Safety and Immunogenicity of a Pneumococcal Conjugate Vaccine When Administered Concomitantly With Routine Pediatric Vaccines in Healthy Toddlers and Infants*

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KEY TAKEAWAYS

- All PCV21 formulations showed acceptable safety profiles comparable with PCV13
- PCV21 and PCV13 showed generally comparable immunogenicity for shared serotypes, with numerically greater immunogenicity in the PCV21 groups than in the PCV13 group for the additional serotypes
- This study supports the evaluation of the PCV21 formulation that had the highest antigen content for selected serotypes for phase 3 assessment

BACKGROUND

Pneumococcal disease, caused by *S. pneumoniae,* remains a major global health threat among children under 5 years of age, accounting for an estimated 294,000 deaths worldwide in 2015[1,2]

Although multivalent pneumococcal conjugate vaccines (e.g., PCV13) have reduced disease from vaccine serotypes, infections due to non-vaccine serotypes have increased over time[3,4]

Emerging serotypes necessitate development of pneumococcal vaccines with expanded coverage beyond PCV13, leading to newer vaccines such as PCV15, PCV20, and investigational PCV21[5,6]

PCV21 includes 13 serotypes shared with PCV13, plus 8 additional serotypes that have become increasingly prevalent across North America and Europe[7,8]

OBJECTIVE

To assess the safety and immunogenicity of three PCV21 formulations compared with PCV13 when administered with routine pediatric vaccines in healthy toddlers and infants

STUDY CONDUCT

Study design

Phase 2 randomized, observer-blind (double-blind across PCV21 formulations), active-controlled study

Study duration and location

22 centers in the United States between May 22, 2020, and September 23, 2021

Inclusion criteria

- No prior history of *S. pneumoniae* infection or IPD
- Toddlers: With 3 prior doses of PCV13 and DTaP-IPV/Hib in infancy
- Infants: pneumococcal vaccine-naive

Study vaccines

All study vaccines contained 2.2 µg of antigen per serotype, except for certain serotypes that were formulated at an increased antigen concentration of 4.4 µg including:

- **PCV13 and PCV21 #1**: serotype 6B
- **PCV21 #2**: serotypes 3, 6B, 19A, and 19F
- **PCV21 #3**: serotypes 3, 4, 6B, 9V, 19A, and 19F

Cohort 1: Toddlers (aged 12–15 months) **140**

Cohort 2: Infants (aged 42–89 days) **712**

Randomized (1:1:1:1)

A single dose of one of the three PCV21 or PCV13 was given concomitantly DTaP5-IPV/Hib

First three doses of PCV21 or PCV13 given concomitantly with DTaP5-IPV/Hib and rotavirus vaccines at 2, 4, and 6 months; hepatitis B vaccine administered per local recommendations

Fourth dose at 12–15 months administered concomitantly with MMR and varicella vaccines

ENDPOINTS

Safety:

Safety profile of PCV21 formulations and PCV13 after each vaccination was determined by the occurrence of:

- Unsolicited systemic AEs/ARs (within 30 minutes)
- Solicited local/systemic reactions (within 7 days)
- Unsolicited AEs/ARs (up to 30 days)
- SAEs & AESIs (up to 6 months post-final dose)

Immunogenicity:

- Immune response in terms of serotype-specific **IgG GMCs** using ECL assay were assessed as primary endpoints
  Cohort 1: IgG GMCs and GMCRs at Day 30 (1-month post-dose)
  Cohort 2: IgG response rates (≥0.35 µg/mL per WHO) and GMCs at Day 150 (1-month post-dose 3) and Day 330 (1-month post-dose 4)
- Functional immune response in terms of serotype-specific **OPA GMTs** at D30 and OPA ≥LLOQ at each time point were evaluated as secondary endpoints

Statistical analysis:

- All analyses were descriptive, with no statistically powered hypothesis testing. Safety analyses were conducted in the safety analysis set
- Immunogenicity analyses were conducted in the per-protocol analysis set, for which results are reported and in the full analysis set

RESULTS

Baseline characteristics

- Comparable across groups within each cohort, with no major differences observed

Safety

- Overall, all three PCV21 formulations were well tolerated; with safety profiles comparable to PCV13
- Most adverse events were mild-to-moderate; no vaccine-related SAEs or AESIs were identified

Immunogenicity

Cohort 1 (Toddlers):

Overall IgG responses

- All three PCV21 formulations elicited IgG responses for all 21 serotypes
- Formulation with higher antigen content led to numerically higher IgG levels (for serotypes 3, 4, 9V)

Shared vs. additional serotypes

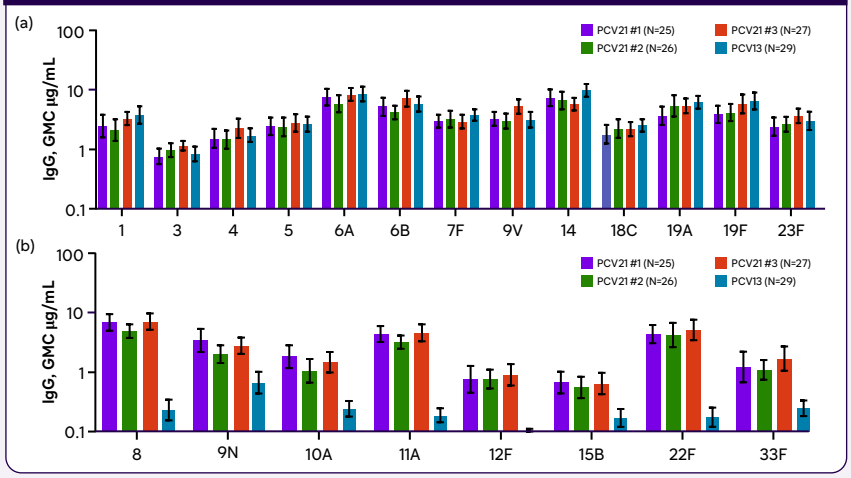
- Shared serotypes: IgG responses were comparable to PCV13
- Additional serotypes: PCV21 generated robust and higher IgG responses

Functional activity (OPA)

OPA GMTs increased for all serotypes, with:

- Comparable values to PCV13 for shared serotypes and higher values for additional serotypes

Serotype-specific IgG GMC for (a) shared serotypes with PCV13 and (b) additional serotypes not included in PCV13 for cohort 1



Cohort 2 (Infants):

After primary series (2, 4, 6 months)

- All PCV21 formulations generated immune responses across all serotypes
- Formulation with higher antigen content again resulted in numerically higher response rates and IgG levels (notably for 3, 4, 9V)

Shared vs. additional serotypes

- Shared serotypes: IgG GMCs and response rates were comparable to PCV13
- Additional serotypes: PCV21 induced higher IgG GMCs as well as response rates

After fourth dose (12–15 months)

Booster vaccination yielded responses

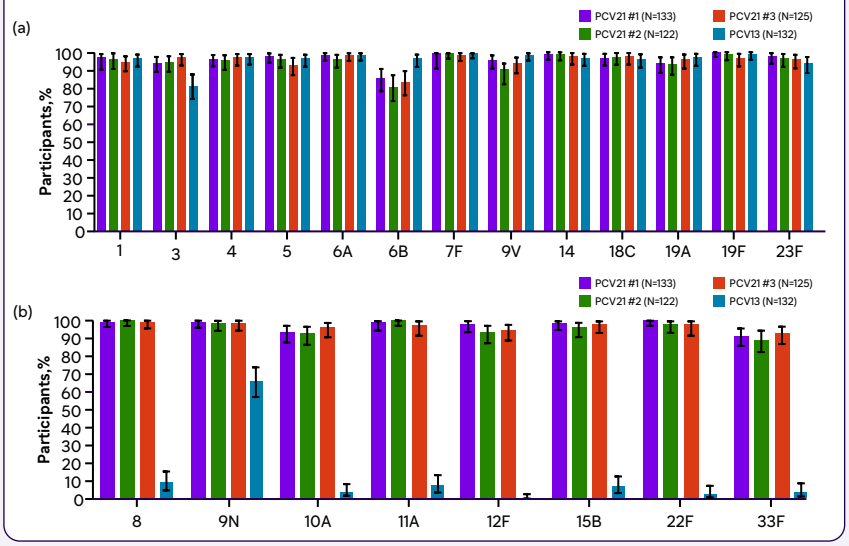
- Comparable to PCV13 for shared serotypes
- Sustained and strong for additional serotypes

Functional activity (OPA)

OPA responses followed similar trend, showing

- Comparable responses to PCV13 for shared serotypes and higher for all additional serotypes

Serotype-specific immune response rate for (a) shared serotypes with PCV13 and (b) additional serotypes not included in PCV13 for cohort 2



STRENGTHS

- Randomized study design ensuring robust methodology
- Use of an active comparator (PCV13) for meaningful comparison
- Concomitant administration of routine pediatric vaccines, reflecting real-world clinical practice

LIMITATIONS

- Descriptive study; not powered for formal hypothesis testing
- PCV13 used as the active control, as the study was initiated before the approval of PCV15 and PCV20
- Phase 3 trials required to confirm immunogenicity and safety

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†Pichon S, Monfredo C, Mari K, Personnic S, Pouzet C, Manson C, Silhadi W, and Minutello AM are employees of Sanofi. Pandey A was an employee of Sanofi at the time of the study

Abbreviations: AE, adverse event; AR, adverse reaction; AESI, adverse event of special interest; DTaP-IPV/Hib, diphtheria, tetanus, pertussis, poliovirus and haemophilus influenzae type b; ECL, electrochemical luminescence; GMC, geometric mean concentration; GMCR, geometric mean concentration ratio; GMT, geometric mean titers; IgG, immunoglobulin type G; IPD, invasive pneumococcal disease; MMR, measles-mumps-rubella; LLOQ, lower limit of quantitation; OPA, opsonophagocytic activity; PCV, pneumococcal conjugate vaccine; SAE, serious adverse events; *S. pneumoniae*, Streptococcus pneumoniae; WHO, World Health Organization

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