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

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Background

- Opsonophagocytic activity (OPA) antibodies against *Streptococcus pneumoniae* induced by pneumococcal vaccines have been shown to have a stronger correlation with protection in various pneumococcal vaccine studies compared with assessments of antibody levels by enzyme-linked immunosorbent assay (ELISA).[1]
- Pneumococcal serogroups consist of structurally related serotypes.[2] Serotype-specific antibodies can cross-react against other serotypes with similar capsular composition.[2,3]
- Serotype 6C has structural similarity with serotype 6A and, to a lesser extent, serotype 6B.[3,4]
- 13-valent pneumococcal conjugate vaccine (PCV13; Prevenar 13™; Pfizer Inc.), which contains serotypes 6A and 6B, induces cross-reactive OPA antibodies to serotype 6C. The use of PCV13 has been associated with an observed decrease in 6C disease incidence in some populations.[4,5]
- V114 (VAXNEUVANCE™, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA) is a 15-valent pneumococcal conjugate vaccine (PCV) containing the 13 serotypes in PCV13 plus two additional serotypes, 22F and 33F.[6,7]
- This study evaluated whether V114 elicits cross-reactive OPA antibodies to serotype 6C.

Methods

- Adults ≥50 years of age and toddlers 12–15 months of age who received V114 or PCV13 in the adult and paediatric V114 Phase 2 proof-of-concept studies (NCT02547649 and NCT02987972, respectively) were included in this analysis (**Figure 1**).
- Serotype-specific immune responses induced by V114 and PCV13 to serotypes 6A, 6B and 6C were evaluated separately via validated multiplexed opsonophagocytic killing assay (MOPA) to quantify OPA antibodies.[8]
  - OPA geometric mean titres (GMTs) against serotypes 6A, 6B and 6C were measured pre-vaccination and 30 days post-vaccination (single dose) in adults ≥50 years of age, and pre-dose 4 and 30 days post-dose 4 in toddlers 12–15 months of age.
  - OPA GMTs were calculated by exponentiating the estimates of the mean of the natural log values. The within-group confidence intervals (CIs) were obtained by exponentiating the CIs of the mean of the natural log values based on the t-distribution.
- The degree of inhibition of antibody activity in OPA assays for serotypes 6A, 6B and 6C after adsorption with purified polysaccharide (PS) of serogroup 6 was evaluated in adult serum samples (**Figure 2**).
  - Pre-selected post-vaccination adult samples (n=40 for each arm) were tested for 6A, 6B and 6C antibodies, each in the presence of no PS; 6A PS, 6B PS and 6C PS homologous pools; and a heterologous PS pool (inhibition assay).
  - Owing to limitations in blood volume, pre-adsorption tests were not performed in toddler samples.
  - The average inhibition rate was calculated by 1 − exponentiating the mean of the natural log ratio of post- and pre-adsorption MOPA titre. The within-group CIs were obtained by 1 − exponentiating the corresponding CIs based on the t-distribution.

Figure 1. Immunogenicity evaluation

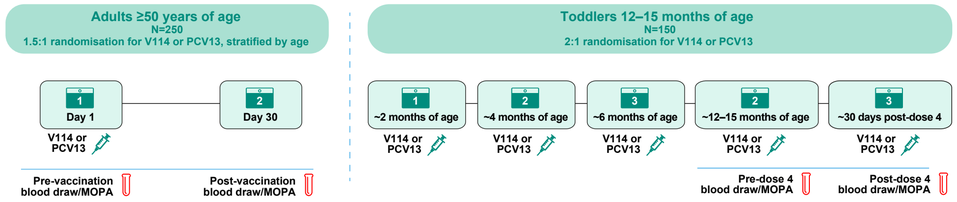
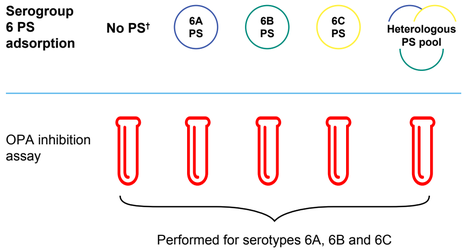


Figure 2. Serogroup 6 PS adsorption



Adult samples only.
†No PS adsorption to provide uninhibited control.

Results

Participants

- Demographic and baseline characteristics were generally comparable across the two intervention groups for both adult (**Table 1**) and paediatric participants, except for sex in the paediatric subset (**Table 2**).

Table 1. Adult participant demographics

	V114 (N=150) n (%)	PCV13 (N=100) n (%)
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 (50.0–81.0)	63.3 (51.0–85.0)
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

Table 2. Paediatric participant demographics

	V114 (N=100) n (%)	PCV13 (N=50) n (%)
Sex		
Male	39 (39.0)	31 (62.0)
Female	61 (61.0)	19 (38.0)
Age (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)	8 (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)

Immunogenicity results

- In both the adult and paediatric populations, observed OPA GMTs to serotypes 6A, 6B and 6C were comparable across both vaccination groups (post-single dose in adults and from pre-vaccination to post-dose 4 in paediatric participants; **Figures 3** and **4**).
  - The cross-reactive response to serotype 6C was stronger in toddlers than adults. However, the sample size for todders (N=150) was relatively smaller than the sample size for adults (N=250).
- The inhibition analysis demonstrated the specificity of antibody responses (**Figure 5**).
  - In adults ≥50 years of age, the degrees of inhibition following adsorption of a given serogroup 6 PS were generally comparable between both vaccination groups.
  - For all three serotypes, antibody activity was inhibited the most following adsorption with the homologous PS.
  - However, for serotype 6C, inhibition by serotype 6A PS was almost as much as by serotype 6C PS in both vaccination groups.
  - For all three serotypes, antibody activity was least inhibited following adsorption with a heterologous PS pool.

Figure 3. OPA GMTs at pre-vaccination and 30 days post-vaccination in adults ≥50 years of age

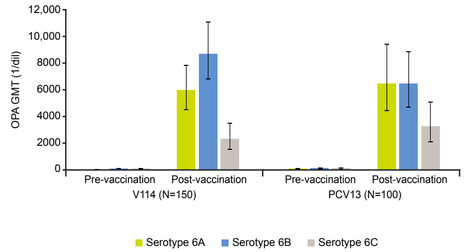


Figure 4. OPA GMTs at pre- and 30 days post-dose 4 in toddlers 12–15 months of age

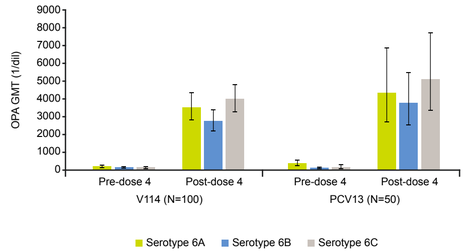
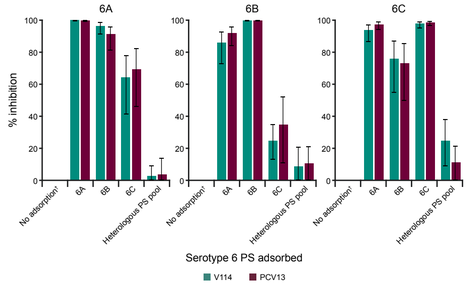


Figure 5. Inhibition of antibody activity for serotypes 6A, 6B and 6C after adsorption of serogroup 6 PS at Day 30 in adults ≥50 years of age



†No PS adsorption to provide uninhibited control.

Conclusions

- Observed OPA responses to serotypes 6A, 6B and 6C were comparable in both vaccination groups in both the adult and paediatric populations.
- Based on OPA inhibition studies, V114 induces cross-reactive antibodies to serotype 6C in adult and paediatric populations that are specific and comparable to those induced by PCV13.
- Based on the experience with PCV13, V114 may therefore 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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Disclosures

YS, KN, RM, NB, LM and UB 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. RB is minority owner of SunFire Biotechnologies.

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