

The 15-valent pneumococcal conjugate vaccine V114 induces cross-reactive antibodies against pneumococcal serotype 6C

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ABSTRACT

Pneumococcal serogroups consist of structurally related serotypes, and serotype-specific antibodies can cross-react against other serotypes within the same serogroup. Cross-reactivity of vaccine-induced serotype 6A antibodies, and, to a lesser extent, serotype 6B antibodies, to serotype 6C has been demonstrated following receipt of the 13-valent pneumococcal conjugate vaccine (PCV13), which contains serotypes 6A and 6B. V114 is a 15-valent PCV containing the 13 PCV13 serotypes plus two additional serotypes, 22F and 33F. This study assessed cross-reactivity to serotype 6C in recipients of V114 and PCV13 as well as specificity of opsonophagocytic activity (OPA) responses in serogroup 6. Following receipt of V114 or PCV13, the observed OPA geometric mean titers to serotypes 6A, 6B, and 6C were comparable across both vaccination groups (post-single dose in adults ≥ 50 years of age [$n = 250$] and from pre- to post-dose 4 in pediatric participants 12–15 months of age [$n = 150$]). Based on OPA inhibition studies, V114 induced cross-reactive antibodies to serotype 6C in adult and pediatric populations that were specific and comparable to those induced by PCV13. Based on experience with PCV13, V114 may also provide comparable protection against pneumococcal disease caused by serotype 6C; however, this will have to be evaluated in real-world studies.

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Serotypes of *Streptococcus pneumoniae* are characterized by the structure of their capsular polysaccharides (PS), with each pneumococcal serogroup consisting of structurally related serotypes.¹ Serotype-specific antibodies can cross-react against other serotypes with similar capsular composition to induce immune responses, but the quality of cross-reactive antibodies can differ between serotypes.^{1,2} Pneumococcal vaccines are designed to cover serotypes associated with the highest burden of disease,^{3,4} and data on serotype distribution following widespread implementation of these vaccines suggested that these vaccines may have an impact on non-vaccine serotypes within a serogroup.⁵ A 7-valent pneumococcal conjugate vaccine (PCV7; Prevnar7[®]; Pfizer Inc.) was the first pneumococcal conjugate vaccine (PCV) licensed in the United States in 2000 and included serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.⁶ Following the widespread use of PCV7, reductions in pneumococcal disease and colonization attributable to serotype 6A were observed despite serotype 6A not being contained in PCV7, likely due to cross-protection with vaccine-induced antibodies against serotype 6B.^{7,8} Serotype 6C shares many epitopes with serotype 6A and was indistinguishable from serotype 6A using conventional serotyping reagents until it was independently characterized in 2007.⁹ As serotype 6C has structural similarity with serotype 6A and, to a lesser extent, serotype 6B,^{1,2,9,10} cross-reactivity was anticipated between these serotypes. However, surveillance studies in the post-PCV7 era have shown little impact on serotype 6C colonization and, in fact, showed that rates of colonization and

invasive pneumococcal disease (IPD) caused by serotype 6C increased in individuals ≥ 5 years of age.^{1,2,8} Retrospective studies carried out using specific methodologies to distinguish between serotypes 6A and 6C have demonstrated a similar increase in the prevalence of serotype 6C in the United States.^{8,11–14} In 2010, a 13-valent PCV (PCV13; Prevnar 13[™]; Pfizer Inc.) was introduced and expanded the serotype coverage to contain six additional serotypes, including serotype 6A.^{15,16} The incidence of IPD due to serotype 6A following the introduction of PCV13, already reduced in the post-PCV7 era, has decreased further in adults in most regions and is consistently low in children.⁷ Cross-reactivity of vaccine-induced antibodies to serotype 6C has been demonstrated following receipt of PCV13,^{1,2} and the use of PCV13 has been associated with an observed decrease in the incidence of disease caused by serotype 6C in some populations.^{17–19} However, serotype 6C remains a significant contributor to the residual burden of pneumococcal disease in some populations and regions.^{7,11,20,21}

V114 (VAXNEUVANCE[™], Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA) is a 15-valent PCV containing the 13 serotypes in PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) and two additional serotypes (22F and 33F). V114 was first approved for use in adults in 2021 and then for use in infants and children 6 weeks through 17 years of age in 2022.^{22–24} Opsonophagocytic activity (OPA) of antibodies against *S. pneumoniae* induced by pneumococcal vaccines has been shown to correlate with

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immune protection in various studies of pneumococcal vaccines.²⁵ Moreover, levels of cross-reactive immunoglobulin G (IgG) against a vaccine-related serotype may not reflect the opsonic capacity of antibodies against this serotype,²⁶ supporting the use of OPA in evaluating responses to vaccine-related serotypes. The objectives of this post-hoc study were to assess cross-reactive antibody responses to serotype 6C in adult and pediatric recipients of V114 and PCV13, and to evaluate the specificity of OPA responses in serogroup 6. This study was presented, in part, at the 12th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD-12), Toronto, Canada, in 2022 (abstract #235).

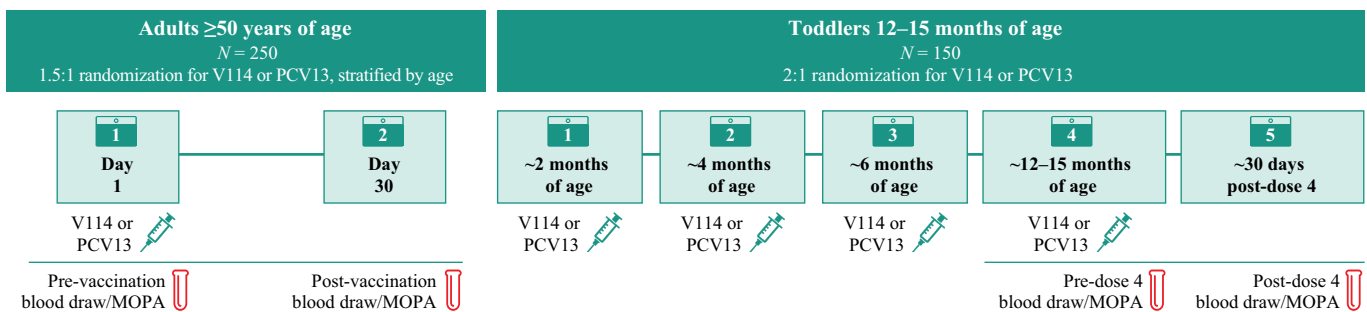
The study design is described in Figure 1. The sera from a subset of adult and pediatric participants from two Phase II randomized, double-blind, proof-of-concept V114 trials were randomly selected using the RANUNI function in SAS[®] software, version 9.4 of the SAS System for Unix (Cary, NC, USA). The adult trial (NCT02547649) compared the safety, tolerability, and immunogenicity of a single dose of two different formulations of V114 with PCV13 in pneumococcal vaccine-naïve adults ≥ 50 years of age.²⁷ The sera from 250 adult participants (V114 = 150; PCV13 = 100) with the remaining pre-

and post-vaccination samples were randomly selected and stratified by age group (50–64, 65–74, and ≥ 75 years of age), based on the proportion of participants in each age subgroup in the original study. The pediatric trial (NCT02987972) compared the safety, tolerability, and immunogenicity profiles of two different lots of V114 compared with PCV13 in healthy infants 6–12 weeks of age at enrollment; vaccines were administered at approximately 2, 4, 6, and 12–15 months of age.²⁸ In total, the sera from 150 pediatric participants (V114 = 100; PCV13 = 50) with available pre- and post-dose 4 samples were randomly selected. Written informed consent for post-hoc testing and analyses using the remaining sera samples had been obtained from all participants or parents/guardians before the participants were enrolled in the original clinical studies.

For the immunogenicity evaluation, serotype-specific immune responses induced by V114 and PCV13 to serotypes 6A, 6B, and 6C were each evaluated separately via multiplexed opsonophagocytic killing assay (MOPA) to quantify OPA or functional antibodies 30 days after vaccination.²⁹

To assess the relative contributions of serotype-specific antibodies to cross-reactivity, post-vaccination samples from 80

(a) Immunogenicity evaluation



(b) Serogroup 6 PS absorption – adult samples only (n = 80)

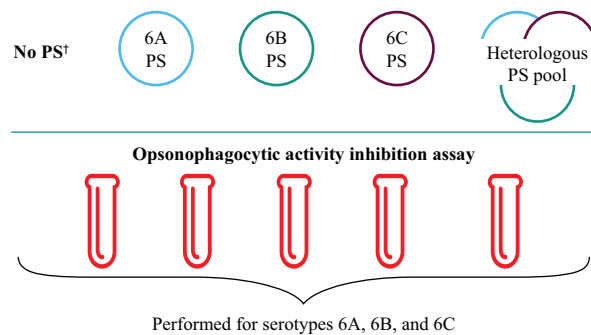


Figure 1. Study design. (a) For the 250 adult participants (V114 = 150; PCV13 = 100) with available pre- and post-vaccination sera samples, OPA GMTs against serotypes 6A, 6B, and 6C were measured prior to, and 30 days following, vaccination with a single dose of V114 or PCV13. For the 150 pediatric participants (V114 = 100; PCV13 = 50) with available pre- and post-dose 4 sera samples, OPA GMTs against serotypes 6A, 6B, and 6C were measured pre-dose 4 and 30 days post-dose 4. OPA GMTs were calculated by exponentiating the estimates of the mean of the natural log values. The within-group CIs were obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution. (b) Eighty adult participants (40 in each vaccination group) were further tested for the additional inhibition analysis for serogroup 6. Sera were tested for 6A, 6B, and 6C opsonophagocytic antibody activity after no PS absorption (control), after absorption with homologous 6A, 6B, or 6C PS, or after absorption with a heterologous PS pool. The 6A, 6B, and 6C PS stock reagents were diluted from 400 mg/L in the MOPA assay to final concentrations of 100 mg/mL for each PS. Stocks of the heterologous PS pools were mixed at 4.8 mg/mL, and equal volumes of each were combined to make 400 mg/L of each PS. The solutions were then diluted 4-fold when added to the sera to achieve final 100 mg/mL concentrations of each PS in the MOPA. The average inhibition rate was calculated by $1 - \text{exponentiating the mean of the natural log ratio of post- and pre-absorption MOPA titer}$. The within-group CIs were obtained by $1 - \text{exponentiating the corresponding CIs based on the t-distribution}$. Owing to limitations in the blood volume, pre-absorption tests were not performed in pediatric samples. [†]No PS absorption to provide uninhibited control. CI = confidence interval; GMT = geometric mean titer; MOPA = multiplexed opsonophagocytic killing assay; OPA = opsonophagocytic activity; PCV13 = 13-valent pneumococcal conjugate vaccine; PS = polysaccharide; V114 = 15-valent pneumococcal conjugate vaccine.

adults were re-tested by OPA after absorbing sera with purified PS of serogroup 6 serotypes (6A, 6B, and 6C); the endpoint was the degree of inhibition of OPA antibody activity following absorption with these three serotypes. Sera were tested for 6A, 6B, and 6C antibody activity after no PS absorption (control), after absorption with homologous serogroup 6 PS, or after absorption with a heterologous control PS pool (which included all V114 serotypes except for those that may potentially cross-react with serogroup 6 [serotypes 6A, 6B, 6C, and 19A]).³⁰

Demographic and baseline characteristics were generally comparable across the two intervention groups for both adult and pediatric participants (Table 1). In the pediatric study, more males were selected in the PCV13 group (62%) and more females in the V114 group (61%) due to sample availability.

In both the adult and pediatric populations, the observed OPA geometric mean titers (GMTs) to serotypes 6A, 6B, and 6C were comparable across both vaccination groups (post-single dose in adults and post-dose 4 in pediatric participants; Figure 2). The cross-reactive response to serotype 6C, as assessed by levels of OPA GMTs, was relatively stronger

in toddlers than in adults, while the responses to serotypes 6A and 6B were relatively stronger in adults than in toddlers. While the immunological mechanisms underlying these differences and their clinical implications are not known, the evaluation of cross-reactivity in children followed the fourth dose of the PCV, reflecting a memory response, whereas adults received only one dose of V114 or PCV13; furthermore, pneumococcal vaccine-induced antibodies in adults build on the B-cell repertoire developed due to natural exposure and nasopharyngeal colonization over time³¹ and may therefore be different than the antibodies induced in children.

In adults ≥ 50 years of age, the degrees of inhibition following absorption of a given serogroup 6 PS were comparable between both vaccination groups (Figure 3). For all three serotypes, antibody activity was inhibited the most following absorption with the homologous PS. However, for serotype 6C responses, inhibition by serotype 6A PS was almost as much as that caused by serotype 6C PS in both vaccination groups. Conversely, the inhibition of serotype 6B response by serotype 6C PS was closer to that seen following absorption with the heterologous PS pool than inhibition associated with 6B PS. For all three serotypes, the antibody activity was least inhibited following absorption with the heterologous PS pool (containing all V114 serotypes except serogroup 6 and serotype 19A).

The results of this post-hoc study demonstrate that V114 induces cross-reactive functional antibodies to serotype 6C that are specific and at levels comparable to those induced by PCV13 in adults and toddlers. Serotype 6C emerged as the predominant serotype associated with serogroup 6 IPD in the pre-PCV13 period following the widespread use of PCV7, while cases associated with serotypes 6A and 6B decreased.¹¹ Our results align with those from studies on the cross-reactivity of serotypes 6A- and 6B-induced antibodies in recipients of PCV13, which have demonstrated the vaccine-elicited induction of cross-reactive antibodies to serotype 6C.^{1,2} Observational data following the implementation of PCV13 into routine vaccination recommendations have shown a decrease in the incidence of disease caused by serotype 6C,^{17–19,32} providing evidence of PCV13-induced cross-protection against serotype 6C.

The specificity of these cross-functional OPA responses was demonstrated using the OPA inhibition analysis, with the greatest inhibition of antibody activity for a given serotype occurring after absorption with the homologous PS and the least inhibition occurring after absorption with the heterologous PS pool. Notably, the inhibition of serotype 6C by serotype 6A PS was almost the same as the inhibition by serotype 6C PS in both vaccination groups, while the inhibition of serotype 6B response by serotype 6C PS was less than the inhibition associated with 6A and 6B PS and closer to that seen following absorption with the heterologous PS pool. This can be explained by the fact that serotype 6A has greater structural similarity to serotype 6C than to serotype 6B, with one galactose residue in serotype 6A being exchanged for a glucose residue in serotype 6C.^{1,9}

The OPA inhibition results are consistent with real-world evidence that cross-functional antibody responses

Table 1. Demographics of (a) adult and (b) pediatric participants.

	V114 (n = 150) n (%)	PCV13 (n = 100) n (%)
(a) Adult participants		
Sex		
Male	60 (40.0)	46 (46.0)
Female	90 (60.0)	54 (54.0)
Age (years)		
50–64	77 (51.3)	51 (51.0)
65–74	58 (38.7)	38 (38.0)
≥ 75	15 (10.0)	11 (11.0)
Mean, years (range)	63.0 (50–81)	63.3 (51–85)
Race		
White	123 (82.0)	85 (85.0)
Black or African American	25 (16.7)	14 (14.0)
American Indian/Alaska Native	0	1 (1.0)
Asian	1 (0.7)	0
Multiple	1 (0.7)	0
Ethnicity		
Not Hispanic/Latino	109 (72.7)	73 (73.0)
Hispanic/Latino	40 (26.7)	27 (27.0)
Not reported	1 (0.7)	0
	V114 (n = 100) n (%)	PCV13 (n = 50) n (%)
(b) Pediatric participants		
Sex		
Male	39 (39.0)	31 (62.0)
Female	61 (61.0)	19 (38.0)
Age at enrollment (weeks)		
6	3 (3.0)	0
7	4 (4.0)	2 (4.0)
8	43 (43.0)	17 (34.0)
9	37 (37.0)	19 (38.0)
10	7 (7.0)	9 (18.0)
11	5 (5.0)	2 (4.0)
12	1 (1.0)	1 (2.0)
Mean, weeks (range)	8.6 (6.0–12.0)	8.9 (7.0–12.0)
Race		
White	85 (85.0)	42 (84.0)
Black or African American	7 (7.0)	3 (6.0)
American Indian/Alaska Native	2 (2.0)	0
Multiple	6 (6.0)	5 (10.0)
Ethnicity		
Not Hispanic/Latino	95 (95.0)	49 (98.0)
Hispanic/Latino	5 (5.0)	1 (2.0)

PCV13 = 13-valent pneumococcal conjugate vaccine; V114 = 15-valent pneumococcal conjugate vaccine.

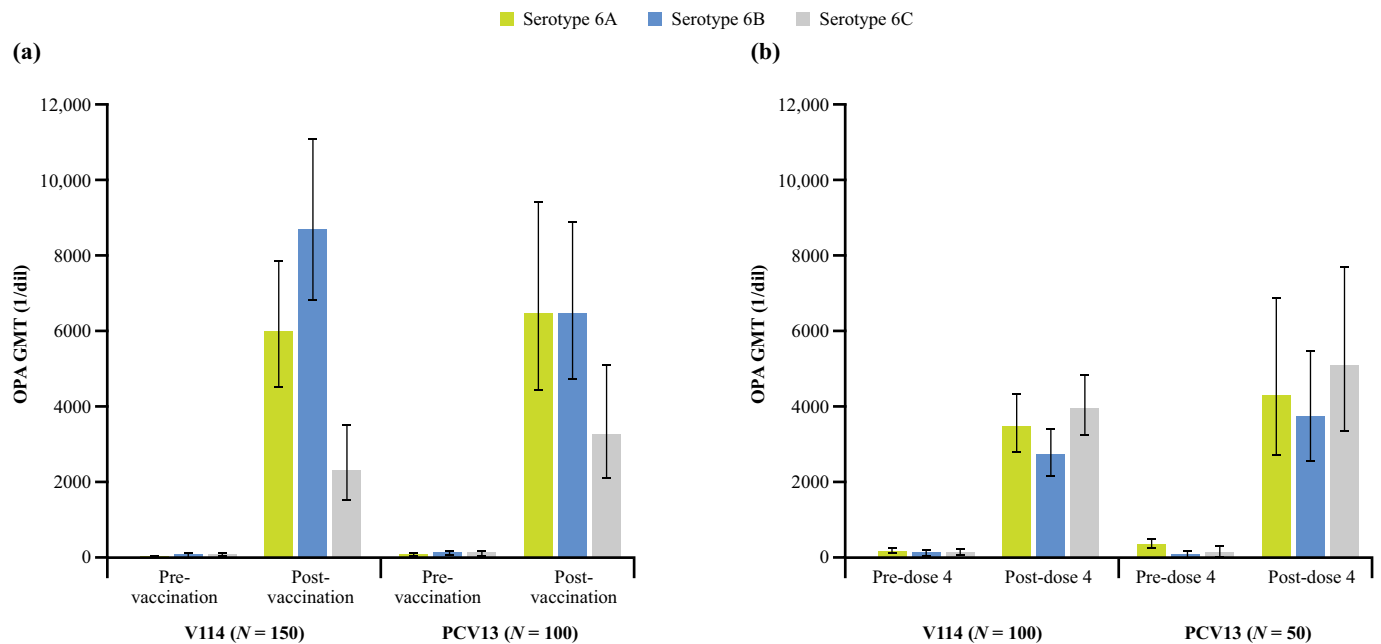


Figure 2. Opsonophagocytic antibody activity at (a) pre-vaccination and 30 days post-vaccination in adults ≥ 50 years of age and (b) at pre- and 30 days post-dose 4 in toddlers 12–15 months of age. GMT = geometric mean titer; OPA = opsonophagocytic activity; PCV13 = 13-valent pneumococcal conjugate vaccine; V114 = 15-valent pneumococcal conjugate vaccine.

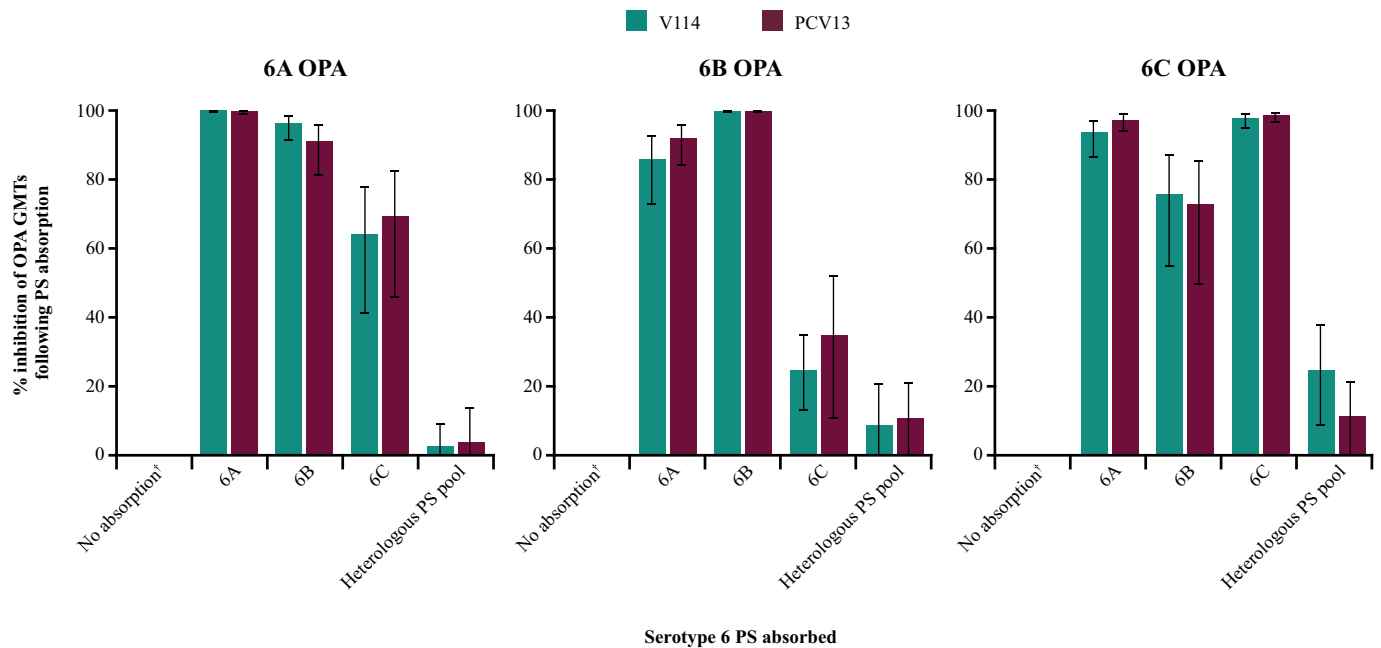


Figure 3. Inhibition of opsonophagocytic antibody activity for serotypes 6A, 6B, and 6C after absorption of serogroup 6 PS at 30 days post-vaccination in adults ≥ 50 years of age. [†]No PS absorption to provide uninhibited control. GMT = geometric mean titer; OPA = opsonophagocytic activity; PCV13 = 13-valent pneumococcal conjugate vaccine; PS = polysaccharide; V114 = 15-valent pneumococcal conjugate vaccine.

to serotype 6C seem to be primarily elicited by the serotype 6A antigen.^{17,32} In a European surveillance study comparing vaccine effectiveness of PCV13 and 10-valent PCV (PCV10) (which contains serotype 6B but not 6A) in children < 5 years of age from 2012 to 2018, PCV13 provided protection against serotype 6C, whereas PCV10 effectiveness against serotype 6C was not observed, despite the inclusion of serotype 6B in the vaccine.³² In a US surveillance study comparing IPD incidence in the

pre-PCV13 era (2007–2008) to the period following PCV13 introduction (2013–2014), a significant decrease in non-vaccine-type IPD was seen in healthy adults 19–64 years of age. As serotype 6C was one of the main non-vaccine-type serotypes causing IPD in the pre-PCV13 era, this decrease was likely attributable to cross-protection of serotype 6A against serotype 6C.¹⁷

This post-hoc study was primarily limited by its small sample size. While the cross-reactive response to serotype 6C

was quantitatively higher in toddlers than in adults, the sample size for toddlers ($n = 150$) was relatively smaller than the sample size for adults ($n = 250$). In addition, owing to limitations in blood volume in toddlers, pre-absorption tests were only performed on adult samples.

In conclusion, V114 induces cross-reactive functional antibodies to serotype 6C in adult and pediatric populations that are specific and comparable to those induced by PCV13, as demonstrated by observed OPA responses to serotypes 6A, 6B, and 6C, as well as the results of the OPA inhibition assays. Based on experience with PCV13, V114 may also have a beneficial impact on disease caused by serotype 6C; however, this will have to be evaluated in real-world studies.

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Author contributions

All authors are responsible for the work described in this paper and meet ICMJE authorship criteria. All authors were involved in at least one of the following: conception, design of work or acquisition, analysis, interpretation of data, drafting the manuscript and/or revising/reviewing the manuscript for important intellectual content. 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.

Disclosure statement

R.B. is an employee and co-founder of SunFire Biotechnologies LLC, which received funding from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA to perform this project. R.D. M. and L.M. were employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA at the time of the study and may own stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA. All other authors are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and may own stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA.

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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 through the EngageZone site or via e-mail to dataaccess@merck.com.

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