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Phase 1 trial of a 20-valent pneumococcal conjugate vaccine in healthy adults

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ABSTRACT

Introduction: Streptococcus pneumoniae is a leading cause of bacteremia, bacterial pneumonia, and meningitis, and is associated with substantial morbidity and mortality, particularly in those under 2 years of age and those over 65 years of age. While significant progress against *S. pneumoniae*-related disease has been made as a result of the introduction of pneumococcal conjugate vaccines (PCV7, PCV10 and PCV13), there remains value in further expanding pneumococcal vaccine serotype coverage. Here we present the first report of a 20-valent pneumococcal conjugate vaccine (PCV20) containing capsular polysaccharide conjugates present in PCV13 as well as 7 new serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) which are important contributors to pneumococcal disease.

Methods: This Phase I first-in-human study was a randomized, controlled, observer-blinded study with a two-arm parallel design to assess the safety, tolerability, and immunogenicity of PCV20 in adults. A total of 66 healthy adults 18–49 years of age with no history of pneumococcal vaccination were enrolled and randomized to receive a single dose of PCV20 or a licensed tetanus, diphtheria, acellular pertussis combination vaccine (Tdap) control. Local injection site reactions, select systemic symptoms, laboratory studies, and adverse events were assessed. Opsonophagocytic activity (OPA) titers and IgG concentrations were measured in sera collected prior to, and approximately one month (28–35 days) after vaccination.

Results: Vaccination with PCV20 elicited substantial IgG and functional bactericidal immune responses as demonstrated by increases in IgG geometric mean concentrations (GMCs) and OPA geometric mean titers (GMTs) to the 20 vaccine serotypes. The overall safety profile of PCV20 was similar to Tdap, and generally consistent with that observed after PCV13 administration.

Conclusions: Vaccination with PCV20 was well tolerated and induced substantial functional (OPA) and IgG responses to all vaccine serotypes. There were no safety issues identified in this Phase 1 study, and the data supported further evaluation of PCV20.

1. Introduction

Streptococcus pneumoniae, a Gram-positive encapsulated diplococcus causing bacteremia, meningitis, and community-acquired pneumonia [1–3]. is associated with substantial morbidity and mortality, particularly in those under two and over 65 years of age [1–3]. The CDC estimated that in 2016 there were 30,400 (9.4/100,000) cases of IPD associated with 3690 (1.14/100,000) deaths in the United States [4]. However, pneumococcal disease affects the populations of both high- and low-resource countries. Based on data from 195 countries, The Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study results estimate that *S. pneumoniae* was the most common cause of bacterial lower respiratory infection in 2015, and led to 1,517,388 deaths, or 55.4% of the 2.74 million total deaths related to respiratory tract infections across all ages [5]. Moreover, in a recent global meta-analysis of 56 studies of bacterial meningitis, *S. pneumoniae* was shown to be the predominant pathogen in both children (22.5–41.1%) and adults (9.6–75.2%) [6].

In the United States, healthcare utilization and disease data from 2004 estimated that 445,000 hospitalizations, 2.3 million hospital days, 5.0 million outpatient visits, and 774,000 emergency

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department visits were attributable to *S. pneumoniae* [7]. More recent surveillance indicates that *S. pneumoniae* remains among the most common pathogens identified in children and adults hospitalized with community-acquired pneumonia (CAP). In 2004, *S. pneumoniae* was estimated to be the etiologic agent in nearly 600,000 cases of pneumonia in US adults aged ≥18 years of age [7]. Although *S. pneumoniae* remains the most commonly identified cause of bacterial CAP, the estimated proportion of disease attributed to *S. pneumoniae* has decreased since the introduction of pneumococcal conjugate vaccines for use in children and adults [8–10].

S. pneumoniae expresses a polysaccharide capsule which is an important virulence factor, and also allows for classification based on serotype. To date there have been more than 90 serotypes identified, although a relatively small subset of these serotypes are responsible for the majority of disease.

Unconjugated polysaccharide vaccines, such as 23-valent pneumococcal polysaccharide vaccine (PPSV23), elicit a T-cell–independent response and as a result, do not induce robust responses in certain populations (eg, immunocompromised persons, children <2 years of age, and adults >65 years of age), nor do they generate immunologic memory, and their protective effect wanes over 2–5 years [11–14]. Another limitation of an initial vaccination with PPSV23 is that functional responses to subsequent pneumococcal vaccination are often lower compared with those after the initial dose, a phenomenon called immunological hyporesponsiveness [15–17].

Significant progress against pneumococcal disease has been made in the last two decades as a result of the development and introduction of pneumococcal conjugate vaccines (PCV). By covalently linking (conjugating) the purified capsular polysaccharide to an immunogenic protein carrier the immune response is converted from a T cell–independent response to a T cell–dependent immune response [14]. In 2000, a 7-valent pneumococcal conjugate vaccine (PCV7) containing seven polysaccharide conjugates of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F was licensed and introduced into the United States' infant vaccination program. Although overall pneumococcal disease decreased substantially, pneumococcal disease due to serotypes not in PCV7 persisted in adults and children [18]. To address this significant remaining disease burden, further vaccine development ensued and in 2010, PCV7 was replaced with a 13-valent pneumococcal conjugate vaccine (PCV13), which added coverage for the additional serotypes 1, 3, 5, 6A, 7F and 19A. Initially licensed for use in infants and children, PCV13 was subsequently licensed in adults and has been introduced in more than 130 countries [19,20]. A ten-valent pneumococcal conjugate vaccine (PCV10, Synflorix, GlaxoSmithKline) using different carrier proteins than PCV7/13 and containing only 10 of the serotypes covered by PCV13 was licensed in some countries, although not in the United States.

Significant direct and indirect impacts on public health (including further decreases in the rates of pneumonia and IPD) have been documented after the introduction of PCV13 vaccination, both in the United States and around the world [21–24]. However, due to the number of serotypes not covered by existing vaccines that continue to cause an important burden of pneumococcal disease across geographic regions, various age groups, and multiple clinical manifestations, there remains a substantial medical need that can be addressed by a pneumococcal conjugate vaccine with expanded serotype coverage.

Here we present the first report of a novel PCV20 containing the capsular polysaccharide conjugates present in PCV13 and pneumococcal capsular polysaccharides of 7 additional serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F), each covalently linked to CRM197. These 7 additional serotypes were selected to expand global pneumococcal serotype coverage based on their relative prevalence as a cause of IPD and pneumonia, their generalized geographic distribution, and other factors such as an association with antibiotic resistance (11A, 15B), outbreaks (8, 12F), and a tendency to cause more severe disease (eg, association with meningitis or increased mortality rate [10A, 11A, 22F]) [25–30].

2. Methods

2.1. Study design and subjects

This was a Phase I first-in-human, randomized, controlled, observer-blinded study with a two-arm parallel design performed to determine the safety, tolerability, and immunogenicity of PCV20 in healthy adults. This study was sponsored by Pfizer and conducted at the Pfizer Clinical Research Unit (PCRU) in New Haven, CT. Healthy adults 18–49 years of age with no history of pneumococcal vaccination, and no history of Tdap vaccination within the prior 12 months were enrolled into the study from November 2016 to January 2017 and randomized 1:1 to receive a single dose of PCV20 or Tdap control on Day 1 of the study (Day 1, Visit 1). Subjects were screened (Visit 0, 2–30 days prior to vaccination), vaccinated (Visit 1), and followed up for safety one to five days after vaccination (Visit 1), two weeks (Visit 2), one month (Visit 3), and six months after vaccination (Visit 4). The visits for safety follow-up at two weeks (Visit 2), and six months after vaccination (Visit 4) were conducted by telephone. Blood was drawn for immunogenicity assessments prior to vaccination (Visit 1, Day 1) and one month after vaccination (Visit 3). Subjects that were pregnant, or had any major disease or clinically significant laboratory abnormality were excluded from the study, as were those with a history of invasive pneumococcal disease. Written informed consent was obtained from all subjects prior to enrollment in the study and before any study-related procedures were performed. This study was conducted in compliance with the ethical principles originating in, or derived from, the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants.

2.2. Vaccines administered

PCV20 contains polysaccharides of pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19F, 19A, 22F, 23F, and 33F individually conjugated to a nontoxic variant of diphtheria toxin cross-reactive material 197 (CRM197). Each 0.5 mL dose contains 2.2 μg of each serotype, except type 6B (4.4 μg), and is formulated in 5.0 mM succinate and 0.85% sodium chloride at pH 5.8 with 0.125 mg aluminum (as aluminum phosphate) and 0.02% polysorbate 80. Tdap (brand name Adacel, Sanofi Pasteur, Swiftwater, PA) is a sterile isotonic suspension of tetanus and diphtheria toxoids and pertussis antigens adsorbed on aluminum phosphate. Both PCV20 and Tdap were provided to the site in pre-filled syringes and stored at 2–8 °C. Subjects received a single dose (0.5 mL) of PCV20 or Tdap intramuscularly into the deltoid muscle, preferentially in the right arm on Day 1 (Visit 1) of the study. Standard vaccination practices were followed.

2.3. Immunogenicity assessments

Blood samples for immunogenicity evaluation were collected from all subjects prior to vaccination on Day 1 and approximately one month (28–35 days) after vaccination. Functional serum antibody titers (measured by OPA) used serotype-specific validated assays for 13 of the serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C,

19A, 19F, and 23F), and qualified serotype-specific assays for the seven new serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F). Although a specific level of OPA antibody has not been shown to correlate with protection against pneumococcal disease in adults, OPA antibody responses are generally accepted as a correlate of vaccine-induced protection [17,31,32]. A titer is defined as the interpolated reciprocal serum dilution that results in complement- and neutrophil-mediated killing of 50% of the bacteria in the assays. Serum concentrations of anti-capsular IgG for each of the 20 pneumococcal serotypes were determined by a Luminex-based direct immunoassay (dLIA) and expressed as micrograms per milliliter of serum. The assay uses poly-L-lysine (PLL)-conjugated polysaccharides, and each serotype polysaccharide is chemically coupled to spectrally distinct Luminex microspheres. The development and validation of the dLIA for the 13 pneumococcal capsular serotypes has been described previously and the 7 new serotypes dLIA were developed similarly [33].

2.4. Safety evaluation

Blood was collected at screening, on the day before vaccination, and during or at five days after vaccination for hematology, and assessments of hepatic, renal, and cardiac organ systems.

Subjects were admitted to the investigator site on the day before vaccination and discharged from the site five days after vaccination upon confirmation that there were no clinically significant laboratory abnormalities. Subjects were observed for the first 30 min after investigational product administration. Local reactions and systemic events were collected by the subjects in an electronic diary (e-diary) for 14 days after vaccination. Subjects measured their oral temperature in the evening daily for 14 days following vaccination and at any time during the 14 days that fever (temperature >100.4°F [38.0 °C]) was suspected. All adverse events (AEs) were collected for one month after vaccination, and serious adverse events (SAEs) and newly diagnosed chronic medical conditions (NDCMCs) were collected through 6 months after vaccination.

2.5. Statistical analysis

Approximately 33 adults per vaccine group were planned to be randomized. No formal statistical comparisons between vaccine groups were planned in this first in human study. All analyses for the safety and immunogenicity data were descriptive in nature. The safety population included all subjects who received one dose of PCV20 or Tdap. The population for immunogenicity analyses included those subjects who met all inclusion criteria, received vaccine as assigned, had blood drawn at Visits 1 and 3, had a valid OPA titer or IgG concentration for at least one serotype at both Visits 1 and 3, and had no major protocol deviations. Results with exact 2-sided 95% CIs (Clopper-Pearson CIs) were provided by vaccine group for all primary safety endpoints, i.e., proportions of subjects reporting local reactions, systemic events, and AEs. The GMT (or GMC) was calculated as the mean of the assay results after making the natural logarithm transformation and then back transformation to its original scale. Two (2)-sided 95% CIs were constructed by back transformation of the CI for the mean of the logarithmically transformed assay results computed based on the Student t distribution.

3. Results

3.1. Disposition and baseline characteristics of the study population

A total of 66 subjects were randomized and vaccinated and 63 (95.5%) subjects completed the last study visit six months after vaccination. Two subjects in the PCV20 group were lost to follow-up and were withdrawn from the study (Fig. 1), one prior to the visit one month after vaccination (Visit 3) and one prior to the visit six months after vaccination (Visit 4). Another subject in the PCV20 group was withdrawn after the follow-up visit one month after vaccination due to death (a motor vehicle accident), which was not considered to be related to study vaccine. Overall, the study population was 57.6% female and the majority of participants (63.6%) were between the ages of 18 and 34 (Table 1).

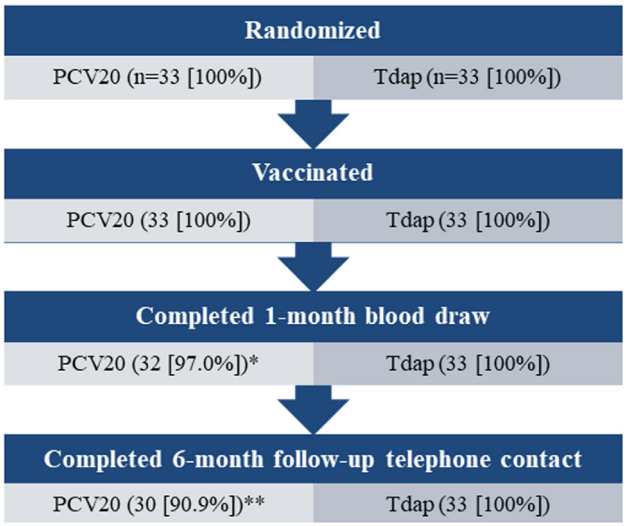

Fig. 1. Subject disposition. *One subject in the PCV20 group was lost to follow-up at the time of the visit 1 month after vaccination and. **A subject in the 20vPnC group was withdrawn after the follow-up visit 1 month after vaccination due to death (a motor vehicle accident) not related to study vaccine, and the another subject was lost to follow-up at the 6-month follow-up telephone call.

Table 1
Demographic characteristics.

	Vaccine Group (as Administered)		
	PCV20 (N[a] = 33) n[b] (%)	Tdap (N[a] = 33) n[b] (%)	Total (N[a] = 66) n[b] (%)
Sex			
Male	10 (30.3)	18 (54.5)	28 (42.4)
Female	23 (69.7)	15 (45.5)	38 (57.6)
Race			
White	11 (33.3)	17 (51.5)	28 (42.4)
Black or African American	19 (57.6)	16 (48.5)	35 (53.0)
American Indian or Alaska Native	2 (6.1)	0	2 (3.0)
Other	1 (3.0)	0	1 (1.5)
Ethnicity			
Hispanic/Latino	5 (15.2)	11 (33.3)	16 (24.2)
Non-Hispanic/non-Latino	28 (84.8)	22 (66.7)	50 (75.8)
Age group			
18–34 years	21 (63.6)	21 (63.6)	42 (63.6)
35–49 years	12 (36.4)	12 (36.4)	24 (36.4)
Age at vaccination (years)			
Mean (SD)	32.4 (8.6)	31.7 (8.1)	32.1 (8.3)
Median	31.0	29.0	30.0
Min, max	(18.0, 48.0)	(20.0, 48.0)	(18.0, 48.0)

[a] N = number of subjects in the vaccine group or total sample. These values are used as the denominators for percentages.
[b] n = Number of subjects in the specified category.

3.2. Safety

Local reactions (defined as redness, swelling, pain at the injection site, and limitation of arm movement) were reported by a similar proportion of subjects in the PCV20 group (69.7%) and the Tdap group (63.6%). The percentage of subjects reporting local reactions and the severity of local reactions reported within 14 days after vaccination are presented in Fig. 2. The most commonly reported local reactions in both the PCV20 and Tdap groups were pain at the injection site (69.7% and 63.6%, respectively), and limitation of arm movement (36.4% and 18.2%, respectively). The majority of local reactions were either mild or moderate in severity.

Systemic events (defined as fatigue, headache, chills, nausea/vomiting, new muscle pain, aggravated muscle pain, new joint pain, and aggravated joint pain) were reported by a higher proportion of subjects in the PCV20 group (72.7%) compared to the Tdap group (57.6%) The percentage of subjects reporting systemic events and the severity of systemic events reported within 14 days after vaccination are presented in Fig. 3. PCV20 demonstrated a safety profile consistent with pneumococcal conjugate vaccines in this population. The most commonly reported systemic event in the PCV20 and Tdap groups was new muscle pain (45.5% and 42.4%, respectively), followed by fatigue and headache (each reported by 39.4% and 30.3% of subjects in the PCV20 and Tdap group, respectively). Fever of 100.8°F was reported by 1 subject in the PCV20 group and fever 101.3°F was reported by 1 subject in the Tdap group. The majority of systemic events were mild or moderate in severity.

There were no clinically significant findings in the laboratory assessments conducted within five days after vaccination. There were 4 SAEs including 1 death (automobile accident), all of which were judged to be not related to study vaccine or procedures.

3.3. Immunogenicity

Pneumococcal OPA GMTs before and one month after vaccination, are presented in Fig. 4 and supplementary Table S1. OPA GMTs measured one month after vaccination were substantially higher in the group receiving PCV20 compared to the responses in the Tdap control group. The OPA geometric mean fold rises (GMFRs) 1 month after vaccination were higher for all 20 pneumococcal serotypes in the PCV20 group compared to the Tdap group.

There was also a substantial increase in IgG GMCs measured one month after vaccination in the PCV20 group; this increase was not observed in the Tdap control group (Fig. 5 and Table S2).

4. Discussion

Pneumococcal conjugate vaccines contain polysaccharides that are covalently linked (conjugated) to a carrier protein. This modification results in T-cell–dependent immune responses, which have been shown to be protective in young children, older adults, and populations with high-risk conditions, and against both invasive and noninvasive pneumococcal disease [34]. The past introduction of PCVs has led to a reduction in nasopharyngeal carriage of the pneumococcal serotypes included in these vaccines, which in turn has led to significant reductions in circulation and disease caused by these serotypes [18,35]. Despite widespread recommendations for the use of the pneumococcal vaccines, pneumococcal disease currently accounts for over 1.5 million deaths and millions of healthcare visits annually, resulting in a substantial global public health burden [5,7].

Pneumococcal disease due to serotypes that are not in PCV13 has the potential to increase both in terms of the relative proportion of disease, and in the rates of serotype-specific increases due to serotype replacement. For these reasons, the continued development of PCVs to protect against additional pneumococcal serotypes of interest is important given the residual pneumococcal disease burden that could be addressed by a pneumococcal conjugate vaccine with expanded serotype coverage.

The annual incidence of hospitalized CAP for adults ≥65 years old in the United States, as estimated by a surveillance study conducted in Louisville, Kentucky, was found to be approximately 2300 per 100,000 person-years [36]. The United States census bureau estimates that there are approximately 49 million adults ≥65 years old, which translates into 1.1 million patients being hospitalized with CAP each year [37]. It has also been estimated through both urine antigen and conventional testing that

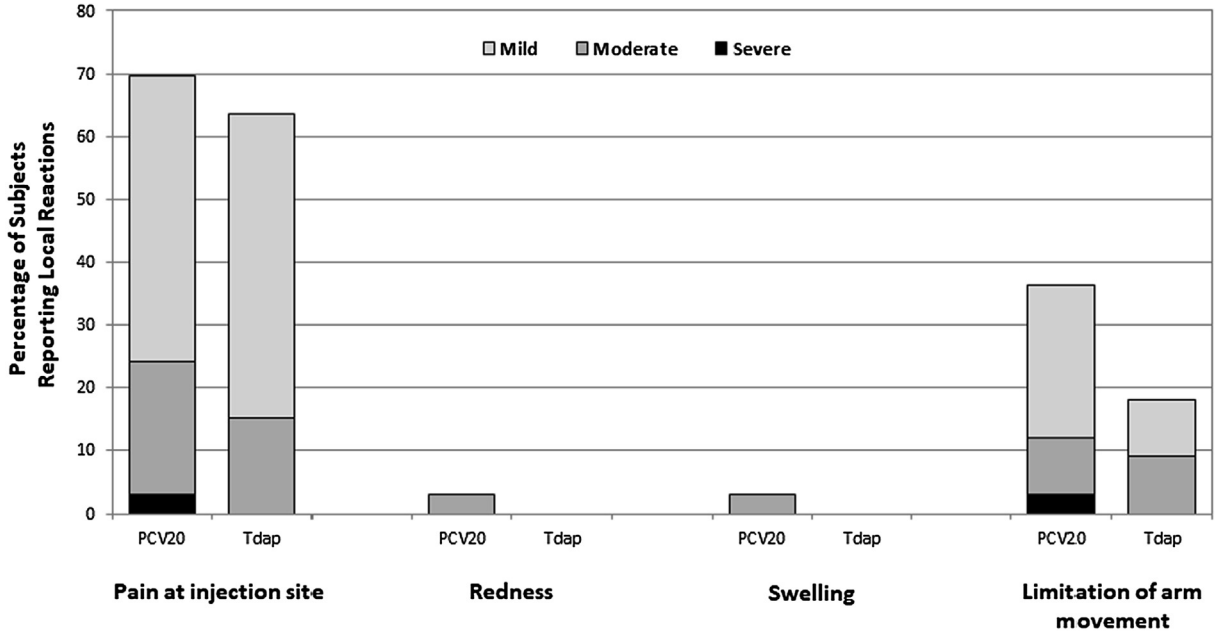

Fig. 2. Summary of local reactions reported within 14 days of vaccination by maximum severity.

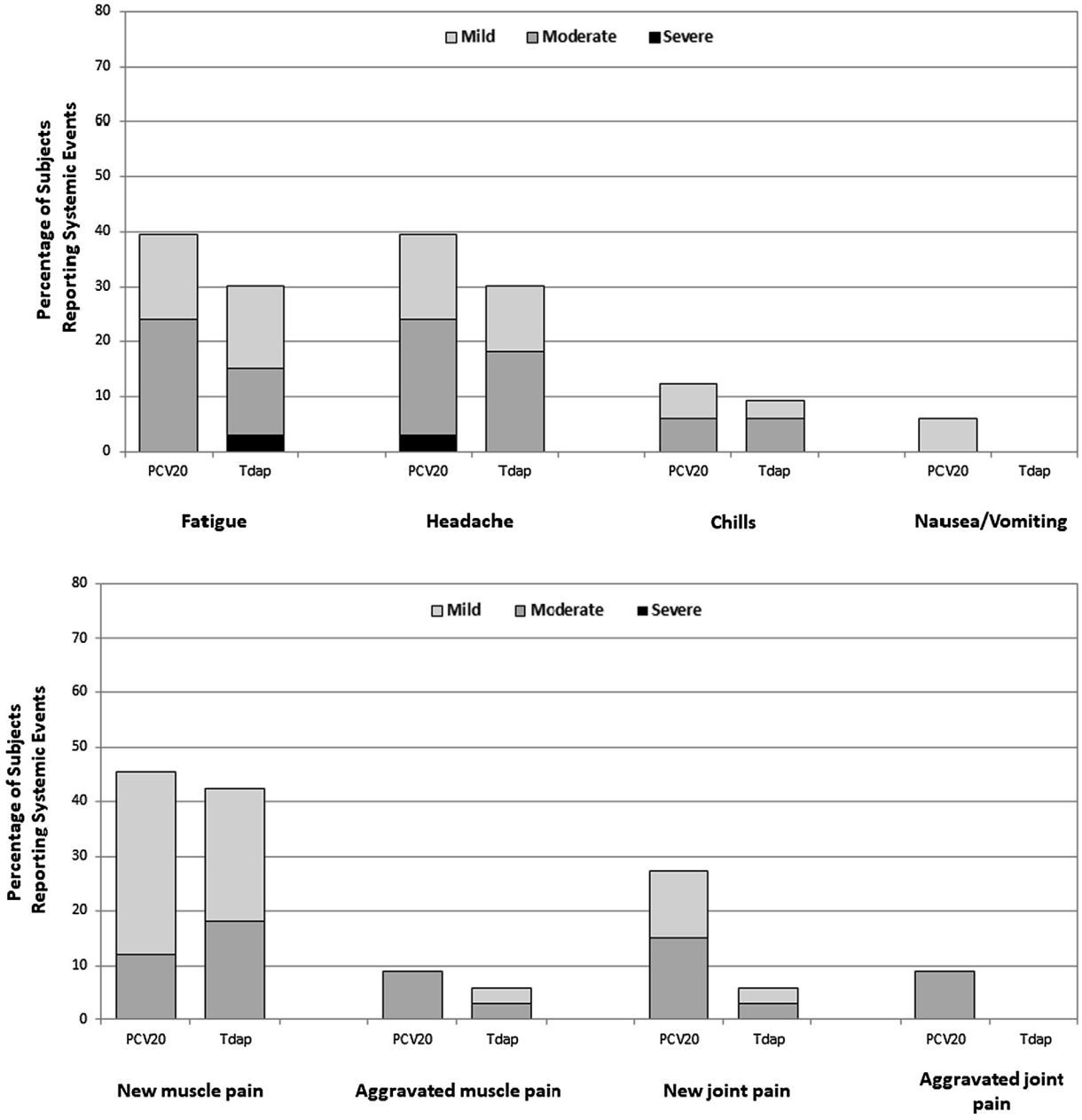

Fig. 3. Summary of systemic events reported within 14 days of vaccination by maximum severity.

approximately 7% of hospitalized CAP is due to serotypes in the PCV20 vaccine (manuscript in preparation). This would translate into approximately 79,000 cases of adult CAP annually due to the serotypes in the PCV20 vaccine in the United States. Assuming a similar effectiveness of PCV20 compared to PCV13 (ranging from 45% to 73% [38,39]), PCV20 could have the potential to prevent a significant portion of that disease.

In this first clinical study, PCV20 was shown to have an acceptable safety profile in healthy adults 18–49 years of age, consistent with that expected of a PCV in this population. No subclinical or clinical signals indicative of hematologic, hepatic, renal, or cardiac effects associated with PCV20 administration were observed in this study. The overall safety profile of PCV20 was similar to Tdap, a vaccine licensed and recommended for adults in this age group, and consistent with the historical profile of PCV13 in 18–49 year olds [40]. The data also demonstrate that PCV20 was immunogenic in healthy adults 18–49 years of age, and that both binding IgG and functional OPA antibodies were elicited in the PCV20 group for all 20 vaccine serotypes.

As this was a Phase 1 study at a single site with a relatively small sample size (33 per group) of adult volunteers 18–49 years of age, there are limitations in the ability to make extrapolations regarding PCV20 immune responses from this study to young children and older adults. Furthermore, the control group was given a licensed vaccine recommended in this age population to serve as a benchmark for safety in this small study, so this study did not generate data to allow a comparison of responses to other pneumococcal vaccines.

PCV20 had an acceptable safety profile, and was well tolerated and immunogenic in healthy adults 18–49 years of age. The safety and immunogenicity results in this study supported further

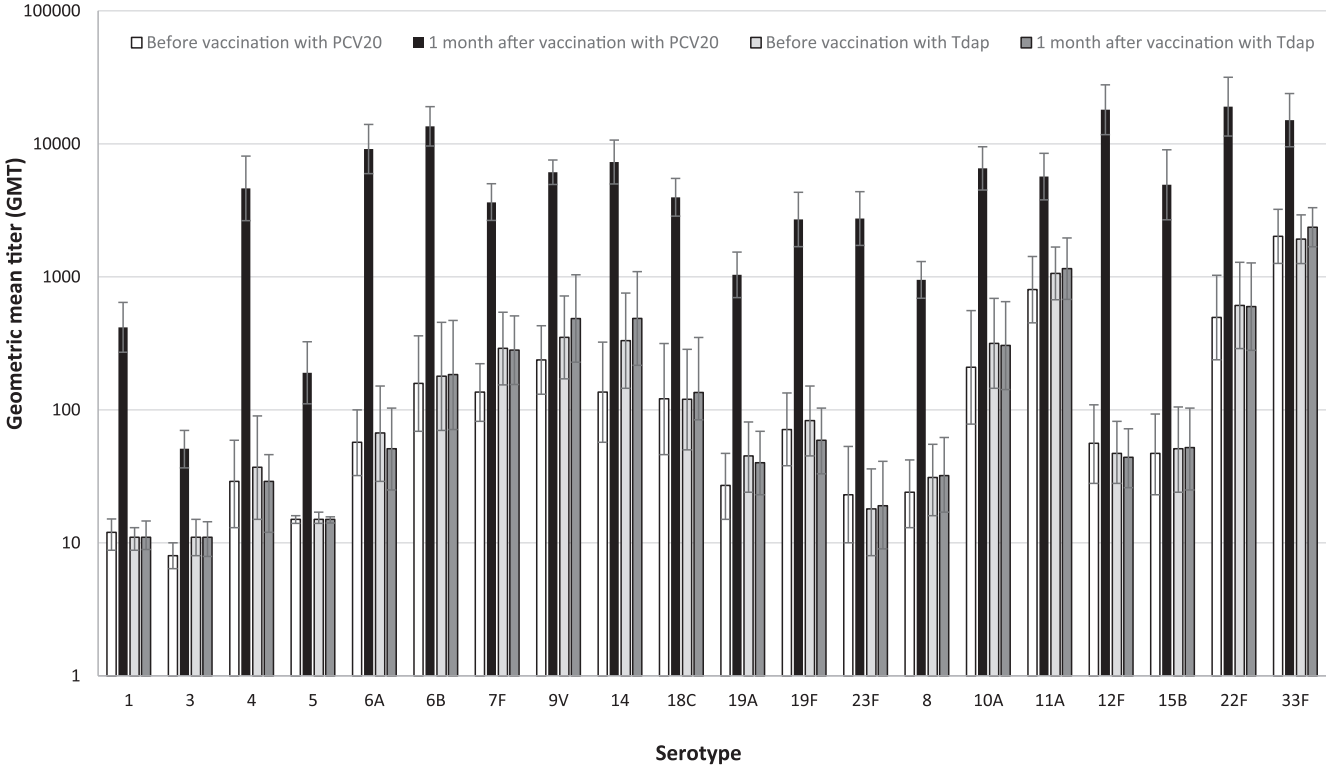

Fig. 4. Serotype-specific OPA GMTs before and 1 month after vaccination.

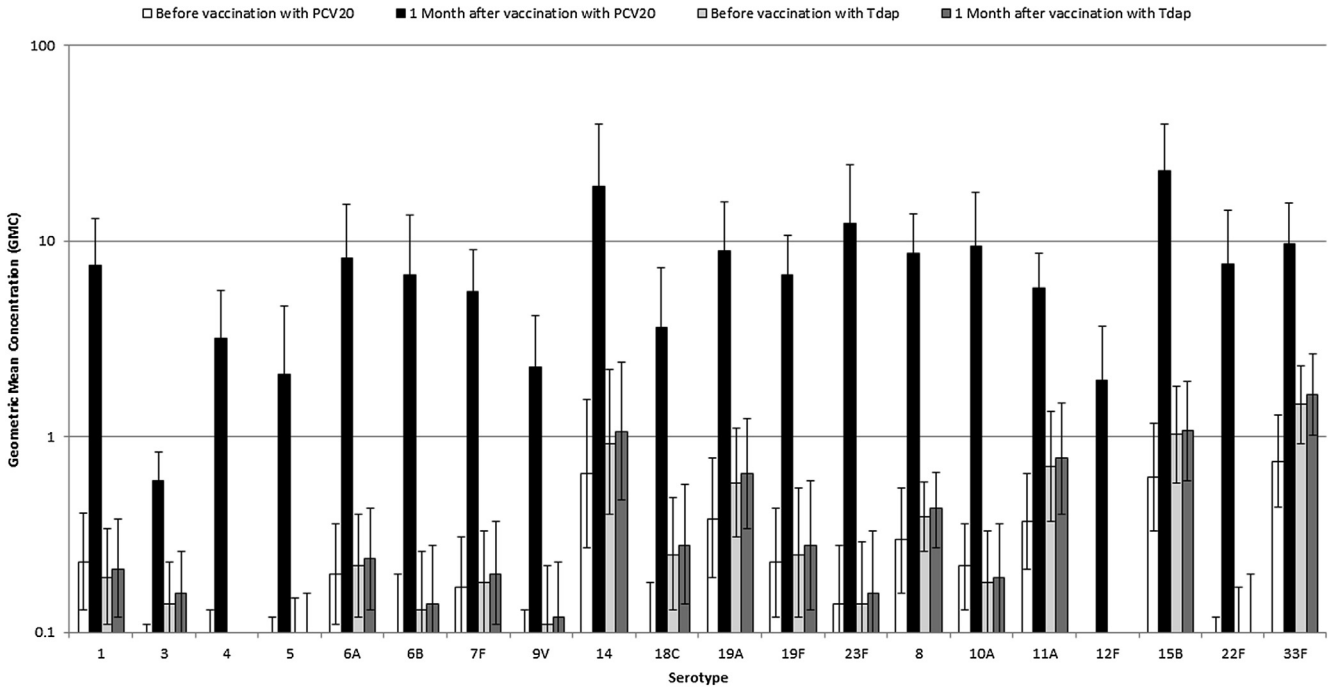

Fig. 5. Serotype-specific IgG GMCs before and 1 month after vaccination.

evaluation of PCV20 in larger comparative studies in other populations (NCT03313037, NCT03512288, NCT03642847, NCT03760146).

Author contributions

All authors met ICMJE criteria for authorship and participated in the study design, data interpretation, writing of the manuscript, and agree to be accountable for all aspects of the work.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

This work was sponsored by Pfizer, Inc. All authors are employees of Pfizer, Inc. and may hold stock or other investments in the company.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.08.048.

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