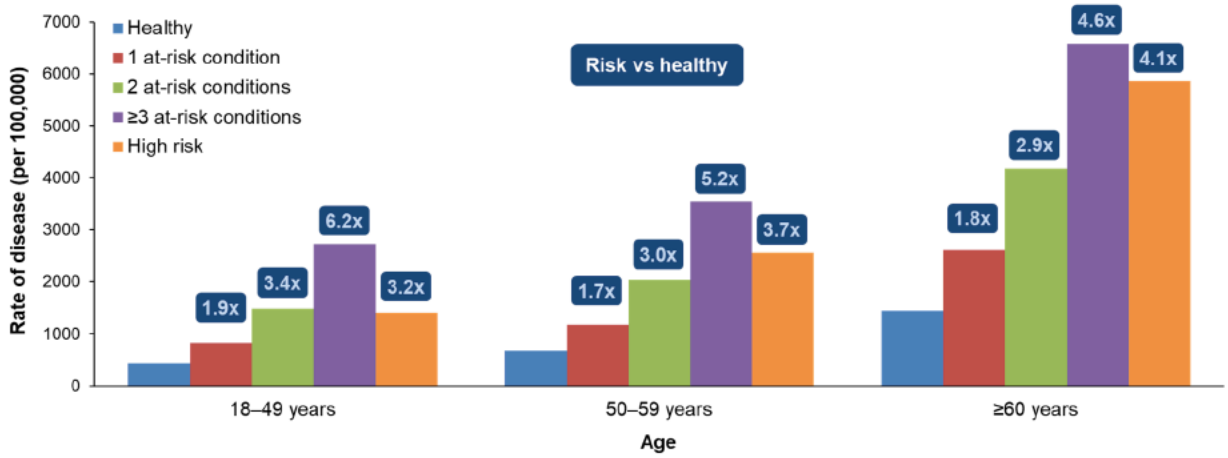
Other conditions that increase the risk of invasive pneumococcal disease in children include chronic heart disease, lung disease (including asthma if treated with high-dose oral corticosteroid therapy), liver disease, CSF leak, and having a cochlear implant. Rates are also increased among children of certain racial and ethnic groups, including Alaska Natives, African Americans, and certain American Indian groups (Navajo and White Mountain Apache). The reason for this increased risk by race and ethnicity is not known with certainty but has also been noted for invasive Haemophilus influenzae infection (also an encapsulated bacterium). Attendance at a childcare center has also been shown to increase the risk of invasive pneumococcal disease and acute otitis media 2- or 3-fold among children younger than age 5 years. Children with a cochlear implant are at increased risk for pneumococcal meningitis.[115]

Studies have been published confirming that both 7vPnC and 13vPnC are safe and immunogenic in children at increased risk of pneumococcal disease (infants born prematurely and in children with SCD, HSCT, and HIV infection). Such studies with 7vPnC and 13vPnC were generally small, as these populations may be difficult to enroll, and often are noncomparative, as it may be unethical to include a control group of unvaccinated participants. The large number of safety and immunogenicity studies of 7vPnC and 13vPnC in high-risk paediatric and adult populations generally reflected the safety profile observed for 7vPnC and 13vPnC in the general population.[116,117] As would be expected, immune responses were lower in immunocompromised individuals; however, the potential for significant benefit in this vulnerable paediatric population is recognized, and recommendations for pneumococcal conjugate vaccines in immunocompromised and other high-risk individuals exist in a number of countries.[45,118,119]

Use in adults at high risk of pneumococcal disease:

The incidence of pneumococcal disease in adults increases substantially after 50 years of age, as does the mortality. The US Advisory Committee on Immunization Practices (ACIP) and national and regional governmental recommending bodies across Europe have identified factors in addition to age in immunocompetent adults that can increase the risk of pneumococcal disease.[119-121] Data from 3 large US health care claims databases indicate that adults 18 through 64 years of age with the most common at-risk conditions/factors, including diabetes mellitus, asthma, chronic heart disease, and cigarette smoking, had rates of pneumococcal disease approximately 3- to 4-fold higher than the healthy population of the same age; persons with chronic lung disease had a rate 10-fold higher.[122] In a study in Germany, adults 18 to 49 years of age with at least 2 underlying medical conditions or with a high-risk condition were at similar risk for developing pneumococcal disease as healthy adults ≥60 years of age (Figure 1).

Figure 1. Rates of All-Cause Pneumonia Among Adults With Chronic Risk Conditions



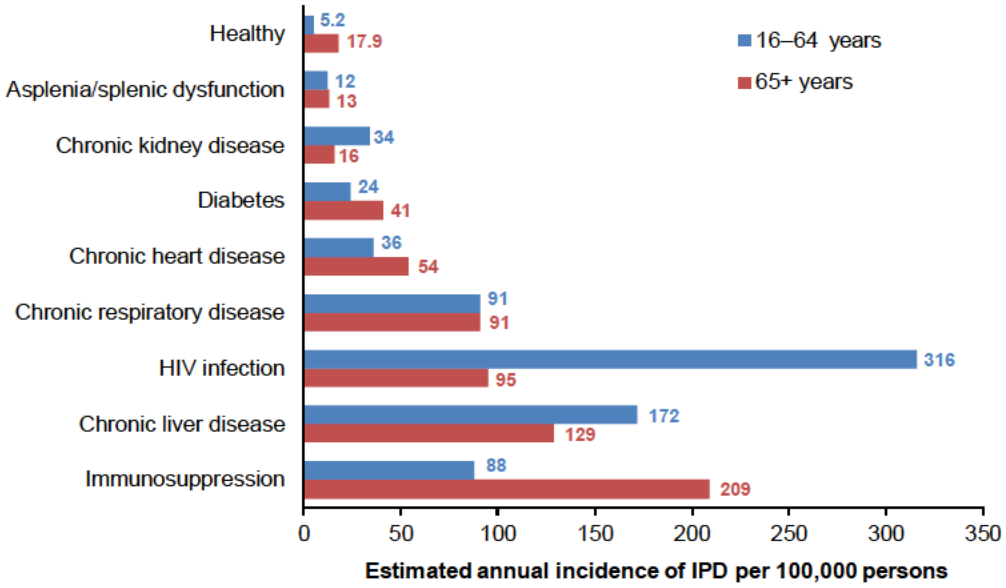
Source: Pelton et al, 2015.[123]

In the aforementioned study in Malmo, Sweden (Table 2), the proportion of CAP due to the 20vPnC serotypes in adults 18 through 64 years of age with a high-risk condition was 25.6%, which was the highest proportion among all the age and risk groups examined. Those 18 through 64 years of age with an at-risk condition also had a higher proportion of 20vPnC serotypes detected (25.0%) compared with all adults ≥65 years of age (15.2%).

As shown in Table 3, the proportion of CAP due to the 20vPnC serotypes in US adults 18 through 64 was also comparable to those ≥65 years of age (8.7% vs 7.0%), though data by risk status was not provided.

The risk of IPD is also increased in adults with certain comorbid conditions. Figure 2 shows data from a retrospective cohort study from the national dataset of laboratory confirmed IPD cases in England and Wales (2008–2009). Irrespective of age, immunosuppressed adults, or adults with chronic conditions such as diabetes; asthma; alcoholism; chronic cardiovascular, liver, or pulmonary disease; or smoking are at an increased risk for IPD when compared with healthy adults. For certain conditions (chronic kidney disease, HIV infection, chronic liver disease), the rates of IPD were higher in those 16 through 64, compared with those ≥65 years of age.

Figure 2. Risk of IPD by Comorbid Condition and Age



Source: van Hoek et al, 2012.[124]

The main existing treatment options:

The currently available pneumococcal conjugate vaccines for infant immunisation in the EU are Prevenar 13 and Synflorix (10-valent pneumococcal conjugate vaccine). Vaxneuvance (15-valent pneumococcal conjugate vaccine, 15vPnC) is approved for an adult indication and recently received European Commission decision for a paediatric indication. Vaxneuvance contains conjugates for the 13vPnC serotypes plus serotypes 22F and 33F.

In addition, PPSV23 is indicated for use in children >2 years of age at increased risk for pneumococcal disease. PPSV23 contains unconjugated pneumococcal capsular polysaccharides for 23 different disease-causing serotypes (including the 7 additional capsular polysaccharides in 20vPnC). Unconjugated polysaccharide vaccines elicit a T-cell–independent immune response. As a result, they do not induce robust responses in certain populations (eg, immunocompromised individuals and children <2 years of age), and do not generate immunologic memory, so that their protective effect wanes over 2 to 5 years.[125-128]

Given the limitations of unconjugated vaccines and the current and global emerging burden of pneumococcal disease due to the 7 additional serotypes of 20vPnC not covered by 13vPnC, and specifically the 5 additional serotypes not covered by Vaxneuvance, a medical need exists for a pneumococcal conjugate vaccine with expanded coverage in the paediatric population. 20vPnC is expected to address that unmet need, providing greater protection than existing therapies.

The currently available pneumococcal vaccines for adults are PPSV23, 13vPnC, 15vPnC, and 20vPnC.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

S. pneumoniae are gram-positive encapsulated diplococci and a significant cause of disease associated with mortality and morbidity among children and adults.[129,85] The capsular polysaccharides of *S. pneumoniae* play important roles in virulence and immune evasion mechanisms and are used to classify pneumococcal serotypes. Currently, 100 different serotypes have been identified, which vary both by the chemical structure of their seroreactive capsular polysaccharides and in their ability to cause disease, with the majority of invasive disease caused by a relatively limited number of serotypes.[130,131]

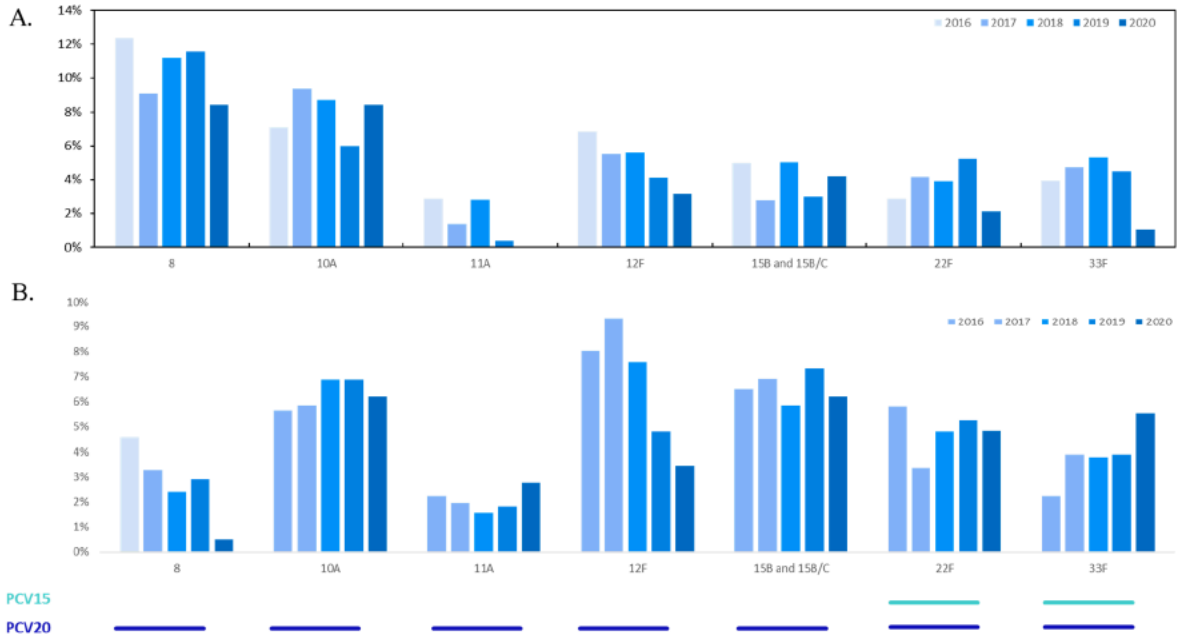
In a human host, *S. pneumoniae* colonizes the nasopharynx and can present with a variety of clinical manifestations. The clinical forms vary in prevalence, severity, and associated sequelae and can be grouped into 2 broad classifications:[132]

- invasive disease, such as meningitis, bacteremic pneumonia, or primary bacteremia, and
- noninvasive (or mucosal) disease, which includes nonbacteremic pneumonia, sinusitis, and AOM.

Invasive Pneumococcal Disease: Serotypes causing pneumococcal disease are evolving, highlighting the need to expand protection against additional medically relevant serotypes and to maintain protection against the 13vPnC serotypes. A global meta-analysis of surveillance data from 42 sites with mature 13vPnC paediatric programs estimated that the 7 additional 20vPnC serotypes account for ~36% of IPD cases in children <5 years of age.[133] Eight serotypes accounted for ~52% of IPD in 13vPnC-using sites, including serotypes 15B/C (9.5%), 12F (5.8%), 10A (5.5%), 22F (5.3%), and 33F (4.3%).

In Europe, an estimated 35% and 33% of IPD in 2019 are due to the 7 additional 20vPnC serotypes among children <1 and 1 through 4 years of age, respectively, based on IPD surveillance from 26 European countries.[134] The most common 20vPnC serotypes were 8 and 10A among children <1 year of age and 10A and 15B/C among children 1 to 4 years of age in 2019 (Figure 3). In 2020 during the COVID-19 pandemic, a substantial decline in the number of IPD cases was observed but IPD rates have rebounded to at or above pre-COVID levels.[135,136]

Figure 3. Proportion of IPD Due to 20vPnC non-13vPnC Serotypes Among Children Less Than 1 Year of Age (A) and 1 to 4 Years of Age (B) in 26 Countries in Europe[a,b]



a. Proportions based on reported serotype-specific IPD cases from Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom.

b. Countries may report 15B and the closely related, cross-reactive serotype 15C separately or as a group. If grouped, 15B/C included in analysis.

Source: Pfizer analysis of data available from European Center for Disease Prevention and Control Surveillance Atlas for Infectious Disease, Invasive Pneumococcal Disease, 2020.[134]

Pneumonia: A substantial burden of bacteremic pneumonia including parapneumonic effusions and empyemas are caused by the 20vPnC serotypes.[7,11,26] While the serotype distribution of nonbacteraemic pneumonia currently cannot be determined due to the lack of sensitive and specific diagnostic tests,[137] evidence of the substantial proportion of bacteraemic pneumonia due to the 20vPnC serotypes and the impact of pneumococcal conjugate vaccines on all-cause pneumonia suggest 20vPnC will likely help protect against childhood pneumonia. [21,26]

Acute Otitis Media: AOM is a common infection in young children worldwide — one of the most common reasons for clinic visits and antimicrobial prescriptions in developed countries. The majority of AOM is due to bacteria, and among bacterial OM globally, *S pneumoniae* is one of the most common causes, causing 24% and ~26% of cases as reported from studies in the USA and Israel, respectively, during the 13vPnC period.[28,138] Studies in France, Germany, Israel, and USA during the 13vPnC period found that 12% to 31% of acute or complicated pneumococcal OM cases were caused by the 7 additional 20vPnC serotypes not covered by 13vPnC (Ben-Shimol, Pichichero, JMI Laboratories, and Kaplan datasets on

file).[139-142] While mortality is rare, certain clinical presentations of OM, especially those caused by *S pneumoniae*, are associated with significant morbidity given their severity, complexity, and propensity for sequelae including hearing loss.[143]

Overall: The unmet need in Europe for paediatric pneumococcal disease is substantial. A modeling analysis of 9 European countries (Austria, Finland, France, Germany, Italy, Netherlands, Spain, Sweden, United Kingdom) estimated that 1082 IPD cases, 65,124 pneumonia cases, 780,236 AOM cases per year in children <5 years of age are caused by 20vPnC serotypes, representing an annual direct healthcare cost of approximately €166 million per year.[144]

The 7 additional serotypes were not only selected based on their prevalence in IPD and mucosal disease around the world, but also on characteristics that make them medically important, including antibiotic resistance (10A, 11A, 15B and the closely related 15C, 22F, and 33F),[145-148] association with outbreaks (8, 12F),[149-152] and a tendency to greater disease severity such as an association with meningitis[60,153,154] or higher case fatality rates (10A, 11A, 12F, 15B/C, 22F, 33F)[155,156] (Table 5).

Table 5. Epidemiological Characteristics of the 7 Additional Pneumococcal Serotypes of 20vPnC in Children

Epidemiological Characteristic	8	10A	11A	12F	15B/C*	22F	33F
Cause of any IPD[a]**	++	++	+	++	+++	++	++
Case fatality ratio for IPD[b]	+	++++	++	++	++++	+++	++
Cause of any non-IPD[a]**	+	+++	+	+	++++	NR	+
Cause of pneumococcal meningitis**	+++	++	+	++	++++	+++	++
Cause of pneumococcal bacteremic pneumonia[a]	++	++	+	++	++	+	++
Cause of pneumococcal AOM[a]	+	+++	+++	+	++++	++	+

* 15B and 15C are reported together.
** In settings with later-period 13vPnC programs.
a. +: ≤2%; ++: 3-5%; +++: 6-8%; ++++: >8%.
b. +: all studies ≤1%; ++: ≥1 study 2-5%; +++: ≥1 study >5%; ++++: all studies >5% or 1 study >10%.
Source: Manuscript in preparation; Pfizer data on file.

In summary, 7vPnC and 13vPnC have substantially reduced the burden of disease due to *S. pneumoniae* globally. Nevertheless, pneumococci remain an important cause of IPD, pneumonia, and AOM in children age <5 years in Europe and globally. The 20vPnC serotypes are among the most important causes of IPD, pneumococcal pneumonia, and AOM among children, and the 7 additional serotypes also have the potential to cause more severe disease, outbreaks, and antibiotic resistance. Thus, 20vPnC, with its expanded coverage for these 7 important serotypes has the potential to address this substantial unmet need in Europe and in the global paediatric population.

Please also refer to 'Pneumococcal CAP in Adults' above for a discussion of pneumococcal pneumonia complications, long-term sequelae in all age groups, and mortality rates.

Important co-morbidities:

It is widely accepted that the risk of pneumococcal infection is elevated among individuals who are either immunocompetent but have chronic medical conditions and/or have immunocompromising conditions. These individuals are frequently referred to by health agencies and vaccine recommending bodies as “at-risk” and “high-risk,” respectively.[122,157,158]

Persons at highest risk of IPD include all persons with functional or anatomic asplenia (eg, from sickle cell disease or splenectomy), HIV infection, leukaemia, lymphoma, Hodgkin disease, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, or other conditions associated with immunosuppression (eg, organ or bone marrow transplantation) and those receiving immunosuppressive chemotherapy, including long-term corticosteroids. At-risk conditions include asthma, chronic heart disease, chronic liver disease, chronic lung disease, chronic use of oral steroids, diabetes, trisomy 21, neuromuscular/seizure disorders, prematurity and low birth weight.[157,158]

Please also refer above for a discussion of pneumococcal infection in high risk/at risk population (see also Table 2, Figure 1, and Figure 2).[77,123,124]

Module SII. Non-Clinical Part of the Safety Specification

The key studies in the nonclinical toxicity assessment for 20vPnC consisted of a GLP-compliant pivotal repeat-dose toxicity study, a fertility and developmental toxicity study, and a series of repeat-dose investigative studies in NZW rabbits. The investigative studies were conducted to evaluate an unexpected finding in the pivotal repeat-dose toxicity study.

Expected findings related to 20vPnC administration in the initial pivotal repeat-dose study were consistent with those seen in rabbits administered an aluminum-containing vaccine, including injection site findings, increased fibrinogen and CRP, and expansion of germinal centers in the spleen and iliac and inguinal lymph nodes, and were not considered adverse.

An unexpected microscopic heart finding observed in a small number of rabbits administered 20vPnC in the initial pivotal repeat-dose toxicity study drove heart-focused investigative studies and an extensive toxicity assessment. Ultimately, it was determined that the heart finding was not related to the vaccine or vaccine components.

This conclusion was based on evidence that comparable heart findings can occur independent of the test article in rabbits, heart findings were not due to direct or immune-mediated cardiotoxicity, and comparable findings may be induced in rabbits with increased handling and study procedures suggesting the potential contribution of extrinsic factors such as stress, in the development of heart findings. Further, there is extensive safety experience with the vaccine components in marketed vaccines and/or biotherapeutic products, and no myocardial inflammation was identified in any species in the repeat-dose toxicity studies conducted with 13vPnC or with the 7 new serotypes in c7vPnC. Finally, there have been no cardiac safety signals or cTnI elevations in human clinical trials with 20vPnC (when tested). The totality of the nonclinical and clinical data supports the conclusion that heart is not a target organ for 20vPnC.

In a combined fertility and developmental toxicity study conducted in NZW rabbits, there were no 20vPnC-related effects on fertility, pregnancy, or the offspring.

In summary, the nonclinical safety findings related to 20vPnC administration represent an expected immune reaction to vaccine administration and are clinically manageable or acceptable risks in the intended population. The key safety findings from nonclinical studies and their relevance to human usage are presented in Table 6.

Table 6. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
• **Toxicity** (key issues identified from acute or repeat-dose toxicity studies) *Single-Dose Toxicity* A separate single-dose toxicity study with 20vPnC has not been conducted; however, single-dose toxicity was evaluated after IM administration of the first of 5 doses of 20vPnC to male and female NZW rabbits in the initial pivotal 59-day (1 dose/2 weeks) toxicity study (Study 12GR385). There were no adverse test article-related effects following single-dose administration. *Repeat-Dose Toxicity* In the initial pivotal repeat-dose toxicity study in rabbits, no 20vPnC-related clinical signs of toxicity were observed during the dosing or recovery phases (12GR385). 20vPnC-related changes in acute phase proteins and microscopic findings at the injection site and in the draining lymph nodes and spleen were consistent with those seen with administration of aluminum-containing vaccines. However, in a small number of rabbits administered 20vPnC, microscopic inflammation with degeneration/necrosis of cardiac myocytes or myocardial fibrosis was observed. Further investigations support that these cardiac findings were likely related to toxicity study procedures and handling, not directly related to 20vPnC, and unlikely to have any translational relevance to humans.	- Findings related to 20vPnC administration were consistent with the administration of an aluminium-containing vaccine, including injection site findings, increased FIB and CRP, and expansion of germinal centres in the spleen and iliac and inguinal lymph nodes, and were not adverse. In clinical trials conducted to date with 20vPnC, no serious unexpected, adverse reactions have been detected in healthy people. Additionally, no cardiac safety signals or cTnI were noted in human clinical trials with 20vPnC (when tested); CSR B7471001.
Reproductive/developmental toxicity No vaccine-related effects on female fertility or the development of fetuses or offspring were observed in a fertility and developmental toxicity study of 20vPnC in rabbits.	No effects are anticipated in pregnant women or their offspring.
• **Genotoxicity**[a] NA	-
• **Carcinogenicity**[a] NA	-

Table 6. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Safety pharmacology[a] - *Cardiac* Findings of inflammation with degeneration/necrosis of cardiac myocytes or myocardial fibrosis in the hearts of a small number of rabbits administered 20vPnC were observed in the initial pivotal repeat-dose toxicity study. Subsequent additional repeat-dose investigative studies, including a saline-only rabbit study, and a detailed root cause analysis on the vehicle constituents indicated that the heart findings were not related to the vaccine conjugates or other vaccine components. Heart findings were not due to direct or immune-mediated cardiotoxicity, and comparable findings may be induced in rabbits with increased handling and study procedures, suggesting the potential contribution of factors such as stress in the development of heart findings. - *Respiratory and neurologic* No clinical signs indicative of respiratory or neurologic system effects were observed in the pivotal repeat-dose toxicity study in rabbits.	No cardiac safety signals or cTnI elevations were noted in human clinical trials with 20vPnC (when tested). The totality of the nonclinical and clinical data supports the conclusion that heart is not a target organ for 20vPnC.
Other toxicity-related information or data: NA	-

a. No genotoxicity, carcinogenicity, safety pharmacology, or studies evaluating pharmacodynamic drug interactions were conducted. These studies are generally not considered necessary to support the development and licensure of vaccine products for infectious diseases.[159,160].

Module SIII. Clinical Trial Exposure

The clinical development of 20vPnC for paediatric and adult immunisation was modelled upon the experience and clinical data of 13vPnC. The immunogenicity, safety, and postlicensure data on effectiveness with 13vPnC are relevant to 20vPnC since the vaccines are manufactured and formulated similarly and contain the same 13 polysaccharide conjugates

Paediatric population

The paediatric clinical development program for 20vPnC consists of 5 completed clinical trials (1 phase 2 and 4 phase 3 studies), as outlined below:

Phase 2 studies	
	B7471003: A phase 2, randomized, double-blind trial to evaluate the safety and immunogenicity of a multivalent pneumococcal conjugate vaccine in healthy infants
Phase 3 studies	
-	B7471011: A phase 3, randomized, double-blind trial to evaluate the safety and immunogenicity of a 20-valent pneumococcal conjugate vaccine in healthy infants
-	B7471012:[a] A phase 3, randomized, double-blind trial to evaluate the safety and immunogenicity of a 20-valent pneumococcal conjugate vaccine given as a series of 2 infant doses and 1 toddler dose in healthy infants
-	B7471013:[a] A phase 3, randomized, double-blind trial to evaluate the safety of a 20-valent pneumococcal conjugate vaccine in healthy infants
-	B7471014: A phase 3, single-arm trial to evaluate the safety and immunogenicity of a 20-valent pneumococcal conjugate vaccine in healthy children 15 months through 17 years of age

a. Study sites in the EU.

Across all 5 clinical trials, 5987 paediatric participants received at least 1 study vaccination: 3664 participants received 20vPnC and 2323 received control vaccine. Additionally, four participants were randomized to 13vPnC but received at least one dose of 20vPnC (Dose 1: 1 in B7471013; Dose 2: 2 in B7471011; Dose 4: 1 in B7471011). Those were included in the exposure summaries based on the first time they were exposed to 20vPnC in the studies. They were excluded from the safety summaries from the first analysis period as they received incorrect study vaccination.

Table 7. Exposure (by Indication)

Exposure	No. of Participants Exposed to 20vPnC	Total Vaccine Doses
Indication 1 – Studies in Participants 6 Weeks to <5 Years of Age		
2+1 regimen	601	1782
3+1 regimen	2236	8476
Other[a]	425	425
Total (Indication 1)	3262	10683
Indication 2 – Studies in Participants 5 to <18 Years of Age		
Other[b]	406	406
Total (Indication 2)	406	406
Total Exposure	**3668**	**11089**

a. Included are cohort 1 and cohort 2 from study B7471014 who received at least 3 prior doses of 13vPnC and a single dose of 20vPnC.
b. Included are cohort 3 and cohort 4 from study B7471014. In this category the participants received a single dose of 20vPnC.
[redacted] Source Data: adsl Output File: ./b747_pediatric_sec/B747_PED_RMP/exp_rmp Date of Generation: 21OCT2022 (09:33)

Table 8. Exposure by Age Group and Gender (by Indication)

	No. of Participants Exposed to 20vPnC			Total Vaccine Doses		
Age Group	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
Indication 1 – Studies in Participants 6 Weeks to <5 Years of Age						
<2 months	365	314	679	1282	1117	2399
2 - <4 months	1089	1069	2158	3938	3921	7859
15 - <24 months	117	92	209	117	92	209
2 - <5 years	106	110	216	106	110	216
Total (Indication 1)	1677	1585	3262	5443	5240	10683
Indication 2 – Studies in Participants 5 to <18 Years of Age						
5 - <12 years	132	119	251	132	119	251
12 - <18 years	91	64	155	91	64	155
Total (Indication 2)	223	183	406	223	183	406
Total Exposure	**1900**	**1768**	**3668**	**5666**	**5423**	**11089**

[redacted] Source Data: adsl Output File: ./b747_pediatric_sec/B747_PED_RMP/exp_rmp_agegrp Date of Generation: 21OCT2022 (09:38)

Table 9. Exposure by Racial Origin (by Indication)

Racial Origin	No.of Participants Exposed to 20vPnC	Total Vaccine Doses
Indication 1 – Studies in Participants 6 Weeks to <5 Years of Age		
White	2710	8901
Black or African American	253	758
Multiracial	149	502
Not reported	74	252
Asian	58	208
American Indian or Alaska Native	13	47
Native Hawaiian or Other Pacific Islander	5	15
Total (Indication 1)	3262	10683
Indication 2 – Studies in Participants 5 to <18 Years of Age		
White	352	352
Black or African American	39	39
Multiracial	14	14
Native Hawaiian or Other Pacific Islander	1	1
Total (Indication 2)	406	406
Total Exposure	**3668**	**11089**

[redacted] Source Data: adsl Output File: ./b747_pediatric_sec/B747_PED_RMP/exp_rmp_race Date of Generation: Date of Generation: 21OCT2022 (09:50)

Table 10. Exposure by Ethnicity (by Indication)

Ethnicity	No. of Participants Exposed to 20vPnC	Total Vaccine Doses
Indication 1 – Studies in Participants 6 Weeks to <5 Years of Age		
Hispanic	804	2785
Non-Hispanic	2396	7679
Not reported	62	219
Total (Indication 1)	3262	10683
Indication 2 – Studies in Participants 5 to <18 Years of Age		
Hispanic	74	74
Non-Hispanic	329	329
Not reported	3	3
Total (Indication 2)	406	406
Total Exposure	**3668**	**11089**

[redacted] Source Data: adsl Output File: ./b747_pediatric_sec/B747_PED_RMP/exp_rmp_ethnic Date of Generation: 21OCT2022 (09:39)

Adult population

The adult clinical development program for 20vPnC consisted of 6 completed trials: 2 Phase 1, 1 Phase 2 and 3 Phase 3 safety and immunogenicity studies, as below.

Phase 1 studies:	
-	B7471001: Phase 1, first-in-human, randomized, controlled, observer-blinded study with a 2-arm parallel design.
-	B7471005: Phase 1b, randomized, controlled, double-blind study with a 3-arm parallel design, in adults of Japanese descent.
Phase 2 studies	
	B7471002: Phase 2, multicenter, randomized, active-controlled, double-blind study with a 2-arm parallel design.
Phase 3 studies	
-	B7471007[a]: Phase 3, multicenter, randomized, double-blind study with an age-based 3-cohort design.
-	B7471006[a]: Phase 3, multicenter, randomized, open-label study with a 3-cohort design based on prior pneumococcal vaccination status.
-	B7471008: Phase 3, multicenter, randomized, double-blind, lot consistency study with a 4-arm parallel design.

a. The study has sites in the EU (Sweden)

Across all 6 clinical trials, 7048 adult participants received at least 1 study vaccination: 4552 participants received 20vPnC and 2496 received control vaccine.

Table 11. Exposure (by Indication)

Indication 3 – Studies in Adults (≥18 Years)[a,b]	No. of Participants Exposed to 20vPnC	Total Vaccine Doses
1 dose	4552	4552
Total Exposure	4552	4552

a. Included are studies B7471001, B7471002, B7471005, B7471006, B7471007, and B7471008.
b. All studies in this category received a single dose of 20vPnC.
PFIZER CONFIDENTIAL Source Data: adsl Output File:
./b747 adult sec/B747 ADULT RMP LABEL ADHOC/exp rmp Date of Generation: 02JUL2020 (17:20)

Table 12. Exposure by Age Group and Gender (by Indication)

Indication 3 – Studies in Adults (≥18 Years)[a,b]	No. of Participants Exposed to 20vPnC			Total Vaccine Doses		
Age Group	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
Adults (18 to 64 years)	1261	2153	3414	1261	2153	3414
18-49 years	637	1228	1865	637	1228	1865
50-59 years	139	195	334	139	195	334
60-64 years	485	730	1215	485	730	1215
Elderly (≥65 years)	513	625	1138	513	625	1138
65-69 years	306	362	668	306	362	668
70-79 years	165	233	398	165	233	398
≥80 years	42	30	72	42	30	72
Total Exposure	**1774**	**2778**	**4552**	**1774**	**2778**	**4552**

a. Included are studies B7471001, B7471002, B7471005, B7471006, B7471007, and B7471008.
b. All studies in this category received a single dose of 20vPnC.
[redacted] Source Data: adsl Output File: ./b747_adult_sec/B747_ADULT_RMP_LABEL_ADHOC/exp_rmp_age Date of Generation: 02JUL2020 (17:04)

Table 13. Exposure by Racial and Ethnic Origin (by Indication)

Indication 3 – Studies in Adults (≥18 Years)[a,b]	No. of Participants Exposed to 20vPnC	Total Vaccine Doses
Racial origin		
White	3674	3674
Black or African American	607	607
Asian	131	131
American Indian or Alaska Native	31	31
Native Hawaiian or other Pacific Islander	10	10
Other	1	1
Multiracial	61	61
Not reported	37	37
Ethnic origin		
Hispanic/Latino	409	409
Non-Hispanic/non-Latino	4077	4077
Not reported	66	66

Table 13. Exposure by Racial and Ethnic Origin (by Indication)

Indication 3 – Studies in Adults (≥18 Years)[a,b]	No. of Participants Exposed to 20vPnC	Total Vaccine Doses
Total Exposure	**4552**	**4552**

a. Included are studies B7471001, B7471002, B7471005, B7471006, B7471007, and B7471008.
b. All studies in this category received a single dose of 20vPnC.
[redacted] Source Data: adsl Output File: ./b747_adult_sec/B747_ADULT_RMP_LABEL_ADHOC/exp_rmp_race Date of Generation: 06JUL2020 (16:03)

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Participants Aged 6 Weeks to <18 Years

Infants, children, and adolescents eligible for the studies of 20vPnC were determined to be healthy by clinical assessment, including medical history, physical examination, and clinical judgment.

Table 14. Exclusion Criteria in Pivotal Clinical Studies (Paediatric Participants)

Criterion	Reason for exclusion	Missing information (Yes/No)/ Justification for not being considered Missing information[a]
Previous vaccination with any licensed or investigational pneumococcal vaccine, or planned receipt through study participation.	To ensure the correct study population for measurement of safety endpoints and immunogenicity (ie, ensures that assessments are not confounded by previous PnC vaccination).	No. Criterion is study specific and not relevant for the proposed indication. Information on prior vaccination is provided in SmPC (Section 5.1 *Pharmacodynamic properties*).
Prior receipt of diphtheria, tetanus, pertussis, poliomyelitis, and/or Hib vaccine.	To ensure the correct study population for measurement of immunogenicity endpoints for concomitant study vaccines.	No. Criterion is study specific and not relevant for the proposed indication. Information on the possibility to administer 20vPnC with these vaccines is provided in the SmPC Section 4.5 *Interaction with other medicinal products and other forms of interaction* for infants and children 6 weeks to less than 5 years of age.
History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of investigational product or any diphtheria toxoid–containing vaccine.	To ensure the safety of the study population.	No. Information on hypersensitivity is provided in SmPC (Sections 4.3 *Contraindication,* 4.4 *Special warnings and precautions for use* and in Section 4.8 *Undesirable effects*)

Table 14. Exclusion Criteria in Pivotal Clinical Studies (Paediatric Participants)

Criterion	Reason for exclusion	Missing information (Yes/No)/ Justification for not being considered Missing information[a]
Significant neurological disorder or history of seizure including febrile seizure or significant stable or evolving disorders such as cerebral palsy, encephalopathy, hydrocephalus, or other significant disorders. Does not include resolving syndromes due to birth trauma, such as Erb's palsy and/or hypotonic-hyporesponsive episodes	To ensure the safety of the study population.	No. Information concerning seizure is provided in the SmPC Section 4.8, *Undesirable effects.* For other disorders, the safety profile is not expected to differ in these populations when compared with the study populations studied.
Major known congenital malformation or serious chronic disorder.	To avoid confounding the assessment of safety and immunogenicity endpoints in the study population.	No. The safety profile is not expected to differ in these populations when compared with study populations studied, eg, those with stable chronic disease and immunocompromising diseases.
History of microbiologically proven invasive disease caused by *S. pneumoniae*.	To avoid confounding the assessment of immunogenicity endpoints in the study population.	No. Criterion is study specific and not relevant for the proposed indication (contraindication).
Known or suspected immunodeficiency or other conditions associated with immunosuppression, including, but not limited to, immunoglobulin class/subclass deficiencies, DiGeorge syndrome, generalized malignancy, human immunodeficiency virus (HIV) infection, leukemia, lymphoma, or organ or bone marrow transplant.	To avoid confounding the assessment of immunogenicity endpoints in the study population.	No. Information for use of 20vPnC can be assumed to be similar to that for 13vPnC in these populations. [See EU SmPC Section 4.2 *Posology and method of administration (Special populations)*, 4.4 *Special warnings and precautions for use (Immunocompromised individuals),* Section 4.8 *Undesirable effects (Additional information in special populations in studies with Prevenar 13),* and Section 5.1 *Pharmacodynamic properties (Immune responses in special populations)*].

Table 14. Exclusion Criteria in Pivotal Clinical Studies (Paediatric Participants)

Criterion	Reason for exclusion	Missing information (Yes/No)/ Justification for not being considered Missing information[a]
Received treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, or planned receipt through the last postvaccination blood draw. If systemic corticosteroids were administered short term (<14 days) for treatment of an acute illness, participants were not to be enrolled into the trial until corticosteroid therapy was discontinued for at least 28 days before investigational product administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin, eyes, or ears) corticosteroids were permitted.[b]	To avoid confounding the assessment of immunogenicity endpoints in the study population.	No. Information for use of 20vPnC can be assumed to be similar to that for 13vPnC in these populations. (See SmPC Section 4.4 *Special warnings and precautions for use*.)
Receipt of blood/plasma products or immunoglobulins (including hepatitis B immunoglobulin) or planned receipt through the last planned blood draw in the study.	To avoid confounding the assessment of immunogenicity endpoints in the study population.	No. Criterion is study specific and not relevant for the proposed indication.

a. Please note that safety and immunogenicity of Prevenar 13 are relevant to 20vPnC since the vaccines are manufactured and formulated similarly and contain 13 of the same polysaccharide conjugates.
b. Applies for study B7471003 and B7471013.

Adults Aged 18 Years and Older

Table 15. Exclusion Criteria in Pivotal Clinical Studies (Adults)

Criterion	Reason for exclusion	Missing information (Yes/No)/ Justification for not being considered Missing information.[a]
Previous vaccination with any licensed or investigational pneumococcal vaccine, or planned receipt through study participation.	To ensure the correct study population for measurement of safety endpoints and immunogenicity (ie, ensures that assessments are not confounded by previous PnC vaccination).	No. Information on prior vaccination is provided in SmPC (Section 5.1 *Pharmacodynamic properties*).
History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of 20vPnC, 13vPnC, or any other diphtheria toxoid–containing vaccine, or PPSV23.	To ensure safety of the study population.	No. Information concerning this criterion is provided in the SmPC Sections 4.4 *Special warnings and precautions for use* and Section 4.8 *Undesirable effects.*

Table 15. Exclusion Criteria in Pivotal Clinical Studies (Adults)

Criterion	Reason for exclusion	Missing information (Yes/No)/ Justification for not being considered Missing information.[a]
Serious chronic disorder (including metastatic malignancy, severe chronic obstructive pulmonary disease requiring supplemental oxygen, end-stage renal disease with or without dialysis, clinically unstable cardiac disease), or any other disorder that, in the investigator's opinion, excluded the participant from participating in the study.	To avoid confounding the assessment of safety and immunogenicity endpoints in the study population.	No. Information concerning this criterion is provided in the SmPC Section 4.4 *Special warnings and precautions for use.*
Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.	To avoid confounding the assessment of safety endpoints in the study population.	No. Information concerning this criterion is provided in the SmPC Section 4.4 *Special warnings and precautions for use.*
History of microbiologically proven invasive disease caused by *S. pneumoniae*.	To avoid confounding the assessment of immunogenicity endpoints in the study population.	No. Criterion is study specific and not relevant for the approved indication (contraindication).
Subjects with known or suspected immunodeficiency or other conditions associated with immunosuppression, including, but not limited to, immunoglobulin class/subclass deficiencies, generalized malignancy, human immunodeficiency virus (HIV) infection, leukemia, lymphoma, or organ or bone marrow transplant.	To avoid confounding the assessment of immunogenicity endpoints in the study population.	No. Information for use of 20vPnC can be assumed to be similar to that for 13vPnC in these populations. [See EU SmPC Section 4.4 *Special warnings and precautions for use (Immunocompromised individuals),* Section 4.8 *Undesirable effects (Additional information in special populations in studies with Prevenar 13), and* Section 5.1 *Pharmacodynamic properties* (*Prevenar 13 Immune responses in special populations*).
Subjects who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, or planned receipt through the last blood draw.	To avoid confounding the assessment of immunogenicity endpoints in the study population.	No. Information for use of 20vPnC can be assumed to be similar to that for 13vPnC in these populations. (See SmPC Section 4.4 *Special warnings and precautions for use*.)

Table 15. Exclusion Criteria in Pivotal Clinical Studies (Adults)

Criterion	Reason for exclusion	Missing information (Yes/No)/ Justification for not being considered Missing information.[a]
Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may have increased the risk associated with study participation or investigational product administration or may have interfered with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.	To ensure the enrolled subjects are appropriate and to avoid confounding the assessment of safety and immunogenicity endpoints in the study population.	No. Criterion study specific and not relevant for the approved indication.
Receipt of blood/plasma products or immunoglobulin, from 60 days before investigational product administration, or planned receipt through study participation.	To avoid confounding the assessment of immunogenicity endpoints in the study population.	No. Criterion study specific and not relevant for the approved indication.
Pregnant female subjects or breastfeeding female subjects (known or suspected).	To ensure safety of the study population	No. Based on the clinical and post marketing safety experience of 13vPnC, no different safety profile during pregnancy/ lactation is anticipated for 20vPnC. Information regarding use during pregnancy and lactation is provided in the SmPC Section 4.6 *Fertility, pregnancy and lactation*.
Participation in other studies involving investigational drug(s), investigational vaccines, or investigational devices within 28 days prior to study entry and/or during study participation.	To ensure safety of the study population and to avoid confounding the assessment of safety and immunogenicity endpoints	No. Criterion study specific and not relevant for the approved indication.

a. Please note that safety and immunogenicity of Prevenar 13 are relevant to 20vPnC since the vaccines are manufactured and formulated similarly and contain 13 of the same polysaccharide conjugates.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Table 16. SIV.2. Limitations to Detect Adverse Reactions

Ability to Detect Adverse Reactions	Limitation of Trial Programme	Discussion of Implications for Target Population
Which are rare	The limitations from clinical trials to detect rare AEs are compensated for by the extensive (>10 years) 13vPnC product post-marketing exposure.	Following over 10 years of post-authorisation exposure in standard medical practice to 13vPnC, the implication of this limitation is considered to be low.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 17. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women/ Breastfeeding women	Not included in the clinical development program. As of the DLP of this RMP, 8 reports of pregnancy had been received from clinical trials [B7471007 (2), B7471008 (6)]; none reported associated clinical adverse events (AEs). In 4 cases 'Maternal exposure during pregnancy' was reported. In 3 other cases, the pregnancy occurred a while after vaccination (PT Maternal exposure before pregnancy). In 1 case, spontaneous abortion was reported. The pregnancy outcome included the delivery of healthy infants in 5 cases and was unknown in 2 cases. There were no cases reporting 20vPnC administration during breastfeeding.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular disease • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	Please refer to Table 10 and Table 13 for exposure information by ethnic origin from the studies.
Subpopulations carrying relevant genetic polymorphisms	No host genetic polymorphism has been identified that would have a substantial influence on the immune response to pneumococcal conjugate vaccines.
Other	NA.

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

Due to various dosage regimens and country-specific vaccination schedules, it is not possible to determine with certainty the number of individuals who received 20vPnC vaccine at the data-lock point of this RMP. Estimated worldwide units' distribution may serve as a reasonable indicator of patient exposure.

With these caveats in mind, the estimated cumulative worldwide units' distribution for 20vPnC from launch to 07 December 2023 is approximately 23,815,524 doses.

Cumulative estimated exposure by gender, age group, and region based on the MAH's internal sales data and factored, as applicable, by data from IQVIA from launch through 07 June 2023, is summarized in Table 18 and Table 19, separately for US/Puerto Rico (PR) and ROW (excl. US and PR), and Table 20.

In addition, beginning with the release of 1Q22 data, IQVIA medical data moved from NDTI (National Disease and Therapeutic Index, used to capture data in the US) to NMTA (National Medical and Treatment Audit), used to capture data in the US and Puerto Rico. NMTA uses different methodologies for data, sample and projection compared to NDTI. Due to the change in methodology, it is observed a trend break in data for indication, formulation, region, gender, age and dose. As part of this update, the NMTA audit can only produce patient age information in 5-year age bands due to data privacy concerns for older age groups. The 5-year age bands do not align with the age breakdown for paediatric population according to ICH E11 (R1) recommendation. In this report, the demographic data for US and Puerto Rico are presented according to 5 years bands mimicking as close as possible ICH recommendation for the paediatric population (0-15; 16-20 years). There is no impact on elderly population aged >65 years.

[redacted]

Table 19. Cumulative Estimated Exposure in ROW (excl. US and PR) for 20vPnC (# of Doses)

Total	Sex (% of Rx)		Age (years, % of Rx)			
	M	F	0-16	17-65	>65	Unspecified
3,367,349	50.1%	49.9%	0.0%	41.7%	57.5%	0.8%
	1,687,042	1,680,307	-	1,404,185	1,936,226	26,938

M= Male; F= Female; Rx = prescription; PR=Puerto Rico; US=United States.

Table 20. Cumulative Estimated Exposure for 20vPnC by Region Worldwide (# of Doses)

Region/Country/Other	% of Doses	Total
North America	87.3%	20,799,841
Western EU	12.3%	2,919,283
Central and Eastern Europe	0.2%	51,045
Asia (excl Japan)	0.1%	19,737
Africa/Middle East	0.1%	17,084
Latin America	0.0%	8,000
Australia/New Zealand	0.0%	534
Total	**100%**	**23,815,524**

The estimated cumulative unit distributions for 20vPnC by European countries are provided in Table 21.

Table 21. Cumulative Estimated Exposure for 20vPnC by EU/EEA Countries

European/EEA Country	Total Number of Doses
Total	**2,876,426**

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

No potential for drug abuse or dependence with 20vPnC is expected.

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Table 22 lists the safety concerns at the initial RMP submission for 20vPnC.

Table 22. Safety concerns at the initial submission

Safety concerns	
Important identified risk	None.
Important potential risk	None.
Missing information	Concomitant use of 20vPnC with quadrivalent inactivated influenza vaccine or COVID-19 mRNA vaccine.[a]

a. In adults ≥65 years of age.

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

A review of the safety data from the 3 completed Phase 3 trials of 20vPnC in adults (B7471006, B7471007, B7471008) did not identify any risks beyond those already known for 13vPnC/20vPnC and as such are not included in the list of safety concerns.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk: None

Important Potential Risk: None.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

There are no new important identified/potential risks for 20vPnC. Upon completion of the coadministration studies B7471004 and B7471026 and based upon review of the immunogenicity and safety results, the MAH no longer considers the concomitant use of 20vPnC with quadrivalent inactivated influenza vaccine (QIV) or COVID-19 mRNA vaccine as missing information. (See also Module SVII.3.2).

B7471004 (quadrivalent inactivated influenza vaccine coadministration):

Study Summary and Conclusion: A total of 1796 healthy adults ≥65 years of age were stratified by prior pneumococcal vaccine status (no previous pneumococcal vaccine [naï ve], receipt of at least 1 dose of PPSV23 only, receipt of at least 1 dose of 13vPnC only, or receipt of at least 1 dose each of PPSV23 and 13vPnC) and randomized in 1:1 ratio to 1 of 2 groups to receive 20vPnC concomitantly administered with a seasonal quadrivalent influenza

vaccine (QIV; surface antigen, inactivated, adjuvanted) (Group 1, N = 898) or 20vPnC administered 1 month after receiving QIV (Group 2, N = 898). 1752 (97.6%) were vaccinated at Visit 2, and 1727 (96.2%) completed the study. The immune responses to all 20 serotypes elicited by 20vPnC when coadministered with QIV were noninferior to those elicited by 20vPnC when administered 1 month after QIV. Of note, numerically lower titres were observed for all pneumococcal serotypes included in 20vPnC when given concomitantly with QIV compared to when 20vPnC was given alone. The clinical relevance of this finding is unknown. Immune responses to all 4 influenza strains elicited by QIV when coadministered with 20vPnC were noninferior to those elicited by QIV alone.

20vPnC was observed to have a similar safety profile when coadministered with or administered 1 month after QIV. The results from this study and the consistency of findings with prior influenza vaccine studies, provide support for the general concept that 20vPnC may be administered with influenza vaccines in adults ≥18 years of age.

<u>B7471026 (COVID-19 mRNA vaccine coadministration study)</u>

Study Summary and Conclusion: 20vPnC elicited robust immune responses to all 20 serotypes 1 month after coadministration with COVID-19 mRNA vaccine (nucleoside modified) and when administered alone. A booster dose of COVID-19 mRNA vaccine elicited robust immune responses to SARS-CoV-2 1 month after coadministration with 20vPnC and when administered alone. When 20vPnC was coadministered with COVID-19 mRNA vaccine, the tolerability profile generally resembled that of the COVID-19 mRNA vaccine administered alone. There were a few differences in the safety profile when compared to administration of 20vPnC alone: pyrexia (13.0%) and chills (26.5%) were reported as "very common" with co administration. There was also one report of dizziness (0.5%) in the co-administration group. The safety and immunogenicity results from this study support coadministration of 20vPnC with COVID-19 mRNA vaccine.

Of note, the following sections of the EU SmPC have been updated to reflect immunogenicity and safety outcomes of studies B7471004 and B7471026.

- Section 4.5 *Interaction with other medicinal products and other forms of interaction* of the EU SmPC has been updated to include the following:

  'Prevenar 20 may be administered concomitantly with seasonal influenza vaccine (QIV; surface antigen, inactivated, adjuvanted). In subjects with underlying conditions associated with a high risk of developing life-threatening pneumococcal disease, consideration may be given to separating administrations of QIV and Prevenar 20 (e.g., by approximately 4 weeks). In a double-blind, randomised study (B7471004) in adults 65 years of age and older, the immune response was formally non-inferior, however numerically lower titres were observed for all pneumococcal serotypes included in Prevenar 20 when given concomitantly with seasonal influenza vaccine (QIV, surface antigen, inactivated, adjuvanted) compared to when Prevenar 20 was given alone. The clinical relevance of this finding is unknown.'

'Prevenar 20 can be administered concomitantly with COVID-19 mRNA vaccine (nucleoside modified).'

- Section 4.8 *Undesirable effects* (*Safety with concomitant vaccine administration in adults*) of the EU SmPC states the following:

  '*When Prevenar 20 was administered to adults aged ≥65 years together with the third (booster) dose of a COVID-19 mRNA vaccine (nucleoside modified), the tolerability profile generally resembled that of the COVID-19 mRNA vaccine (nucleoside modified) administered alone. There were a few differences in the safety profile when compared to administration of Prevenar 20 alone. In the phase 3 trial B7471026 (study 1026), pyrexia (13.0%) and chills (26.5%) were reported as "very common" with co-administration. There was also one report of dizziness (0.5%) in the co-administration group.'*

Additionally, the following information was added to the PL, Section 2, *Other medicines/vaccines and Prevenar 20* to address the previously considered missing information *'Concomitant use of 20vPnC with quadrivalent inactivated influenza vaccine or COVID-19 mRNA vaccine'*:

'*Prevenar 20 may be given at the same time as the flu (inactivated influenza) vaccine at different injection sites. Depending on the individual risk assessment of your health care provider, separation of both vaccinations of e.g., 4 weeks might be advised*.'

'*Prevenar 20 can be given at the same time as the COVID-19 mRNA vaccine'.*

Interactions between 20vPnC and QIV, 20vPnC and COVID-19 mRNA vaccine, as well as any other interaction(s) will be monitored via routine pharmacovigilance.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

As stated above, there are no important identified or potential risks for 20vPnC.

SVII.3.2. Presentation of the Missing Information

There are no safety concerns and other concerns due to missing or partially missing information.

Module SVIII. Summary of the Safety Concerns

There are no important identified/potential risks or missing information for 20vPnC.

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities (PVAs) beyond adverse events' reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires for safety concerns**:

There are no specific adverse event follow-up questionnaires addressing any of the safety concerns for this RMP. (Annex 4 contains no data).

- **Other forms of routine pharmacovigilance activities for safety concerns**:

Since licensure of 13vPnC, reports from the European countries Denmark, France, Germany, Norway, and UK were submitted annually to the EU Regulatory Authority as part of a post-marketing commitment (MEA 19, previously FUM 19). On 26 June 2014, at the request of the CHMP, this MEA was closed while surveillance data continue to be reported in routine PSURs. Confidential reports from Denmark, France, Germany, UK, and, until recently, Norway, have continued to be included in the report post MEA 19 closure. This activity will also continue with 20vPnC.

Data from the above surveillance systems will include information on serotype and antibiotic resistance, and often includes vaccination history, allowing for assessment of vaccine effectiveness or vaccine failure.

Furthermore, the European Centre for Disease Prevention and Control (ECDC) has established a European surveillance system for IPD that compiles reported cases from 29 EU member states. The surveillance data are available an online as an interactive database (ECDC Surveillance atlas) and allow for customized analysis of serotype distributions by country, year of reporting and age group (<1 year, 1 - 4 years, ≥65 years of age). A summary of the epidemiology of IPD reported by ECDC will be submitted together with the country reports mentioned above to the EU Regulatory Authority.

In addition, a targeted literature search will be conducted, with the objective to identify the most relevant and representative publications and publicly available surveillance data (ECDC, CDC, WHO data, as examples) to document epidemiology of pneumococcal disease. Large population- and hospital-based studies among European and North American adult populations are given priority over other types of studies and regions, with a focus on pneumococcal disease epidemiology, emerging resistance, and vaccine effectiveness. Relevant data will be reported in the routine PSURs.

III.2. Additional Pharmacovigilance Activities

There are no ongoing or planned additional PVAs planned for 20vPnC. A list of completed studies in the PV Plan is provided in Annex 2.

III.3. Summary Table of Additional Pharmacovigilance Activities

There are no ongoing or planned pharmacovigilance activities for 20vPnC. A list of completed studies in the PV plan is provided in Annex 2.

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

Post-authorisation efficacy studies (PAES) which are conditions or specific obligations of the MAA in adults are presented in Table 23.

Table 23. Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations[a]

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorisation				
Study B7471015: A Phase 4 Study Using a Test-Negative Design to Evaluate the Effectiveness of a 20-valent Pneumococcal Conjugate Vaccine Against Vaccine-Type Radiologically Confirmed Community-Acquired Pneumonia in Adults ≥65 Years of Age. Ongoing	Evaluate the long-term effectiveness of 20vPnC for active immunization for the prevention of pneumonia caused by *Streptococcus pneumoniae*	Vaccine efficacy (VE) against vaccine-type (VT) radiologically confirmed community acquired pneumonia (CAP) in adults ≥65 years of age	Submission of final study results by	31/12/2027
European specific analysis results of Study B7471015 (A Phase 4 Study Using a Test-Negative Design to Evaluate the Effectiveness of 20vPnC Against Vaccine-Type Community-Acquired Radiologically-Confirmed Pneumonia in Adults ≥65 Years of Age). Planned	Evaluate the long-term effectiveness of 20vPnC for active immunization for the prevention ofpneumonia caused by *Streptococcus pneumoniae*	VE against VT radiologically confirmed CAP in adults ≥65 years of age	Submission of final study results by	31/12/2030
Phase 4 Observational, Real-World Study of 20-valent Pneumococcal Conjugate Vaccine Effectiveness Against Vaccine-Type Invasive Pneumococcal Disease in Europe. Planned	Evaluate the long-term effectiveness of 20vPnC against vaccine-type invasive pneumococcal disease in adults in the EU.	VE against VT IPD and duration of protection	Feasibility assessment currently ongoing Submission of final study results by	 31/12/2030

Table 23. Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations[a]

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due dates
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None.				

a. Classification: category 1= Annex II D condition; category 2= Annex II E specific obligations; category 3 = All other studies reflected only in the RMP (non-clinical, PK, PASS).

The final protocol for Study B7471015 (Protocol version amendment 1, 26 Sep 2023) is provided in Annex 5.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. Routine Risk Minimisation Measures

Routine risk minimization actions include the use of the SmPC and the package leaflet (PL) to support safe use of the vaccine.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage safe use of the vaccine. No additional risk minimisation measures are proposed.

V.3. Summary of Risk Minimisation Measures

Routine risk minimisation actions include the use of SmPC and package leaflet (PL) to support safe use of the vaccine. There are no additional risk minimisation measures.

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Prevenar 20 (20-valent Pneumococcal Polysaccharide Conjugate Vaccine [20vPnC])

This is a summary of the risk management plan (RMP) for Prevenar 20. The RMP details important risks of Prevenar 20, how these risks can be minimised, and how more information will be obtained about Prevenar 20's risks and uncertainties (missing information).

Prevenar 20's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Prevenar 20 should be used.

This summary of the RMP for Prevenar 20 should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Prevenar 20's RMP.

I. The Medicine and What It Is Used For

Prevenar 20 is a vaccine for:

- Active immunisation for the prevention of invasive disease, pneumonia, and acute otitis media caused by *Streptococcus pneumoniae* in infants, children, and adolescents from 6 weeks to less than 18 years of age.

- Active immunisation for the prevention of invasive disease and pneumonia caused by *Streptococcus pneumoniae* in individuals ≥18 years of age (see SmPC for the full indication);

Prevenar 20 contains pneumococcal polysaccharide conjugate vaccine (20-valent, adsorbed) as the active substance, and it is given by IM route of administration.

Further information about the evaluation of Prevenar 20's benefits can be found in Prevenar 20's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/Prevenar 20.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Prevenar 20, together with measures to minimise such risks and the proposed studies for learning more about Prevenar 20's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals

- Important advice on the medicine's packaging

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly

- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Prevenar 20 is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Prevenar 20 are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Prevenar 20. Potential risks are concerns for which an association with the use of this vaccine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

There are no important identified/potential risks or missing information for Prevenar 20.

II.B. Summary of Important Risks

Not applicable.

II.C. Post-Authorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

The following post-authorisation efficacy studies are conditions of the marketing authorisation for Prevenar 20 in adults:

- **Study B7471015: A Phase 4 Study Using a Test-Negative Design to Evaluate the Effectiveness of a 20-valent Pneumococcal Conjugate Vaccine Against Vaccine-Type Radiologically Confirmed Community-Acquired Pneumonia in Adults ≥65 Years of Age**

- **European specific analysis results of Study B7471015**

  Purpose of the study: Evaluate the long-term effectiveness of 20vPnC against vaccine-type radiologically confirmed community acquired pneumonia in adults ≥65 years of age.

- **Phase 4 Observational, Real-World Study of 20-valent Pneumococcal Conjugate Vaccine Effectiveness Against Vaccine-Type Invasive Pneumococcal Disease in Europe**

  Purpose of the study: Evaluate the long-term effectiveness of 20vPnC against vaccine-type invasive pneumococcal disease in adults in the EU.

II.C.2. Other Studies in Post-Authorisation Development Plan

None.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2 – Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 - Protocols for proposed and on-going studies in RMP Part IV

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 - Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

REFERENCES

1. Klugman KP, Black S, Dagan R, et al. Pneumococcal conjugate vaccine and pneumococcal common protein vaccines. In *Vaccines*. Edited by: Plotkin SA, Orenstein WA, Offit PA. Sixth Edition. China: Elsevier Saunders; 2013. p. 504-41.

2. Schilder AG, Chonmaitree T, Cripps AW, et al. Otitis media. Nat Rev Dis Primers. 2016;2:16063.

3. WHO. Pneumonia Updated 11 November 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/pneumonia. Accessed on: 04 January 2022.

4. Olarte L, Jackson MA. Streptococcus pneumoniae. Pediatr Rev. 2021;42(7):349-59.

5. Chapman R, Sutton K, Dillon-Murphy D, et al. Ten year public health impact of 13-valent pneumococcal conjugate vaccination in infants: A modelling analysis. Vaccine. 2020;38(45):7138-45.

6. Ladhani SN, Collins S, Djennad A, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000–17: a prospective national observational cohort study. The Lancet Infectious Diseases. 2018;18(4):441-51.

7. Tagarro A, Benito A, Sanchez A, et al. Bacteremic Pneumonia before and after Withdrawal of 13-Valent Pneumococcal Conjugate Vaccine from a Public Vaccination Program in Spain: A Case-Control Study. J Pediatr. 2016;171:111-5 e1-3.

8. Levy C, Varon E, Picard C, et al. Trends of pneumococcal meningitis in children after introduction of the 13-valent pneumococcal conjugate vaccine in France. Pediatr Infect Dis J. 2014;33(12):1216-21.

9. Slotved HC, Dalby T, Hoffmann S. The effect of pneumococcal conjugate vaccines on the incidence of invasive pneumococcal disease caused by ten non-vaccine serotypes in Denmark. Vaccine. 2016;34(6):769-74.

10. Steens A, Bergsaker MA, Aaberge IS, et al. Prompt effect of replacing the 7-valent pneumococcal conjugate vaccine with the 13-valent vaccine on the epidemiology of invasive pneumococcal disease in Norway. Vaccine. 2013;31(52):6232-8.

11. Azzari C, Serranti D, Nieddu F, et al. Significant impact of pneumococcal conjugate vaccination on pediatric parapneumonic effusion: Italy 2006-2018. Vaccine. 2019;37(20):2704-11.

12. Savulescu C, Krizova P, Lepoutre A, et al. Effect of high-valency pneumococcal conjugate vaccines on invasive pneumococcal disease in children in SpIDnet countries: an observational multicentre study. Lancet Respir Med. 2017;5(8):648-56.

13. Statens Serum Institute. Invasive Pneumococcal Disease 2018-2019 Updated 26 Mar 2020. Available from: https://en.ssi.dk/surveillance-and-preparedness/surveillance-in-

denmark/annual-reports-on-disease-incidence/invasive-pneumococcal-disease-2018-2019. Accessed on: 15 Feb 2022.

14. Hanquet G, Krizova P, Dalby T, et al. Serotype Replacement after Introduction of 10-Valent and 13-Valent Pneumococcal Conjugate Vaccines in 10 Countries, Europe. Emerg Infect Dis. 2022;28(1):137-38.

15. Moore MR, Link-Gelles R, Schaffner W, et al. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance. The Lancet Infectious diseases. 2015;15(3):301-09.

16. Naucler P, Galanis I, Morfeldt E, et al. Comparison of the Impact of Pneumococcal Conjugate Vaccine 10 or Pneumococcal Conjugate Vaccine 13 on Invasive Pneumococcal Disease in Equivalent Populations. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2017;65(11):1780-89.

17. Andrews N, Kent A, Amin-Chowdhury Z, et al. Effectiveness of the seven-valent and thirteen-valent pneumococcal conjugate vaccines in England: The indirect cohort design, 2006–2018. Vaccine. 2019;37(32):4491-98.

18. Dagan R, Patterson S, Juergens C, et al. Comparative immunogenicity and efficacy of 13-valent and 7-valent pneumococcal conjugate vaccines in reducing nasopharyngeal colonization: a randomized double-blind trial. Clin Infect Dis. 2013;57(7):952-62.

19. Pirez MC, Algorta G, Cedres A, et al. Impact of universal pneumococcal vaccination on hospitalizations for pneumonia and meningitis in children in Montevideo, Uruguay. Pediatr Infect Dis J. 2011;30(8):669-74.

20. Simonsen L, Taylor RJ, Young-Xu Y, et al. Impact of pneumococcal conjugate vaccination of infants on pneumonia and influenza hospitalization and mortality in all age groups in the United States. mBio. 2011;2(1):e00309-10.

21. Griffin MR, Zhu Y, Moore MR, et al. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. The New England journal of medicine. 2013;369(2):155-63.

22. Angoulvant F, Levy C, Grimprel E, et al. Early Impact of 13-Valent Pneumococcal Conjugate Vaccine on Community-Acquired Pneumonia in Children. Clinical Infectious Diseases. 2014;58(7):918-24.

23. Becker-Dreps S, Amaya E, Liu L, et al. Changes in childhood pneumonia and infant mortality rates following introduction of the 13-valent pneumococcal conjugate vaccine in Nicaragua. Pediatr Infect Dis J. 2014;33(6):637-42.

24. Griffin MR, Mitchel E, Moore MR, et al. Declines in pneumonia hospitalizations of children aged <2 years associated with the use of pneumococcal conjugate vaccines - Tennessee, 1998-2012. MMWR Morb Mortal Wkly Rep. 2014;63(44):995-8.

25. Lau WC, Murray M, El-Turki A, et al. Impact of pneumococcal conjugate vaccines on childhood otitis media in the United Kingdom. Vaccine. 2015;33(39):5072-9.

26. Olarte L, Barson WJ, Barson RM, et al. Pneumococcal Pneumonia Requiring Hospitalization in US Children in the 13-Valent Pneumococcal Conjugate Vaccine Era. Clinical Infectious Diseases. 2017;64(12):1699-704.

27. Kawai K, Adil EA, Barrett D, et al. Ambulatory Visits for Otitis Media before and after the Introduction of Pneumococcal Conjugate Vaccination. J Pediatr. 2018;201:122-27 e1.

28. Pichichero M, Kaur R, Scott DA, et al. Effectiveness of 13-valent pneumococcal conjugate vaccination for protection against acute otitis media caused by Streptococcus pneumoniae in healthy young children: a prospective observational study. Lancet Child Adolesc Health. 2018;2(8):561-68.

29. Ouldali N, Levy C, Minodier P, et al. Long-term Association of 13-Valent Pneumococcal Conjugate Vaccine Implementation With Rates of Community-Acquired Pneumonia in Children. JAMA Pediatr. 2019;173(4):362-70.

30. Zhou X, de Luise C, Gaffney M, et al. National impact of 13-valent pneumococcal conjugate vaccine on ambulatory care visits for otitis media in children under 5 years in the United States. International Journal of Pediatric Otorhinolaryngology. 2019;119:96-102.

31. Triadou D, Givon-Lavi N, Greenberg D, et al. Pneumococcal conjugate vaccines decrease community-acquired alveolar pneumonia with and without pleural effusion in children <60 months in Southern Israel, 2002-2016. Infect Dis (Lond). 2020;52(3):186-95.

32. Gambia Pneumococcal Surveillance G, Mackenzie GA, Hill PC, et al. Impact of the introduction of pneumococcal conjugate vaccination on invasive pneumococcal disease and pneumonia in The Gambia: 10 years of population-based surveillance. Lancet Infect Dis. 2021;21(9):1293-302.

33. Ben-Shimol S, Givon-Lavi N, Leibovitz E, et al. Impact of Widespread Introduction of Pneumococcal Conjugate Vaccines on Pneumococcal and Nonpneumococcal Otitis Media. Clin Infect Dis. 2016;63(5):611-8.

34. Ubukata K, Morozumi M, Sakuma M, et al. Etiology of Acute Otitis Media and Characterization of Pneumococcal Isolates After Introduction of 13-Valent Pneumococcal Conjugate Vaccine in Japanese Children. The Pediatric Infectious Disease Journal. 2018;37(6):598-604.

35. Sapir A, Ziv O, Leibovitz E, et al. Impact of the 13-valent pneumococcal conjugate vaccine (PCV13) on acute mastoiditis in children in southern Israel: A 12-year retrospective comparative study (2005-2016). Int J Pediatr Otorhinolaryngol. 2021;140:110485.

36. Dagan R, Van Der Beek BA, Ben-Shimol S, et al. Effectiveness of the 7- and 13-Valent Pneumococcal Conjugate Vaccines Against Vaccine-Serotype Otitis Media. Clin Infect Dis. 2021;73(4):650-58.

37. Dagan R, Van Der Beek BA, Ben-Shimol S, et al. Corrigendum to: Effectiveness of the 7- and 13-Valent Pneumococcal Conjugate Vaccines Against Vaccine-Serotype Otitis Media. Clin Infect Dis. 2022;74(2):372.

38. van Hoek AJ, Sheppard CL, Andrews NJ, et al. Pneumococcal carriage in children and adults two years after introduction of the thirteen valent pneumococcal conjugate vaccine in England. Vaccine. 2014;32(34):4349-55.

39. Rodgers GL, Klugman KP. Surveillance of the impact of pneumococcal conjugate vaccines in developing countries. Hum Vaccin Immunother. 2016;12(2):417-20.

40. Baxter R, Aukes L, Pelton SI, et al. Impact of the 13-Valent Pneumococcal Conjugate Vaccine on Invasive Pneumococcal Disease After Introduction Into Routine Pediatric Use. J Pediatric Infect Dis Soc. 2021;10(2):141-50.

41. Gierke R, Farley MM, Schaffner W, et al. 1299. Epidemiology of Invasive Pneumococcal Disease (IPD) in the United States 2011-2019. Open Forum Infect Dis. 2021;8(Supplement_1):S737-S38.

42. Wahl B, O'Brien KL, Greenbaum A, et al. Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15. Lancet Glob Health. 2018;6(7):e744-e57.

43. Talbot TR, Hartert TV, Mitchel E, et al. Asthma as a risk factor for invasive pneumococcal disease. N Engl J Med. 2005;352(20):2082-90.

44. Yildirim I, Shea KM, Little BA, et al. Vaccination, Underlying Comorbidities, and Risk of Invasive Pneumococcal Disease. PEDIATRICS. 2015;135(3):495-503.

45. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among children aged 6-18 years with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2013;62(25):521-4.

46. Vestjens S, Sanders E, Vlaminckx B, et al. Twelve years of pneumococcal conjugate vaccination in the Netherlands: Impact on incidence and clinical outcomes of invasive pneumococcal disease. Vaccine. 2019;37(43):6558-65.

47. Naucler P, Galanis I, Morfeldt E, et al. Comparison of the Impact of Pneumococcal Conjugate Vaccine 10 or Pneumococcal Conjugate Vaccine 13 on Invasive Pneumococcal Disease in Equivalent Populations. Clin Infect Dis. 2017;65(11):1780-89.

48. Statens Serum Institut. Invasive pneumococcal disease 2018–2019. Statens Serum Institut, Updated 26 Mar 2020. Available from: https://en.ssi.dk/surveillance-and-preparedness/surveillance-in-denmark/annual-reports-on-disease-incidence/invasive-pneumococcal-disease-2018-2019. Accessed on: 5 Jun 2020.

49. Finnish Institute for Health and Welfare. Incidence of invasive pneumococcal disease in Finland. Finnish Institute for Health and Welfare, Updated 07 May 2020. Available from: https://thl.fi/en/web/thlfi-en/research-and-expertwork/projects-and-programmes/monitoring-the-population-effectiveness-of-pneumococcal-conjugate-vaccination-in-the-finnish-national-vaccination-programme/incidence-of-invasive-pneumococcal-disease-in-finland. Accessed on: 5 Jun 2020.

50. Centre National de Référence des Pneumocoques. Batah J and Varon E. Rapport d'activité 2018, Epidémiologie 2017. Available from: https://cnr-pneumo.com/docman/rapports/39-2018-epidemiologie-2017/file. Accessed on: 5 Jun 2020.

51. Houseman C, Chapman KE, Manley P, et al. Decreasing case fatality rate following invasive pneumococcal disease, North East England, 2006-2016. Epidemiol Infect. 2019;147:e175.

52. Backhaus E, Berg S, Andersson R, et al. Epidemiology of invasive pneumococcal infections: manifestations, incidence and case fatality rate correlated to age, gender and risk factors. BMC Infect Dis. 2016;16:367.

53. Harboe ZB, Dalby T, Weinberger DM, et al. Impact of 13-valent pneumococcal conjugate vaccination in invasive pneumococcal disease incidence and mortality. Clin Infect Dis. 2014;59(8):1066-73.

54. Wagenvoort G, Sanders EA, Vlaminckx B, et al. Invasive pneumococcal disease: Clinical outcomes and patient characteristics 2-6 years after introduction of 7-valent pneumococcal conjugate vaccine compared to the pre-vaccine period, the Netherlands. Vaccine. 2016;34(8):1077-85.

55. Centers for Disease Control and Prevention. *Streptococcus pneumoniae*, 2017. In Active Bacterial Core Surveillance Report. Emerging Infections Program Network. 2019.

56. Polkowska A, Toropainen M, Ollgren J, et al. Bacterial meningitis in Finland, 1995-2014: a population-based observational study. BMJ Open. 2017;7(5):e015080.

57. Lepoutre A, Varon E, Georges S, et al. Impact of the pneumococcal conjugate vaccines on invasive pneumococcal disease in France, 2001-2012. Vaccine. 2015;33(2):359-66.

58. Castelblanco R, Lee M, Hasbun R. Epidemiology of bacterial meningitis in the USA from 1997 to 2010: a population-based observational study. Lancet Infect Dis. 2014;14(9):813-9.

59. Jacobs DM, Yung F, Hart E, et al. Trends in pneumococcal meningitis hospitalizations following the introduction of the 13-valent pneumococcal conjugate vaccine in the United States. Vaccine. 2017;35(45):6160-65.

60. Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial Meningitis in the United States, 1998–2007. New England Journal of Medicine. 2011;364(21):2016-25.

61. Jit M. The risk of sequelae due to pneumococcal meningitis in high-income countries: a systematic review and meta-analysis. J Infect. 2010;61(2):114-24.

62. European Centre for Disease Prevention and Control. Surveillance Atlas for Infectious Diseases, Invasive Pneumococcal Disease, 2018. Available from: https://www.ecdc.europa.eu/en/data-tools. Accessed on: 17 Jul 2020.

63. Grant L, Suaya J, Pugh S. Coverage of the 20-valent conjugate vaccine against invasive pneumococcal disease by age group in the United States, 2017 [online ePoster/abstract 237]. ISPPD-12 2020 Digital Library. Available from: https://cslide.ctimeetingtech.com/isppd20/attendee/eposter/poster/237. Accessed on: 26 Jun 2020.

64. van Hoek AJ, Andrews N, Waight PA, et al. Effect of serotype on focus and mortality of invasive pneumococcal disease: coverage of different vaccines and insight into non-vaccine serotypes. PLoS One. 2012;7(7):e39150.

65. Hausdorff WP, Feikin DR, Klugman KP. Epidemiological differences among pneumococcal serotypes. Lancet Infect Dis. 2005;5(2):83-93.

66. Richter SS, Diekema DJ, Heilmann KP, et al. Changes in pneumococcal serotypes and antimicrobial resistance after introduction of the 13-valent conjugate vaccine in the United States. Antimicrob Agents Chemother. 2014;58(11):6484-9.

67. Varon E, Cohen R, Béchet S, et al. Invasive disease potential of pneumococci before and after the 13-valent pneumococcal conjugate vaccine implementation in children. Vaccine. 2015;33(46):6178-85.

68. Janoir C, Lepoutre A, Gutmann L, et al. Insight Into Resistance Phenotypes of Emergent Non 13-valent Pneumococcal Conjugate Vaccine Type Pneumococci Isolated From Invasive Disease After 13-valent Pneumococcal Conjugate Vaccine Implementation in France. Open Forum Infect Dis. 2016;3(1):ofw020.

69. Cohen R, Biscardi S, Levy C. The multifaceted impact of pneumococcal conjugate vaccine implementation in children in France between 2001 to 2014. Hum Vaccin Immunother. 2016;12(2):277-84.

70. Ikuse T, Habuka R, Wakamatsu Y, et al. Local outbreak of Streptococcus pneumoniae serotype 12F caused high morbidity and mortality among children and adults. Epidemiol Infect. 2018;146(14):1793-96.

71. Linkevicius M, Cristea V, Siira L, et al. Outbreak of invasive pneumococcal disease among shipyard workers, Turku, Finland, May to November 2019. Euro Surveill. 2019;24(49):1900681.

72. Sings HL. Pneumococcal conjugate vaccine use in adults - Addressing an unmet medical need for non-bacteremic pneumococcal pneumonia. Vaccine. 2017;35(40):5406-17.

73. Pick H, Daniel P, Rodrigo C, et al. Pneumococcal serotype trends, surveillance and risk factors in UK adult pneumonia, 2013-18. Thorax. 2020;75(1):38-49.

74. Vestjens S, Wagenvoort G, Grutters J, et al. Changes in pathogens and pneumococcal serotypes causing community-acquired pneumonia in The Netherlands. Vaccine. 2017;35(33):4112-18.

75. Pletz MW, von Baum H, van der Linden M, et al. The burden of pneumococcal pneumonia - experience of the German competence network CAPNETZ. Pneumologie. 2012;66(8):470-5.

76. Menéndez R, España PP, Pérez-Trallero E, et al. The burden of PCV13 serotypes in hospitalized pneumococcal pneumonia in Spain using a novel urinary antigen detection test. CAPA study. Vaccine. 2017;35(39):5264-70.

77. Theilacker C, Hansen K, Rünow E. Pneumococcal serotype distribution in adults hospitalized with radiologically-confirmed community-acquired pneumonia in Malmö, Sweden [online ePoster/abstract 904]. ISPPD-12 2020 Digital Library. Available from: https://cslide.ctimeetingtech.com/isppd20/attendee/eposter/poster/904. Accessed on: 26 Jun 2020.

78. Said MA, Johnson HL, Nonyane BA, et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. PLoS One. 2013;8(4):e60273.

79. Wunderink R, Self W, Anderson E, et al. Pneumococcal Community-Acquired Pneumonia Detected by Serotype-Specific Urinary Antigen Detection Assays. Clin Infect Dis. 2018;66(10):1504-10.

80. Jain S, Self WH, Wunderink RG, et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. N Engl J Med. 2015;373(5):415-27.

81. Ramirez J, Furmanek S, Pena S, et al. The Louisville pneumonia study group. Impact of microbiological workup on the incidence of hospitalizations due to pneumococcal pneumonia. ISPPD-12 2020, #809. [abstract].

82. Morrill HJ, Caffrey AR, Noh E, et al. Epidemiology of pneumococcal disease in a national cohort of older adults. Infect Dis Ther. 2014;3(1):19-33.

83. Ramirez J, Furmanek S, Pena S, et al. Association of *S pneumoniae* serotypes with myocardial infarction and other cardiac events in hospitalized patients with pneumococcal pneumonia. ISPPD 2020. #805 [abstract].

84. Self W, Lindsell C, Rouphael N, et al. Quality of life following pneumococcal and all-cause pneumonia: results from the PNEUMO study. ISPPD-12 2020, #809 [abstract].

85. Drijkoningen J, Rohde G. Pneumococcal infection in adults: burden of disease. Clin Microbiol Infect. 2014;20 Suppl 5:45-51.

86. Han J, Lindsell C, Rouphael N, et al. Cognitive function following pneumococcal and all-cause pneumonia: results from the PNEUMO study. ISPPD-12 2020, #353 [abstract].

87. Cillóniz C, Liapikou A, Martin-Loeches I, et al. Twenty-year trend in mortality among hospitalized patients with pneumococcal community-acquired pneumonia. PLoS One. 2018;13(7):e0200504.

88. van Mens SP, van Deursen AMM, de Greeff SC, et al. Bacteraemic and non-bacteraemic/urinary antigen-positive pneumococcal community-acquired pneumonia compared. Eur J Clin Microbiol Infect Dis. 2015;34(1):115-22.

89. Klein EY, Monteforte B, Gupta A, et al. The frequency of influenza and bacterial coinfection: a systematic review and meta-analysis. Influenza Other Respir Viruses. 2016;10(5):394-403.

90. McCullers JA. Insights into the interaction between influenza virus and pneumococcus. Clin Microbiol Rev. 2006;19(3):571-82.

91. Peltola VT, McCullers JA. Respiratory viruses predisposing to bacterial infections: role of neuraminidase. Pediatr Infect Dis J. 2004;23(1 Suppl):S87-97.

92. Martin-Loeches I, Schultz M, Vincent J, et al. Increased incidence of co-infection in critically ill patients with influenza. Intensive Care Med. 2017;43(1):48-58.

93. Brundage JF. Interactions between influenza and bacterial respiratory pathogens: implications for pandemic preparedness. Lancet Infect Dis. 2006;6(5):303-12.

94. MacIntyre CR, Chughtai AA, Barnes M, et al. The role of pneumonia and secondary bacterial infection in fatal and serious outcomes of pandemic influenza a(H1N1)pdm09. BMC Infect Dis. 2018;18(1):637.

95. Brundage JF, Shanks GD. Deaths from bacterial pneumonia during 1918-19 influenza pandemic. Emerg Infect Dis. 2008;14(8):1193-9.

96. Morris DE, Cleary DW, Clarke SC. Secondary Bacterial Infections Associated with Influenza Pandemics. Front Microbiol. 2017;8:1041.

97. Garcia-Vidal C, Sanjuan G, Moreno-Garcia E, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect. 2021;27(1):83-88.

98. Amin-Chowdhury Z, Aiano F, Mensah A, et al. Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic on Invasive Pneumococcal Disease and Risk of Pneumococcal Coinfection With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): Prospective National Cohort Study, England. Clin Infect Dis. 2021;72(5):e65-e75.

99. Westblade LF, Simon MS, Satlin MJ. Bacterial Coinfections in Coronavirus Disease 2019. Trends Microbiol. 2021;29(10):930-41.

100. Rouze A, Martin-Loeches I, Povoa P, et al. Early Bacterial Identification among Intubated Patients with COVID-19 or Influenza Pneumonia: A European Multicenter Comparative Clinical Trial. Am J Resp Crit Care. 2021;204(5):546-56.

101. Langford BJ, So M, Raybardhan S, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. Clinical Microbiology and Infection. 2020;26(12):1622-29.

102. Musuuza JS, Watson L, Parmasad V, et al. Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: A systematic review and meta-analysis. Plos One. 2021;16(5):e0251170.

103. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: Implications for pandemic influenza preparedness. Journal of Infectious Diseases. 2008;198(7):962-70.

104. Lewnard JA, Bruxvoort KJ, Fischer H, et al. Prevention of Coronavirus Disease 2019 Among Older Adults Receiving Pneumococcal Conjugate Vaccine Suggests Interactions Between Streptococcus pneumoniae and Severe Acute Respiratory Syndrome Coronavirus 2 in the Respiratory Tract. Journal of Infectious Diseases. 2021;225(10):1710-20.

105. Mitsi E, Reine J, Urban BC, et al. Streptococcus pneumoniae colonization associates with impaired adaptive immune responses against SARS-CoV-2. J Clin Invest. 2022;132(7):e157124.

106. Lewnard JA, Bruxvoort KJ, Hong VX, et al. Effectiveness of Pneumococcal Conjugate Vaccination Against Virus-Associated Lower Respiratory Tract Infection Among Adults: A Case-Control Study. Journal of Infectious Diseases. 2023;227(4):498-511.

107. Carniel BF, Marcon F, Rylance J, et al. Pneumococcal colonization impairs mucosal immune responses to live attenuated influenza vaccine. Jci Insight. 2021;6(4):e141088.

108. Pride MW, Huijts SM, Wu K, et al. Validation of an immunodiagnostic assay for detection of 13 Streptococcus pneumoniae serotype-specific polysaccharides in human urine. Clin Vaccine Immunol. 2012;19(8):1131-41.

109. Kalina WV, Souza V, Wu K, et al. Qualification and Clinical Validation of an Immunodiagnostic Assay for Detecting 11 Additional Streptococcus pneumoniae Serotype-specific Polysaccharides in Human Urine. Clin Infect Dis. 2020;71(9):e430-e38.

110. Isturiz RE, Ramirez J, Self WH, et al. Pneumococcal epidemiology among us adults hospitalized for community-acquired pneumonia. Vaccine. 2019;37(25):3352-61.

111. Grant L, Ramirez J, Self W. *Streptococcus pneumoniae* serotype distribution and coverage of pneumococcal conjugate vaccines in adults hospitalized with community-acquired pneumonia in the United States [online ePoster/abstract 311]. ISPPD-12 2020 Digital Library. Available from: https://cslide.ctimeetingtech.com/isppd20/attendee/person/311. Accessed on: 26 Jun 2020.

112. Bollaerts K, Fletcher M, Suaya J. Vaccine-preventable clinical versus radiologically- or etiologically-confirmed disease in pneumococcal conjugate vaccine efficacy trials: A systematic literature review and re-analysis [online ePoster/abstract 762]. ISPPD-12 2020 Digital Library. . Available from: https://cslide.ctimeetingtech.com/isppd20/attendee/person/persons?q=Bollaerts. Accessed on: 05 Aug 2020.

113. Gessner BD, Jiang Q, Van Werkhoven CH, et al. A public health evaluation of 13-valent pneumococcal conjugate vaccine impact on adult disease outcomes from a randomized clinical trial in the Netherlands. Vaccine. 2019;37(38):5777-87.

114. Perdrizet J, Chilson E, Wasserman M, et al. Current and future pneumococcal conjugate vaccine serotype-specific burden in the United States adult population [online ePoster/abstract 287]. ISPPD-12 2020 Digital Library. Available from: https://cslide.ctimeetingtech.com/isppd20/attendee/person/226. Accessed on: 5 Aug 2020.

115. Gierke R, Wodi PA, Kobayashi M. Pneumococcal Disease. In *The Pink Book: Course Textbook*. Edited by: CDC. 14th Edition. 2021.

116. Fletcher MA, Balmer P, Bonnet E, et al. PCVs in individuals at increased risk of pneumococcal disease: a literature review. Expert Rev Vaccines. 2015;14(7):975-1030.

117. Chilson E, Scott DA, Schmoele-Thoma B, et al. Immunogenicity and safety of the 13-valent pneumococcal conjugate vaccine in patients with immunocompromising conditions: a review of available evidence. Hum Vaccin Immunother. 2020;16(11):2758-72.

118. Yildirim I, Shea KM, Pelton SI. Pneumococcal Disease in the Era of Pneumococcal Conjugate Vaccine. Infectious disease clinics of North America. 2015;29(4):679-97.

119. Castiglia P. Recommendations for pneumococcal immunization outside routine childhood immunization programs in Western Europe. Advances in therapy. 2014;31(10):1011-44.

120. Centers for Disease Control and Prevention. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 1997;46(RR-8):1-24.

121. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 2012;61(40):816-9.

122. Shea KM, Edelsberg J, Weycker D, et al. Rates of pneumococcal disease in adults with chronic medical conditions. Open Forum Infect Dis. 2014;1(1):ofu024.

123. Pelton SI, Shea KM, Farkouh RA, et al. Rates of pneumonia among children and adults with chronic medical conditions in Germany. BMC Infect Dis. 2015;15:470.

124. van Hoek AJ, Andrews N, Waight PA, et al. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. J Infect. 2012;65(1):17-24.

125. Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. N Engl J Med. 1991;325(21):1453-60.

126. Stein KE. Thymus-independent and thymus-dependent responses to polysaccharide antigens. J Infect Dis. 1992;165 Suppl 1:S49-52.

127. Borrow R, Heath PT, Siegrist CA. Use of pneumococcal polysaccharide vaccine in children: what is the evidence? Curr Opin Infect Dis. 2012;25(3):292-303.

128. Iyer AS, Ohtola JA, Westerink MA. Age-related immune response to pneumococcal polysaccharide vaccination: lessons for the clinic. Expert Rev Vaccines. 2015;14(1):85-97.

129. Janoff EN, Musher DM. Streptococcus pneumoniae. In *Mandell Douglas and Bennett's Principles and Practice of Infectious Diseases*. Edited by: Bennett JE, Dolin R, Blaser MJ, et al. 8th edition. Philadelphia, PA: Elsevier Saunders; 2015. p. 2310-27.

130. Geno KA, Gilbert GL, Song JY, et al. Pneumococcal Capsules and Their Types: Past, Present, and Future. Clin Microbiol Rev. 2015;28(3):871-99.

131. Ganaie F, Saad J, McGee L, et al. A New Pneumococcal Capsule Type, 10D, is the 100th Serotype and Has a Large cps Fragment from an Oral Streptococcus. mBio. 2020;11(3):e00937-20.

132. Henriques-Normark B, Tuomanen EI. The pneumococcus: epidemiology, microbiology, and pathogenesis. Cold Spring Harb Perspect Med. 2013;3(7):a010215.

133. Quesada MG, Hetrich M, Knoll MD. 1181. Serotype Distribution by Age of Remaining Invasive Pneumococcal Disease After Long-Term PCV10/13 Use: The PSERENADE Project. Open Forum Infect Dis. 2021;8(Supplement_1):S683-S84.

134. ECDC. Surveillance Atlas for Infectious Diseases, Invasive Pneumococcal Disease. European Centre for Disease Prevention and Control. Available from: http://atlas.ecdc.europa.eu/public/index.aspx. Accessed on: 18 July 2022.

135. Amin-Chowdhury Z, Bertran M, Sheppard CL, et al. Does the rise in seasonal respiratory viruses foreshadow the return of invasive pneumococcal disease this winter? Lancet Respir Med. 2022;10(1):e1-e2.

136. Perniciaro S, van der Linden M, Weinberger DM. Reemergence of Invasive Pneumococcal Disease in Germany During the Spring and Summer of 2021. Clin Infect Dis. 2022;75(7):1149-53.

137. Dowell SF, Garman RL, Liu G, et al. Evaluation of Binax NOW, an assay for the detection of pneumococcal antigen in urine samples, performed among pediatric patients. Clin Infect Dis. 2001;32(5):824-5.

138. Paker M, Pichkhadze E, Miron D, et al. Two decades of otitis media in northern Israel: Changing trends in the offending bacteria and antibiotic susceptibility. Int J Pediatr Otorhinolaryngol. 2022;152:110940.

139. Hulten KG, Barson W, Lin PL, et al. 1373. Vaccine Effectiveness and Pneumococcal Serotypes in Pediatric Otitis Media in the Era of Routine 13-valent Pneumococcal Vaccination in the United States. Open Forum Infect Dis. 2020;7(Supplement_1):S696-S97.

140. Ben-Shimol S, Givon-Lavi N, Kotler L, et al. Post-13-Valent Pneumococcal Conjugate Vaccine Dynamics in Young Children of Serotypes Included in Candidate Extended-Spectrum Conjugate Vaccines. Emerg Infect Dis. 2021;27(1):150-60.

141. Imohl M, Perniciaro S, Busse A, et al. Bacterial Spectrum of Spontaneously Ruptured Otitis Media in a 7-Year, Longitudinal, Multicenter, Epidemiological Cross-Sectional Study in Germany. Front Med (Lausanne). 2021;8(675225):1-17.

142. Levy C, Varon E, Ouldali N, et al. Bacterial causes of otitis media with spontaneous perforation of the tympanic membrane in the era of 13 valent pneumococcal conjugate vaccine. PLoS One. 2019;14(2):e0211712.

143. Dagan R, Pelton S, Bakaletz L, et al. Prevention of early episodes of otitis media by pneumococcal vaccines might reduce progression to complex disease. The Lancet Infectious Diseases. 2016;16(4):480-92.

144. Wasserman MD, Perdrizet J, Grant L, et al. Clinical and Economic Burden of Pneumococcal Disease Due to Serotypes Contained in Current and Investigational Pneumococcal Conjugate Vaccines in Children Under Five Years of Age. Infect Dis Ther. 2021;10(4):2701-20.

145. Mendes RE, Hollingsworth RC, Costello A, et al. Noninvasive Streptococcus pneumoniae serotypes recovered from hospitalized adult patients in the United States in 2009 to 2012. Antimicrob Agents Chemother. 2015;59(9):5595-601.

146. Metcalf BJ, Gertz RE, Jr., Gladstone RA, et al. Strain features and distributions in pneumococci from children with invasive disease before and after 13-valent conjugate vaccine implementation in the USA. Clin Microbiol Infect. 2016;22(1):60.e9-60.e29.

147. Tomczyk S, Lynfield R, Schaffner W, et al. Prevention of Antibiotic-Nonsusceptible Invasive Pneumococcal Disease With the 13-Valent Pneumococcal Conjugate Vaccine. Clinical Infectious Diseases. 2016;62(9):1119-25.

148. Amin-Chowdhury Z, Groves N, Sheppard CL, et al. Invasive pneumococcal disease due to 22F and 33F in England: A tail of two serotypes. Vaccine. 2021;39(14):1997-2004.

149. Zulz T, Wenger JD, Rudolph K, et al. Molecular characterization of Streptococcus pneumoniae serotype 12F isolates associated with rural community outbreaks in Alaska. J Clin Microbiol. 2013;51(5):1402-07.

150. Ikuse T, Habuka R, Wakamatsu Y, et al. Local outbreak of Streptococcus pneumoniae serotype 12F caused high morbidity and mortality among children and adults. Epidemiol Infect. 2018;146(14):1793-96.

151. Zivich PN, Grabenstein JD, Becker-Dreps SI, et al. Streptococcus pneumoniae outbreaks and implications for transmission and control: a systematic review. Pneumonia (Nathan). 2018;10:11.

152. Rokney A, Ben-Shimol S, Korenman Z, et al. Emergence of Streptococcus pneumoniae Serotype 12F after Sequential Introduction of 7- and 13-Valent Vaccines, Israel. Emerg Infect Dis. 2018;24(3):453-61.

153. Olarte L, Barson WJ, Barson RM, et al. Impact of the 13-Valent Pneumococcal Conjugate Vaccine on Pneumococcal Meningitis in US Children. Clinical Infectious Diseases. 2015;61(5):767-75.

154. Amin-Chowdhury Z, Collins S, Sheppard C, et al. Characteristics of Invasive Pneumococcal Disease Caused by Emerging Serotypes After the Introduction of the 13-Valent Pneumococcal Conjugate Vaccine in England: A Prospective Observational Cohort Study, 2014-2018. Clin Infect Dis. 2020;71(8):e235-e43.

155. Oligbu G, Collins S, Sheppard CL, et al. Childhood Deaths Attributable to Invasive Pneumococcal Disease in England and Wales, 2006-2014. Clin Infect Dis. 2017;65(2):308-14.

156. Harboe ZB, Thomsen RW, Riis A, et al. Pneumococcal serotypes and mortality following invasive pneumococcal disease: a population-based cohort study. PLoS medicine. 2009;6(5):e1000081.

157. Lynch JP, 3rd, Zhanel GG. Streptococcus pneumoniae: epidemiology, risk factors, and strategies for prevention. Semin Respir Crit Care Med. 2009;30(2):189-209.

158. Centers for Disease Control and Prevention. Pneumococcal Disease: Epidemiology and prevention of vaccine-preventable diseases. In *The pink book: course textbook*. Edited by: CDC. 12th Edition. Washington DC: 2012. p. 291-300.

159. World Health Organization. Annex 1 - WHO guidelines on non clinical evaluation of vaccines. WHO Technical Report Series No 927. Geneva, Switzerland. 2005. p. 31-63.

160. World Health Organization. Annex 2 - Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines. WHO Technical Report Series No 987. Geneva, Switzerland. 2014. p. 59-100.

ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.