NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	An observational safety study for Prevenar 13 among Chinese children
Protocol Number	B1851193
Protocol Version Identifier	1.2
Date of Last Version of Protocol	30 January 2019
Active Substance	PF-06414256/13-valent pneumococcal vaccine
Medicinal Product	Prevenar 13®
Research Question and Objectives	The objective of this study is to expand the understanding of the safety profile of Prevenar 13 in Chinese pediatric populations.
Author	PPD , PhD, MPH PPD , Epidemiology Worldwide Safety & Regulatory Pfizer Inc 235 East 42nd Street New York, NY 10017 United States

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
13vPnC	13-valent pneumococcal conjugate vaccines
7vPnC	7-valent pneumococcal conjugate vaccine
AE	Adverse Event
AEFIS	Adverse event following immunization information system
AEM	Adverse event monitoring
CDC	Centers for disease control and prevention
EHR	Electronic health record
EMR	Electronic medical record
HCP	Healthcare Professional
HGRAC	Human Genetic Resources Administration of China
Hib	Haemophilus influenzae type b
ICD-10	International classification of diseases, tenth revision
IEC	Independent ethics committee
IPD	Invasive pneumococcal disease
IPV	Inactivated polio
IRB	Institutional review board
NID	National identification
NIS	Non-interventional study
NMPA	National Medical Products Administration
PAC	Post authorization commitment
PPV	Positive predictive value

Abbreviation	**Definition**
RV	Rotavirus
SAP	Statistical analysis plan
SOI	Safety outcome of interest
SOP	Standard operating procedure

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
PPD, MD, PhD	PPD	PPD	PPD China
PPD, PhD, MPH	PPD Epidemiology Worldwide Safety & Regulatory	Pfizer Inc	235 East 42nd Street New York, NY 10017 United States

Investigators

Name, degree(s)	Title	Affiliation	Address
PPD, PhD, MS	PPD	PPD	PPD, China
PPD, BS	PPD	PPD	PPD, China
PPD, BS	PPD	PPD	PPD, China
PPD, PhD, MS	PPD, Epidemiology Worldwide Safety & Regulatory	Pfizer Inc	235 East 42nd Street New York, NY 10017 United States
PPD, MS	Medical advisor Vaccine Medical Affair	Pfizer Inc	PPD China
PPD, BS	PPD	PPD	PPD, China

3. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	12 December 2018	Substantial	• Section 1, 5, 6, 8, and 9. • Section 2. • Section 7.	• Editorial changes by abbreviating some terms such as safety outcomes of interest, changing CFDA to NMPA. • Changed names of three investigators. • Re-estimated the study size based on the new data.	• To update the protocol and make it concise. • To reflect on the change in study personnel. • The original study size was estimated based on the annual birth rate and the coverage for Prevenar 7. The new exposure data showed the coverage for Prevenar 13 is much higher than Prevenar 7. In order to renew the HGRAC application, it is necessary to re-estimate the study size.
2	30 January 2019	Administrative	• Section 7	• Re-estimated the study size based on the more current data.	• In order to renew the HGRAC application, it is necessary to re estimate the study size.

4. MILESTONES

Milestone	Planned date
Start of data collection (first data cut)*	15 December 2018
End of data collection (last data cut)*	30 September 2020
Study progress report 1	15 April 2018
Study progress report 2	15 April 2019
Study progress report 3	15 April 2020
Final study report	15 April 2021

*For the main study.

5. RATIONALE AND BACKGROUND

Pneumococcal disease is a leading cause of serious illness throughout the world.[1] It is an infection caused by *Streptococcus pneumoniae* bacteria ("pneumococcus"). These bacteria can result in both invasive diseases such as bacteremic pneumonia, septicemia, and meningitis, and non-invasive diseases, such as pneumonia, otitis media, and sinus infections. One of the key risk factors of pneumococcal diseases is age, with children younger than 2 years of age and the elderly being at the highest risk of developing pneumococcal-related infection.[1] Pneumococcal disease is estimated to be the leading cause of vaccine-preventable morbidity and mortality among children younger than 5 years both globally and in China.[1] At least 1 million children die of pneumococcal disease every year, most of these being young children in developing countries.[2] In China alone, approximately 30 thousand children in this age group die due to pneumococcal disease every year.[3]

Currently, several approved vaccines to prevent *S. pneumoniae* infections are available on the market, including the 10-, and 13-valent pneumococcal conjugate vaccines (10vPnC; Synflorix, GlaxoSmithKline and 13vPnC; Prevnar 13, Pfizer, respectively), and the 23-valent pneumococcal polysaccharide vaccine (PPSV23; Pneumovax, SanofiPasteurMSD [in the US, Merck]). 13vPnC was approved in the European Union in December 2009 for the prevention of Invasive Pneumococcal Disease (IPD), pneumonia and acute otitis media caused by *S. pneumoniae* in infants, children and adolescents from 6 weeks to 17 years of age, and in the United States in February 2010 for the prevention of IPD and otitis media caused by *S. pneumoniae* in children 6 weeks through 5 years of age.

13vPnC is in use in the national childhood immunization programs in many countries and contains polysaccharides from the 7 serotypes included in the original 7vPnC (4, 6B, 9V, 14, 18C, 19F, and 23F) and an additional 6 serotypes (1, 3, 5, 6A, 7F, and 19A), all conjugated to cross-reactive material 197. It has been shown that the 6 additional serotypes in 13vPnC increase coverage for IPD prevention in children <5 years of age from 74% to 88% globally.[4] Importantly, the additional serotypes in 13vPnC are associated with a high percentage of pneumococcal disease in the developing world.[5,6]

In October 2016, 13vPnC was approved in China for the prevention of invasive disease (including bacteremic pneumonia, meningitis, septicemia, and bacteremia) caused by *Streptococcus pneumoniae* for infants and children aged 6 weeks to 15 months. 13vPnC is recommended as a series of four doses, one dose at each of these ages: 2 months; 4 months; 6 months; 12 through 15 months. Vaccines in China are classified into two categories. Type I vaccines are mandatory and provided for citizens by the government free of charge, and infants and children should get immunized according to the government's regulations. These vaccines include tuberculosis (Bacillus Calmette–Guérin), diphtheria/tetanus/pertussis, oral polio, measles/mumps/rubella, hepatitis B, hepatitis A, meningococcal, and Japanese encephalitis. Type II vaccines are ones available on the private market for use on a voluntary base at the purchaser's expense. They consist of Haemophilus influenzae type b (Hib), pneumococcal conjugate, rotavirus (RV), inactivated polio (IPV), varicella, human papillomavirus, and influenza vaccines. In China, all type I and type II vaccines are

administrated at China Centers for Disease Control and Prevention (CDC) immunization clinics.

13vPnC has a favorable benefit-risk profile. Based on data from clinical trials and the worldwide safety experiences after authorization, convulsions/seizures, fever, apnea, and anaphylaxis/hypersensitivity are identified as known or potential risks associated with 13vPnC among young children.[7,8]

To monitor these known and potential risks for 13vPnC among Chinese children receiving 13vPnC in China, an observational study using a population-based electronic health record (EHR) database from 1 May 2017 to 31 July 2020 in Yinzhou district of Ningbo city in China is conducted in a real world setting. Yinzhou is one of the largest districts in economically developed Ningbo city. Children exposed to 13vPnC in Yinzhou district are representative of those children likely receiving 13vPnC in China given that only families with sufficient financial resources can afford 13vPnC. In addition, the coverage for 7-valent pneumococcal conjugate vaccine (7vPnC) in Yinzhou district was similar to that in the published literature in China.[9] As a population-based database, Yinzhou EHR database consists of complete immunization records and healthcare data of all children in the district. This allows for the possibility of monitoring the safety of 13vPnC in the context of routine medical care from outpatient visits to inpatient care and provides greater generalizable findings.

This observational safety study is a post authorization commitment (PAC) to fulfill the key monitoring activity requirement of the China National Medical Products Administration (NMPA).

6. RESEARCH QUESTION AND OBJECTIVES

This observational study using a population-based EHR database in Yinzhou district of Ningbo city is to expand the understanding of the safety profile of 13vPnC in Chinese pediatric populations.

Objectives of the study are to:

- Estimate incidence rates (per 1,000 person-days at risk and per 1,000 doses) of safety outcomes of interest (SOIs) including seizures (including febrile seizures), urticaria and angioedema, apnea, and fever for the periods of 0 through 3 days (with 0 indicating the day of vaccination), 4 through 7 days, and 0 through 7 days after the 13vPnC vaccination by all doses and by each dose in the main study based on Yinzhou EHR database between 1 May 2017 and 31 July 2020.

- Estimate the incidence rates (per 1,000 person-days at risk and per 1,000 doses) of SOIs mentioned above for the same periods after the 13vPnC vaccination by all doses and by each dose in a sub-population of the main study through a prospective cohort study between 1 August 2018 and 31 July 2020.

All SOIs are acute events and are likely to occur within 7 days post-vaccination based on the known safety profile of 13vPnC as well as biologic plausibility of these events occurring after vaccination.[7,8]

7. RESEARCH METHODS

7.1. Study Design

This is an observational study based on a population-based EHR database. In addition, a validation study including validation of International classification of diseases, tenth revision (ICD-10) codes or ICD-10 code based algorithm for identifying all SOIs and a prospective cohort study in a sub-population of the main study will be conducted in order to offset the potential biased results from the main study because of potential misclassification of the SOIs due to miscoding and/or undercoding of ICD-10 codes used to identify the SOIs in the EHR database.

7.2. Study Population

The main study population consists of eligible children aged 1-24 months receiving at least one dose of 13vPnC recorded in Yinzhou EHR database between 1 May 2017 and 24 July 2020 (ie, one week prior to the end of the study) (Figure 1).

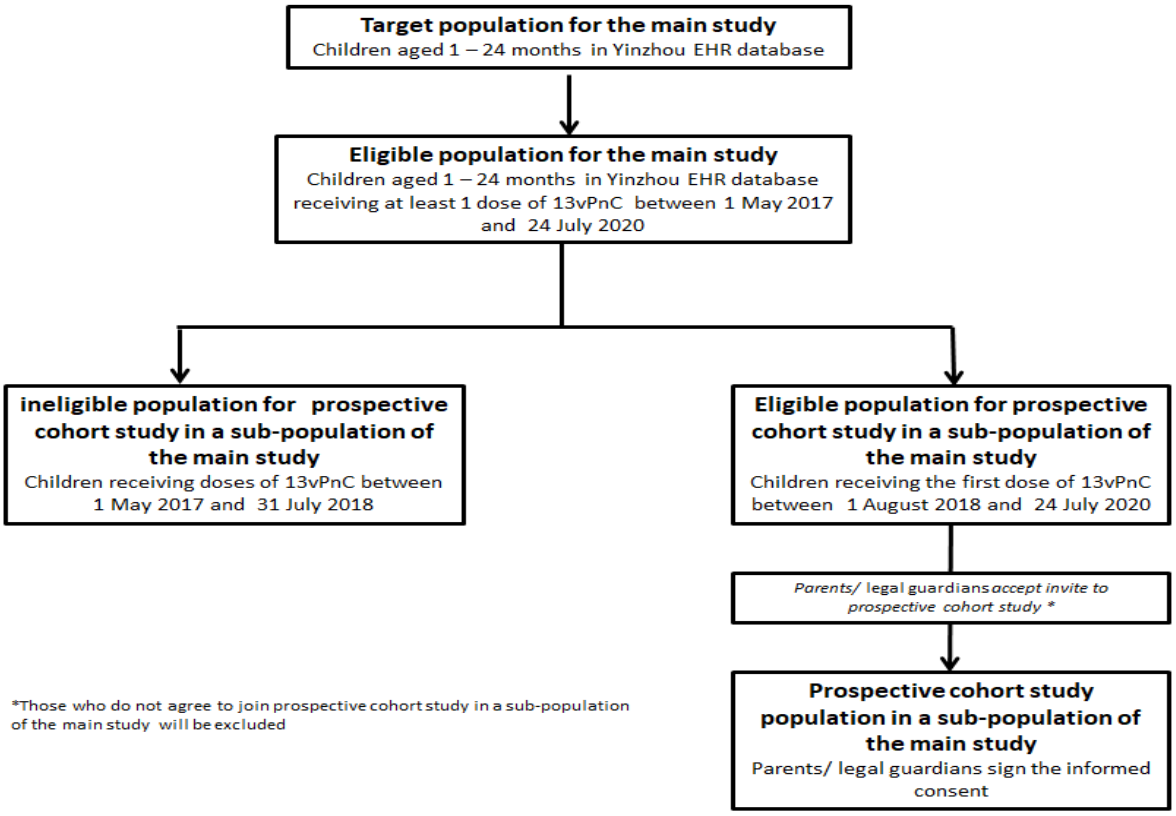
7.2.1. Inclusion Criteria

To be eligible for the main study, children in Yinzhou population-based EHR database must be aged 1 to 24 months and receive at least one dose of 13vPnC between 1 May 2017 and 24 July 2020 where the first dose is received before or on 24July 2020 since a 7-day post-vaccination follow-up for each dose in each child receiving 13vPnC is needed. For the prospective cohort in a sub-population of the main study, eligible children for the main study must receive the first dose of 13vPnC between 1 August 2018 and 24 July 2020 and an informed consent must be obtained from parents/legal guardians (Figure 1).

7.2.2. Exclusion Criteria

There are no exclusion criteria for this study.

Figure 1. Flow Chart for Study Populations



7.3. Variables

The exposure of interest is 13vPnC vaccine administered in CDC immunization clinics in Yinzhou district. SOIs are seizures, urticaria and angioedema, apnea and fever. Dates and doses of 13vPnC vaccination are recorded in Yinzhou CDC Immunization Administration Registry which is integrated into Yinzhou EHR database at an individual level. SOIs are documented in Yinzhou EHR database according to ICD coding in the database except ones in the CDC Adverse Event Following Immunization Information System (AEFIS). The events in AEFIS are recorded in text format based on a diagnosis. Variables and their descriptions are shown on Table 1. ICD codes or algorithm of ICD codes and diagnoses used to identify the SOIs in the study will be developed and documented in the statistical analysis plan (SAP).

Table 1. Variables and Roles

Variable	Role
Age at each dose of 13vPnC vaccination	Demographic
Gender	Demographic
Residency Status	Demographic
Smoking in the family (only the prospective cohort in a sub-population)	Covariate
Known allergies (only the prospective cohort in a sub-population)	Medical history
Preterm	Medical history
Low birth weight	Medical history
Sickle cell disease	Medical history
History of febrile seizure	Medical history
History of other seizures	Medical history
History of urticaria	Medical history
History of angioedema	Medical history
History of apnea	Medical history
Fever at the date prior to 13vPnC vaccination	Medical history
Other vaccines administrated the same date with 13vPnC	Co-administration
Season of diagnosis for each safety outcome of interest	Covariate
Hospitalization for each safety outcome of interest	Covariate
Date of each dose of 13vPnC vaccination (based on barcode scanning)	Exposure
Seizures (including febrile seizures)	Outcome
Urticaria and angioedema	Outcome
Apnea	Outcome
Fever	Outcome
Highest temperature for each day fever is reported (only the prospective cohort in a sub-population)	Outcome
Use of antipyretics post-vaccination (only the prospective cohort in a sub-population)	Covariate

7.4. Data Sources

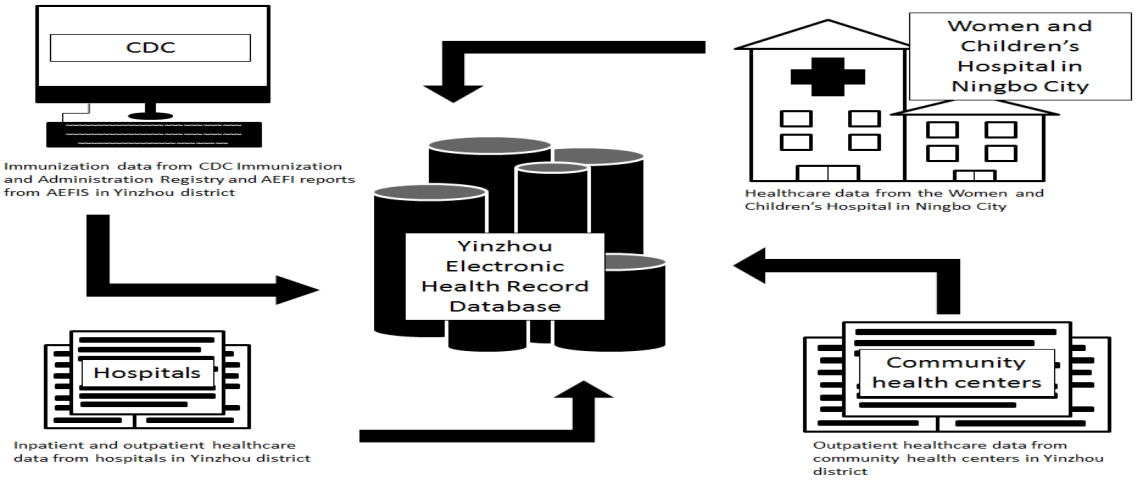
EHRs provide real-world clinical data with broad patient populations and have been increasingly used for post-approval drug safety studies over the past two decades in Europe and North America. In China, there are three major types of electronic healthcare databases including population-based EHR, electronic medical records (EMRs), and national claims. Since 2014, via collaboration with academic institutions in China, Pfizer has been evaluating these data sources and has determined that they provide potential value to post-marketing drug safety studies, particularly population-based EHRs.[10] Yinzhou EHR database is selected for this study because this population-based EHR database consists of complete immunization records and healthcare data of all children in the district.

7.4.1. Yinzhou EHR Database

Yinzhou is one of the largest districts of economically developed Ningbo city in Zhejiang province, China and consists of approximately 1.6 million populations (740,000 permanent residents and 860,000 temporary residents). The Yinzhou EHRs include data from three main sources (Figure 2):

- Yinzhou CDC databases;
- Healthcare data including EMRs, claims and e-prescriptions from hospitals and community health centers within the district;
- Healthcare data including EMRs, claims and e-prescriptions from the Women and Children's hospital of Ningbo city.

Figure 2. Components of Yinzhou EHR Database



Data from these data sources are entered into Yinzhou EHR database in real time. These data sources are linked via each individual's unique personal identification number (termed the national identification (NID) number) used by each resident throughout life in China. In a situation where children do not yet have a NID number, data of those children are matched by names of children, dates of birth, names of parents/legal guardians, or home addresses.

Yinzhou CDC database: There are two CDC databases (ie, Immunization Administration Registry and CDC AEFIS) in the district. The Immunization Administration Registry includes immunization data at CDC immunization clinics for both type I and type II vaccines for all children aged <7 years. The AEFIS is a passive surveillance system and collects AEFIs reports. All cases reported to AEFIS are to be investigated, with the exception of common adverse reactions that have a clear diagnosis (eg, fever, redness, and swelling on the injection site; induration).

Healthcare data from hospitals and community health centers within the district:
Yinzhou district collect healthcare data of its residents from hospitals (3 tertiary general hospitals and 1 specialized hospital) and community health centers (20) within the district including inpatient and outpatient visits from all hospitals and outpatient visits from all community health centers within the district.

Healthcare data from the Women and Children's Hospital of Ningbo city: The Women and Children's Hospital of Ningbo city is the only children hospital in the city. It is essential to have data from this hospital being part of Yinzhou EHR database because this hospital is very likely to be the hospital of choice if families would seek medical care for their children outside hospitals of Yinzhou district.

7.4.2. Evaluation of Yinzhou EHR Database

Yang et al conducted a detailed assessment of characteristics of Yinzhou EHR database in 2016 and concluded that Yinzhou database has the necessary attributes for post-marketing drug safety surveillance and pharmacoepidemiologic studies,[10] however, the data quality and its suitability for a post-approval vaccine safety study among pediatric populations was not assessed previously. It was therefore essential to conduct a pilot study before moving forward with a full-scale study using Yinzhou EHR database. Therefore, Pfizer, collaborating with Fudan University and Yinzhou CDC, performed a pilot study to further evaluate the Yinzhou EHR database from September to December 2017. Preliminary results of the pilot study indicated that the Yinzhou EHR database can be used to fulfill the requirement of this PAC, despite some limitations identified at the pilot study such as sub-classifications of some ICD codes used in the database are either omitted and/or combined with a few related or unelated diagnoses and a large number of children from transient families (temporary residents) move in or out of the district within a short period of time. To address these limitations, a validation study will be conducted.

7.5. Validation Study

To minimize potential biased estimates in the main study, a validation study will be conducted. This validation study consists of two parts: validation of ICD codes used to identify all SOIs in the main study and a prospective cohort study in a sub-population of the main study.

7.5.1. Validation of ICD Codes

To evaluate the accuracy of the ICD-10 codes or ICD-10 codes based algorithm for identifying all SOIs in the main study, relevant medical records of children having the ICD codes for these events are going to be obtained from hospitals within Yinzhou district and Women and Children's hospital of Ningbo city and outpatient medical records from community health centers within the district by Yinzhou CDC. A data abstraction form will be used to abstract data from the medical records. The abstracted data will be sent to an adjudication committee to determine whether the identified case is a true case. Then the adjudicated outcomes will be entered to the validation study database for analyses. The Positive Predicted Value (PPV) of the ICD code or ICD code algorithms will be calculated for the SOIs, using an adjudicated safety outcome based on the medical record as the gold

standard. Although this study will attempt to obtain all relevant medical records of all children having the ICD codes from these hospitals and community health centers, it is possible that some medical records of these children may not be available for various reasons. Procedures for this component are shown on Figure 3.

7.5.2. A Prospective Cohort Study in a Sub-Population

A prospective cohort study in a sub-population of the main study was initiated on 1 August 2018 after obtaining the approval of Human Genetic Resources Administration of China (HGRAC) application. The prospective cohort study will end on 31 July 2020. Potential participants are enrolled at the time of a visit to CDC immunization clinics after the informed consent is obtained. An initial questionnaire for the first dose is administered to parents/legal guardians of children in the office by healthcare professionals (HCPs) at the immunization clinics when a child receives the 13vPnC vaccination. A follow-up questionnaire at 7 days post-vaccination is administered by the HCPs either via a telephone or face-to-face interview to parents/legal guardians of the children. The initial questionnaires and follow-up questionnaire are completed for each dose of the 13vPnC vaccination. It should be noted that responsibilities of HCPs at the CDC immunization clinics are to administer vaccines to children and they are not children's treating HCPs.

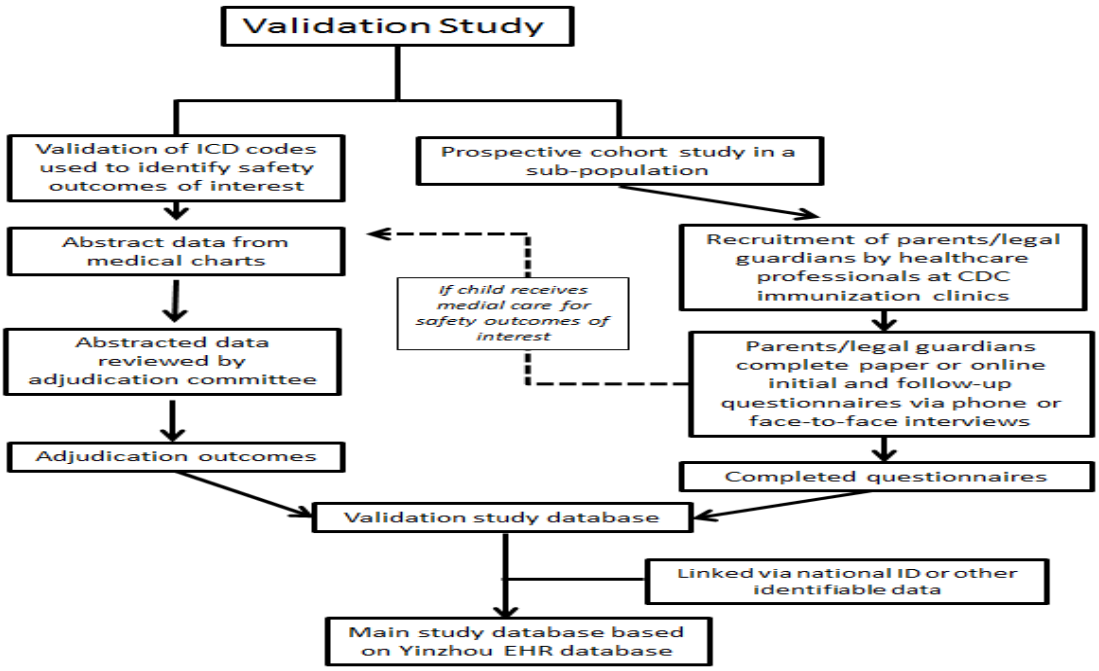
Both a web-based questionnaire and a paper-based questionnaire are made available to the HCPs for their preference. The HCPs at CDC immunization clinics have access to the web-based questionnaire via their work computers. Based on the feedback from Yinzhou CDC, the HCPs would be likely to use the web-based questionnaire for a face-to-face interview and a paper-based questionnaire for a phone interview. However, if a paper questionnaire is used at an interview, the HCP will be instructed to transfer the data from the completed paper questionnaire by completing a web-based questionnaire. A copy of the completed paper questionnaire will be uploaded to the validation study database. It is expected that completion of the initial questionnaire and the follow-up questionnaire will take approximately 20 minutes and 15 minutes respectively.

The questionnaires are pretested on a sample of HCPs and parents/legal guardians and revised to ensure clarity. Data elements on the questionnaire are similar to that in the main study based on Yinzhou EHR database including: demographic information; household characteristics; medical history; and occurrences of the SOIs. Questions on the questionnaires consist of both yes/no and multiple-choice answers. For questions related to SOIs, information on the date of onset, visits to a healthcare facility, the doctor's diagnosis, etc. is collected. The questionnaires do not solicit adverse events (AEs) other than the SOIs. There are no open-ended questions. Any product safety information that is otherwise volunteered will be handled in the manner described in the Section 9.3.

In addition, a child's medical records will be abstracted by Yinzhou CDC and reviewed by the adjudication committee if the parent/guardian indicates that the child visits a healthcare facility for one of the SOIs. The adjudicated outcomes will be subsequently entered and stored in the validation study database that is housed by Wanda Inc, the database builder and manager of Yinzhou EHR database. Although this study will attempt to obtain all relevant medical records of all children indicated a visit to a healthcare facility for the SOIs, it is

possible that some medical records of these children may not be available for various reasons. Procedures for this prospective cohort study are shown on Figure 3.

Figure 3. Procedures for the Validation Study



7.6. Study Size

This study includes all children 1 to 24 months of age who have received at least one dose of 13vPnC in the Yinzhou EHR database. Although the number of children in the Yinzhou EHR database varies from year to year, the birth rate in Yinzhou district has been steady with approximately 8,000 live-births each year. The coverage for the 7vPnC dose 1 vaccine in China was approximately 10% for children under 24 months.[9] Assuming the same coverage for the 13vPnC dose 1 in Yinzhou district, the study size was originally estimated to be 3,200 children exposed to at least one dose of 13vPnC during the approximately three-year study period. However, as of 30 January 2019, approximately 10,000 children 1 to 24 months of age in the Yinzhou EHR database have already received at least one dose of 13vPnC since the start of the main study (ie, 1 May 2017). Based on the newly available data, the study size is now re-estimated to be approximately 22,000 for the approximately three-year study period.

7.7. Data Management

All data for the main study are collected through the routine data collection practices of the Yinzhou EHR database. The data in the Yinzhou EHR database are updated continually. The principal investigator or his delegates at Fudan University will have access to de-identified study specific data generated by the data builder and manager of the Yinzhou EHR database (Wanda Inc) via a secure server. Data for the main study will be stored in the form of SAS® datasets at the secure server.

Data obtained from the validation study will also be housed and managed by Wanda Inc. Fudan University and Pfizer have full access to the de-identified study database. Although identifiable data such as children's NID numbers, their dates of birth, their names, etc. will be collected in one part of the validation study (ie, the prospective cohort study in a sub-population of the main study), these identifiable data will only be used by Wanda Inc to link children who participate in both the main study and the validation study for the purpose of analyses. The identifiable data will not be shared with Fudan University, Pfizer, or other third parties.

The first annual progress report to NMPA presented the study status since the HGRAC application for the study was pending. To prepare the subsequent annual progress reports to NMPA, the main study database is to be queried to identify the number of eligible children who have received a 13vPnC vaccination. For these children, routinely collected data are abstracted for the study variables: demographics; medical history; coadministration of other type I and type II vaccines if any, and the SOIs. Counts of the study variables in the main study will be included in the 2019 progress report and descriptive analyses will be conducted for the 2020 progress report.

Eligible children are followed in the Yinzhou EHR from the date of the first dose of the 13vPnC vaccination until 7 days after the last dose of the 13vPnC vaccination, moving out of the district, death, loss to follow-up, or the end of the study (whichever occurs first) for the occurrence of the SOIs.

All data will be maintained by a trained group of data managers from Wanda Inc ensuring compliance with national regulations in China. SAS® will be used for the statistical analyses.

7.8. Data Analysis

All analyses for the study will be descriptive. The descriptive analyses will include frequency distributions of age at the time receiving each dose of 13vPnC, gender, residential status, year of 13vPnC vaccinations, co-administration of other vaccines at the same date, and medical history. In addition, frequency distributions of the number of SOIs by age, gender, residential status, season of diagnosis, hospitalization, and year of 13vPnC vaccinations will also be described. The frequency distributions mentioned above will be tabulated for both the main study and the prospective cohort study in the sub-population of the main study.

Incidence rates per 1,000 person-days at risk and per 1,000 doses and its 95% CIs of the SOIs will be calculated in three different time periods (ie, 0-3 days, 4-7 days, and 0-7 days post-vaccination) by all doses and by each dose. Additional analyses (eg, stratification by gender, residency, and co-administration of other vaccines) will be performed. The incident rates will be estimated for both the main study and the prospective cohort study in the sub-population of the main study.

The percentage of children's medical charts that are available for the validation study will be described. The PPV of an ICD-10 code or ICD-10 code based algorithm used to identify the SOIs against adjudicated SOIs based on the information from medical records of children as a gold standard will be calculated for the validation of these codes in the main study. Additionally, the PPV of a reported SOI by parents/legal guardians that requires medical attentions against the adjudicated SOI based on the information from medical records of children as a gold standard will be also calculated in the prospective cohort study in the sub-population of the main study. Finally, among children who participate in both the main study and the prospective cohort study, sensitivity and specificity of an ICD code or ICD-10 code based algorithm identifying seizures or apnea in the main study will be calculated using the adjudicated seizures or apnea in the prospective cohort as a reference standard (ie, a gold standard). A positive percent of agreement and a negative percent of agreement will be estimated between an ICD code or ICD-10 code based algorithm identifying fever or urticaria and angioedema in the main study and the reported fever or urticaria and angioedema by parents/legal guardians in the prospective cohort as a non-reference standard (ie, a non-gold standard).

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

7.9. Quality Control

Fudan University and the database builder for the Yinzhou EHR database are responsible for following Pfizer's standard operating procedures (SOPs) as well as any of their own SOPs whenever appropriate to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables, description of available data, and extent of validation of endpoints.

7.10. Adjudication Committee

An adjudication committee consisting of three physicians will be set-up for the duration of the study. The primary role of the adjudication committee will be to:

- Review and endorse the adjudication charter.
- Agree case criteria for the SOIs.
- Adjudicate cases of the SOIs against the case criteria.

The detailed role and responsibility of the adjudication committee as well as the adjudication process will be documented in the adjudication committee charter.

7.11. Strengths and Limitations of the Research Methods

As one of the first of its kind to utilize a population-based EHR database in China for the purpose of post-approval safety studies, one of the key strengths of this study is completeness of vaccination record which is linked to healthcare data at hospitals and community health centers. It allows for the possibility of monitoring the safety of 13vPnC in the context of routine medical care from outpatient visits to inpatient care. In addition, observational data using real-world data (like the data in the Yinzhou EHR database) may provide insight regarding safety outcomes in children who are underrepresented in clinical trials. Furthermore, results based on this population-based study would be more generalizable than those obtained from clinical trials.

Nevertheless, there are several limitations to this study. First, one main potential source of confounding is co-administration of multiple vaccines. Although co-administration of type I and type II vaccines is not recommended by China CDC, it exists in practice. Additionally, it is possible that other type II vaccines may be administrated simultaneously with 13vPnC. For example, Hib, Pentaxim, RV1, and IPV vaccines can be given at the same time as 13vPnC in Children aged 2 months and 4 months based on China CDC recommended vaccine schedule. It may not be possible to differentiate safety outcomes of these vaccines although there is a plan to conduct analyses to estimate the incidence rates of the safety outcomes for those receiving 13vPnC only and for those receiving 13vPnC plus co-administration of other vaccines (Section 7.8). Second, it is possible that some children may receive medical care from hospitals outside of the catchment area. This information will not be captured by Yinzhou EHR except the care under Women and Children's hospital of Ningbo city. However, it is reasonable to assume that the vast majority of families are likely to go to the Women and Children's hospital of Ningbo city for the care since the next nearest Children's hospital is about two hour away while the Women and Children's hospital of Ningbo is less than a half hour away. Third, similar to any studies using secondary data sources, misclassification of SOIs may exist, since Yinzhou EHR is not designed for the research purpose. SOIs not requiring medical attentions tend to be systematically undercoded (eg, low fever and mild urticaria and angioedema) in these data sources. Although the prospective cohort study in a sub-population of the main study will be able to ascertain some of these events not requiring medical attention, it is possible that a small percentage of the events may be still under-reported. Fourth, like the rest of China, it is expected that a small percentage (approximately 10%) of children from families with sufficient financial resources may receive 13vPnC in Yinzhou district, It is possible that children receiving 13vPnC may be from tails of the target children population on either ends that may not be the same as the rest of the target population in terms of health status. As a result, the incidence of safety outcomes of interest in the study may be either substantially lower or higher than that in countries that 13vPnC is included in the national childhood immunization programs or covered by private insurance. Furthermore, SOIs requiring treatment may be miscoded. But, the validation study will allow evaluation of the magnitude of misclassification as well as provide more accurate estimation of the incidence rates of SOIs. Last, some children in Yinzhou EHR don't have a NID number during the study period. Healthcare data of these children will be mapped based on a combination of dates of birth, names of children, names of parents/legal guardians, or home addresses in the EHR

database. There is a chance of mismatching among the children although the likelihood is low.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Patient Information and Consent

The informed consent is not applicable for the main study based on Yinzhou EHR database.

All parties will ensure protection of child personal data and will not include a child's names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. The principal investigator or his delegates at Fudan University will not have access to the personal identification numbers since all data for the study are de-identified prior to being uploaded to the server that is created by the database builder.

The informed consent is required for one part under the validation study (ie, a prospective cohort). The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in the prospective cohort study in sub-population of the main study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

HCPs at local immunization clinics in Yinzhou district who recruit parents/legal guardians for the prospective cohort study in a sub-population must ensure that each study child, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. HCPs will obtain written informed consent from the child's legally acceptable representative before any study-specific activity is performed for the prospective cohort study in a sub-population. Fudan University will retain the original of each child's signed consent form.

8.2. Patient Withdrawal

Patient withdrawal is not applicable to the main study based on Yinzhou EHR database.

For one component of the validation study (ie, a prospective cohort study), parents/legal guardians may withdraw children from the prospective cohort study in a sub-population at any time at their own request, or they may be withdrawn at any time at the discretion of the HCPs at CDC immunization clinics or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The HCP should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved AEs.

If the parent withdraws from the validation study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

8.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of Fudan University and Yinzhou CDC to have prospective approval of the study protocol, protocol amendments, and other relevant documents, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

8.4. Ethical Conduct of the Study

The study will be conducted in accordance with the NMPA Draft Guidance on the Key Monitoring Activities of Drug Products by Manufacturing Enterprises, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology, Good Epidemiological Practice guidelines issued by the International Epidemiological Association (IEA), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

9.1. Main Study Using Yinzhou EHR Database

This study includes data that already exist as structured data in an electronic database. In these data sources, it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the *minimum criteria for reporting an AE (ie, identifiable patient, identifiable reporter, a suspect product, and event) are not available* and AEs are not reportable as individual AE reports.

9.2. Validation Study to Validate ICD Codes through Medical Chart Abstraction

In addition, this study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report AEs with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to any Pfizer drug that appear in the reviewed information must be recorded on the data abstraction form and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these safety events with an explicit attribution to or associated with use of, respectively, a Pfizer product, the data captured in the medical record will constitute all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All research staff members will complete the Pfizer requirements regarding training on the following: "Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)" and any relevant Your Reporting Responsibilities supplemental training. This training must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer. Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

9.3. Validation Study to Interview Parents/Legal Guardians by HCPs at CDC Immunization Clinics Using Questionnaires

This protocol will use an external adjudication committee wherein, to maintain scientific integrity, adjudication of clinical endpoints defined in the study objectives will be performed. The committee is responsible for ongoing analysis of SOIs and of their adjudication as the SOIs (Section 7.5.2 Figure 3). Events that are adjudicated not to be the SOIs will be handled as described at Section 9.2.

Product safety information unrelated to the SOIs in the study that are volunteered by parents/legal guardians will be handled as described below.

Any safety information for an individual child that is volunteered by a parent/legal guardian of the child during the course of this research must be reported as described below.

The following safety events must be reported on the NISAEM Report Form: serious and non-serious AEs when associated with the use of the Pfizer product, and scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure **(all reportable, regardless of whether associated with an AE)**, when associated with the use of a Pfizer product.

All HCPs at Yinzhou CDC immunization clinics who will administer the interview to the parent/legal guardian and complete the questionnaire tool will complete the Pfizer requirements regarding training on the following: "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)"* and any relevant Your Reporting Responsibilities supplemental training. This training must

be completed by the HCPs at CDC immunization clinics prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. The study vendor will also provide copies of all signed training certificates to Pfizer. Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

The HCPs at CDC immunization clinics will be trained to identify safety event information. In the event that a parent/legal guardian reports a safety event associated with a Pfizer product, the HCP will complete the NIS AEM Report Form and submit to Pfizer within 24 hours of becoming aware of the safety event. Included in the completion of the NIS AEM Report Form is the parent's/legal guardian's contact information; complete contact information should be obtained so that, once the NIS AEM Report Form is transferred to Pfizer, the NIS AEM Report Form can be assessed and processed according to Pfizer's standard operating procedures, including requests for follow-up to the parent/legal guardian.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Three study progress reports and the final study report will be submitted to the NMPA in 2018, 2019, 2020, and 2021 respectively. Information from the study will be communicated to the scientific and medical community through relevant professional association meetings and/or a journal submission.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NIS protocol that the investigator becomes aware of.

11. REFERENCES

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