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Safety, tolerability, and immunogenicity of V114 pneumococcal vaccine compared with PCV13 in a 2+1 regimen in healthy infants: A phase III study (PNEU-PED-EU-2)

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ABSTRACT

Background: This phase III study evaluated safety, tolerability, and immunogenicity of V114 (15-valent pneumococcal conjugate vaccine) in healthy infants. V114 contains all 13 serotypes in PCV13 and additional serotypes 22F and 33F.

Methods: Healthy infants were randomized to two primary doses and one toddler dose (2+1 regimen) of V114 or PCV13 at 3, 5, and 12 months of age; diphtheria, tetanus, pertussis (DTaP), inactivated poliovirus (IPV), *Haemophilus influenzae* type b (Hib), hepatitis B (HepB) vaccine was administered concomitantly. Adverse events (AEs) were collected on Days 1–14 following each vaccination. Serotype-specific anti-pneumococcal immunoglobulin G (IgG) was measured 30 days post-primary series, immediately prior to toddler dose, and 30 days post-toddler dose. Primary objectives included non-inferiority of V114 to PCV13 for 13 shared serotypes and superiority of V114 to PCV13 for serotypes 22F and 33F.

Results: 1191 healthy infants were randomized to V114 (n = 595) or PCV13 (n = 596). Proportions of participants with solicited AEs and serious AEs were comparable between groups. V114 met non-inferiority criteria for 13 shared serotypes, based on difference in proportions with serotype-specific IgG $\geq$0.35 μg/mL (lower bound of two-sided 95% confidence interval [CI] >−10.0) and IgG geometric mean concentration (GMC) ratios (lower bound of two-sided 95% CI >0.5) at 30 days post-toddler dose. V114 met superiority criteria for serotypes 22F and 33F, based on response rates (lower bound of two-sided 95% CI >10.0) and IgG GMC ratios (lower bound of two-sided 95% CI >2.0) at 30 days post-toddler dose.

Antibody responses to DTaP-IPV-Hib-HepB met non-inferiority criteria, based on antigen-specific response rates.

Conclusion: A two-dose primary series plus toddler dose of V114 was well-tolerated in healthy infants. Compared with PCV13, V114 provided non-inferior immune responses to 13 shared serotypes and superior immune responses to additional serotypes 22F and 33F.

Abbreviations: AE, adverse event; APaT, all-participants-as-treated; CI, confidence interval; COVID-19, coronavirus disease 2019; CV, coefficient of variation; DTaP, diphtheria, tetanus, and pertussis; GMC, geometric mean concentration; GMT, geometric mean titer; HBsAg, HepB surface antigen; HepB, hepatitis B; Hib, *Haemophilus influenzae* type b; IgG, immunoglobulin G; IgM, immunoglobulin M; IPD, invasive pneumococcal disease; IPV, inactivated poliovirus; mMOPA, microcolony multiplexed OPA; MMR, measles, mumps, and rubella; OPA, opsonophagocytic activity; PCV, pneumococcal conjugate vaccine; PD, pneumococcal disease; SAE, serious adverse event; WHO, World Health Organization.

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1. Introduction

Pneumococcal disease (PD) is associated with high burden and mortality in children younger than 5 years of age [1]. Although the widespread use of pneumococcal conjugate vaccines (PCVs) in infant immunization programs has led to an overall decrease in incidence of invasive PD (IPD), the subsequent increase in disease caused by non-vaccine serotypes remains a concern [2,3]. Additionally, residual burden persists from certain serotypes included in the 13-valent PCV (PCV13), including serotypes 3 and 19A [2].

In Europe, PCVs are commonly administered to healthy infants as a two-dose primary series at 3 and 5 months or 2 and 4 months, followed by a toddler dose at 11–15 months of age (2+1 regimen) [4]. A three-dose primary series at 2, 4, and 6 months with a toddler dose at 12–15 months is also used in some countries (3+1 regimen) [5,6]. PCVs can be administered concomitantly with other pediatric vaccines, including those containing diphtheria, tetanus, and pertussis (DTaP), inactivated poliovirus (IPV), *Haemophilus influenzae* type b (Hib), and hepatitis B (HepB) antigens, rotavirus, measles, mumps, and rubella (MMR), hepatitis A, and varicella [7,8]. Extensive global data to support the satisfactory safety profile of PCVs are available [9].

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 plus two additional serotypes, 22F and 33F. In Europe in 2017, serotypes 22F and 33F caused 8.4% and 6.7% of IPD in children <1 and 1–4 years of age, respectively [10,11]. Both serotypes have high invasive disease potential [12], and serotype 33F is associated with multidrug resistance [13]. V114 has been approved for the prevention of IPD in children 6 weeks–17 years of age and adults ≥18 years of age in the United States and Canada [6,14]. In the EU, V114 is approved for the prevention of IPD, pneumonia and acute otitis media in children 6 weeks–17 years of age and for the prevention of IPD and pneumonia in adults ≥18 years of age [15,16]. This phase III study compared the safety and immunogenicity of a 2+1 regimen of V114 or PCV13 in healthy infants, when administered concomitantly with DTaP-IPV-Hib-HepB and other licensed pediatric vaccines.

2. Methods

2.1. Study design

This was a phase III, multicenter, randomized, double-blind, active comparator-controlled, parallel-group study to evaluate the safety, tolerability, and immunogenicity of V114 when administered to healthy infants in a 2+1 regimen (two-dose primary series at approximately 3 and 5 months of age, followed by a toddler dose at approximately 12 months of age). The study was conducted at 22 sites in four countries (Denmark, Finland, Italy, and Norway; Supplemental Table 1) from August 2019 to November 2021 (clinicaltrials.gov NCT04016714 and EU at EudraCT 2018–003788-70). The study period coincided with the coronavirus disease 2019 (COVID-19) pandemic.

This study was designed to enroll approximately 1180 participants, randomized in a 1:1 ratio to receive either V114 or PCV13 at approximately 3, 5, and 12 months of age. Participants were also administered concomitant pediatric vaccines (DTaP-IPV-Hib-HepB at 3, 5, and 12 months of age, and MMR and varicella vaccine at 12 months of age). In accordance with local requirements, participants at sites in Norway and Denmark received a second dose of varicella vaccine at approximately 13 months of age.

The study used central randomization and assignment to each vaccination group. This was implemented using an interactive response technology system. The study vaccines were prepared and/or dispensed by an unblinded pharmacist or qualified study site staff who were not involved in any subsequent study-related procedures/assessments (including safety). An unblinded clinical research associate monitored vaccine accountability at the study sites. The participants and the investigator involved in the clinical evaluation of the participants were blinded to the group assignments. DTaP-IPV-Hib-HepB, MMR, and varicella vaccines were administered open-label. The study was conducted in accordance with the principles of Good Clinical Practice and was approved by appropriate Institutional Review Boards and regulatory agencies. An external Data Monitoring Committee conducted periodic reviews of safety and tolerability data. A Scientific Advisory Committee composed of sponsor and non-sponsor scientists contributed to the development of the protocols, formulation of the statistical analysis plan, data analysis, interpretation of the data, and authoring of this manuscript.

2.2. Participants

Pneumococcal-vaccine naïve healthy infants from 70 to 111 days of age at enrollment were eligible for the study. Written informed consent was obtained from a legally acceptable representative prior to any study procedure. Key exclusion criteria included: birth prior to 37 weeks of gestation, history of IPD or other culture-positive pneumococcal disease, recent febrile illness, history of immunodeficiency or autoimmune disease, known or suspected impairment of immunological function, a positive HepB surface antigen test (HBsAg) or HIV infection (participant or participant's mother), and prior receipt of any pertussis-based combination, Hib conjugate or poliovirus vaccine, or >1 dose of HepB vaccine. Non-study medications were permitted prior to, or during, the study, with a few exceptions (recent systemic corticosteroids, or receipt of blood transfusion products [including immunoglobulin]). Immunization with any live vaccines within 30 days before, or any non-live vaccines within 14 days before, the study vaccine was not permitted, with the exception of rotavirus vaccine, which could be administered according to local guidelines.

2.3. Vaccines and administration

V114 (VAXNEUVANCE™, Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA) is a 15-valent PCV. Each 0.5 mL dose contains 2 μg of pneumococcal capsular polysaccharide from each of serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F, 22F, and 33F, and 4 μg from serotype 6B, all conjugated to CRM_{197} carrier protein and adjuvanted with 125 μg aluminum phosphate [14].

PCV13 (Prevnar 13; Wyeth LLC., marketed by Pfizer, New York, NY, USA) is a 13-valent PCV. Each 0.5 mL dose contains 2.2 μg capsular polysaccharide from each of serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, and 23F, and 4.4 μg from serotype 6B, all conjugated to CRM_{197} carrier protein and adjuvanted with 125 μg aluminum phosphate [8]. The pediatric vaccines used in this study were DTaP-IPV-Hib-HepB (VAXELIS™, manufactured by Sanofi Pasteur ltd., Toronto, Canada), and MMR (M–M–R® II) and varicella (VARIVAX®) vaccines (both manufactured by Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA) [17–19].

All vaccines were supplied as sterile suspensions. V114 (lots #0000957291 and #0001069325) and PCV13 (lots #AA4507, #AD5372, and #DP5064) were supplied in pre-filled syringes, stored at 2–8 °C, and administered intramuscularly as 0.5 mL doses. DTaP-IPV-Hib-HepB (lots #S035976 and #T002924) was administered intramuscularly, and MMR (lot #0000906501) and varicella (lot #0000912315) vaccines were administered subcutaneously, all as 0.5 mL doses.

2.4. Safety assessments

Participants' legally acceptable representatives recorded post-vaccination complaints using electronic Vaccination Report Cards, which were subsequently assessed by study investigators to determine whether they met protocol-defined adverse event (AE) criteria. Injection-site reactions (injection-site pain, injection-site swelling, injection-site induration, and injection-site erythema) and systemic AEs (irritability, drowsiness [somnolence], decreased appetite, and urticaria) occurring from Days 1–14 post-vaccination were solicited. Injection-site AEs for concomitant vaccines were not collected. Participants were also followed for non-solicited AEs from Days 1–14 post-vaccination. Pyrexia was assessed as a non-solicited AE in this study. All injection-site AEs were considered to be related to the study vaccines. For systemic AEs, relatedness to study vaccine was assessed by study investigators.

Solicited daily maximum body temperatures were collected on Days 1–7 post-vaccination (and on Days 8–14 if fever was suspected). Where appropriate, rectal temperature was the preferred measurement when obtaining a participant's temperature. Axillary (underarm) was an acceptable method, but temperature would need to be confirmed by rectal measurement if fever was detected. Temperature readings were taken at approximately the same time each day.

Serious AEs (SAEs), discontinuations due to an AE, and deaths, regardless of whether the events were considered to be related to the vaccine by study investigators, were collected from time of signed consent through to end of study (approximately 6 months following final vaccination). AEs were considered serious if they were life-threatening, required hospitalization or extended an existing hospitalization, resulted in persistent or significant disability/incapacity, were congenital anomalies/birth defects in an offspring of a participant, or resulted in death.

All solicited and non-solicited events were assessed by investigators for intensity and were recorded along with AE duration in days. For injection-site erythema, injection-site induration, and injection-site swelling, intensity was assigned according to size as follows: mild events were those measuring 0–≤1 in. (∼2.5 cm), moderate events were >1–≤3 in. (∼7.5 cm), and severe events were >3 in.

2.5. Immunogenicity assessments

Serum samples were drawn 30 days post-dose 2 (post primary series), prior to administration of the toddler dose, and 30 days post-toddler dose to assess immune responses. Serotype-specific pneumococcal capsular polysaccharide immunoglobulin G (IgG) antibodies were evaluated using a validated electrochemiluminescence assay with intermediate assay precision ranging from 16.8% to 24.1% geometric coefficient of variation (CV) across the 15 serotypes [20]. Functional anti-pneumococcal antibodies were measured using serotype-specific opsonophagocytic activity (OPA) using a validated microcolony multiplexed OPA (mMOPA), with intermediate assay precision ranging from 32.5% to 51.3% CV across the serotypes [21].

IgG antibodies to diphtheria toxoid, tetanus toxoid, and pertussis antigens (pertussis toxin, filamentous hemagglutinin, pertactin, and fimbriae types 2/3) were evaluated using the DTP-6 IgG Luminex assay. Functional antibodies to poliovirus serotypes 1, 2, and 3 were evaluated using a micrometabolic inhibition test-based virus neutralization assay. IgG antibodies to Hib polyribosylribitol phosphate were measured using an IgG enzyme-linked immunosorbent assay, and antibodies to HBsAg were measured using an enhanced chemiluminescence assay.

2.6. Study endpoints and statistical methods

2.6.1. Determination of study sample size

The planned study size of 1180 participants (590 per vaccination group) would provide >95% power for the primary hypotheses at a one-sided 2.5% alpha level to demonstrate non-inferiority of V114 to PCV13 for the 13 shared serotypes and superiority for the two additional serotypes in V114 based on serotype-specific IgG response rates and IgG geometric mean concentration (GMC) ratios. The power for the secondary non-inferiority hypotheses regarding concomitant administration of DTaP-IPV-Hib-HepB would be approximately 90%.

2.6.2. Analysis populations

Safety analyses were conducted on the all-participants-as-treated (APaT) population, comprising all randomized participants who received relevant study vaccine for timepoint of interest. The per-protocol population was the primary population used for analysis of immunogenicity data, comprising all randomized participants without protocol deviations that could substantially affect the results of immunogenicity endpoints.

2.6.3. Primary safety endpoint and statistical methods

The primary safety objective was to evaluate the safety and tolerability of V114 with respect to the proportion of participants with AEs. Safety endpoints included proportions of participants with solicited injection-site AEs and solicited systemic AEs from Days 1–14 post-vaccination, and vaccine-related SAEs through the completion of the study.

Point estimates were provided for all safety endpoints and 95% confidence intervals [CIs] were provided for between-treatment differences in the proportion of participants with solicited injection-site and solicited systemic AEs. The broad AE categories consisted of the proportion of participants with any AE, any vaccine-related AE, any SAE, any vaccine-related SAE, discontinuation due to an AE, death, and maximum body temperature measurements, using the unstratified Miettinen & Nurminen method [22]. No multiplicity adjustments were made for safety comparisons.

2.6.4. Primary immunogenicity endpoints and statistical methods

The co-primary immunogenicity objectives were to compare V114 to PCV13 for non-inferiority of immune responses for shared serotypes and superiority for the two additional serotypes in V114 at 30 days post-toddler dose (primary hypotheses). This was assessed via anti-pneumococcal polysaccharide IgG response rates, defined as the proportion of participants meeting the serotype-specific threshold of ≥0.35 μg/mL and IgG GMC ratios. The statistical criterion for non-inferiority of IgG response rates required the lower bound of the two-sided 95% CI of the difference in response rates (V114 minus PCV13) to be >−10.0, and the statistical criterion for superiority required this to be >10.0. The statistical criteria for non-inferiority and superiority of IgG GMCs required the lower bound of the two-sided 95% CI of the GMC ratio to be >0.5 and >2.0, respectively. The study was designed to test each of the hypotheses at a one-sided 0.025 significance level and predicate study success on all primary immunogenicity hypotheses having been met. Therefore, the overall one-sided type I error rate was controlled at 0.025.

IgG response rates with corresponding 95% CIs and p-values were estimated using the Miettinen & Nurminen method [22]. IgG GMCs with corresponding 95% CIs and p-values were calculated using the *t*-distribution with variance estimate from a serotype-specific linear model, utilizing the natural log-transformed antibody concentrations as response and a single term for vaccination group.

2.6.5. Secondary and tertiary immunogenicity endpoints and statistical methods

A secondary immunogenicity objective was to compare the V114 group to the PCV13 group for non-inferiority of immune responses to each antigen in DTaP-IPV-Hib-HepB at 30 days post-toddler dose based on antigen-specific threshold values (secondary hypothesis). The statistical criterion for non-inferiority required the lower bound of the two-sided 95% CI of the difference in percentages to be greater than −5.0 for tetanus toxoid and poliovirus types 1–3, and −10.0 for all other antigens, at a one-sided 0.025 significance level.

Other secondary immunogenicity objectives included evaluation of anti-pneumococcal OPA response rates, defined according to serotype-specific dilutions, geometric mean titers (GMTs) at 30 days post-toddler dose, and anti-pneumococcal polysaccharide IgG response rates and GMCs at 30 days post-dose 2. A tertiary objective was to evaluate anti-pneumococcal polysaccharide IgG GMCs immediately prior to administration of the toddler dose.

Response rates to DTaP-IPV-Hib-HepB antigens with corresponding 95% CIs and p-values were estimated using the Miettinen & Nurminen method [22]. IgG response rates and GMCs were calculated as described for the primary objective. OPA response rates and within-group 95% CIs were based on the exact binomial method proposed by Clopper and Pearson [23], and OPA GMTs were obtained by exponentiating the CIs of the mean of the natural log values based on the *t*-distribution.

2.7. Analysis software

All analyses were performed using SAS© software, version 9.4, of the SAS System for Unix. Copyright© 2012 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc (Cary, NC, USA).

3. Results

A total of 1191 healthy infants 70–111 days of age were randomized to receive V114 (n = 595) or PCV13 (n = 596). All participants received the first dose of either V114 or PCV13 and were included in the APaT population (Fig. 1). The most common reason for discontinuations was withdrawal by parent/guardian (2.4%). A subset of discontinuations (n = 6; 0.5%) was associated with the COVID-19 pandemic. In total, 572 (96.1%) participants vaccinated with V114 and 580 (97.3%) participants vaccinated with PCV13 completed the study.

Demographic and baseline characteristics were generally comparable between vaccination groups (Table 1). The mean age at baseline was 12.4 weeks (range 10–15) in the V114 group and 12.5 weeks (range 10–15) in the PCV13 group; 54.3% and 51.5% of participants, respectively, were male.

3.1. Safety

The proportions of participants with at least one AE following any dose of study vaccine were 99.3% in the V114 group and 99.7% in the PCV13 group; 99.2% in each group experienced at least one vaccine-related AE (Table 2). The most commonly reported AEs

Table 1
Participant demographics and baseline characteristics.

Characteristic	V114 (N = 595)	PCV13 (N = 596)	Total (N = 1191)
Mean age (range), weeks	12.4 (10–15)	12.5 (10–15)	12.4 (10–15)
Sex, n (%)			
Female	272 (45.7)	289 (48.5)	561 (47.1)
Male	323 (54.3)	307 (51.5)	630 (52.9)
Race, n (%)			
American Indian/Alaska Native	1 (0.2)	1 (0.2)	2 (0.2)
Asian	2 (0.3)	4 (0.7)	6 (0.5)
Multiple	13 (2.2)	12 (2.0)	25 (2.1)
White	579 (97.3)	579 (97.1)	1158 (97.2)
Ethnicity, n (%)			
Hispanic or Latino	26 (4.4)	22 (3.7)	48 (4.0)
Not Hispanic or Latino	564 (94.8)	570 (95.6)	1134 (95.2)
Not reported	3 (0.5)	3 (0.5)	6 (0.5)
Unknown	2 (0.3)	1 (0.2)	3 (0.3)

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

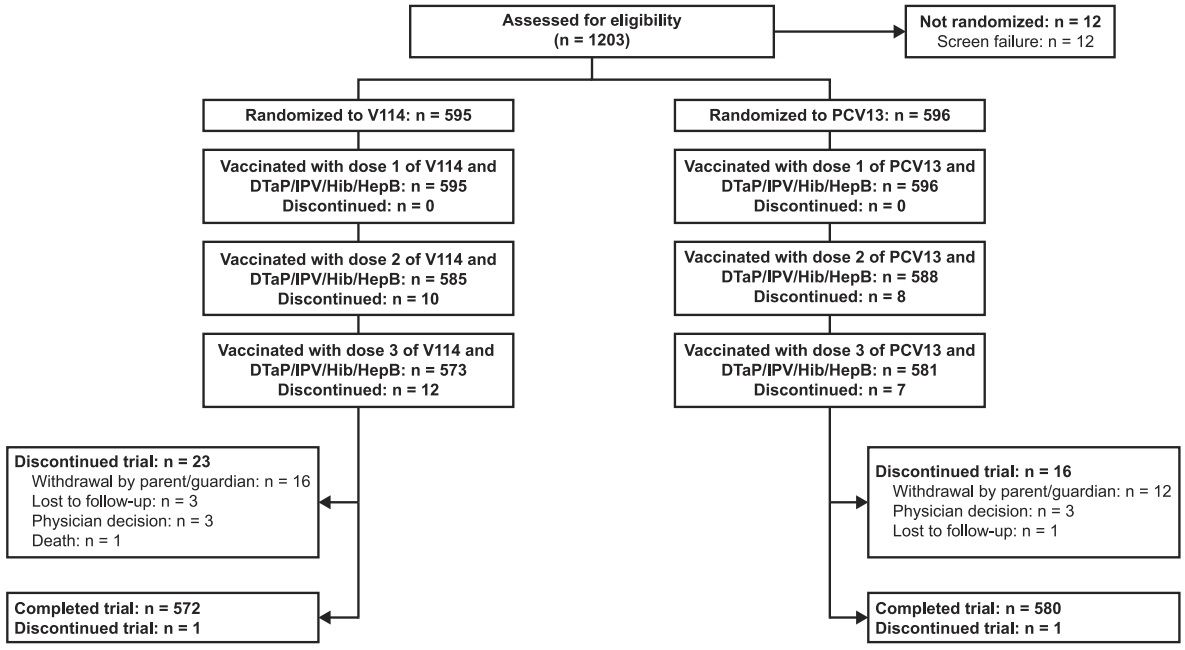


Fig. 1. Participant disposition. DTaP, diphtheria, tetanus, and pertussis; HepB, hepatitis B; Hib, *Haemophilus influenzae* type b; IPV, inactivated poliovirus; PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.

Table 2
Proportions of participants with AEs following any vaccination.

	V114 (N = 595) n (%)	PCV13 (N = 594) n (%)	Difference in percent V114−PCV13 (95% CI)
Any AE	591 (99.3)	592 (99.7)	−0.3 (−1.4, 0.6)
Injection-site	525 (88.2)	531 (89.4)	
Systemic	588 (98.8)	587 (98.8)	
Any vaccine-related AEs	590 (99.2)	589 (99.2)	0.0 (−1.2, 1.2)
Injection-site	525 (88.2)	531 (89.4)	
Systemic	581 (97.6)	579 (97.5)	
Any SAEs	30 (5.0)	28 (4.7)	0.3 (−2.2, 2.8)
Deaths	1 (0.2)	0 (0.0)	0.2 (−0.5, 0.9)
Discontinuation due to an AE	3 (0.5)	1 (0.2)	0.3 (−0.5, 1.3)
Discontinuation due to a vaccine-related AE	1 (0.2)	1 (0.2)	
Solicited injection-site AEs (Day 1 to Day 14)			
Injection-site pain	375 (63.0)	354 (59.6)	3.4 (−2.1, 8.9)
Injection-site swelling	276 (46.4)	262 (44.1)	2.3 (−3.4, 7.9)
Injection-site erythema	357 (60.0)	389 (65.5)	−5.5 (−11.0, 0.0)
Injection-site induration	339 (57.0)	351 (59.1)	−2.1 (−7.7, 3.5)
Solicited systemic AEs (Day 1 to Day 14)			
Irritability	573 (96.3)	559 (94.1)	2.2 (−0.2, 4.7)
Somnolence	460 (77.3)	463 (77.9)	−0.6 (−5.4, 4.1)
Decreased appetite	326 (54.8)	346 (58.2)	−3.5 (−9.1, 2.2)
Urticaria	100 (16.8)	127 (21.4)	−4.6 (−9.1, −0.1)

AE, adverse event; CI, confidence interval; PCV13, 13-valent pneumococcal conjugate vaccine; SAE, serious adverse event; V114, 15-valent pneumococcal conjugate vaccine.

in both groups were those solicited in the trial, and included irritability, somnolence, injection-site pain, and injection-site erythema. The majority of these solicited AEs had a maximum intensity of mild or moderate (Fig. 2) and the majority were of short duration (≤3 days), or moderate duration (>3–≤5 days) (Supplemental Table 2).

SAEs were reported for 30 (5.0%) participants in the V114 group and 28 (4.7%) participants in the PCV13 group (Table 2). Of these, two participants in each group were considered by the investigators to have had SAEs related to the study vaccine. In the V114 group, two participants experienced an SAE of pyrexia. One participant had pyrexia of mild intensity with a maximum temperature of 38.2°C (100.8°F), which started on the day of dose 2; the participant consequently discontinued the study. The other participant experienced an SAE of pyrexia of mild intensity with a temperature ranging from 37.6°C (99.7°F) to 39.9°C (103.8°F), which started on day 15 relative to dose 2. In the PCV13 group, one participant experienced an SAE of febrile convulsion of severe intensity with a maximum temperature of 40.0°C (104.0°F), which occurred on day 2 relative to dose 3. Another participant in the PCV13 group had an SAE of pyrexia of severe intensity with a maximum temperature of 39.0°C (102.2°F), which started on the day of dose 1; the participant consequently discontinued the study.

The majority of participants (74.8% in the V114 group and 74.4% in the PCV13 group) had a maximum body temperature of <39.0°C (102.2°F) in the 7 days post-vaccination (Supplemental Table 3). Two participants (0.3 %) in each group had a maximum body temperature of ≥40.5°C (104.9°F).

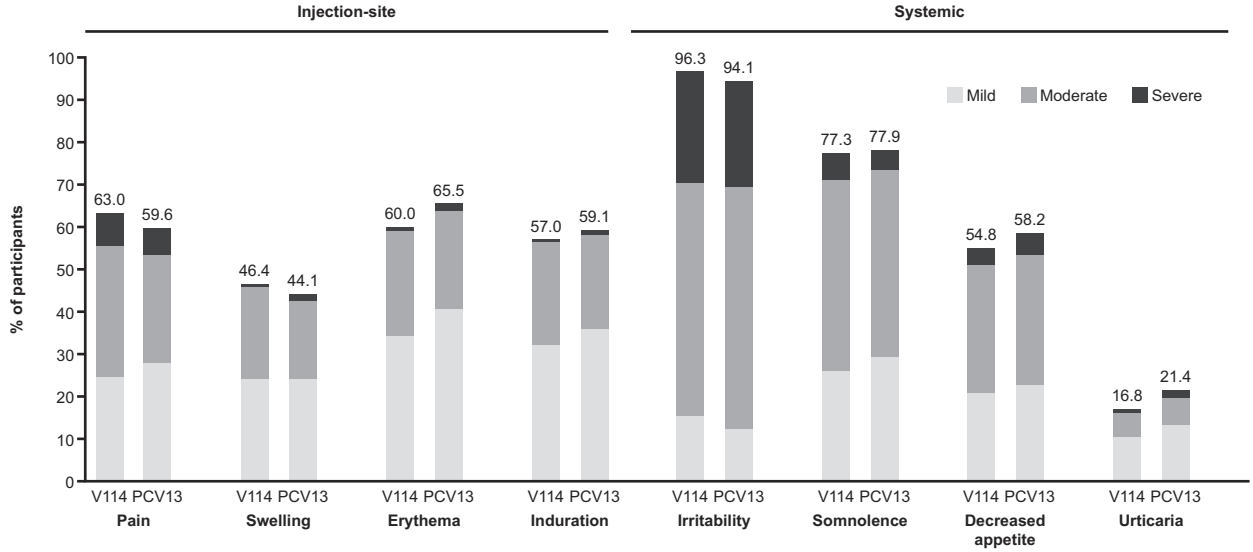


Fig. 2. Proportions of participants with solicited AEs by intensity after any vaccination. Solicited AEs collected Days 1–14 post any dose are shown with intensity grades (V114: n = 595; PCV13: n = 594). The height of the stacked bar represents the total percentage of participants reporting the AE. The intensity grades (mild, moderate, or severe) within the bar indicate the proportion of the total attributed to each respective category. AE, adverse event; PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.

The unsolicited AE of pyrexia was observed in 53.8% (320/595) and 55.7% (331/594) of participants in the V114 and PCV13 groups, respectively (data not shown).

Three participants in the V114 group and one in the PCV13 group discontinued the study due to an AE. One participant in the V114 group died during the study due to a brain neoplasm, which was not considered by the investigator to be related to the study vaccine.

3.2. Immunogenicity

V114 met non-inferiority criteria for the 13 serotypes shared with PCV13 as assessed by IgG response rates at 30 days post-toddler dose (Fig. 3). The lower bound of the two-sided 95% CI for the difference in percentage (V114−PCV13) was >−10.0 for all shared serotypes. Superiority criteria were met for the additional two serotypes in V114 (22F and 33F), as the lower bound of the two-sided 95% CI was >10.0.

Non-inferiority criteria for shared serotypes were also met when assessed by IgG GMC ratios at 30 days post-toddler dose (Fig. 4). The lower bound of the two-sided 95% CI for the GMC ratio was >0.5 for each serotype. IgG GMC superiority criteria were met for both serotypes 22F and 33F, as the lower bound of the two-sided 95% CI for the GMC ratio was >2.0. The distribution of IgG concentrations at 30 days post-toddler dose (as displayed by reverse cumulative distribution curves) was generally comparable between groups for the 13 shared serotypes but was higher for the two additional serotypes in the V114 group (Supplemental Fig. 1).

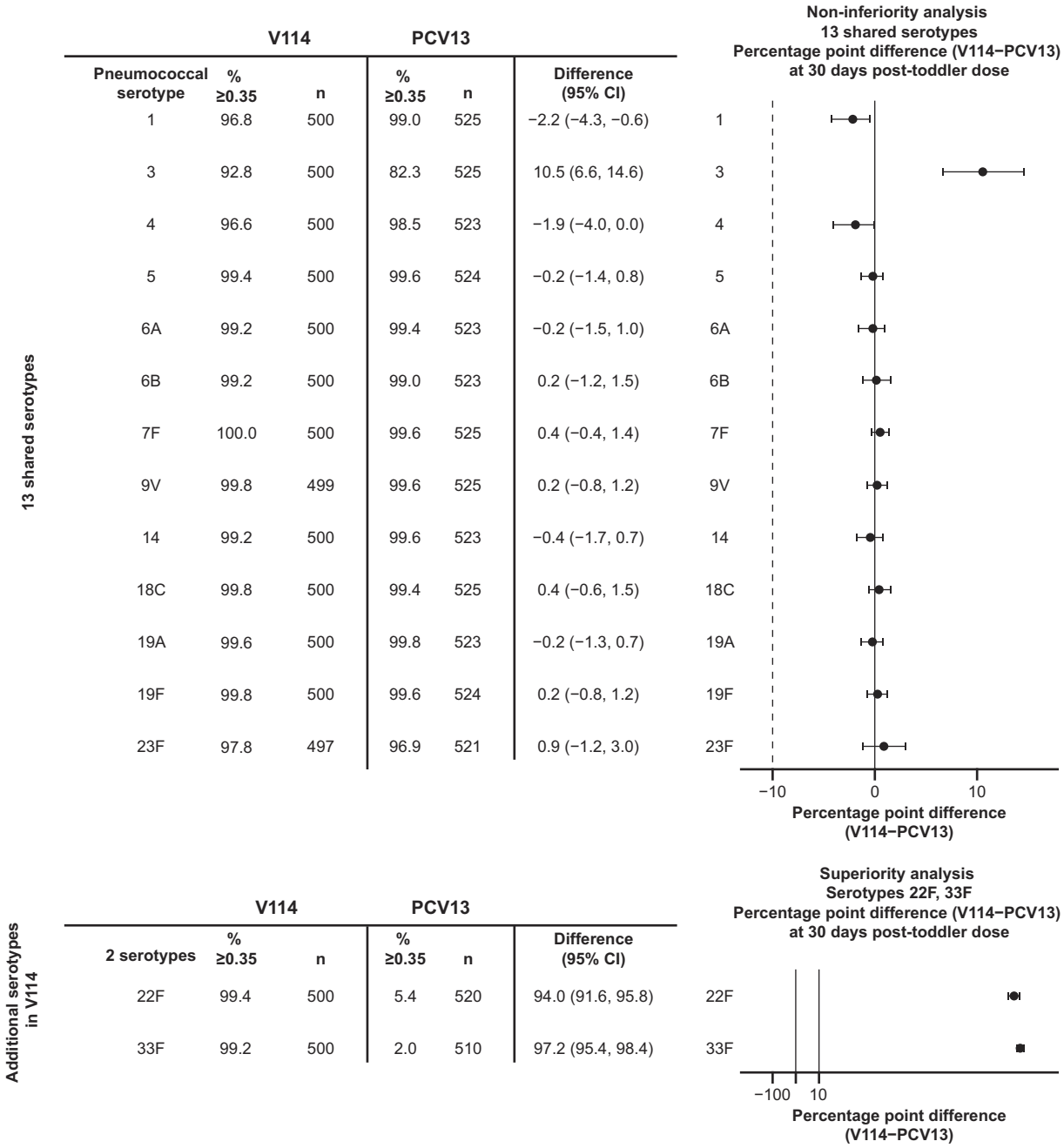
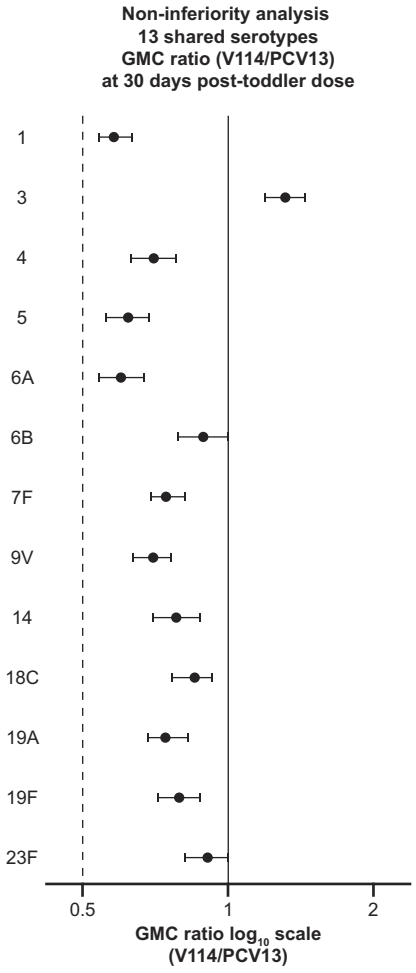


Fig. 3. Proportions of participants with IgG ≥0.35 μg/mL at 30 days post-toddler dose. Forest plot depicts the difference in proportions with IgG ≥0.35 μg/mL with the corresponding 95% CIs. N range 497–500 for V114 and 510–525 for PCV13. CI, confidence interval; IgG, immunoglobulin G; PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.

13 shared serotypes

Pneumococcal serotype	V114 GMC	V114 n	PCV13 GMC	PCV13 n	GMC ratio (95% CI)
1	1.28	500	2.20	525	0.58 (0.54, 0.63)
3	0.85	500	0.65	525	1.31 (1.20, 1.43)
4	1.41	500	2.00	523	0.70 (0.63, 0.78)
5	2.08	500	3.35	524	0.62 (0.56, 0.68)
6A	3.21	500	5.36	523	0.60 (0.54, 0.67)
6B	4.56	500	5.12	523	0.89 (0.79, 1.00)
7F	2.78	500	3.74	525	0.74 (0.69, 0.81)
9V	2.14	499	3.07	525	0.70 (0.64, 0.76)
14	5.35	500	6.83	523	0.78 (0.70, 0.87)
18C	2.10	500	2.48	525	0.85 (0.77, 0.92)
19A	4.74	500	6.38	523	0.74 (0.68, 0.82)
19F	4.08	500	5.18	524	0.79 (0.72, 0.87)
23F	1.58	497	1.77	521	0.90 (0.81, 1.00)



Additional serotypes in V114

2 serotypes	V114 GMC	V114 n	PCV13 GMC	PCV13 n	GMC ratio (95% CI)
22F	500	6.06	0.09	520	68.34 (61.73, 75.65)
33F	500	3.28	0.07	510	48.99 (44.45, 54.01)

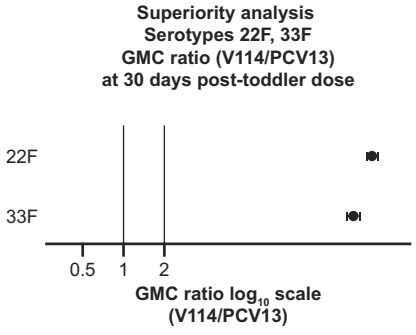


Fig. 4. IgG GMCs at 30 days post-toddler dose. Forest plot depicts the V114/PCV13 GMC ratios with the corresponding 95% CIs. N range 497–500 for V114 and 510–525 for PCV13. CI, confidence interval; GMC, geometric mean concentration (μg/mL); IgG, immunoglobulin G; PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.

Antigen-specific immune response rates were non-inferior in the V114 group compared with the PCV13 group for all antigens in the DTaP-IPV-Hib-HepB vaccine, as the lower bound of the two-sided 95% CI for the difference in percentage (V114−PCV13) was greater than the prespecified non-inferiority margins for each antigen 30 days post-toddler dose (Fig. 5).

OPA response rates and OPA GMTs at 30 days post-toddler dose were comparable between vaccination groups for the 13 shared serotypes (Supplemental Tables 4 and 5). OPA GMTs were higher in the V114 group than the PCV13 group for serotypes 22F and 33F. OPA response rates were higher in the V114 group than the PCV13 group for serotype 22F; however, OPA response rates were similar between groups for serotype 33F, as assessed by the proportion with dilution ≥1:20. Using an alternative dilution to reduce non-specific assay results (1:9291, based on the 95th percentile of OPA titers in the PCV13 group at 30 days post-toddler dose), OPA response rates to serotype 33F were higher with V114 (66.7%) than PCV13 (5.3%).

At 30 days post-dose 2, serotype-specific IgG response rates and IgG GMCs were generally comparable between groups for most shared serotypes and higher in the V114 group than the PCV13 group for the two additional serotypes in V114 (Supplemental Tables 6 and 7). Immediately prior to the toddler dose, serotype-specific IgG GMCs were generally comparable for shared serotypes and higher with V114 than PCV13 for serotypes 22F and 33F (Supplemental Table 7). For most serotypes, IgG GMCs decreased from

		V114		PCV13		
Antigen	Criterion	%	n	%	n	Difference (95% CI)
Diphtheria toxoid	% ≥0.1 IU/mL	100.0	514	99.8	543	0.2 (−0.6, 1.0)
Tetanus toxoid	% ≥0.1 IU/mL	100.0	514	99.8	543	0.2 (−0.6, 1.0)
Pertussis – PT	% ≥5 EU/mL	100.0	514	99.8	543	0.2 (−0.6, 1.0)
Pertussis – FHA	% ≥5 EU/mL	100.0	514	99.8	543	0.2 (−0.6, 1.0)
Pertussis – FIM 2/3	% ≥20 EU/mL	99.8	514	99.6	543	0.2 (−0.8, 1.2)
Pertussis – PRN	% ≥5 EU/mL	99.8	514	99.6	543	0.2 (−0.8, 1.2)
Hib – PRP	% ≥0.15 µg/mL	96.8	495	97.9	523	−1.1 (−3.3, 0.9)
HBsAg	% ≥10 mIU/mL	99.0	495	99.6	523	−0.6 (−2.0, 0.5)
Poliovirus 1	% with NAb ≥1:8 dilution	99.8	502	99.8	529	−0.0 (−0.9, 0.9)
Poliovirus 2	% with NAb ≥1:8 dilution	100.0	499	99.8	518	0.2 (−0.6, 1.1)
Poliovirus 3	% with NAb ≥1:8 dilution	100.0	503	100.0	529	0.0 (−0.8, 0.7)

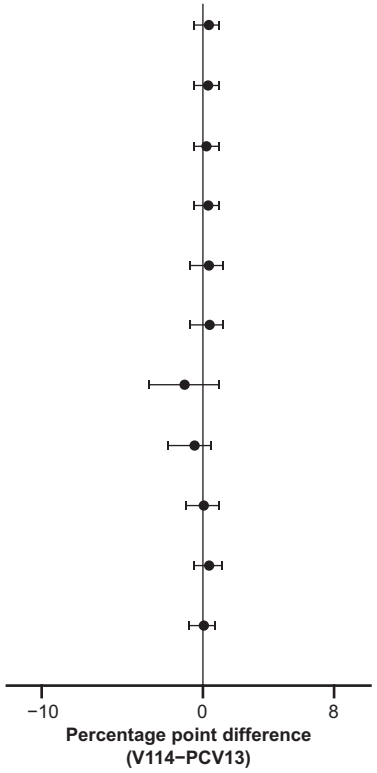


Fig. 5. Immune responses to DTaP-IPV-Hib-HepB antigens at 30 days post-toddler dose. Forest plot depicts the difference in proportions with a response with the corresponding 95% CIs. N range 495–514 for V114 and 518–543 for PCV13. CI, confidence interval; EU, endotoxin unit; FHA, filamentous hemagglutinin; FIM 2/3, fimbriae types 2 and 3; HBsAg, hepatitis B surface antigen; Hib, *Haemophilus influenzae* type b; IU, international unit; Nab, neutralizing antibodies; PCV13, 13-valent pneumococcal conjugate vaccine; PRN, pertactin; PRP, polyribosylribitol phosphate; PT, pertussis toxin; V114, 15-valent pneumococcal conjugate vaccine.

post-dose 2 to pre-toddler dose, and then increased again after the toddler dose.

4. Discussion

In healthy infants, V114 administered at approximately 3, 5, and 12 months of age, concomitantly with other pediatric vaccines, was well-tolerated and elicited robust immune responses to all 15 pneumococcal serotypes, both binding (IgG) and functional (OPA) antibodies. The safety profile of V114 was generally comparable to that of PCV13. V114 was non-inferior to PCV13 for the 13 shared serotypes and superior to PCV13 for the two additional serotypes (22F and 33F), as assessed by serotype-specific IgG response rates and GMCs at 30 days post-toddler dose. Results were consistent at 30 days post-dose 2. Kinetics of vaccine-induced immune responses showed a decline in serotype-specific immune responses between post-dose 2 and pre-toddler dose, followed by an increase at 30 days post-toddler dose for most serotypes in both vaccination groups, thus supporting the establishment of immune memory following the primary infant series in recipients of V114 and PCV13. Induction of immune memory is an important attribute of PCVs for use in infant populations, as noted in World Health Organization (WHO) recommendations for PCV quality assurance [24]. Furthermore, antibody responses to the antigens included in the DTaP-IPV-Hib-HepB vaccine were non-inferior in participants vaccinated with V114 when compared with the PCV13 group. Taken together, these findings suggest that V114 has the potential to provide broad protection against vaccine serotypes in infants, including serotypes 22F and 33F, and show that it can be administered concomitantly with DTaP-IPV-Hib-HepB vaccine without interference.

The majority of AEs reported were solicited events with a maximum intensity of mild or moderate, and a short (≤3 days) or moderate (>3 days and ≤5 days) duration. This is consistent with the safety profile of V114 observed in infants in other studies [15,25]. Furthermore, the proportion of participants with a maximum body temperature of ≥39.0°C (102.2°F) was low in the 7 days post-vaccination.

In this study, V114 was administered in a 2+1 regimen, as recommended by the WHO [26]. A 2+1 regimen is widely used across Europe, either with administration of the primary doses at 3 and 5 months of age, as in this study, or at 2 and 4 months of age [4]. Responses to V114 using the latter regimen have been assessed in the PNEU-PED-EU-1 study (V114-025) [27]. Immune responses to V114 administered as a three-dose primary series plus a toddler dose (3+1 regimen) have also been assessed in the PNEU-PED study (V114-029) [28]. The 3+1 regimen is commonly used in North America [5,6].

Induction of functional antibodies, which cause complement-mediated bactericidal killing of *Streptococcus pneumoniae*, is also an important measure of PCV quality, as protection against PD is primarily mediated by phagocytosis [29]. In this study, V114 elicited a functional antibody response to all 15 vaccine serotypes, as assessed by OPA responses and GMTs at 30 days post-toddler dose.

Although OPA response rates to serotype 33F were comparable between the V114 and PCV13 groups at 30 days post-toddler dose

using a dilution threshold of 1:20, a larger proportion of participants responded with V114 compared with PCV13 using the alternative dilution threshold of 1:9291, indicating that a higher OPA GMT threshold value may be needed for serotype 33F. This may be due to the high sensitivity of the specific bacterial strain used for serotype 33F in the mMOPA assay, as this was not observed for other serotypes tested by the mMOPA assay and was also not observed for IgG responses to serotype 33F. Alternatively, as immunoglobulin M (IgM) is known to increase during the first year of life, these findings may be due to the contribution of IgM to the mMOPA assay measurements [30,31]. Similar observations have been reported in other V114 trials for serotype 33F [32], and in studies comparing PCV7 and PCV13 for serotype 7F [33].

Vaccine-induced immune responses to individual serotypes within a PCV have previously been shown to differ, and certain serotypes may need three doses to reach the peak antibody response after the infant series [34,35]. For the descriptive evaluation of IgG GMC post infant series, the response was relatively low to serotype 33F. However, an increase in IgG GMCs was observed pre-dose 3, followed by a larger increase post-dose 3. When comparing results from previous studies, it seems that the vaccine-induced immune response observed here with serotype 33F follows similar kinetics to that observed with serotype 6B [35]. These results suggest that serotype 33F may be slower to reach its peak immune response following the infant series and instead responses increase over time. It is important to consider that immune responses to each serotype are unique to each respective serotype, which can occur as a result of two variables. The first is that the interaction with antigen-presenting cells can vary between serotypes, particularly in the setting of an immature immune system (i.e., infants). The second is that differences can appear in the antibody response to varying capsular-type polysaccharides in conjugate vaccines. Furthermore, Kaur et al. recently estimated the correlate of protection for acute otitis media for serotype 33F at ~0.25 mcg/mL [36], suggesting that the level seen here is protective.

It is important to note that this study was limited in scope with regards to safety and immunogenicity. Real-world evidence will be required to demonstrate vaccine effectiveness. In addition, the study only assessed immune responses to one non-PCV pediatric vaccine (DTaP-IPV-Hib-HepB); although other pediatric vaccines were permitted during the study, immune responses to the antigens in these vaccines were not evaluated.

5. Conclusions

In healthy infants, V114 administered as a two-dose primary series plus toddler dose was generally well-tolerated and induced immune responses for all 15 pneumococcal serotypes, supporting the use of this schedule in routine immunization programs. In addition, administration of V114 concomitantly with other pediatric vaccines, including DTaP-IPV-Hib-HepB, was well-tolerated and no immune interference was observed.

CRediT authorship contribution statement

Conception, design, or planning of the study (conceptualization): Peter Richmond, Robert Lupinacci, Luwy Musey, Kara Bickham, Richard McFetridge, Swati Mercer, Frederick Wittke, Jun Park. Acquisition of the data: Thomas Benfield, Mika Rämet, Piero Valentini, Ilkka Seppä, Peter Richmond, Luwy Musey, Jun Park. Formal analysis: Swati Mercer, Clay Churchill, Robert Lupinacci, Jun Park, Natalie Banniettis, Luwy Musey, Kara Bickham, Janusz Kaminski, Thomas Benfield. Data interpretation: Thomas Benfield, Mika Rämet, Ilkka Seppä, Ron Dagan, Peter Richmond, Swati Mercer, Clay Churchill, Robert Lupinacci, Jun Park, Frederick Wittke, Natalie Banniettis, Luwy Musey, Kara Bickham, Janusz Kaminski. Drafting of the manuscript (Writing – original draft, Writing – review & editing): Thomas Benfield, Ilkka Seppä, Peter Richmond, Clay Churchill, Natalie Banniettis, Luwy Musey, Kara Bickham, Janusz Kaminski.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: T.B. reports grants from Novo Nordisk Foundation, Lundbeck Foundation, Simonsen Foundation, GSK, Pfizer, Gilead, Kai Hansen Foundation and Erik and Susanna Olesen's Charitable Fund, and personal fees from GSK, Pfizer, Boehringer Ingelheim, Gilead, MSD, Pentabase ApS, Becton Dickinson, Janssen and AstraZeneca, outside the submitted work.

M.R. and I.S. are employed by the Vaccine Research Center of Tampere University, which conducts clinical vaccine studies for many major vaccine pharmaceutical companies, companies, including Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

R.D. has received grants from Pfizer, MSD, and MedImmune/AstraZeneca. He serves as 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 GSK.

P.R. has participated in scientific advisory boards for Merck & Co., Inc., Pfizer and GSK and has received institutional funding for investigator-initiated research from GSK Biologicals and Merck & Co., Inc.

S.M., C.C., R.L., J.P., and N.B. 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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R.M., L.M. and K.B. were employees of Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA at the time of this study.

J.K. is an employee of MSD, United Kingdom and may hold stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA.

P.V. reports no potential conflicts of interest.

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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 https://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.02.041.

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