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A phase III, multicenter, randomized, double-blind, active comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of catch-up vaccination regimens of V114, a 15-valent pneumococcal conjugate vaccine, in healthy infants, children, and adolescents (PNEU-PLAN)

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ABSTRACT

Background: Despite widespread use of pneumococcal conjugate vaccines (PCVs) in children, morbidity and mortality caused by pneumococcal disease (PD) remain high. In addition, many children do not complete their PCV course on schedule. V114 is a 15-valent PCV that contains two epidemiologically important serotypes, 22F and 33F, in addition to the 13 serotypes present in PCV13, the licensed 13-valent PCV.
Methods: This phase III descriptive study evaluated safety and immunogenicity of catch-up vaccination with V114 or PCV13 in healthy children 7 months–17 years of age who were either pneumococcal vaccine-naïve or previously immunized with lower valency PCVs (NCT03885934). Overall, 606 healthy children were randomized to receive V114 (n = 303) or PCV13 (n = 303) via age-appropriate catch-up vaccination schedules in three age cohorts (7–11 months, 12–23 months, or 2–17 years).
Results: Similar proportions of children 7–11 months and 2–17 years of age reported adverse events (AEs) in the V114 and PCV13 groups. A numerically greater proportion of children 12–23 months of age reported AEs in the V114 group (79.0%) than the PCV13 group (59.4%). The proportions of children who reported serious AEs varied between different age cohorts but were generally comparable between vaccination groups. No vaccine-related serious AEs were reported, and no deaths occurred. At 30 days after the last PCV dose, serotype-specific immunoglobulin G geometric mean concentrations were comparable between vaccination groups for the 13 shared serotypes and higher in the V114 group for 22F and 33F.
Conclusions: Catch-up vaccination with V114 in healthy individuals 7 months–17 years of age was generally well tolerated and immunogenic for all 15 serotypes, including those not contained in PCV13, regardless of prior pneumococcal vaccination. These results support V114 catch-up vaccination in children with incomplete or no PCV immunization per the recommended schedule.

Abbreviations: **AE**, **adverse event**; **CI**, **confidence interval**; **ELISA**, **enzyme-linked immunosorbent assay**; **eVRC**, **electronic Vaccination Report Card**; **GMC**, **geometric mean concentration**; **GMFR**, **geometric mean fold rise**; **IgG**, **immunoglobulin G**; **IPD**, **invasive pneumococcal disease**; **PCV**, **pneumococcal conjugate vaccine**; **PCV10**, **10-valent pneumococcal conjugate vaccine**; **PCV13**, **13-valent pneumococcal conjugate vaccine**; **PCV7**, **7-valent pneumococcal conjugate vaccine**; **PCV9**, **9-valent pneumococcal conjugate vaccine**; **PD**, **pneumococcal disease**; **Pn ECL**, **pneumococcal electrochemiluminescence**; **PnP**, **pneumococcal polysaccharide**; **SAE**, **serious adverse event**; **V114**, **15-valent pneumococcal conjugate vaccine**.

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[1] Our colleague Richard McFetridge passed away during the approval stage of this manuscript.

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1. Introduction

Streptococcus pneumoniae can cause non-invasive mucosal disease (including sinusitis and acute otitis media), as well as invasive pneumococcal disease (IPD), such as meningitis, bacteremia, bacteremic pneumonia, and osteoarticular infection [1–4]. *S. pneumoniae* is a major cause of morbidity and mortality in children <5 years of age. In 2016, there were an estimated 44.7 million global episodes of pneumococcal disease (PD) and 0.3 million PD-related deaths in this age group. *S. pneumoniae* is globally also the most common etiology of lower respiratory tract infections in children <5 years of age, with about 52.3% of all lower respiratory tract infection-related deaths attributed to pneumococcal pneumonia [5]. Although infants are at the greatest risk of PD, older children, including those ≥2 years of age, are also vulnerable and the burden of disease is substantial [6].

The widespread implementation of pneumococcal conjugate vaccines (PCVs) in childhood vaccination schedules has helped to reduce the burden of PD in infants and children; however, it has led to an increase in non-PCV serotype PD [7–11]. Therefore, there is unmet need for pneumococcal vaccines with broader serotype coverage. Pneumococcal vaccination is widely recommended for infants and, despite high coverage rates in several industrialized countries, there is still a substantial number of children who have not received the recommended PCV schedule [12–15]. The World Health Organization and United States Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) currently recommend routine PCV vaccination at the earliest opportunity for all infants followed by booster doses in toddlers, and catch-up vaccinations for healthy children who start late or fall behind the immunization schedule for any reason [4,16].

V114 (VAXNEUVANCE™, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA [MSD]) is a 15-valent PCV, currently approved in individuals ≥6 weeks of age, that contains all 13 serotypes in 13-valent PCV (PCV13 [Prevnar 13®]; 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F), as well as serotypes 22F and 33F [17],[18], which are important contributors to residual PD [19]. Serotypes 22F and 33F have high potential to cause invasive disease in children, causing 3% and 4% of IPD in children <5 years of age globally, and 11% and 13% of IPD in this population in the United States, respectively [11,20]. Previous studies have shown V114 to be well tolerated and immunogenic in infants, toddlers, and young adults (<18 years of age) [19,22,22].

This study evaluated the safety, tolerability, and immunogenicity of catch-up vaccination regimens of V114 in healthy infants, children, and adolescents who were either pneumococcal vaccine-naïve or who had previously received a partial regimen (7-valent PCV [PCV7], 10-valent PCV [PCV10], or PCV13) or full regimen of a lower valency PCV (PCV7 or PCV10).

2. Methods

2.1. Study design

This was a phase III, descriptive, multicenter, randomized, double-blind, active comparator-controlled study to describe the safety, tolerability, and immunogenicity of catch-up vaccination regimens of V114 in healthy infants, children, and adolescents who were either PCV-naïve or who previously received a partial regimen (PCV7, PCV10, or PCV13) or full regimen of a lower-valency PCV (PCV7 or PCV10) (protocol V114-024; Table 1). The study was conducted at 25 sites (Finland [10], Malaysia [2], Poland [6], the Russian Federation [3], and Thailand [4]), from June 2019 to December 2020. The study is registered with ClinicalTrials.gov as NCT03885934 and in the European Union as EudraCT number 2018-003706-88.

Children were vaccinated according to three age-appropriate catch-up schedules recommended by the ACIP and utilized by many countries globally [16]. Vaccination was based on age at randomization and prior PCV status: Cohort 1 (7–11 months of age; PCV-naïve) received two doses plus a toddler dose at ≥12 months of age; Cohort 2 (12–23 months of age; PCV-naïve) received two vaccine doses 8–12 weeks apart; and Cohort 3 (2–17 years of age; PCV-naïve, or partial or full prior PCV vaccination) received a single dose of PCV (Table 1). Non-study routine pediatric vaccines were permitted to be administered concomitantly according to local guidelines.

The study was designed to enroll approximately 600 participants randomized in a 1:1 ratio to receive either V114 or PCV13. Randomization was stratified by age at enrollment into three age cohorts (Fig. 1). Participants 2–17 years of age were further stratified based on a prior history of PCV vaccination (naïve and previously vaccinated) and age (2–5 years and 6–17 years of age). Intervention allocation and randomization occurred centrally using an interactive response technology system. The study vaccines were dispensed and administered by unblinded study personnel who were not involved in any subsequent participant assessments. The participant and the investigator involved in the clinical evaluation of the participants were blinded to the vaccination group assignments.

A Scientific Advisory Committee comprising external scientists and scientists from MSD contributed to the development of the study protocol, formulation of the statistical analysis plan, analysis, and interpretation of study data, and authoring of this manuscript. The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate Institutional Review Boards and regulatory agencies. An external Data Monitoring Committee conducted interim reviews of safety and tolerability data.

2.2. Participants

Eligible participants were male or female, in generally good health, and were 7 months–17 years of age (inclusive). Participants had a legally acceptable representative who understood the study procedures, alternate treatments available, and risks involved with the study, and voluntarily agreed to have their child participate by giving written informed consent prior to any study procedure.

Key exclusion criteria were as follows: history of IPD or other culture-positive PD; known hypersensitivity to any component of PCV or any diphtheria toxoid-containing vaccine; recent febrile illness; and impairment of immunological function, immunodeficiency, or autoimmunity. Participants were also excluded if they had received any dose of a pneumococcal polysaccharide vaccine or received other licensed non-live vaccines within the 14 days or licensed live virus vaccine within the 30 days prior to receipt of first dose of study vaccine. Participants 7–23 months of age were excluded if they had received a dose of a pneumococcal vaccine prior to study entry. Participants ≥2 years of age could have received a PCV at least 8 weeks prior to study entry as follows: a

Table 1
Catch-up vaccination schedule.

Age at randomization	PCV status	V114/PCV13 dose schedule
7–11 months (n = 128)	Naïve	**Dose 1:** At randomization **Dose 2:** 4–8 weeks after Dose 1 **Dose 3:** 8–12 weeks after Dose 2 at or after the 1st birthday
12–23 months (n = 126)	Naïve	**Dose 1:** At randomization **Dose 2:** 8–12 weeks after Dose 1
	Naïve	
2–17 years (n = 352)	Partial regimen of PCV7 (Prevnar®), PCV10 (Synflorix™), or PCV13 (Prevnar 13®) Complete regimen of PCV7 or PCV10	**Dose 1:** At randomization[a]

PCV = pneumococcal conjugate vaccine; PCV7 = 7-valent pneumococcal conjugate vaccine; PCV10 = 10-valent pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; V114 = 15-valent pneumococcal conjugate vaccine.
[a] At least 8 weeks after the previous dose of PCV.

partial regimen PCV7, PCV10, or PCV13, or a full regimen of PCV7 or PCV10, based on local guidelines.

2.3. Vaccines and administration

V114 (VAXNEUVANCE™, MSD) is a 15-valent PCV; each 0.5 mL dose contains 2 μg of pneumococcal capsular polysaccharide from serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F, 22F, and 33F, as well as 4 μg of serotype 6B, all conjugated to CRM197 carrier protein and adjuvanted with 125 μg of aluminum phosphate.

PCV13 (Prevnar 13®, Wyeth LLC, marketed by Pfizer, Philadelphia, PA, USA) is a 13-valent PCV; each 0.5 mL dose contains 2.2 μg of pneumococcal capsular polysaccharide from serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, as well as 4.4 μg of serotype 6B, all conjugated to CRM197 carrier protein and adjuvanted with 125 μg of aluminum phosphate.

V114 and PCV13 were supplied as sterile suspensions. V114 was supplied in either pre-filled syringes or vials, and PCV13 was supplied in pre-filled syringes. All study vaccines were stored at 2–8 °C. A 0.5 mL dose of V114 (lot number 00068572) or PCV13 (lot number AA4507) was administered intramuscularly using needles suited for intramuscular injection.

2.4. Safety assessments

Participants or their legally acceptable representative were provided with an electronic Vaccination Report Card (eVRC) to record safety data, including solicited injection-site reactions (erythema, pain, swelling, and induration), solicited systemic adverse events (AEs), unsolicited injection-site AEs, and unsolicited systemic reactions on Days 1–14 post-vaccination, and maximum body temperature on Days 1–7 post-vaccination. The eVRC device was programmed to collect distinct sets of age-appropriate solicited systemic AEs for participants either <3 or ≥3 years of age. For participants 7 months to <3 years of age, solicited systemic AEs included irritability, somnolence, decreased appetite, and urticaria; for those ≥3 years of age, these included myalgia, arthralgia, headache, fatigue, and urticaria.

Information for serious adverse events (SAEs), deaths, and discontinuation due to an AE, regardless of whether the events were considered to be related to the vaccine by the investigator, were collected from the time of signed consent through the end of the study follow-up period (approximately 6 months after administration of the last study vaccination). Solicited systemic AEs and solicited injection-site pain were assessed for intensity by the investigator and categorized as mild, moderate, or severe. Injection-site erythema, induration, and swelling were reported by maximum size, with mild events measuring 0 to ≤1 inches (0 to ≤2.5 cm), moderate events measuring >1 to ≤3 inches (>2.5 to ≤7.5 cm), and severe events measuring >3 inches (>7.5 cm). All injection-site AEs were considered to be related to the study vaccine; for systemic AEs, relatedness to study vaccine was assessed by the site investigator. Duration of all solicited AEs in days was also recorded.

2.5. Immunogenicity assessments

Serum samples were taken at 30 days post-final vaccination with PCV in all participants to assess immune responses across all age cohorts. Serum samples were taken pre-vaccination with

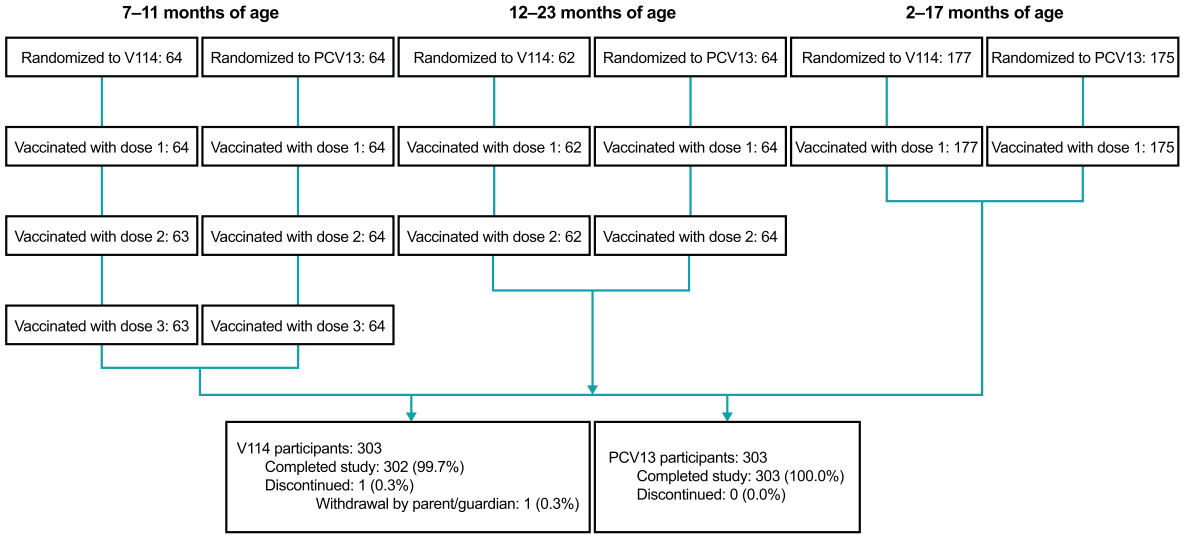

Fig. 1. Participant disposition.
PCV13 = 13-valent pneumococcal conjugate vaccine; V114 = 15-valent pneumococcal conjugate vaccine.

PCV on Day 1 for participants ≥2 years of age only, as children in this age group are more likely to have circulating serotype-specific pneumococcal antibodies due to prior pneumococcal vaccination or exposure to *S. pneumoniae*. Serotype-specific pneumococcal capsular polysaccharide immunoglobulin G (IgG) antibodies were evaluated using a validated multiplexed pneumococcal electrochemiluminescence (Pn ECL) assay described by Nolan et al. [23] and developed by MSD. The Pn ECL intermediate assay precision ranged from 16.8% to 24.1% geometric coefficient of variation across the 15 serotypes [23]. Anti-pneumococcal polysaccharide (PnP) IgG geometric mean concentrations (GMCs) were calculated. The serotype-specific response rates, assessed as the proportion of participants meeting an IgG concentration threshold of ≥0.35 μg/mL 30 days after the last dose of vaccine, were summarized for each vaccine serotype. For participants ≥2 years of age, serotype-specific geometric mean fold rises (GMFRs) from pre-vaccination to 30 days following final vaccination for IgG responses were evaluated.

2.6. Study endpoints and statistical analysis

2.6.1. Analysis populations

Safety analyses were conducted in the all participants-as-treated population, which consisted of all randomized participants who received at least one dose of the study vaccine. The per-protocol population served as the primary population for the analysis of immunogenicity data; this included all randomized participants without deviations from the protocol that could have substantially affected immunogenicity results. All safety and immunogenicity analyses were conducted by age at the time of randomization (7–11 months of age, 12–23 months of age, and 2–17 years of age).

2.6.2. Primary safety endpoints and statistical methods

The primary safety objective was to evaluate the safety and tolerability of V114 or PCV13 determined by the proportions of participants with solicited injection-site AEs and solicited systemic AEs from Day 1 to Day 14 post-vaccination, as well as the proportions of participants with vaccine-related SAEs. Point estimates were provided for the safety endpoints, and within-group 95% confidence intervals (CIs) were derived by the method of Clopper and Pearson [24].

2.6.3. Primary immunogenicity endpoints and statistical methods

The primary immunogenicity objective was to evaluate serotype-specific IgG GMCs for the 15 serotypes included in V114 at 30 days post-vaccination with the final dose of V114 or PCV13. Descriptive statistics with point estimates and within-group 95% CIs were provided; the within-group 95% CIs were obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.

2.6.4. Secondary immunogenicity endpoints and statistical methods

The secondary immunogenicity objective was to evaluate serotype-specific IgG response rates (the proportion of participants meeting the IgG threshold value of ≥0.35 μg/mL) for the 15 serotypes included in V114 at 30 days post-vaccination with the final dose of V114 or PCV13. The within-group CIs were derived by the method of Clopper and Pearson [24].

2.6.5. Exploratory immunogenicity endpoints

The exploratory immunogenicity objective was to evaluate serotype-specific GMFRs in IgG responses for the 15 serotypes included in V114 from pre-vaccination (Day 1) to 30 days post-vaccination (Day 30) with the final dose of V114 or PCV13 in participants ≥2 years of age only.

2.6.6. Subgroup analyses

Subgroup analyses of safety endpoints and the primary immunogenicity endpoint by age and prior PCV status (participants ≥ 2 years of age only) and by sex were summarized using the same methods as the corresponding endpoints.

2.6.7. Analysis software

Analyses were performed using SAS© software, version 9.4 of the SAS System for Unix (Cary, NC, USA).

3. Results

3.1. Study population

A total of 606 participants were randomized, with 303 in each group (Fig. 1). All randomized participants were vaccinated with V114 or PCV13, and all but one completed the study; one participant discontinued due to withdrawal by their parent or guardian. Both vaccination groups were generally comparable within each age cohort in terms of baseline characteristics (Table 2). All participants 7–11 and 12–23 months of age were PCV-naïve, and the majority were Asian. Of the participants 2–17 years of age, 57.1% (n = 201) were PCV-naïve, 64.2% (n = 226) were 2–5 years of age, and most were White and of non-Hispanic or Latino ethnicity. Of the participants who had received prior PCV, approximately 80% received at least one prior dose of PCV10, 15% received at least one prior dose of PCV13, and 6% received at least one prior dose of PCV7 (data not shown).

3.2. Safety

The proportions of participants with AEs were generally comparable between the V114 and PCV13 groups for participants 7–11 months and 2–17 years of age. A numerically greater proportion of participants 12–23 months of age experienced AEs in the V114 group compared with the PCV13 group (Tables 3 and 4). The proportions of participants with AEs and SAEs following each vaccine dose were generally comparable between the groups for participants 7–11 months of age, with the exception of systemic AEs following the second dose, of which there was a higher proportion of these in the V114 group. For participants 12–23 months of age, the proportions of participants with AEs following each vaccine dose were generally higher in the V114 group compared with the PCV13 group (**Supplemental Tables 1 and 2**). No deaths occurred during the study, and there were no vaccine-related SAEs. The proportions of participants with SAEs were generally comparable between vaccination groups for each age group (Tables 3 and 4).

The three most frequently reported solicited AEs following V114 vaccination for participants 7–11 months of age were irritability, somnolence, and injection-site erythema; for participants 12–23 months of age, the most common were irritability, injection-site pain, and somnolence (Fig. 2**A,B** and Table 3). The three most frequently reported AEs following V114 vaccination for participants 2–17 years of age were injection-site pain, myalgia, and injection-site swelling (Fig. 2**C** and Table 4). The majority of solicited AEs following PCV vaccination were mild or moderate in intensity and were of a short duration (≤3 days) across intervention groups (Fig. 2 and **Supplemental Tables 3–5**).

The majority of participants 7–11 and 12–23 months of age had a maximum body temperature of <101.3 °F (38.5 °C) across intervention groups. The majority of participants 2–17 years of age had a maximum body temperature of <100.4 °F (38.0 °C) (Tables 3 and 4).

V114 was well tolerated in participants 2–5 and 6–17 years of age, regardless of prior PCV status; participants 2–5 years of age

Table 2
Baseline characteristics and clinical characteristics.

	7–11 months		12–23 months		2–17 years	
	V114	PCV13	V114	PCV13	V114	PCV13
Participants in population, n	64	64	62	64	177	175
Sex, n (%)						
Male	35 (54.7)	31 (48.4)	32 (51.6)	26 (40.6)	92 (52.0)	92 (52.6)
Female	29 (45.3)	33 (51.6)	30 (48.4)	38 (59.4)	85 (48.0)	83 (47.4)
Age, n (%)						
7–11 months	64 (100.0)	64 (100.0)	NA	NA	NA	NA
12–23 months	NA	NA	62 (100.0)	64 (100.0)	NA	NA
2–5 years	NA	NA	NA	NA	114 (64.4)	112 (64.0)
6–17 years	NA	NA	NA	NA	63 (35.6)	63 (36.0)
Mean (±SD)	8.6 months (1.4)	8.8 months (1.6)	17.7 months (3.2)	17.8 months (3.3)	6.5 years (4.7)	6.5 years (4.7)
Race, n (%)						
Asian	53 (82.8)	53 (82.8)	52 (83.9)	53 (82.8)	60 (33.9)	56 (32.0)
White	11 (17.2)	11 (17.2)	10 (16.1)	11 (17.2)	117 (66.1)	118 (67.4)
Multiple	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.6)
Ethnicity, n (%)						
Hispanic or Latino	0 (0)	0 (0)	0 (0)	1 (1.6)	0 (0)	0 (0)
Not Hispanic or Latino	64 (100.0)	64 (100.0)	62 (100.0)	63 (98.4)	176 (99.4)	174 (99.4)
Not reported	NA	NA	NA	NA	1 (0.6)	1 (0.6)
PCV-naïve < 6 years of age, n (%)						
Yes	64 (100.0)	64 (100.0)	62 (100.0)	64 (100.0)	63 (55.3)[a]	62 (55.4)[a]
No	0 (0)	0 (0)	0 (0)	0 (0)	51 (44.7)[a]	50 (44.6)[a]
PCV-naïve 6–17 years of age, n (%)						
Yes	NA	NA	NA	NA	39 (61.9)[b]	37 (58.7)[b]
No	NA	NA	NA	NA	24 (38.1)[b]	26 (41.3)[b]

NA = not applicable; PCV = pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; SD = standard deviation; V114 = 15-valent pneumococcal conjugate vaccine.
[a] Percentages based on total number of participants 2–5 years of age (V114: n = 114; PCV13: n = 112).
[b] Percentages based on total number of participants 6–17 years of age (V114: n = 63; PCV13: n = 63).

Table 3
Safety summary for participants 7–11 and 12–23 months of age following any dose of PCV.

	7–11 months of age				12–23 months of age			
	V114 (n = 64)		PCV13 (n = 64)		V114 (n = 62)		PCV13 (n = 64)	
	n (%)	95% CI[a]	n (%)	95% CI[a]	n (%)	95% CI[a]	n (%)	95% CI[a]
Any AEs	49 (76.6)	64.3–86.2	50 (78.1)	66.0–87.5	49 (79.0)	66.8–88.3	38 (59.4)	46.4–71.5
Injection-site	25 (39.1)		27 (42.2)		32 (51.6)		24 (37.5)	
Systemic	45 (70.3)		43 (67.2)		40 (64.5)		29 (45.3)	
Any vaccine-related AEs[b]	41 (64.1)	51.1–75.7	41 (64.1)	51.1–75.7	42 (67.7)	54.7–79.1	31 (48.4)	35.8–61.3
Injection-site	25 (39.1)		27 (42.2)		32 (51.6)		24 (37.5)	
Systemic	33 (51.6)		30 (46.9)		30 (48.4)		19 (29.7)	
Any SAEs (duration of study)	7 (10.9)	4.5–21.2	5 (7.8)	2.6–17.3	4 (6.5)	1.8–15.7	4 (6.3)	1.7–15.2
Any vaccine-related SAEs[b]	0 (0)	0.0–5.6	0 (0)	0.0–5.6	0 (0)	0.0–5.8	0 (0)	0.0–5.6
Death	0 (0)	0.0–5.6	0 (0)	0.0–5.6	0 (0)	0.0–5.8	0 (0)	0.0–5.6
Solicited injection-site AEs (Days 1–14)								
Injection-site erythema	18 (28.1)	17.6–40.8	22 (34.4)	22.9–47.3	13 (21.0)	11.7–33.2	14 (21.9)	12.5–34.0
Injection-site pain	12 (18.8)	10.1–30.5	5 (7.8)	2.6–17.3	21 (33.9)	22.3–47.0	15 (23.4)	13.8–35.7
Injection-site swelling	12 (18.8)	10.1–30.5	10 (15.6)	7.8–26.9	9 (14.5)	6.9–25.8	8 (12.5)	5.6–23.2
Injection-site induration	11 (17.2)	8.9–28.7	9 (14.1)	6.6–25.0	5 (8.1)	2.7–17.8	6 (9.4)	3.5–19.3
Solicited systemic AEs (Days 1–14)								
Irritability	21 (32.8)	21.6–45.7	28 (43.8)	31.4–56.7	22 (35.5)	23.7–48.7	14 (21.9)	12.5–34.0
Somnolence	14 (21.9)	12.5–34.0	10 (15.6)	7.8–26.9	15 (24.2)	14.2–36.7	11 (17.2)	8.9–28.7
Decreased appetite	10 (15.6)	7.8–26.9	12 (18.8)	10.1–30.5	14 (22.6)	12.9–35.0	12 (18.8)	10.1–30.5
Urticaria	1 (1.6)	0.0–8.4	3 (4.7)	1.0–13.1	0 (0)	0 (0)	0 (0)	
Maximum temperature[c]								
<100.4 °F (38 °C)	8 (12.5)		16 (25.0)		27 (43.5)		31 (48.4)	
≥100.4 °F (38 °C) to < 102.2 °F (39 °C)	46 (71.9)		41 (64.1)		27 (43.5)		27 (42.2)	
≥102.2 °F (39 °C)	10 (15.6)		7 (10.9)		8 (12.9)		6 (9.4)	

AE = adverse event; CI = confidence interval; PCV = pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; SAE = serious adverse event; V114 = 15-valent pneumococcal conjugate vaccine.
[a] Estimated CIs are calculated based on the exact binomial method proposed by Clopper and Pearson and are provided in accordance with the statistical analysis plan.
[b] Determined by the investigator to be related to the vaccine.
[c] All participants reported temperature data. Includes participants whose temperature methods were unreported or unable to be converted to rectal equivalent for Days 1–7 following vaccination. Multiple occurrences of maximum temperature are counted only once.

reported fewer AEs than participants 6–17 years of age. PCV-naïve participants 2–5 years of age reported fewer AEs than participants with prior PCV vaccination, regardless of intervention group (**Supplemental Table 6**). Catch-up vaccination with V114 was well tolerated, and similar safety profiles were observed regardless of participant sex (data not shown).

Table 4
Safety summary for participants 2–17 years of age following any dose of PCV.

	2–17 years of age			
	V114 (n = 177)		PCV13 (n = 175)	
	n (%)	95% CI[a]	n (%)	95% CI[a]
Any AEs	132 (74.6)	67.5–80.8	134 (76.6)	69.6–82.6
Injection-site	118 (66.7)		119 (68.0)	
Systemic	93 (52.5)		92 (52.6)	
Any vaccine-related AEs[b]	125 (70.6)	63.3–77.2	125 (71.4)	64.1–78.0
Injection-site	118 (66.7)		119 (68.0)	
Systemic	73 (41.2)		62 (35.4)	
Any SAEs (duration of study)	4 (2.3)	0.6–5.7	4 (2.3)	0.6–5.7
Any vaccine-related SAEs[b]	0 (0)	0.0–2.1	0 (0)	0.0–2.1
Death	0 (0)	0.0–2.1	0 (0)	0.0–2.1
Solicited injection-site AEs (Days 1–14)				
Injection-site erythema	34 (19.2)	13.7–25.8	37 (21.1)	15.3–27.9
Injection-site pain	97 (54.8)	47.2–62.3	99 (56.6)	48.9–64.0
Injection-site swelling	37 (20.9)	15.2–27.6	42 (24.0)	17.9–31.0
Injection-site induration	12 (6.8)	3.6–11.5	26 (14.9)	9.9–21.0
Solicited systemic AEs (Days 1–14)				
Irritability[c]	5 (2.8)	0.9–6.5	7 (4.0)	1.6–8.1
Somnolence[c]	5 (2.8)	0.9–6.5	5 (2.9)	0.9–6.5
Decreased appetite[c]	4 (2.3)	0.6–5.7	5 (2.9)	0.9–6.5
Urticaria	2 (1.1)	0.1–4.0	2 (1.1)	0.1–4.1
Myalgia[d]	42 (23.7)	17.7–30.7	29 (16.6)	11.4–22.9
Fatigue[d]	28 (15.8)	10.8–22.0	30 (17.1)	11.9–23.6
Headache[d]	21 (11.9)	7.5–17.6	24 (13.7)	9.0–19.7
Arthralgia[d]	0 (0)	0.0–2.1	3 (1.7)	0.4–4.9
Maximum temperature[e]				
<100.4 °F (38 °C)	167 (94.4)		167 (95.4)	
≥100.4 °F (38 °C) to <102.2 °F (39 °C)	7 (4.0)		8 (4.6)	
≥102.2 °F (39 °C)	3 (1.7)		0 (0)	

AE = adverse event; CI = confidence interval; PCV = pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; SAE = serious adverse event; V114 = 15-valent pneumococcal conjugate vaccine.
[a] Estimated CIs are calculated based on the exact binomial method proposed by Clopper and Pearson and are provided in accordance with the statistical analysis plan.
[b] Determined by the investigator to be related to the vaccine.
[c] Only solicited from participants 2 to <3 years of age.
[d] Only solicited from participants ≥3 years of age.
[e] All participants reported temperature data. Includes participants whose temperature methods were unreported or unable to be converted to oral equivalent for Days 1–7 following vaccination. Multiple occurrences of maximum temperature are counted only once.

3.3. Immunogenicity

Anti-PnP serotype-specific IgG GMCs at 30 days post-final dose were generally comparable between the vaccination groups for the 13 shared serotypes in V114 and PCV13 for participants 7–11 months of age, 12–23 months of age, and 2–17 years of age (Fig. 3 and **Supplemental Tables 7–9**). Anti-PnP IgG GMCs for the two serotypes (22F and 33F) unique to V114 at 30 days post-final dose were higher in the V114 group than in the PCV13 group (Fig. 3 and **Supplemental Tables 7–9**). The reverse cumulative distribution curves of anti-PnP IgG concentrations for each age group were consistent with results from the primary immunogenicity analyses (**Supplemental Fig. 1**).

In the V114 group, the proportion of immunological responders (individuals achieving serotype-specific IgG concentration threshold of ≥0.35 μg/mL) for participants 7–11 months of age, 12–23 months of age, and 2–17 years of age to each of the 15 serotypes contained in V114 ranged from 95–100%, 83–100%, and 95–100%, respectively (Tables 5**A–C**). Across all age groups, serotype-specific IgG response rates at 30 days post-final dose were generally comparable between the intervention groups for the 13 shared serotypes in V114 and PCV13. IgG response rates for the two serotypes unique to V114 (22F and 33F) at 30 days post-final dose were higher with V114 (94–100%) than with PCV13 (6–37%) across all age groups. More than 70% of participants 2–17 years of age had a ≥4-fold rise in IgG concentrations for 14 out of the 15 serotypes (excluding serotype 5) in the V114 group from Day 1 to Day 30. Of the participants 2–17 years of age in the PCV13 group, >70% had a ≥4-fold rise in IgG concentrations for 11 of the 13 serotypes contained in PCV13 (excluding serotypes 3 and 5; **Supplemental Table 10**). Increases in serotype-specific IgG GMCs from Day 1 to Day 30 were also observed in the PCV13 group for the 13 shared serotypes, with generally no change seen for serotypes 22F and 33F (**Supplemental Table 10**).

Subgroup analyses of anti-PnP IgG GMCs at Day 30 were performed by age and prior PCV status, by sex, and by race. In participants 2–5 and 6–17 years of age, anti-PnP IgG GMC results for both V114 and PCV13 groups were generally consistent with those in the overall population of participants 2–17 years of age but showed an age-dependent response for some serotypes (**Supplemental Table 11**). Anti-PnP IgG GMCs were higher for many shared serotypes in participants previously vaccinated with PCV compared with PCV-naïve participants, regardless of intervention group. These trends were observed for more serotypes in participants 2–5 years of age compared with those 6–17 years of age, regardless of the PCV received (**Supplemental Table 12**). In both males and females, anti-PnP IgG GMCs were generally consistent with those calculated in the overall study population (**Supplemental Tables 13–15**). Similarly, results within Asian or white participants were generally consistent with the results in the overall population of each age group (data not shown).

4. Discussion

In this study of healthy children 7 months–17 years of age with or without history of prior PCV exposure, catch-up vaccination with V114 was generally well tolerated and elicited a robust

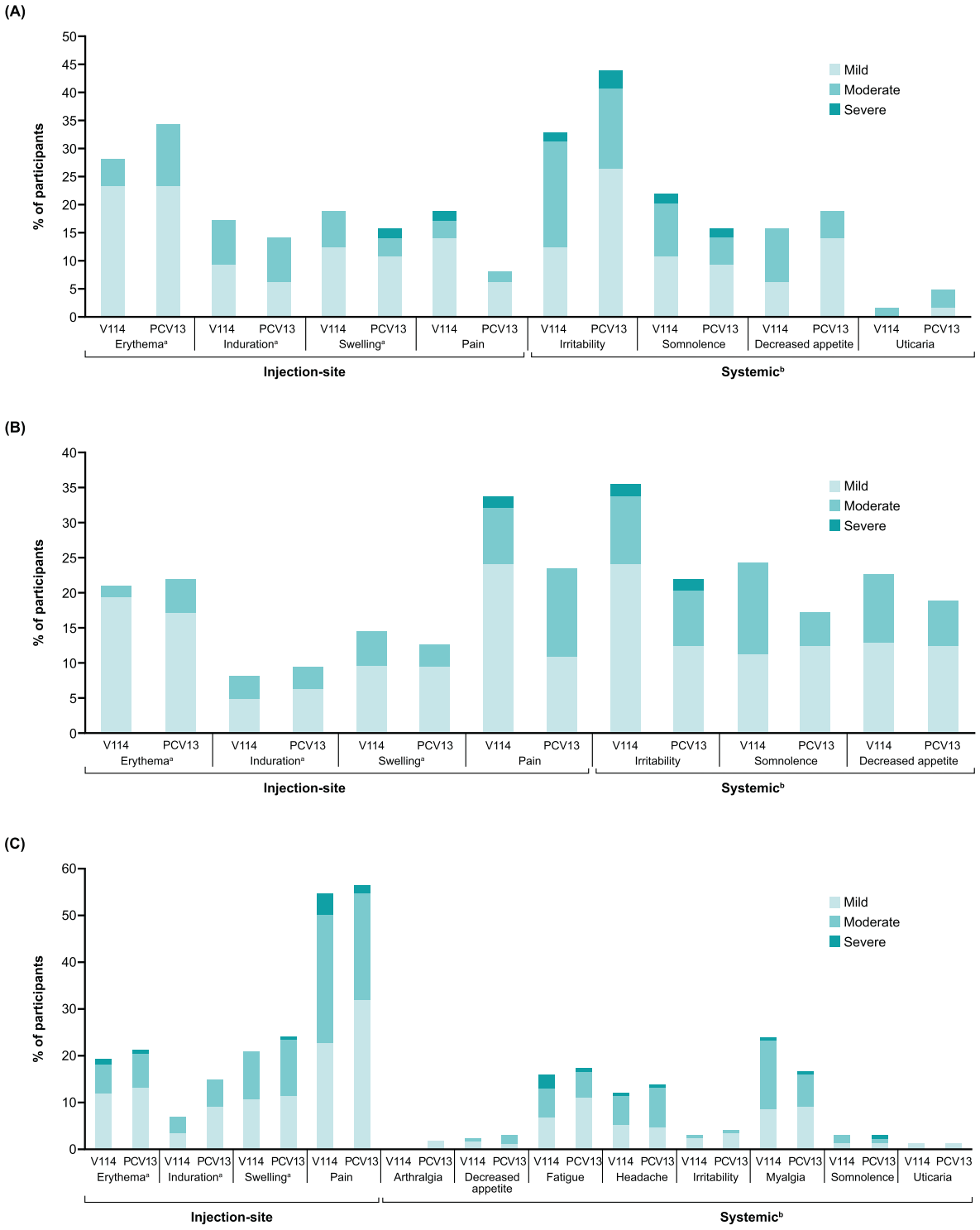

Fig. 2. Assessment of solicited adverse events for participants (A) 7–11 months of age, (B) 12–23 months of age, and (C) 2–17 years of age.
Injection-site erythema, induration, and swelling events were solicited from Days 1–14 following any vaccination. Injection-site pain and systemic events were solicited from Days 1–14 following each vaccination. The height of the stacked bar represents the total percentage of participants reporting the AE. The severity grades (mild, moderate, or severe) within the bar indicate the proportion of the total attributed to each respective category. [a]For the severity of solicited injection-site erythema, induration, and swelling, mild events measured >0 to ≤1 inches (0 to ≤ 2.5 cm), moderate events measured > 1 to ≤3 inches (>2.5 to ≤7.5 cm), and severe events measured >3 inches (>7.5 cm). [b]For participants 2 to <3 years of age, decreased appetite, irritability, somnolence, and urticaria were solicited from Days 1–14 following vaccination. For participants ≥3 to 17 years of age, arthralgia, fatigue, headache, myalgia, and urticaria were solicited from Days 1–14 following vaccination. AE = adverse event; PCV13 = 13-valent pneumococcal conjugate vaccine; V114 = 15-valent pneumococcal conjugate vaccine.

immune response to all 15 serotypes included in the vaccine, as assessed by IgG GMCs and IgG response rates at 30 days following the last dose of study intervention, regardless of prior PCV vaccination. The safety profile of catch-up vaccination with V114 was generally comparable to that of PCV13 and was consistent with previous PCV13 studies in similar populations [25–27]. Frequen-

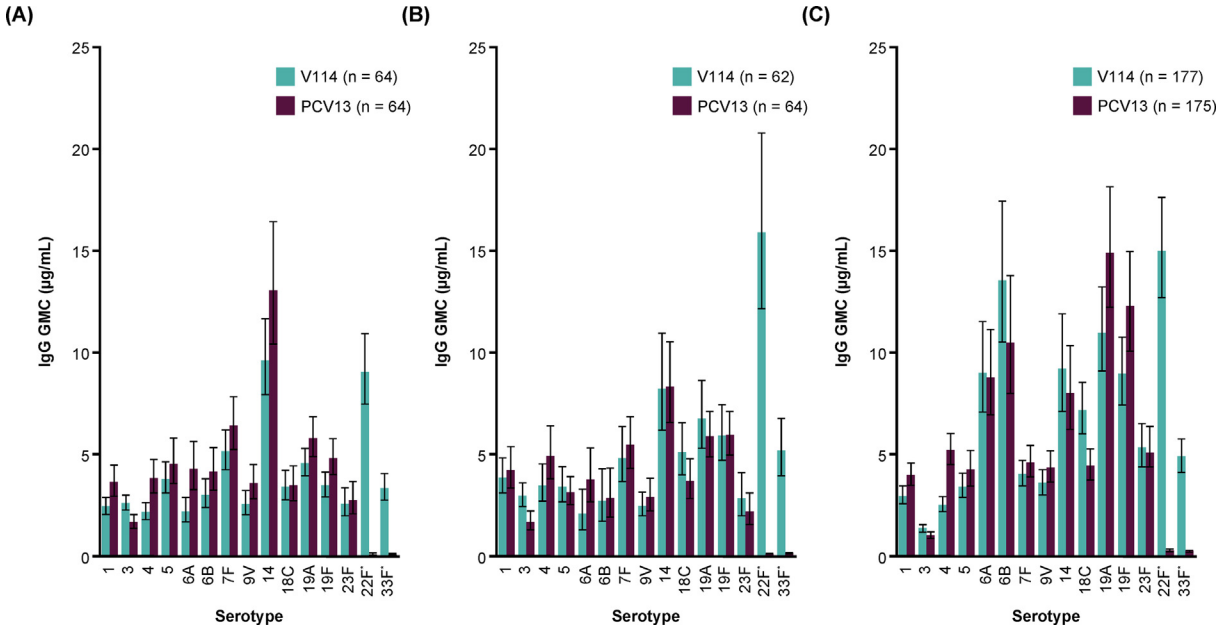

Fig. 3. Estimated serotype-specific anti-PnP IgG GMCs 30 days after final vaccination with PCV for participants (A) 7–11 months of age, (B) 12–23 months of age, and (C) 2–17 years of age.

GMC = geometric mean concentration; IgG = immunoglobulin G; n = number of participants randomized to each individual age cohort; PCV = pneumococcal conjugate vaccine; PnP = pneumococcal polysaccharide.

cies of participants with systemic AEs, body temperature ≥ 100.4 °F (38 °C), and body temperature ≥ 102.2 °F (39 °C) inversely correlated with increase in age. There were no vaccine-related SAEs, discontinuations due to AEs, or deaths during the study. Small differences in the frequencies of some AEs between groups were observed in participants <2 years of age after any dose, with no discernable pattern. Given that the majority of reported AEs were mild or moderate in intensity and transient (<3 days) and sample sizes of participants 7–11 months and 12–23 months of age were small, these differences are unlikely to be clinically meaningful. The observed safety profile is consistent with other studies of V114 in similar populations [19,22,22].

Overall, catch-up vaccination with V114 elicited serotype-specific anti-pneumococcal IgG responses to all 15 serotypes in healthy children 7 months–17 years of age. Although numerical differences in antibody responses were observed for some serotypes between recipients of V114 and PCV13 in some age cohorts, serotype-specific pneumococcal antibodies were generally comparable between the vaccination groups for the 13 shared serotypes and higher among recipients of V114 than PCV13 for the two additional serotypes in V114. A relatively lower response against serotype 6A was seen in participants 12–23 months of age who received two doses of V114 or PCV13, a trend not observed in the other age cohorts, albeit the sample size was small in this cohort. The reason for this is unclear, as is why >70% of participants 2–17 years of age in the V114 group had a ≥4-fold rise in IgG GMCs from Day 1 to Day 30 for all serotypes except serotype 5. While serotype 5, shared by both PCV13 and V114, is not a serotype that contributes significantly to the residual burden of disease in the post-PCV era, rates of IPD attributable to serotype 5 in children <5 years of age have remained unchanged following the introduction of PCV13 into childhood vaccination schedules compared with the pre-PCV13 period [28]. Overall, however, there have been marked decreases in cases of PD attributable to vaccine serotypes since the introduction of PCVs into pediatric vaccination recommendations. Conversely, cases of PD caused by serotypes not contained in PCV13 have increased in recent years, particularly in countries with high PCV13 uptake [28–31].

Differences in immune responses between different subgroups, including by age and number of doses, are likely indicative of age-related differences in the maturity of the immune system [32]. The small between-group differences in serotype-specific IgG responses observed for some shared serotypes within each age cohort are not anticipated to impact the effectiveness of V114. The variability in vaccine-elicited antibody concentrations observed within vaccination groups is consistent with previous studies [33–36].

The proportion of participants who achieved the serotype-specific IgG concentration threshold of ≥0.35 µg/mL after the last dose in the catch-up schedule was high (83.9–100%) across all three age cohorts, for all shared serotypes in both vaccination groups. This IgG concentration threshold was derived from infants enrolled in three studies evaluating the clinical efficacy of PCV7/9-valent PCV (PCV9) using the original enzyme-linked immunosorbent assay (ELISA) method, and has since been recommended for use as a benchmark when comparing immune responses between vaccines; however, the estimated antibody concentrations that correlate with protection against PD vary between serotypes and can be lower or higher than 0.35 µg/mL [33,38,38]. As such, IgG concentrations below this threshold may be clinically meaningful for some serotypes, and participants designated as "non-responders" for these serotypes in this study may have sufficient protection against them. Notably, this threshold is of limited value in older children who generally have more robust immune responses to PCVs (Fig. 3).

The safety and immunogenicity profiles of V114 and PCV13 were comparable among participants 2–5 and 6–17 years of age and were consistent with the overall population of participants 2–17 years of age. Differences were observed in subgroup analyses of safety and immunogenicity based on prior history of PCV vaccination between the two age cohorts (2–5 years and 6–17 years of age). While no differences were observed when comparing

Table 5
Serotype-specific anti-PnP IgG response rates 30 days after final vaccination with PCV for participants (A) 7–11 months of age, (B) 12–23 months of age, and (C) 2–17 years of age.

(A)

	V114 (n = 64)		PCV13 (n = 64)	
13 shared serotypes	Observed response percentage (m/n)	95% CI[a]	Observed response percentage (m/n)	95% CI[a]
1	100.0 (60/60)	94.0–100.0	100.0 (59/59)	93.9–100.0
3	100.0 (60/60)	94.0–100.0	96.6 (57/59)	88.3–99.6
4	100.0 (60/60)	94.0–100.0	100.0 (59/59)	93.9–100.0
5	100.0 (60/60)	94.0–100.0	100.0 (59/59)	93.9–100.0
6A	95.0 (57/60)	86.1–99.0	98.3 (58/59)	90.9–100.0
6B	96.7 (58/60)	88.5–99.6	100.0 (59/59)	93.9–100.0
7F	100.0 (60/60)	94.0–100.0	100.0 (59/59)	93.9–100.0
9V	98.3 (59/60)	91.1–100.0	100.0 (59/59)	93.9–100.0
14	100.0 (60/60)	94.0–100.0	100.0 (59/59)	93.9–100.0
18C	100.0 (60/60)	94.0–100.0	100.0 (59/59)	93.9–100.0
19A	100.0 (60/60)	94.0–100.0	100.0 (59/59)	93.9–100.0
19F	100.0 (60/60)	94.0–100.0	100.0 (59/59)	93.9–100.0
23F	98.3 (59/60)	91.1–100.0	100.0 (59/59)	93.9–100.0
2 additional serotypes in V114				
22F	100.0 (60/60)	94.0–100.0	13.8 (8/58)	6.1–25.4
33F	100.0 (60/60)	94.0–100.0	11.9 (7/59)	4.9–22.9

(B)

	V114 (n = 62)		PCV13 (n = 64)	
13 shared serotypes	Observed response percentage (m/n)	95% CI[a]	Observed response percentage (m/n)	95% CI[a]
1	100.0 (56/56)	93.6–100.0	98.3 (59/60)	91.1–100.0
3	98.2 (55/56)	90.4–100.0	90.0 (54/60)	79.5–96.2
4	100.0 (56/56)	93.6–100.0	96.7 (58/60)	88.5–99.6
5	98.2 (55/56)	90.4–100.0	98.3 (59/60)	91.1–100.0
6A	83.9 (47/56)	71.7–92.4	95.0 (57/60)	86.1–99.0
6B	89.3 (50/56)	78.1–96.0	88.3 (53/60)	77.4–95.2
7F	98.2 (55/56)	90.4–100.0	100.0 (60/60)	94.0–100.0
9V	98.2 (55/56)	90.4–100.0	96.7 (58/60)	88.5–99.6
14	98.2 (55/56)	90.4–100.0	100.0 (60/60)	94.0–100.0
18C	96.4 (54/56)	87.7–99.6	98.3 (59/60)	91.1–100.0
19A	98.2 (55/56)	90.4–100.0	100.0 (60/60)	94.0–100.0
19F	100.0 (56/56)	93.6–100.0	100.0 (60/60)	94.0–100.0
23F	94.6 (53/56)	81.5–98.9	88.3 (53/60)	77.4–95.2
2 additional serotypes in V114				
22F	100.0 (56/56)	93.6–100.0	6.7 (4/60)	1.8–16.2
33F	94.6 (53/56)	81.5–98.9	15.0 (9/60)	7.1–26.6

(C)

	V114 (n = 177)		PCV13 (n = 175)	
13 shared serotypes	Observed response percentage (m/n)	95% CI[a]	Observed response percentage (m/n)	95% CI[a]
1	99.4 (161/162)	96.6–100.0	100.0 (162/162)	97.7–100.0
3	95.7 (155/162)	91.3–98.2	87.7 (142/162)	81.6–92.3
4	98.8 (160/162)	95.6–99.9	100.0 (162/162)	97.7–100.0
5	99.4 (161/162)	96.6–100.0	99.4 (161/162)	96.6–100.0
6A	98.1 (159/162)	94.7–99.6	98.1 (159/162)	94.7–99.6
6B	98.1 (159/162)	94.7–99.6	96.9 (156/161)	92.9–99.0
7F	99.4 (161/162)	96.6–100.0	100.0 (162/162)	97.7–100.0
9V	100.0 (162/162)	97.7–100.0	98.8 (160/162)	95.6–99.9
14	99.4 (161/162)	96.6–100.0	98.1 (159/162)	94.7–99.6
18C	100.0 (162/162)	97.7–100.0	100.0 (162/162)	97.7–100.0
19A	100.0 (162/162)	97.7–100.0	100.0 (162/162)	97.7–100.0
19F	99.4 (161/162)	96.6–100.0	100.0 (162/162)	97.7–100.0
23F	99.4 (161/162)	96.6–100.0	95.7 (155/162)	91.3–98.2
2 additional serotypes in V114				
22F	100.0 (162/162)	97.7–100.0	37.7 (60/159)	30.2–45.8
33F	99.4 (161/162)	96.6–100.0	37.5 (60/160)	30.0–45.5

CI = confidence interval; IgG = immunoglobulin G; N = number of participants randomized and vaccinated; n = number of participants contributing to the analysis; PCV = pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; PnP = pneumococcal polysaccharide; V114 = 15-valent pneumococcal conjugate vaccine.

[a] The within-group CIs are based on the exact binomial method proposed by Clopper and Pearson.

frequencies of injection-site and systemic AEs between PCV-naïve and PCV-experienced children 6–17 years of age, PCV-naïve children 2–5 years of age reported lower rates than PCV-experienced children for these AEs. It is unclear why there is a higher incidence of AEs in children with prior receipt of PCV. This could be due to the shorter interval between the last PCV vaccination received prior to study entry and the receipt of V114 or PCV13 in this study for children 2–5 years of age compared with those 6–17 years of age. The higher reactogenicity associated with shorter intervals between doses has also been observed in a study of adults given a sequential administration of PCV and 23-valent pneumococcal polysaccharide vaccine (PPSV23) with a 2-month or 6-month interval [39].

In participants 2–17 years of age previously vaccinated with PCV, higher levels of serotype-specific IgG GMCs were observed compared with PCV-naïve participants, regardless of the PCV

received; this difference was observed for more serotypes in participants 2–5 years of age than 6–17 years of age. Observed differences in IgG GMCs between the two age cohorts could be explained by several factors, including maturity of the immune system and higher levels of immune memory cells in subjects with prior receipt of PCV or pneumococcal carriage exposure.

The study has several limitations. It was descriptive and was not powered to assess noninferiority or superiority with respect to immune responses. The study did not evaluate the efficacy of V114 and PCV13 in this target population. An additional limitation was the lack of baseline (pre-vaccination) measurements for participants <2 years of age to allow for assessment of possible differences across all age cohorts. Furthermore, although V114-induced opsonophagocytic activity to all 15 serotypes has previously been observed in phase III adult studies and a phase II pediatric study [21,41,41], functional activity was not measured in this study, as there were limited quantities of blood for measurement of all pneumococcal serotypes. Despite these limitations, the immune responses reported here were consistent with other studies of PCV-induced immunogenicity for V114, as well as other PCVs [21,33].

In conclusion, catch-up vaccination with V114 in healthy children 7 months–17 years of age was generally well tolerated and immunogenic, regardless of prior PCV history. The results from these analyses support a recommendation for V114 catch-up vaccination in children who have not received PCV immunization per the recommended schedule.

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Declaration of competing interests

NB, YS, LG, MP, RL, GT, and CC are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD), and may own stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA. LM and KB are former employees of MSD and own stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA. RM was an employee of MSD at the time the study was conducted. JW and LS have taken part in clinical vaccine trials, served on advisory boards, and presented satellite symposia during medical congresses for GlaxoSmithKline, Pfizer, and MSD . For MR, Tampere University Vaccine Research Center carries out clinical vaccine trials for most major vaccine manufacturers, including MSD. PR has taken part in clinical vaccine trials and served on advisory boards for GlaxoSmithKline, Pfizer, and MSD. RD has received grants from Pfizer, MSD, and MedImmune/AstraZeneca. He serves scientific consultant, on the review/board/advisory committee of Pfizer and MSD. He is also part of the speakers' bureaus of Pfizer, MSD, Sanofi Pasteur, and GlaxoSmithKline. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Author contributions

Banniettis N: conception, design or planning of the study; analysis of the data; interpretation of the results; drafting of the manuscript; review of the manuscript. Wysocki J, Szenborn L: acquisition of the data; review of the manuscript. Phongsamart W, Pitisuttithum P, Rämet M: acquisition of the data; interpretation of the results; review of the manuscript. Richmond P: interpretation of the results; review of the manuscript. Dagan R: interpretation of the results; drafting of the manuscript; review of the manuscript. Good L: conception, design or planning of the study; review of the manuscript. Papa M, Churchill C: conception, design or planning of the study; acquisition of the data; review of the manuscript. Lupinacci R; Bickham K: conception, design or planning of the study; analysis of the data; interpretation of the results; review of the manuscript. Shi Y, Musey L: conception, design or planning of the study; acquisition of the data; analysis of the data; interpretation of the results; drafting of the manuscript; review of the manuscript. All authors provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data sharing

The data sharing policy, including restrictions, of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the Engage Zone site or via email to dataaccess@merck.com.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.09.003.

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