

A phase 3 study of safety and immunogenicity of V114, a 15-valent pneumococcal conjugate vaccine, followed by 23-valent pneumococcal polysaccharide vaccine, in children with HIV

Marissa Wilck^a, Shaun Barnabas^b, Kulkanya Chokephaibulkit^c,
Avy Violari^d, Pope Kosalaraksa^e, Svitlana Yesypenko^f,
Iryna Chukhalova^g, Ron Dagan^h, Peter Richmondⁱ,
Elena Mikviman^a, Leslie Morgan^a, Kristen Feemster^a,
Robert Lupinacci^a, Joseph Chiarappa^a, Shabir A. Madhi^j,
Kara Bickham^a, Luwy Musey^a, on behalf
of the V114-030 Study Group

See related paper on page 1325

Objectives: To evaluate the safety and immunogenicity of V114 [15-valent pneumococcal conjugate vaccine (PCV) containing serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F], followed by 23-valent pneumococcal polysaccharide vaccine (PPSV23) 8 weeks later, in children with HIV.

Design: This phase 3 study (NCT03921424) randomized participants 6–17 years of age with HIV (CD4⁺ T-cell count ≥ 200 cells/ μ l, plasma HIV RNA $< 50\,000$ copies/ml) to receive V114 or 13-valent PCV (PCV13) in a double-blind manner on Day 1, followed by PPSV23 at Week 8.

Methods: Adverse events (AEs), pneumococcal serotype-specific immunoglobulin G (IgG), and opsonophagocytic activity (OPA) were evaluated 30 days after each vaccination.

Results: The proportion of participants experiencing at least one AE post-PCV was 78.8% in the V114 group ($n = 203$) and 69.6% in the PCV13 group ($n = 204$); respective proportions post-PPSV23 were 75.4% ($n = 203$) and 77.2% ($n = 202$). There were no vaccine-related serious AEs. IgG geometric mean concentrations (GMCs) and OPA geometric mean titers (GMTs) were generally comparable between V114 and PCV13 for shared serotypes at Day 30, and were higher for V114 compared with PCV13 for the additional V114 serotypes 22F and 33F. Approximately 30 days after PPSV23, IgG GMCs and OPA GMTs were generally comparable between the V114 and PCV13 groups for all 15 serotypes in V114.

^aMerck & Co., Inc., Rahway, New Jersey, USA, ^bDepartment of Paediatrics, University of Stellenbosch, Cape Town, South Africa, ^cDepartment of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, ^dPerinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, ^eFaculty of Medicine, Khon Kaen University, Khon Kaen, Thailand, ^fOdesa Regional Center for Socially Significant Diseases, Odeska Oblast, ^gDnipropetrovsk Regional Medical Center Of Socially Significant Diseases, Dnipro, Ukraine, ^hThe Shraga Segal Department of Microbiology, Immunology and Genetics Faculty of Health Sciences of the Ben-Gurion University of the Negev Beer-Sheva, Israel, ⁱUniversity of Western Australia, Perth, Australia, and ^jSouth African Medical Research Council Vaccines and Infectious Diseases Analytics Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa.

Correspondence to: Marissa Wilck, Merck & Co., Inc., 351 N Summeytown Pike, PO Box 1000, North Wales, PA 19454, USA.

E-mail: marissa.wilck@merck.com

Received: 19 October 2022; revised: 2 February 2023; accepted: 8 February 2023.

DOI:10.1097/QAD.0000000000003551

ISSN 0269-9370 Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Conclusions: In children with HIV, a sequential administration of V114 followed 8 weeks later with PPSV23 is well tolerated and induces immune responses for all 15 pneumococcal serotypes included in V114.

Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc.

AIDS 2023, **37**:1227–1237

Keywords: children, clinical trial, HIV, pneumococcal infections, pneumococcal vaccines

Introduction

Children with HIV (CWH) are at high risk of invasive pneumococcal disease (IPD), with an incidence >40-fold higher than children without HIV [1–3]. Treatment with antiretroviral therapy (ART) is associated with reduced risk; however, the incidence remains several-fold higher than in children without HIV [2]. Although widespread use of pneumococcal conjugate vaccines (PCVs) in infants has reduced the overall burden of IPD caused by vaccine serotypes, incidence due to non-vaccine serotypes has increased, and a residual burden remains from certain vaccine serotypes, including serotype 3 [4–6]. Therefore, CWH remain at increased risk of morbidity and mortality due to IPD compared with children without HIV in the PCV era [7,8].

In CWH 6–18 years of age in the United States, guidelines recommend one dose of 13-valent PCV (PCV13), followed by one dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23) ≥8 weeks later, with re-immunization with PPSV23 approximately 5 years after the first PPSV23 dose [9]. A sequential strategy with PCV13 followed by PPSV23 is also recommended in other countries [10–13]. The initial conjugated vaccine stimulates a T-cell-dependent immune response [14] and establishment of immune memory [15], and the PPSV23 vaccine allows for broader serotype coverage.

V114 (VAXNEUVANCE, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, New Jersey, USA) is a 15-valent PCV containing serotypes 22F and 33F in addition to the 13 serotypes in PCV13 [16]. Since the introduction of PCVs, serotypes 22F and 33F have emerged as globally important pneumococcal serotypes that contribute to the residual IPD burden in children. Both serotypes have high invasive disease potential [17], and serotype 33F is associated with multidrug resistance [18]. In children under 5 years of age, serotypes 22F and 33F cause 3% and 4%, respectively, of IPD cases globally and 8–13% and 9–10% of IPD cases, respectively, in the United States [5,17,19,20].

V114 is approved for the prevention of IPD in adults at least 18 years of age and children in the United States,

Canada, and Europe [21–23], and was previously studied in adults with HIV [24]. We report results from a phase 3 study evaluating the safety, tolerability, and immunogenicity of V114, followed by PPSV23 8 weeks later, in CWH.

Methods

Study design

This was a phase 3, multicenter, randomized, double-blind, active comparator-controlled, descriptive study to evaluate the safety, tolerability, and immunogenicity of V114, followed by PPSV23 approximately 8 weeks later, in CWH 6–17 years of age (Protocol V114-030; NCT03921424; EudraCT 2019-000341-12). The study was conducted from November 2019 to May 2021 in South Africa, Thailand, and Ukraine (Table 1, Supplemental Digital Content, <http://links.lww.com/QAD/C841>).

Participants were randomized in a 1:1 ratio to receive a single dose of either V114 or PCV13 on Day 1, followed by a single dose of PPSV23 at Week 8. Randomization was stratified by CD4⁺ T-cell count (≥200 to <500, and ≥500 cells/μl).

The study used central randomization implemented using an interactive response technology system. Vaccines were prepared and/or dispensed by unblinded study personnel who were not involved in any subsequent participant safety or immunogenicity assessments. V114 and PCV13 were administered in a blinded fashion and PPSV23 was administered open-label. The study was conducted in accordance with the principles of Good Clinical Practice and was approved by Institutional Review Boards or Ethics Committees of participating sites. An external Data Monitoring Committee (eDMC) 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 protocol, formulation of the statistical analysis plan, data analysis, interpretation of the data, and authoring of this manuscript.

Participants

CWH 6–17 years of age, with CD4⁺ T-cell count ≥ 200 cells/ μ l and plasma HIV RNA $< 50\,000$ copies/ml at screening, were eligible. Participants could be PCV-naive, previously vaccinated with PCV of valency < 13 , partially vaccinated with PCV13, or fully vaccinated with PCV13 at least 3 years prior to enrollment. Participants could be PPSV23-naive or have received one previous PPSV23 vaccination at least 5 years prior to enrollment. Written informed consent was obtained from all parents or legal guardians, and applicable assent from participants, prior to any study procedure.

Key exclusion criteria included: Stage 4 disease, according to World Health Organization (WHO) HIV classification, within the past 12 months, history of active hepatitis with pretreatment aspartate transaminase or alanine transaminase levels elevated to more than 5 times the upper limit of normal within the past 6 months, history of IPD or other culture-positive pneumococcal disease within the previous 3 years, febrile illness within the past 72 h, and receipt of immunosuppressive therapy. Non-study medications and therapies other than blood transfusion, blood products or systemic corticosteroids were permitted. Immunization with any live vaccine within 30 days before/after study vaccine, or any non-live vaccine within 14 days before or 30 days after study vaccine, was not permitted. Inactivated influenza vaccination was allowed if given at least 7 days before or 15 days after study vaccine.

Vaccines and administration

V114 is a 15-valent PCV containing capsular polysaccharide from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 22F, and 33F, all conjugated to CRM₁₉₇ carrier protein and adjuvanted with 125 μ g aluminum phosphate. PCV13 (Prenar 13; Wyeth LLC, marketed by Pfizer, New York, New York, USA) is a 13-valent PCV containing capsular polysaccharide from serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F, all conjugated to CRM₁₉₇ carrier protein and adjuvanted with 125 μ g aluminum phosphate. PPSV23 (PNEU-MOVAX23; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, New Jersey, USA) is an unadjuvanted 23-valent pneumococcal polysaccharide vaccine. Each dose contains 25 μ g of pneumococcal capsular polysaccharide from serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F.

V114 and PCV13 were supplied as sterile suspensions and PPSV23 was supplied as a sterile solution. All vaccines were supplied in prefilled syringes and stored at 2–8°C. They were all administered intramuscularly as 0.5 ml doses.

Safety assessments

Participants or their 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. Participants were prompted to record specific injection-site complaints (injection-site tenderness/pain, injection-site swelling, injection-site hard lump/induration, and injection-site redness/erythema), and specific systemic complaints (muscle pain/myalgia, joint pain/arthritis, headache, tiredness/fatigue, and hives or welts/urticaria), occurring from Days 1–14 after vaccination. All injection-site AEs were considered related to study vaccines. For systemic AEs, relatedness to study vaccine was assessed by the investigator.

Body temperature was measured on Days 1–7 post-vaccination (and on Days 8–14 if fever was suspected). Participants were also followed for non-solicited AEs from Days 1–14 post-vaccination. Serious AEs (SAEs), regardless of whether they were considered related to the vaccine by investigators, were collected from time of signed consent through to end of study (approximately 6 months after first vaccination).

All solicited and non-solicited AEs were assessed by investigators for intensity. For injection-site erythema, injection-site induration, and injection-site swelling, intensity was assigned according to size: mild events were those measuring > 0 to ≤ 1 in. (~ 2.5 cm), moderate events were > 1 to ≤ 3 in. (~ 7.5 cm), and severe events were > 3 in.

Immunogenicity assessments

Serum samples were drawn pre-vaccination with PCV on Day 1, at 30 days post-vaccination with PCV (Day 30), and at 30 days post-vaccination with PPSV23 (Week 12). Functional antibodies were measured by serotype-specific opsonophagocytic activity (OPA) using a validated microcolony multiplexed opsonophagocytic assay [25]. Serotype-specific pneumococcal capsular polysaccharide immunoglobulin G (IgG) antibodies were evaluated using a validated electrochemiluminescence assay [26].

Study endpoints and statistical methods

Determination of study sample size

The study aimed to randomize 400 participants overall (200 per vaccination group). It was assumed that at least 160 participants (based on an 80% evaluability rate) per vaccination group would be sufficient to provide a meaningful and descriptive assessment of the safety and immunogenicity profiles of V114 in this important population.

Analysis populations

Safety analyses were conducted on the All-Participants-as-Treated (APaT) population, comprising all randomized participants who received the study vaccine required for analysis. The per-protocol population was the primary

population for analysis of immunogenicity data, comprising all randomized participants without protocol deviations that could have substantially affected immunogenicity endpoints.

Safety endpoints and statistical methods

Safety endpoints were summarized via descriptive statistics, and no formal statistical comparisons were planned between vaccination groups. The primary safety objective was to evaluate the safety and tolerability of V114 with respect to the proportion of participants with AEs. The secondary safety objective was to evaluate the safety and tolerability of PPSV23 administered 8 weeks after V114 with respect to the proportion of participants with AEs. Safety endpoints included proportions of participants with solicited injection-site and systemic AEs from Days 1–14 following each vaccination, and vaccine-related SAEs through to study completion.

Point estimates and within-group 95% confidence intervals (CIs) were provided for each vaccination group for the proportion of participants with solicited injection-site and solicited systemic AEs, and broad AE categories consisting of the proportion with any AE, any vaccine-related AE, any SAE, any vaccine-related SAE, discontinuation due to an AE, and death, using the exact binomial method proposed by Clopper and Pearson [27], without multiplicity adjustments. Subgroup analyses of post-PCV safety endpoints by age (6–9 years, 10–14 years, and 15–17 years of age), sex (male and female), race (American Indian or Alaska Native, Asian, Black or African American, Multiple, Native Hawaiian or other Pacific Islander, and White), ethnicity (Hispanic or Latino and not Hispanic or Latino), CD4⁺ T-cell count at screening (≥ 200 to < 500 cells/ μ l and ≥ 500 cells/ μ l), prior PCV status (prior PCV and PCV-naïve), and prior PPSV23 status (prior PPSV23 and PPSV23-naïve), were performed for those subgroups with sample size $\geq 5\%$ of the number of randomized participants in each vaccination group.

Immunogenicity endpoints and statistical methods

Immunogenicity endpoints were summarized via descriptive statistics and no formal statistical comparisons were planned between vaccination groups. The primary immunogenicity objective was to evaluate serotype-specific IgG geometric mean concentrations (GMCs) for all 15 serotypes included in V114 at 30 days post-vaccination with V114 or PCV13 (Day 30) by vaccination group. Secondary immunogenicity endpoints were to evaluate serotype-specific OPA geometric mean titers (GMTs) at 30 days post-vaccination with V114 or PCV13 and serotype-specific IgG GMCs and OPA GMTs at 30 days post-PPSV23 (Week 12) by vaccination group. Exploratory objectives included evaluation of serotype-specific geometric mean fold rises (GMFRs) from Day 1 to Day 30 (pre-vaccination and post-vaccination with PCV) for both OPA and IgG responses

by vaccination group. A post hoc analysis was performed to summarize the proportion of participants with an at least four-fold rise in serotype-specific IgG concentrations and OPA titers from Day 1 to Day 30 by vaccination group.

Point estimates of serotype-specific IgG GMCs and OPA GMTs at Day 30 and Week 12 (and corresponding 95% CIs) were provided for each vaccination group. Point estimates were calculated by exponentiating the estimates of the mean of the natural log values. Within-group CIs were derived by exponentiating the CIs of the mean of the natural log values based on the *t*-distribution. Point estimates of serotype-specific GMFRs and associated 95% CIs were calculated based on the *t*-distribution of natural log-transformed fold rise. Evaluation of the proportions of participants with an at least four-fold rise in serotype-specific IgG concentrations and OPA titers included point estimates and within-group 95% CIs (based on the exact binomial method proposed by Clopper and Pearson [27]) for each vaccination group. Subgroup analyses (point estimates and within-group 95% CIs) of serotype-specific IgG GMCs at Day 30 used the same subgroup categories and sample size rule described above for safety subgroup analyses. All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, North Carolina, USA), of the SAS System for Unix.

Results

Study population

Of 407 randomized participants, all received either V114 ($n = 203$) or PCV13 ($n = 204$) and were included in the APaT population following PCV vaccination (Fig. 1). All participants vaccinated with V114 were subsequently vaccinated with PPSV23 and all completed the study. In the PCV13 group, three participants discontinued early (two withdrawn by their parent or guardian prior to PPSV23 administration, and one lost to follow-up after PPSV23 vaccination).

Demographic and baseline characteristics were generally comparable between vaccination groups (Table 1). Median age was 13 years (range 6–17 years). The majority of participants (91.6%) had a CD4⁺ T-cell count of ≥ 500 cells/ μ l at screening, were PCV-naïve (92.6%), and were PPSV23-naïve (99.8%). The majority of participants (99.0%) were receiving antivirals at baseline, the most common medications being combination lopinavir and ritonavir (48.2%), efavirenz (19.9%), lamivudine (19.2%), combination zidovudine and lamivudine (18.2%), combination abacavir sulfate and lamivudine (17.7%), and zidovudine (11.1%). The majority (77%) of participants had HIV viral loads that were below the assay limit (< 20 copies/ml) or undetectable at study entry.

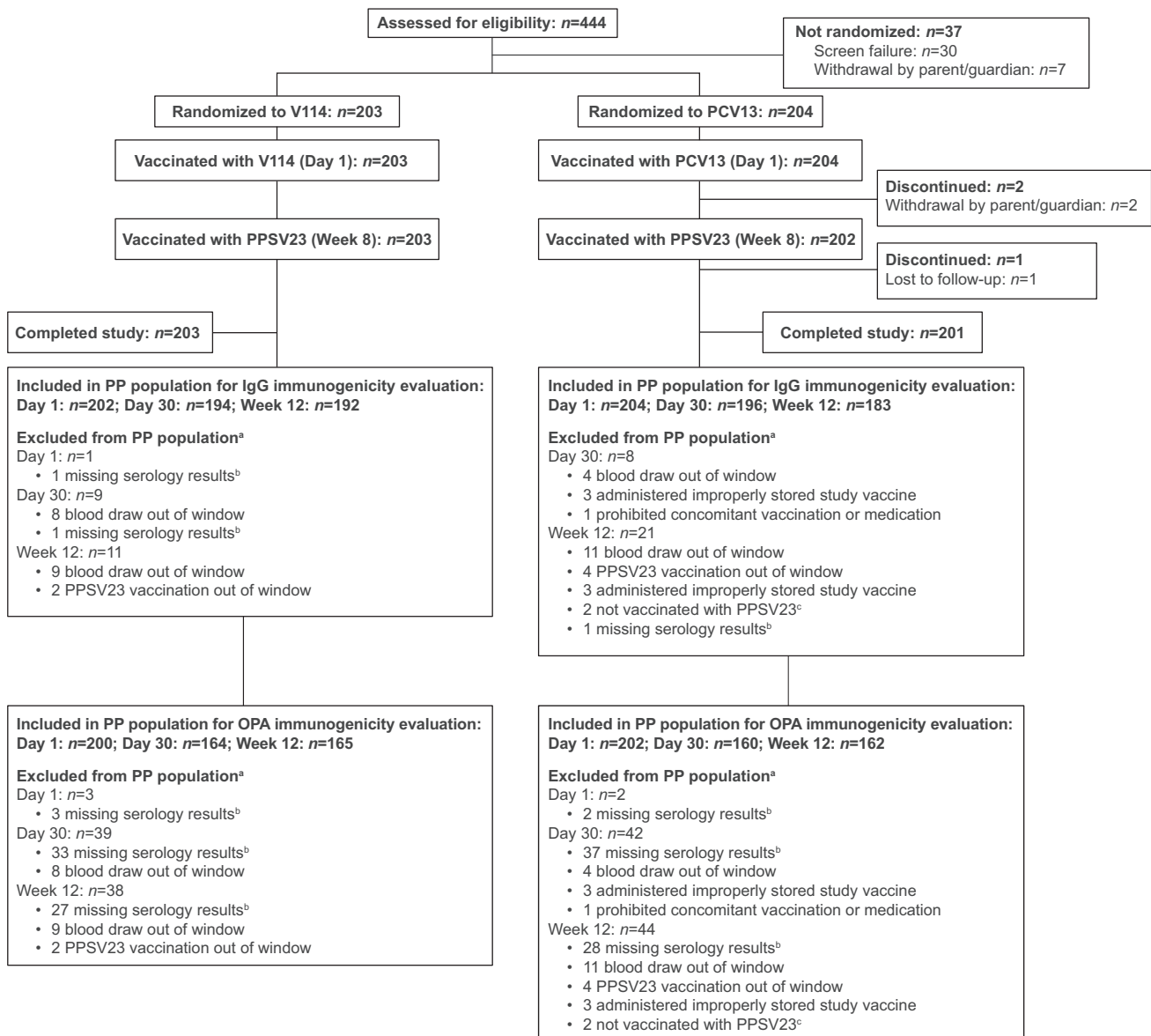


Fig. 1. Participant disposition. ^aParticipants may have more than one reason for exclusion. ^bMissing IgG serology results or missing/failed OPA results for all 15 serotypes, which may be due to discontinuation prior to serum sample collection, failure to provide a serum sample, or serum sample lost or damaged. ^cIncludes participants who discontinued the study prior to receiving PPSV23. These participants are not included under other reasons for exclusion at Week 12. IgG, immunoglobulin G; PCV13, 13-valent pneumococcal conjugate vaccine; PP, per-protocol; PPSV23, 23-valent pneumococcal polysaccharide vaccine; V114, 15-valent pneumococcal conjugate vaccine.

Safety following vaccination with V114 or 13-valent pneumococcal conjugate vaccine

Following PCV vaccination, 78.8% of participants in the V114 group and 69.6% in the PCV13 group experienced at least one AE, and 78.3% and 67.2%, respectively, experienced at least one vaccine-related AE (Table 2, Supplemental Digital Content, <http://links.lww.com/QAD/C841>).

In both groups, the most commonly reported AEs were those solicited in the trial, including injection-site pain, injection-site swelling, and myalgia. The proportions of

participants with solicited injection-site and systemic AEs were generally comparable between groups following vaccination with V114 or PCV13. The majority of solicited injection-site and systemic AEs reported after PCV vaccination had a maximum intensity of mild (Fig. 2) and a maximum duration of ≤ 3 days (Table 3, Supplemental Digital Content, <http://links.lww.com/QAD/C841>).

One participant in each group experienced an SAE (abnormal uterine bleeding in a recipient of V114 and retinal detachment in a recipient of PCV13), but neither

Table 1. Participant demographics and baseline characteristics.

Characteristic	V114 (n = 203)	PCV13 (n = 204)	Total (n = 407)
Age, years			
Median (range)	13 (6–17)	13 (6–17)	13 (6–17)
Mean (SD)	12.7 (2.7)	12.6 (3.0)	12.7 (2.9)
6–9, n (%)	32 (15.8)	35 (17.2)	67 (16.5)
10–14, n (%)	116 (57.1)	113 (55.4)	229 (56.3)
15–17, n (%)	55 (27.1)	56 (27.5)	111 (27.3)
Sex, n (%)			
Female	96 (47.3)	99 (48.5)	195 (47.9)
Male	107 (52.7)	105 (51.5)	212 (52.1)
Race, n (%)			
Asian	62 (30.5)	66 (32.4)	128 (31.4)
Black or African American	88 (43.3)	78 (38.2)	166 (40.8)
Multiple	12 (5.9)	9 (4.4)	21 (5.2)
White	40 (19.7)	49 (24.0)	89 (21.9)
Missing	1 (0.5)	2 (1.0)	3 (0.7)
CD4 ⁺ T-cell count at screening, n (%)			
≥200 to <500 cells/μl	17 (8.4)	17 (8.3)	34 (8.4)
≥500 cells/μl	186 (91.6)	187 (91.7)	373 (91.6)
PCV-naïve			
Yes	188 (92.6)	189 (92.6)	377 (92.6)
No	15 (7.4)	15 (7.4)	30 (7.4)
PPSV23-naïve			
Yes	202 (99.5)	204 (100.0)	406 (99.8)
No	1 (0.5)	0 (0.0)	1 (0.2)

CD4, cluster of differentiation 4; PCV, pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; SD, standard deviation; V114, 15-valent pneumococcal conjugate vaccine.

event was considered by the investigator to be related to study vaccines. The majority (>94%) of participants in both groups had a maximum body temperature of <38.0°C (100.4 °F) (data not shown). One participant discontinued study intervention (did not receive PPSV23) due to vaccine-related AEs of injection-site erythema, injection-site induration, and injection-site swelling following PCV13 administration.

Safety results after PCV vaccination within the different subgroups were generally comparable with those in the overall study population (data not shown).

Safety following vaccination with 23-valent pneumococcal polysaccharide vaccine

Following vaccination with PPSV23, proportions of participants who experienced at least one AE were comparable between groups (75.4% in the V114 group and 77.2% in the PCV13 group; Table 4, Supplemental Digital Content, <http://links.lww.com/QAD/C841>). The most commonly reported AEs after PPSV23 vaccination in both groups were injection-site pain, injection-site swelling, and myalgia. The proportions of participants with solicited injection-site and systemic AEs were generally comparable between groups following vaccination with PPSV23, with the exception of injection-site swelling, which was reported by a larger proportion of participants in the V114 group (47.3%) than the PCV13 group (34.7%). The majority of solicited injection-site and systemic AEs after PPSV23 vaccination had a maximum intensity of mild or moderate (Fig. 2) and a maximum duration of at most 3 days (data not shown).

Two participants in each group experienced SAEs after PPSV23 vaccination (gastrointestinal inflammation and Hodgkin's disease in the V114 group and infectious diarrhea and suicidal ideation in the PCV13 group), none of which were considered by the investigator to be related to study vaccination. There were no deaths during the study.

Immunogenicity

V114 was immunogenic for all 15 serotypes contained in the vaccine, as assessed by IgG GMCs and OPA GMTs at 30 days post-vaccination (Fig. 3). Serotype-specific IgG GMCs and OPA GMTs were generally comparable between the V114 and PCV13 groups for the 13 shared serotypes, and higher with V114 for serotypes 22F and 33F.

At 30 days post-vaccination with PPSV23 (Week 12), serotype-specific IgG GMCs and OPA GMTs were generally comparable between the V114 and PCV13 groups for the 15 serotypes in V114 (Fig. 4). PPSV23 elicited an immune response for serotypes 22F and 33F in the PCV13 group.

Serotype-specific GMFRs and proportions of participants with a ≥4-fold rise in IgG concentrations and OPA titers from Day 1 to Day 30 after V114 or PCV13 vaccination were generally comparable between groups for the 13 shared serotypes, and higher in the V114 group for serotypes 22F and 33F (Table 5, Supplemental Digital Content, <http://links.lww.com/QAD/C841>).

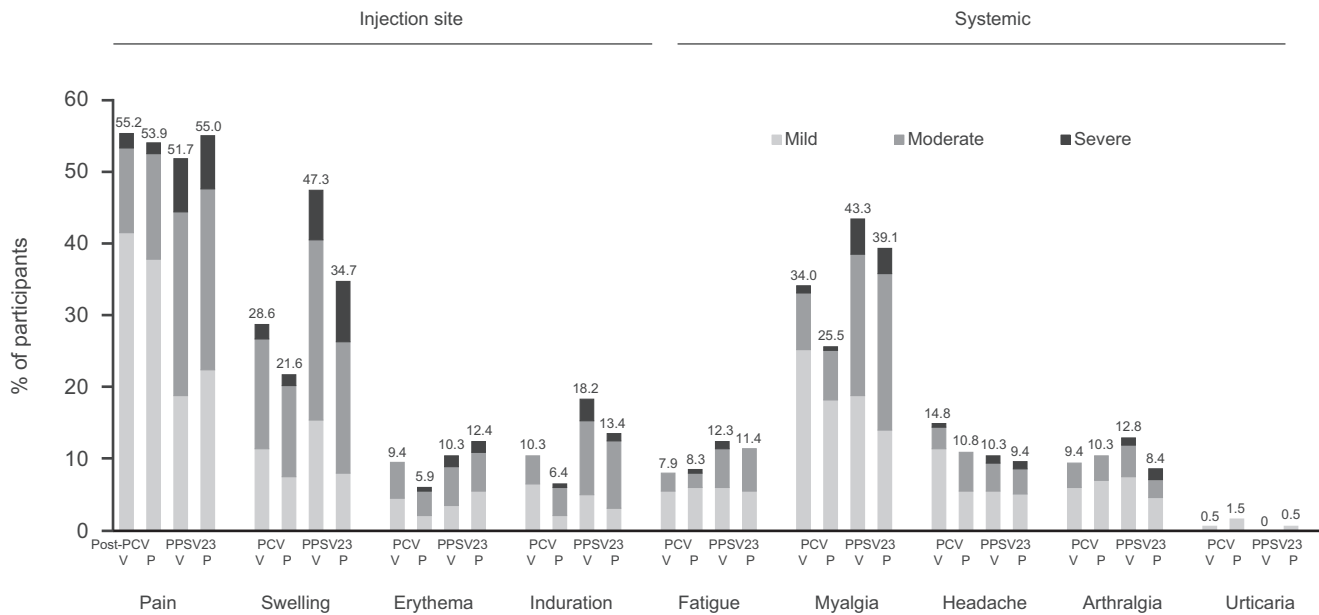


Fig. 2. Proportions of participants with solicited AEs by maximum intensity following vaccination with V114 or PCV13 and following PPSV23. The AEs displayed were solicited from Days 1–14 following each vaccination (V114: $n=203$ following PCV and PPSV23; PCV13: $n=204$ following PCV and 202 following PPSV23). 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. V and P on the x-axis represent V114 and PCV13, respectively. AE, adverse event; PCV, pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; V114, 15-valent pneumococcal conjugate vaccine.

The distributions of serotype-specific IgG concentrations and OPA titers at Day 30 (as displayed by reverse cumulative distribution curves) were consistent with the primary and secondary immunogenicity analyses (Figs. 1 and 2, Supplemental Digital Content, <http://links.lww.com/QAD/C841>).

Subgroup analyses of IgG GMCs at 30 days post-PCV vaccination based on age, sex, and ethnicity, and PPSV23 status, were generally consistent with the results in the overall study population. However, IgG GMCs at Day 30 were generally lower in participants with a CD4⁺ T-cell count of ≥ 200 to <500 cells/ μ l at screening (Table 6, Supplemental Digital Content, <http://links.lww.com/QAD/C841>) and in White participants (data not shown), and were generally higher in participants who received a prior PCV vaccination (Table 7, Supplemental Digital Content, <http://links.lww.com/QAD/C841>), in both the V114 and PCV13 groups compared with the overall study population.

Discussion

In CWH 6–17 years of age, V114 was generally well tolerated and induced immune responses for all 15 serotypes in the vaccine, as assessed by serotype-specific IgG and OPA antibody responses at 30 days post-vaccination. Immune responses were comparable

between V114 and PCV13 recipients for the 13 shared serotypes and higher with V114 for serotypes 22F and 33F. Sequential administration of PPSV23 administered 8 weeks after V114 or PCV13 was well tolerated and immune responses were comparable between groups for the 15 serotypes in V114. These findings show that V114 has the potential to protect against disease caused by the 13 serotypes in PCV13 and against the two additional serotypes in V114. As part of a sequential regimen that includes PPSV23, V114 provides earlier coverage against serotypes 22F and 33F than PCV13. Whilst it may be predicted that the quality of the immune response to 22F and 33F after PPSV23 differs between the two arms, with the establishment of immune memory in the V114 arm [14,15], this study was not designed to demonstrate these differences. The benefit of V114 may be further realized in the many parts of the world where PPSV23 is not routinely given to CWH, who are at increased risk of IPD [4].

Following vaccination with V114, the proportion of participants who reported at least one AE was generally comparable with the PCV13 group. The most common AEs following receipt of V114 were injection-site pain, injection-site swelling, and myalgia; there were no V114-related SAEs. These safety and tolerability profiles of V114 in CWH are generally consistent with those observed in other populations of similar age, either as a catch-up regimen in healthy children [28], or as a single dose in children with sickle cell disease [29].

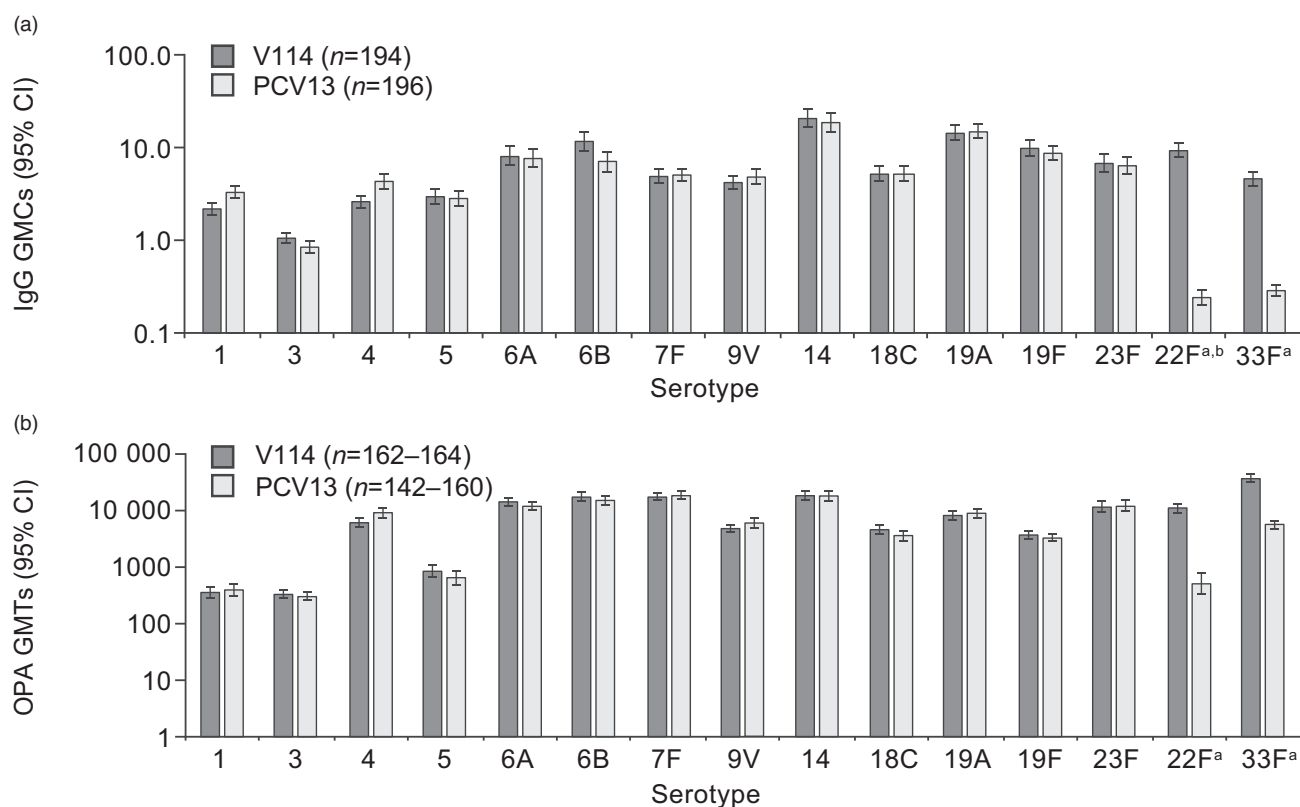


Fig. 3. Serotype-specific immune responses at Day 30: IgG GMCs (a) and OPA GMTs (b). IgG GMCs and OPA GMTs are displayed with the corresponding 95% CIs. ^aSerotypes 22F and 33F are included in V114 but not PCV13. ^b $n=193$ for PCV13. The number of participants differed per serotype for the OPA assay. CI, confidence interval; GMC, geometric mean concentration ($\mu\text{g/ml}$); GMT, geometric mean titer (1/dil); IgG, immunoglobulin G; OPA, opsonophagocytic activity; PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.

Antibody responses post-PPSV23 were comparable in both vaccination groups for all 15 serotypes in V114 and generally similar to those observed at 30 days post-PCV vaccination for the serotypes in the respective PCVs. Consistent with prior studies of sequential V114 and PPSV23 vaccination, the similarity of responses between groups for serotypes 22F and 33F post-PPSV23 is likely due to the fact that, prior to PPSV23 administration, participants who received V114 already had higher levels of antibodies to these serotypes than those who received PCV13 [24,30]. Prior studies of individuals with HIV show that PPSV23 can elicit a similar antibody response to PCVs in persons naive to PPSV23 serotypes [31]. Further studies would be required to determine whether longer intervals between V114 and PPSV23 could lead to higher immune responses to serotypes 22F and 33F post-PPSV23. The optimal interval must balance the potential for higher immune responses to shared serotypes with earlier provision of broader serotype coverage.

Participants with a CD4^+ T-cell count ≥ 200 to < 500 cells/ μl at screening in both vaccination groups had generally lower serotype-specific IgG GMCs at 30 days post-PCV compared with those with a CD4^+ T-cell count ≥ 500 cells/ μl and compared with

the overall study population. The number of participants in the lower CD4^+ T-cell stratum in our study was small; however, findings are consistent with trends observed in adults with HIV [24]. Similar correlations have also been observed among CWH in some studies evaluating other vaccines [32,33]. CD4^+ T-cell count has been shown to be a predictor of immunologic memory in children after vaccination with a sequential PCV and PPSV23 series [34].

There are some limitations to this study. Approximately 7% of participants had previously received a PCV. The effect of this prior vaccine exposure on our findings cannot be fully determined; however, given that the overall proportion of participants with a prior PCV was small, it is unlikely to have had a substantial impact. Underestimation of the frequency of previous PCV receipt is possible; however, prior receipt was determined by participant medical records and known country practices, and any inaccuracies are expected to be small. Immunogenicity of the PCV and PPSV23 sequential series was not evaluated beyond 12 weeks post-PCV and 30 days post-PPSV23 vaccination; thus, additional studies would be needed to fully understand the long-term persistence of antibody responses. Immune responses to

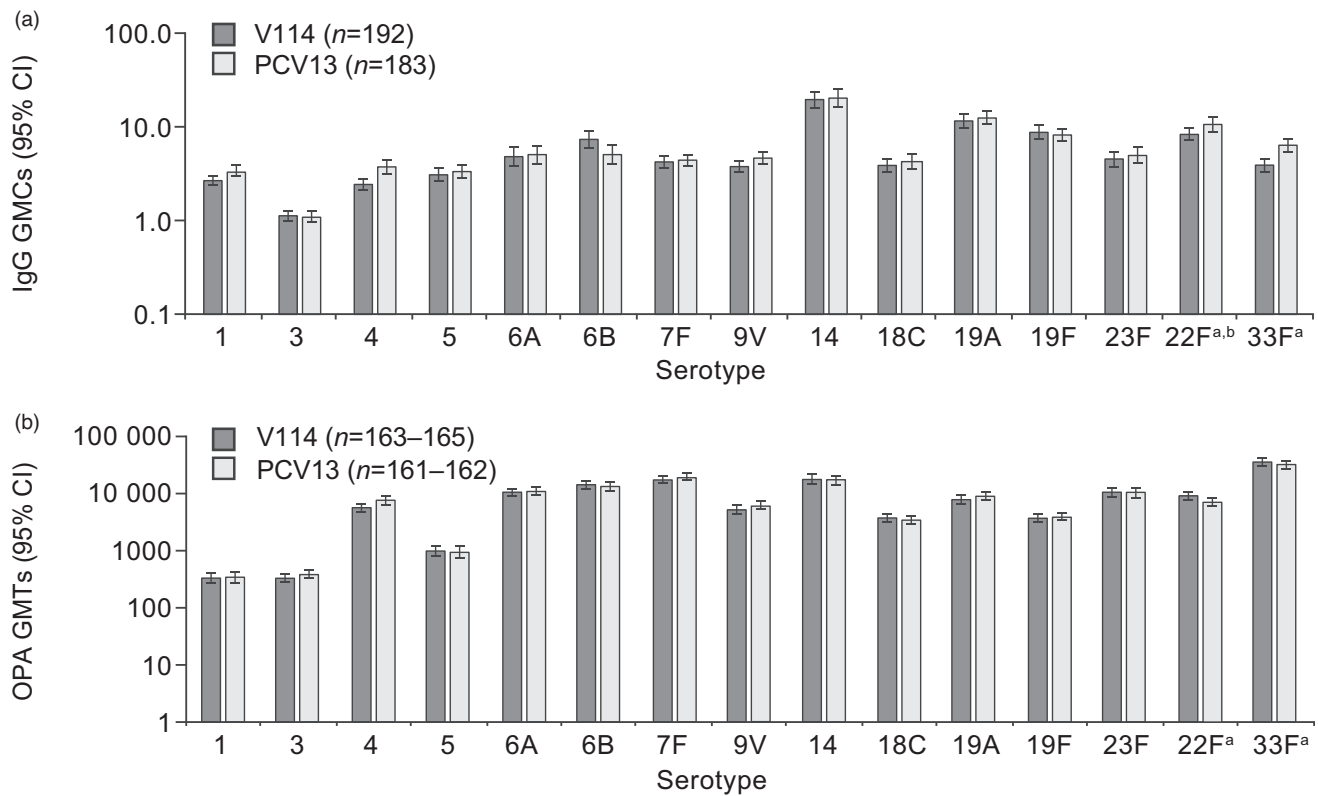


Fig. 4. Serotype-specific immune responses at Week 12: IgG GMCs (a) and OPA GMTs (b). IgG GMCs and OPA GMTs are displayed with the corresponding 95% CIs. ^aSerotypes 22F and 33F are included in V114 but not PCV13. ^b $n = 182$ for PCV13. The number of participants differed per serotype for the OPA assay. CI, confidence interval; GMC, geometric mean concentration ($\mu\text{g/ml}$); GMT, geometric mean titer (1/dil); IgG, immunoglobulin G; OPA, opsonophagocytic activity; PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.

serotypes unique to PPSV23 were not measured. Only participants with a CD4^+ T-cell count of ≥ 200 cells/ μl at screening were included, and results may not be extrapolatable to CWH with lower CD4^+ T-cell counts. Lower immunogenicity to vaccines has been observed in persons with detectable viral loads compared with those with undetectable viral loads [35]. This study was not stratified according to baseline viral load; however, the study was randomized and the majority of participants were on antiretrovirals, with CD4^+ counts ≥ 500 cells/ μl and undetectable HIV viral loads at baseline. Thus, any effect that viral load may have had on the study outcomes would be expected to be minor. This study is limited in scope to safety and immunogenicity; as immune correlates of protection are not well established in this population, real-world evidence is required to demonstrate vaccine effectiveness.

Conclusion

In CWH 6–17 years of age, V114 is generally well tolerated and induces immune responses for all 15 pneumococcal serotypes, as assessed by IgG GMCs and OPA GMTs at 30 days post-vaccination. PPSV23 is well tolerated when given approximately 8 weeks after

V114. These results support the use of V114 in CWH for prevention of pneumococcal disease.

Acknowledgements

The authors would like to thank the participants, their families and all investigators involved in the PNEU-WAY PED study. Principal investigators for this study were Shaun Lawrence Barnabas, Elizabeth Hellstrom, Faezah Patel, and Avy Violari (South Africa), Supaporn Anugulruengkitt, Kulkanya Chokephaibulkit, Pope Kosalaraksa, and Peninnah Oberdorfer (Thailand), and Iryna Chukhalova, Olena Volodymyrivna Kraeva Igor Matkovskiy, Liudmyla Shostakovych-Koretska, and Svitlana Volodymyrivna Yesypenko (Ukraine). Medical writing support, including assisting authors with the development of the initial draft and incorporation of comments was provided by Rachel Wright, PhD, of Scion, London, UK, and Kara S. Cox, MS, of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, New Jersey, USA, and editorial support, including fact checking, referencing, figure preparation, formatting, proofreading, and submission was provided

by Ian Norton, PhD, of Scion, London, all according to Good Publication Practice guidelines (see <https://www.acpjournals.org/doi/10.7326/M22-1460>). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Author contributions: S.B., K.C., A.V., P.K., S.Y., I.C., S.M. contributed to the enrollment of participants and data collection; review of the manuscript. M.W. contributed to the study concept and design; analysis and interpretation of data, preparation of the manuscript; review of the manuscript. E.M., L. Morgan, K.F., R.L., J.C. contributed to the analysis and interpretation of data; preparation of the manuscript; review of the manuscript. R.D., P.R., L. Musey contributed to the study concept and design; analysis and interpretation of data; review of the manuscript. K.B. contributed to the study concept and design; review of the manuscript.

Data sharing: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, New Jersey, USA's data sharing policy, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via e-mail to dataaccess@merck.com.

Funding: This study was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, New Jersey, USA.

Conflicts of interest

M.W., E.M., L. Morgan, K.F., and R.L. 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, New Jersey, USA. J.C., L. Musey and K.B. were employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, New Jersey, USA at the time of this study.

P.K. has received a grant from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, New Jersey, USA through the university to run this study.

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 GlaxoSmithKline.

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

All other authors report no potential conflicts of interest.

References

1. Madhi SA, Petersen K, Madhi A, Khoosal M, Klugman KP. **Increased disease burden and antibiotic resistance of bacteria causing severe community-acquired lower respiratory tract infections in human immunodeficiency virus type 1-infected children.** *Clin Infect Dis* 2000; **31**:170–176.
2. Nunes MC, von Gottberg A, de Gouveia L, Cohen C, Moore DP, Klugman KP, *et al.* **The impact of antiretroviral treatment on the burden of invasive pneumococcal disease in South African children: a time series analysis.** *AIDS* 2011; **25**:453–462.
3. Meiring S, Cohen C, Quan V, de Gouveia L, Feldman C, Karstaedt A, *et al.* **HIV infection and the epidemiology of invasive pneumococcal disease (IPD) in South African adults and older children prior to the introduction of a pneumococcal conjugate vaccine (PCV).** *PLoS One* 2016; **11**:e0149104.
4. European Centre for Disease Prevention and Control. Annual epidemiological report for 2018: invasive pneumococcal disease. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/AER_for_2018_IPD.pdf [Accessed 2 March 2022].
5. Varghese J, Chochua S, Tran T, Walker H, Li Z, Snippes Vagnone PM, *et al.* **Multistate population and whole genome sequence-based strain surveillance of invasive pneumococci recovered in the USA during 2017.** *Clin Microbiol Infect* 2020; **26**:512.e1–512.e10.
6. Balsells E, Guillot L, Nair H, Kyaw MH. **Serotype distribution of *Streptococcus pneumoniae* causing invasive disease in children in the post-PCV era: a systematic review and meta-analysis.** *PLoS One* 2017; **12**:e0177113.
7. Payne H, Judd A, Donegan K, Okike IO, Ladhani SN, Doerholt K, *et al.* **Incidence of pneumococcal and varicella disease in HIV-infected children and adolescents in the United Kingdom and Ireland, 1996–2011.** *Pediatr Infect Dis J* 2015; **34**:149–154.
8. von Mollendorf C, von Gottberg A, Tempia S, Meiring S, de Gouveia L, Quan V, *et al.* **Increased risk for and mortality from invasive pneumococcal disease in HIV-exposed but uninfected infants aged <1 year in South Africa, 2009–2013.** *Clin Infect Dis* 2015; **60**:1346–1356.
9. Centers for Disease Control and Prevention (CDC). Recommended child and adolescent immunization schedule for ages 18 years or younger, United States, 2021. Available at: <https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html> [Accessed 2 March 2022].
10. Public Health England. Chapter 25: Pneumococcal. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/857267/GB_Chapter_25_pneumococcal_January_2020.pdf [Accessed 7 May 2020].
11. Robert Koch-Institut. Statement of the German Standing Committee on Vaccination at the RKI Recommendations of the Standing Committee on Vaccination (STIKO) at the Robert Koch Institute – 2017/2018. Available at: https://www.rki.de/EN/Content/infections/Vaccination/recommendations/34_2017_engl.pdf?__blob=publicationFile [Accessed 2 March 2022].
12. Government of Canada. Immunization of immunocompromised persons: Canadian Immunization Guide. Available at: <https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-3-vaccination-specific-populations/page-8-immunization-immunocompromised-persons.html#a29> [Accessed 14 February 2022].
13. Australian Immunisation Handbook. Pneumococcal disease. Available at: <https://immunisationhandbook.health.gov.au/vaccine-preventable-diseases/pneumococcal-disease> [Accessed 3 August 2020].
14. Avci FY, Li X, Tsuji M, Kasper DL. **A mechanism for glycoconjugate vaccine activation of the adaptive immune system and its implications for vaccine design.** *Nat Med* 2011; **17**:1602–1609.
15. Rose MA, Schubert R, Strnad N, Zielen S. **Priming of immunological memory by pneumococcal conjugate vaccine in children unresponsive to 23-valent polysaccharide pneumococcal vaccine.** *Clin Diagn Lab Immunol* 2005; **12**:1216–1222.
16. Platt HL, Cardona JF, Haranaka M, Schwartz HI, Narejos Perez S, Dowell A, *et al.* **A phase 3 trial of safety, tolerability, and immunogenicity of V114, 15-valent pneumococcal conjugate vaccine, compared with 13-valent pneumococcal conjugate vaccine in adults 50 years of age and older (PNEU-AGE).** *Vaccine* 2022; **40**:162–172.

17. Balsells E, Dagan R, Yildirim I, Gounder PP, Steens A, Munoz-Almagro C, et al. **The relative invasive disease potential of *Streptococcus pneumoniae* among children after PCV introduction: a systematic review and meta-analysis.** *J Infect* 2018; **77**:368–378.
18. Adam HJ, Golden AR, Karlowsky JA, Baxter MR, Nichol KA, Martin I, et al. **Analysis of multidrug resistance in the predominant *Streptococcus pneumoniae* serotypes in Canada: the SAVE study, 2011–15.** *J Antimicrob Chemother* 2018; **73** (Suppl. 7):vii12–vii19.
19. Moore MR, Link-Gelles R, Schaffner W, Lynfield R, Lexau C, Bennett NM, et al. **Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: analysis of multisite, population-based surveillance.** *Lancet Infect Dis* 2015; **15**:301–309.
20. Lo SW, Gladstone RA, van Tonder AJ, Lees JA, du Plessis M, Benisty R, et al. **Pneumococcal lineages associated with serotype replacement and antibiotic resistance in childhood invasive pneumococcal disease in the post-PCV13 era: an international whole-genome sequencing study.** *Lancet Infect Dis* 2019; **19**:759–769.
21. European Medicines Agency. Vaxneuvance summary of product characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/vaxneuvance-epar-product-information_en.pdf [Accessed 29 November 2022].
22. Government of Canada. Pneumococcal vaccine: Canadian immunization guide. Available at: <https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-16-pneumococcal-vaccine.html#a4> [Accessed 7 June 2022].
23. United States Food and Drug Administration. VAXNEUVANCE™ (pneumococcal 15-valent conjugate vaccine) prescribing information. Available at: <https://www.fda.gov/vaccines-blood-biologics/vaccines/vaxneuvance> [Accessed 10 August 2022].
24. Mohapi L, Pinedo Y, Osiyemi O, Supparatpinyo K, Ratanasuwana W, Molina JM, et al. **Safety and immunogenicity of V114, a 15-valent pneumococcal conjugate vaccine, in adults living with HIV.** *AIDS* 2022; **36**:373–382.
25. Nolan KM, Bonhomme ME, Schier CJ, Green T, Antonello JM, Murphy RD. **Optimization and validation of a microcolony multiplexed opsonophagocytic killing assay for 15 pneumococcal serotypes.** *Bioanalysis* 2020; **12**:1003–1020.
26. Nolan KM, Zhang Y, Antonello JM, Howlett AH, Bonhomme CJ, Greway R, et al. **Enhanced antipneumococcal antibody electrochemiluminescence assay: validation and bridging to the WHO reference ELISA.** *Bioanalysis* 2020; **12**:1363–1375.
27. Clopper CJ, Pearson ES. **The use of confidence or fiducial limits illustrated in the case of the binomial.** *Biometrika* 1934; **26**:404–413.
28. Bannietis N, Wysocki J, Szenborn L, Phongsamart W, Pitisuttithum P, Rämets M, et al. **1174. Phase 3 study to evaluate the safety, tolerability, and immunogenicity of catch-up vaccination regimens of V114 in healthy infants, children, and adolescents (PNEU-PLAN).** *Open Forum Infect Dis* 2021; **8** (Suppl. 1):S678–S1678.
29. Musey L, Quinn C, Wiedmann R, Papa M, Shou Q, Dagan R, et al. **A phase 3, multicenter, randomized, double-blind, active comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of V114 in children with sickle cell disease (PNEU-SICKLE).** In: *Pediatric Academic Societies (PAS)*. Denver, CO, USA; 2022.
30. Song JY, Chang CJ, Andrews C, Diez-Domingo J, Oh MD, Dagan R, et al. **Safety, tolerability, and immunogenicity of V114, a 15-valent pneumococcal conjugate vaccine, followed by sequential PPSV23 vaccination in healthy adults aged ≥50 years: a randomized phase III trial (PNEU-PATH).** *Vaccine* 2021; **39**:6422–6436.
31. Garrido HMG, Schnyder JL, Tanck MWT, Vollaard A, Spijker R, Grobusch MP, et al. **Immunogenicity of pneumococcal vaccination in HIV infected individuals: a systematic review and meta-analysis.** *EClinicalMedicine* 2020; **29–30**:100576.
32. Weinberg A, Huang S, Fenton T, Patterson-Bartlett J, Gona P, Read JS, et al. **Virologic and immunologic correlates with the magnitude of antibody responses to the hepatitis A vaccine in HIV-infected children on highly active antiretroviral treatment.** *J Acquir Immune Defic Syndr* 2009; **52**:17–24.
33. Flynn PM, Cunningham CK, Rudy B, Wilson CM, Kapogiannis B, Worrell C, et al. **Hepatitis B vaccination in HIV-infected youth: a randomized trial of three regimens.** *J Acquir Immune Defic Syndr* 2011; **56**:325–332.
34. Abzug MJ, Song LY, Levin MJ, Nachman SA, Borkowsky W, Pelton SI, et al. **Antibody persistence and immunologic memory after sequential pneumococcal conjugate and polysaccharide vaccination in HIV-infected children on highly active antiretroviral therapy.** *Vaccine* 2013; **31**:4782–4790.
35. Bamford A, Kelleher P, Lyall H, Haston M, Zancolli M, Goldblatt D, et al. **Serological response to 13-valent pneumococcal conjugate vaccine in children and adolescents with perinatally acquired HIV infection.** *AIDS* 2014; **28**:2033–2043.