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REVIEW

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PCV15, a pneumococcal conjugate vaccine, for the prevention of invasive pneumococcal disease in infants and children

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ABSTRACT

Introduction: *Streptococcus pneumoniae* is a causative agent of pneumonia and acute otitis media (AOM), as well as invasive diseases such as meningitis and bacteremia. PCV15 (V114) is a new 15-valent pneumococcal conjugate vaccine (PCV) approved for use in individuals ≥6 weeks of age for the prevention of pneumonia, AOM, and invasive pneumococcal disease.

Areas Covered: This review summarizes the V114 Phase 3 development program leading to approval in infants and children, including pivotal studies, interchangeability and catch-up vaccination studies, and studies in at-risk populations. An integrated safety summary is presented in addition to immunogenicity and concomitant use of V114 with other routine pediatric vaccines.

Expert Opinion: Across the development program, V114 demonstrated a safety profile that is comparable to PCV13 in infants and children. Immunogenicity of V114 is comparable to PCV13 for all shared serotypes except serotype 3, where V114 demonstrated superior immunogenicity. Higher immune responses were demonstrated for V114 serotypes 22F and 33F. Results of the ongoing study to evaluate V114 efficacy against vaccine-type pneumococcal AOM and anticipated real-world evidence studies will support assessment of vaccine effectiveness and impact, with an additional question of whether higher serotype 3 immunogenicity translates to better protection against serotype 3 pneumococcal disease.

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1. Introduction

Disease caused by *Streptococcus pneumoniae* (pneumococcus) can be serious and sometimes life threatening. In the 20th century, the pneumococcus was recognized as the chief cause of lobar pneumonia. Pneumococcal pneumonia deaths are declining due to vaccination; however, in 2019 pneumonia was still the leading cause of death in children under 5 years of age worldwide, with the pneumococcus remaining a major causative agent of pneumonia. Pneumococcus also remains a leading cause of bacterial meningitis, sinusitis, and acute otitis media (AOM), despite advances made in the prevention of pneumococcal disease through vaccines [1–6]. Children under one year of age are particularly vulnerable to invasive pneumococcal diseases (IPD) such as meningitis and bacteremia [7].

More than 100 pneumococcal serotypes have been described based on the specific composition of the polysaccharide capsule, the major virulence factor of the bacterium. However, not all serotypes have a similar potential to cause disease. A few serotypes are typically responsible for the majority of disease worldwide, and these can vary with age and geography [8,9]. The introduction of pneumococcal vaccines and other factors have caused a shift in disease-causing serotypes with substantial regional variability. The quest to develop preventative pneumococcal vaccines dates back more than a century [10] with the first polysaccharide vaccine, containing the capsular polysaccharides of 14 serotypes, becoming available in 1977 followed by the 23-valent vaccine (PPSV23) in 1983. PPSV23 remains the pneumococcal vaccine most widely used globally in adults; however, it has poor immunogenicity in infants under 2 years of age. Pneumococcal conjugate vaccines (PCVs) have been developed to address the need for protection against all pneumococcal disease (PD), particularly in infants and children.

To improve the immune response to the capsular polysaccharide in infants and children, following the model established for *Haemophilus influenzae* type b vaccine [11], vaccines in which capsular polysaccharides are conjugated to one of several carrier proteins were developed. PCV7 (Prevnar™) was the first approved and widely used PCV [12]. The conjugation of pneumococcal polysaccharides to a nontoxic carrier protein in PCVs provides an immunogen for induction of T cell-dependent immune responses to the polysaccharides and subsequent increased vaccine immunogenicity in infants. Shortly after the release of PCV7, several studies demonstrated the protective nature of vaccine-induced antibodies raised against the capsular polysaccharide [13,14]. Within a few years of the introduction of PCV7 in infant immunization programs, a > 90% reduction in vaccine type IPD was observed

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Article highlights

- PCV15 (V114) is a 15-valent pneumococcal conjugate vaccine approved in infants, children, and adults for the prevention of pneumonia, AOM, and invasive pneumococcal disease
- This review summarizes the V114 pediatric phase 3 clinical program that included trials in healthy infants and children as well individuals with at-risk conditions, using 2 + 1 and 3 + 1 immunization schedules
- V114 was well tolerated in all studies, with a safety profile similar to the active comparator PCV13
- V114 demonstrated non-inferior immunogenicity to PCV13 for the 13 shared serotypes, and superior immunogenicity for shared serotype 3 and V114 serotypes 22F and 33F
- With a strong safety and immunogenicity profile in infants and children, V114 is expected to maintain protection offered by PCV13 while further reducing pneumococcal disease against additional epidemiologically important serotypes

[15,16]. However, pneumococcal serotypes causing disease have continued to evolve due to natural pressures and in response to vaccine use. Therefore, the ongoing development of new PCVs has been critical to broaden coverage against newly emerging, clinically relevant serotypes for expanded protection globally while maintaining suppression of serotypes included in prior PCVs. Currently, Synflorix® (PCV10, GlaxoSmithKline) [17], Prevnar 13® (PCV13, Pfizer) [18], and more recently Pneumosil® (PCV10, Serum Institute of India) [19], VAXNEUVANCE® (PCV15, Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, U.S.A. [MSD]) [20], and Prevnar 20® (PCV20, Pfizer) [21] are currently available PCVs in various regions globally for use in infants and children.

Post-licensure studies from the post-PCV10 and PCV13 era have shown that PCVs not only significantly reduce the overall incidence of IPD by reducing IPD caused by serotypes contained in the vaccine [2,22–29] but also have a beneficial impact on reducing pneumococcal-related pneumonia [30–35] and AOM [5,23,36–40]. This is accompanied by a reduction in nasopharyngeal colonization of most pneumococcal vaccine serotypes [41–45], which contributes to indirect community protection [46]. All these factors have resulted in significant reductions in pneumococcal-related hospitalizations and deaths in nations with successful PCV national infant immunization programs [32,34,47–49]. As a result of the overall efficacy and effectiveness of PCVs, the World Health Organization (WHO) recommends pneumococcal vaccines be included in childhood vaccination programs globally. As of 2020, 148 countries have instituted PCVs into their national immunization programs, either nationally or subnationally. Despite this, approximately half of infants globally have not received a complete PCV series [50]. Current infant PCV vaccination regimens most widely used include a 3-dose (two primary infant doses and a toddler dose or three infant doses) or 4-dose (3 primary infant doses and a toddler dose) series.

In recent years, several non-vaccine serotypes have become the predominant causes of pediatric PD with associated morbidity/mortality and antibiotic resistance in multiple regions globally, with serotypes 22F and 33F among the leading serotypes [24,25,51–55]. In addition, some serotypes included in currently approved PCVs are still major contributors to residual PD, of which serotypes 3, 19A, and 19F are most prominent. Serotype 3 is a unique case, in that several studies have concluded little to no effect of PCV13 on reducing IPD attributed to this serotype [26,36,56–58]. In a recent analysis of IPD (2014–2019) in children under 5 years of age in 30 high-income countries with PCV national immunization programs (mixed data of PCV10 and PCV13), approximately one quarter of residual IPD was from serotypes 3 and 19A [59]. Furthermore, the prominence of these serotypes has persisted following the COVID-19 pandemic [60,61].

The primary objectives of the development program for PCV15 (also referred to as V114, the name of the clinical development program; contains serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9 V, 14, 18C, 19A, 19F, 23F, 22F, and 33F) were to 1) maintain protection against PD caused by serotypes found in PCV13, 2) induce robust immunogenicity to two key serotypes causing residual disease (22F and 33F), and 3) improve immunogenicity and subsequent protection against serotype 3. For serotype 3, it is well established that unique features of its capsular polysaccharide and a high rate of capsular shedding contribute to lower vaccine-induced immune responses to this serotype [62–64]. These data were considered during V114 development in order to maximize the number of active targets for induction of the serotype 3 immune response.

In the initial Phase 1 and 2 studies, V114 was found to be immunogenic in adults. However, immune responses to some serotypes in infants were suboptimal [65]. As a result, additional formulations were tested to optimize the responses against all 15 serotypes [66]. Subsequently, comprehensive Phase 3 clinical development programs were designed for both pediatric and adult populations to evaluate the tolerability, safety, and immunogenicity in populations in need of PD prevention.

The adult Phase 3 program demonstrated that V114 is well tolerated with a safety profile similar to that of PCV13. V114 induced robust immune responses to all 15 serotypes included in the vaccine after a single dose, which were non-inferior to the immune responses observed with PCV13 for the 13 shared serotypes and higher for serotypes 22F and 33F. This was true in healthy adults ≥18 years of age, as well as older adults ≥65 years of age, and individuals living with HIV or with one or more known risk factors for PD [67–73]. Importantly, V114 was shown to induce superior immune responses to serotype 3 as compared to PCV13 which, pending real-world evidence, has the potential to address the significant burden of disease due to this serotype that remains in many populations worldwide [71]. These findings led to the licensure of V114 for use in adults in many regions globally.

Following proof of concept and formulation adjustments during Phase 2 studies [74], the V114 Phase 3 pediatric development program commenced shortly after the adult program and included a comprehensive set of randomized controlled trials evaluating 3 + 1 and 2 + 1 vaccination regimens in healthy infants, as well as catch-up vaccination and interchangeability with PCV13. Additional studies have evaluated the safety and immunogenicity of V114 in infants and children 6 weeks through 17 years of age with risk conditions of interest for whom pneumococcal vaccination is indicated (Table 1). A global approach was taken to clinical study site selection

Table 1. PCV15 pediatric Phase 3 studies.

Study name	Short description	NCT #	Pubmed ID
V114–023 (PNEU-SICKLE)	PCV15 in children with sickle cell disease	NCT03731182	36383730
V114–024 (PNEU-PLAN)	Catch-up vaccination with PCV15	NCT03885934	36150974
V114–025 (PNEU-PED-EU1)	PCV15 2 + 1 regimen pivotal trial	NCT04031846	37105892
V114–026 (PNEU-PED-EU2)	PCV15 2 + 1 regimen pivotal trial – Nordic	NCT04016714	36841723
V114–027 (PNEU-DIRECTION)	Interchangeabilty of PCV15 and PCV13	NCT03620162	36522265
V114–029 (PNEU-PED)	PCV15 3 + 1 regimen pivotal trial	NCT03893448	36621410
V114–030 (PNEU-WAY PED)	PCV15 in children living with HIV	NCT03921424	36939067
V114–031 (PNEU-LINK)	Safety and tolerability of PCV15	NCT03692871	37309607
V114–032 (PNEU-ERA)	Effectiveness of PCV15 on acute otitis media	NCT04193215	Ongoing
V114–033	Subcutaneous 3 + 1 PCV15 regimen (Japan)	NCT04384107	37344262

for the assessment of V114 in a diverse participant population. As a result, the Phase 3 program included over 350 study sites with participants from 6 continents and 28 countries globally. In all, over 10,000 infants and children have participated in the V114 development program to date. The data derived from this program resulted in the approval and licensing of V114 for use in infants and children in over 30 countries to date, including the United States, Canada, United Kingdom, European Union, Japan, and Australia [75–78] with other approvals currently in process. Herein, a detailed review of the V114 Phase 3 pediatric development program will comprehensively summarize data regarding safety, immunogenicity, concomitant vaccine use, and use within special populations.

2. Body

2.1. Overall study objectives and endpoints

The V114 clinical program was aligned with guidelines from the WHO for the development of new PCVs. This included the use of PCV13 as an active comparator since this was the highest valency PCV licensed in infants and children during the V114 Phase 3 program. Immunogenicity of V114 was bridged to a PCV with established efficacy/effectiveness (through determination of serotype-specific noninferiority of V114 to PCV13) as a means of predicting the effectiveness of V114 since placebo-controlled effectiveness studies are unethical in the post-PCV era. Study designs, populations, endpoints, and statistical criteria were additionally reviewed with multiple regulatory agencies (US FDA, EMA, and Health Canada) for alignment before the initiation of the comprehensive Phase 3 program.

The following endpoints were applied to vaccination with V114 as well as PCV13 for evaluation of V114 safety outcomes. Evaluation of participant safety and tolerability was a primary objective in all V114 clinical trials and included assessment of solicited injection-site and systemic adverse events (AEs), unsolicited AEs, serious AEs (SAEs), and deaths that occurred during the trial. In addition, daily temperature measurements were solicited for 7 days following each study vaccination, and days 8–14 if fever was suspected. AE intensity (measure of impact to function as mild, moderate, or severe which is distinct from serious AE assessment) and duration in days were recorded to characterize AEs within the trial. Electronic vaccination report cards (eVRC) were used with participants and their parents to record safety events for subsequent review by study investigators. SAEs and deaths were recorded from the beginning of the trial to at least 6 months following the last study vaccination. Relatedness to the study vaccines was assessed by the study investigators. In all studies discussed below, baseline demographics were comparable between intervention groups.

Serotype-specific IgG concentration was used to test the primary immunogenicity hypotheses for all participants, in accordance with WHO [79]. Given the established association of IgG responses and functional antibody levels via opsonophagocytic activity (OPA) in children [80–83], the WHO recommends OPA data be generated for a subset of vaccinated children in some or all clinical studies [79]. As such, OPA was descriptively evaluated as a supportive endpoint. IgG was measured using the pneumococcal electrochemiluminescence v2.0 assay, which was bridged to a WHO international reference standard [84,85], and OPA was measured using a validated multiplex opsonophagocytic assay [86]. Immunogenicity endpoints were assessed following the primary infant PCV series (post-primary series, PPS, dose 2 in the 2 + 1 studies and dose 3 in the 3 + 1 studies) and following the toddler dose (post-toddler dose, PTD). Immunogenicity was evaluated for all 15 serotypes contained in V114 in participants who received V114 or PCV13, in order to compare immune responses for the 13 shared serotypes between vaccines and determine whether immune responses to serotypes 22F and 33F were induced following V114. Immunogenicity endpoints included serotype-specific response rates (the proportion of participants meeting the WHO reference IgG concentration ≥0.35 µg/mL for each serotype), IgG geometric mean concentrations (GMCs), and bactericidal activity as measured by OPA geometric mean titers (GMTs) and response rates.

2.2. Pivotal V114 studies

The three pivotal studies (V114–025, V114–026, V114–029) for the V114 program evaluated safety and immunogenicity using 3 + 1 (V114–029 [87]) and 2 + 1 (V114–025 and –026, one using standard [2 and 4 months of age] and the other using alternative [3 and 5 months of age] timing for the primary infant series [88,89]) vaccination regimens. These studies were powered to test hypotheses for noninferiority of serotype-specific immune responses comparing V114 to PCV13 response rates and IgG GMC ratios (V114/PCV13) for the shared serotypes and superiority of serotypes 22F and 33F. The 3 + 1 study had additional immunogenicity hypotheses for noninferiority of serotypes 22F and 33F (immunogenicity was

compared to the lowest observed serotype response in the PCV13 group, excluding serotype 3) and superiority of serotype 3 compared to PCV13. As per WHO recommendations and regulatory requirements, serotype-specific noninferiority for immunogenicity was evaluated at PTD in the 2 + 1 studies and at both PPS and PTD in the 3 + 1 study. In addition to the pivotal studies, a dedicated safety study was performed with over 2,400 infants randomized in a 5:1 ratio (V114: PCV13) such that approximately 2,000 received V114 in a 3 + 1 vaccination regimen (V114–031) for comprehensive safety assessment.

2.2.1. Safety

In the three pivotal studies (V114–025, V114–026, and V114–029) and the dedicated safety study (V114–031) totaling >6,000 participants, V114 was well tolerated with a safety profile consistent with PCV13. All safety outcomes, including proportions of participants with AEs, solicited AEs, vaccine-related AEs, distribution of maximum daily temperature measurements, SAEs, and AE intensity and duration, were generally comparable between groups. In terms of individual solicited AEs, some studies reported higher proportions of participants in the V114 group with injection-site pain, irritability (in V114–025 and V114–031 studies), injection-site erythema, and decreased appetite (in V114–031 study only) when compared to the PCV13 group. However, these differences did not present as a pattern across all studies. In addition, most of these AEs were categorized as mild or moderate in intensity and were of short duration (≤3 days), and therefore these differences are unlikely to be clinically meaningful. Across the four studies (V114–025, V114–026, V114–029, V114–031), vaccine-related SAEs occurred in four participants after V114 (all due to pyrexia) and three participants after PCV13 (two due pyrexia, one due to febrile convulsion). No vaccine-related deaths occurred and only one study discontinuation due to a vaccine-related AE occurred in each group (V114 and PCV13). Finally, no new or unexpected AEs were reported after the administration of V114. An integrated safety summary (ISS) of infants that includes data from V114–025, participants from V114–027 who received a complete vaccination series of V114 or PCV13 (interchangeability study of V114 and PCV13, described below), V114–029, and V114–031 (V114–026 was not included since the study was not complete at the time of the analysis) is shown in Figure 1. Of note is that three of the vaccine-related SAEs discussed above (two after V114 and one after PCV13) occurred in the V114–026 study and therefore are not reported in Figure 1.

Daily maximum temperature measurements were solicited via the eVRC for 7 days following each study vaccination, and days 8–14 if fever was suspected, to monitor for elevated temperatures. Across the studies in the ISS, the majority of participants had a maximum temperature below 39.0°C, and a low proportion of participants (<0.5%) reported maximum temperatures at/above 40.0°C after any study vaccination. The distribution of maximum temperature measurements was comparable between vaccination groups across all studies.

Pyrexia was an unsolicited AE in the program. In the ISS (V114–025, V114–027, V114–029, and V114–031), the rates of the AE of pyrexia were comparable between groups (37.7% [1354/3589] in V114 group, 36.5% [752/2058] in PCV13 group), as well as cases of pyrexia that classified as SAEs (0.3% [11/3589] in V114 group and 0.2% [5/2058] in PCV13 group). Of these, three were considered vaccine-related SAEs, two in the V114 group, and one in the PCV13 group. Per regulatory definitions, these cases were classified as SAEs due to hospitalization of the participant. None of these cases reported a temperature higher than 40.0°C and all were confounded with the concomitant administration of routine pediatric vaccinations. None of the reported vaccine-related SAEs of pyrexia in the V114 group resulted in febrile convulsion. Moreover, the rate of convulsions and febrile convulsions were comparable between arms (0.2% in V114 group and 0.2% in PCV13 group).

Taken together, these data demonstrate that V114 is well tolerated in infants and toddlers, with a comparable safety profile to PCV13.

2.2.2. Immunogenicity

In the 2 + 1 studies, V114 met noninferiority criteria for each of the 13 shared serotypes and superiority criteria for serotypes 22F and 33F, based on IgG response rates and IgG GMC ratios at 30 days PTD as compared to PCV13. In the 3 + 1 study, noninferiority (for all 15 serotypes) and superiority (for serotypes 3, 22F, and 33F) assessments were made at PPS and PTD. V114 met noninferiority criteria for all 15 serotypes at PTD based on IgG GMC, and for all 15 serotypes based on IgG response rates and IgG GMC at PPS, except serotype 6A IgG GMC which narrowly missed the margin by 0.02 (the lower bound of the confidence interval for V114/PCV13 GMC ratio for serotype 6A was 0.48 with a noninferiority cutoff of 0.50). Superiority criteria were met at PPS (for response rates and IgG GMC ratios) and PTD (IgG GMC ratios) for the unique serotypes 22F and 33F, and the shared serotype 3 [87]. In all three pivotal studies, V114 induced robust functional antibodies as measured by OPA to each of the 15 serotypes, at levels which were generally comparable to PCV13 for the 13 shared serotypes and higher for serotypes 22F and 33F, at PPS and PTD. Serotype-specific antibody levels from PPS to prior to the toddler dose waned and then showed boosting PTD, suggesting development of vaccine-induced immune memory. This was true for both 2 + 1 and 3 + 1 vaccination regimens. From these data, it is expected that V114 will be protective for the 15 serotypes included in the vaccine. Importantly, V114 broadens PCV coverage without significant loss of immunogenicity and has improved immunogenicity against serotype 3. Favorable safety and immunogenicity results at PPS from the 3 + 1 study are also informative for PCV recommendations in regions where a 3 + 0 vaccination regimen is used.

2.3. V114 catch-up vaccination and interchangeability

Interchangeability of V114 with PCV13 [90] and catch-up vaccination with V114 [91] were evaluated in two studies. The WHO recommends catch-up vaccination as soon as possible for infants and children who are delayed for any reason in completing the pediatric PCV series [92]. Catch-up vaccination was evaluated in 606 participants composed of three age

a.

	V114 (n=3589) n (%)	PCV13 (n=2058) n (%)
≥1 AE	3363 (93.7)	1912 (92.9)
- Injection-site AEs	2501 (69.7)	1387 (67.4)
- Systemic AEs	3266 (91.0)	1846 (89.7)
Vaccine-related AEs*	3209 (89.4)	1793 (87.1)
- Injection-site AEs	2498 (69.6)	1385 (67.3)
- Systemic AEs	2894 (80.6)	1567 (76.1)
Serious AEs	358 (10.0)	217 (10.5)
- Serious vaccine-related AEs	2 (0.1)	1 (0.0)
Discontinuations due to an AE	0 (0.0)	0 (0.0)
Deaths	2 (0.1)	2 (0.1)

*Determined by the investigator to be related to the vaccine.

b.

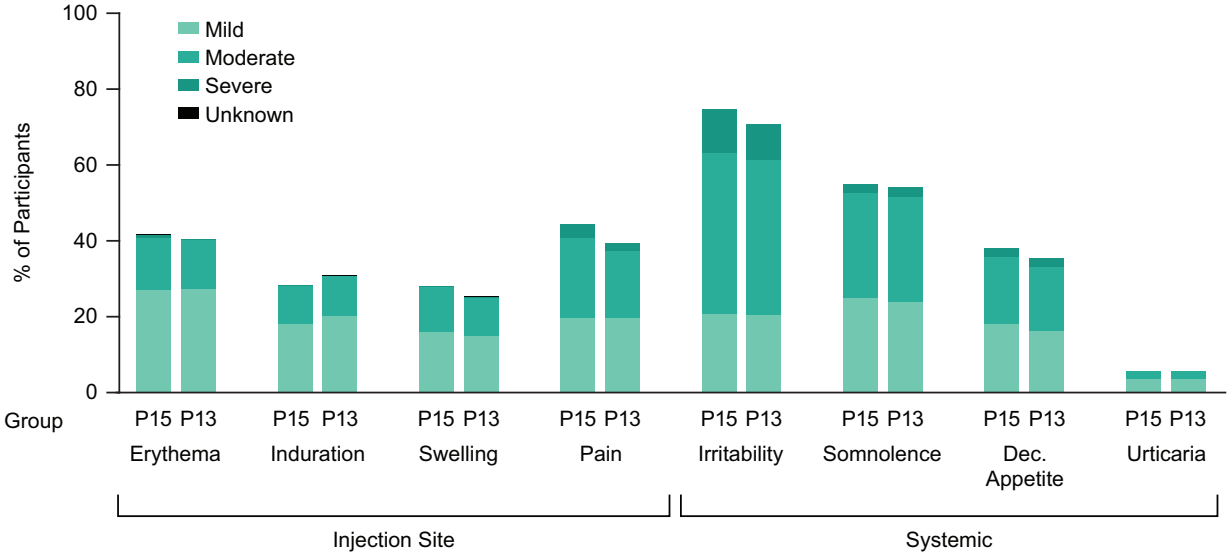

Figure 1. Safety profile of V114 in healthy infants after any study vaccine dose across 4 studies (V114–025, –027, –029, and – 031). For V114–027, groups 1 (complete PCV13 regimen) and 5 (complete V114 regimen) were used for this analysis. Top: the number (n) and proportion (%) of participants included in each safety category. Bottom: solicited AE summary, with proportions of participants experiencing an AE and intensity in the stacked bar in the V114 (P15) and PCV13 (P13) groups. The 2 deaths that occurred in recipients of V114 were due to complications from congenital heart disease and a craniocerebral injury following a motor vehicle accident.

cohorts: 7–11 months (pneumococcal vaccine naïve, received a 3-dose PCV regimen), 12–23 months (PCV naïve, received a 2-dose V114 regimen), and 2–17 years of age (PCV experienced or naïve, received a single V114 dose). Overall, the proportion, duration, and intensity of AEs were similar between groups and no vaccine-related SAEs and/or deaths were reported, demonstrating that V114 was well tolerated. At 30 days after the last PCV dose in all age cohorts, V114 generated robust immune responses to each of the 15 serotypes as assessed by IgG GMCs and response rates, which were comparable to PCV13 for the shared serotypes and higher for serotypes 22F and 33F.

Switching from PCV13 to V114 mid-schedule was evaluated at each of the four doses in the 3 + 1 vaccination regimen in 900 healthy infants. The safety profile of mixed dosing schedules or a complete V114 dosing schedule, including the proportions of participants with AEs, was comparable to participants who received a full 4-dose series of PCV13. No V114-related SAEs occurred during the study, and no deaths were reported. One vaccine-related SAE was reported in the PCV13 group. Immunogenicity data, including serotype-specific response rates and IgG GMCs, were generally comparable for all groups of shared serotypes. Interestingly, the interchangeability study design allowed for the evaluation of immune responses to serotypes

22F and 33F after increasing doses of V114. As shown by response rates, IgG GMCs, and reverse cumulative distribution curves, higher antibodies to both serotypes were observed when at least a single dose of V114 was administered during the infant series and at the toddler age. A single dose of V114 during either the infant primary series or the toddler booster dose was sufficient to induce near-maximal IgG levels against serotype 22F, while serotype 33F immunogenicity increased incrementally with the number of V114 doses received. As has been shown in studies of prior PCVs, individual vaccine serotypes can differ in their immunogenicity profile and the number of doses needed for peak response [93,94].

2.4. V114 concomitant use with other routine pediatric vaccines

In prior PCV development programs, PCVs have been shown to have minimal impact on the immunogenicity of concomitantly administered routine pediatric vaccines [95–98]. While concomitant routine pediatric vaccine administration was allowed throughout the V114 Phase 3 program, four studies had prespecified noninferiority hypotheses regarding immunogenicity of concomitantly administered study vaccines with V114 [87–90]. Concomitant study vaccines tested included pentavalent and hexavalent combination vaccines, rotavirus vaccine, hepatitis A and B vaccines, MMR vaccine, varicella vaccine, and Hib vaccine. Immune responses at PPS and PTD to all vaccine antigens tested in the Phase 3 program had noninferior immunogenicity when co-administered with V114 compared to co-administration with PCV13 (summary in Table 2). These data demonstrate that V114 can be given as part of the pediatric vaccination schedule without interference with the tolerability and immunogenicity of other routine pediatric vaccines.

2.5. V114 in at-risk populations

Infants and children with sickle cell disease (SCD) are at increased risk of IPD [99–102], and IPD due to serotypes 22F and 33F contribute to residual IPD in individuals with SCD [103]. Although relatively understudied compared to healthy children, pneumococcal vaccines have been shown to be immunogenic in children with SCD [104–107]. For V114, the safety and immunogenicity of a single vaccination was evaluated in 104 children 5–17 years of age with SCD [108]. V114 was well tolerated, with a safety profile generally comparable to PCV13. No vaccine-related SAEs were reported, and no deaths occurred during the study. A single dose of V114 induced serotype-specific immune responses (compared to baseline prior to vaccination) to all 15 serotypes; IgG GMCs and OPA GMTs against the 13 shared serotypes were comparable to PCV13 and higher for serotypes 22F and 33F. Although PCV was not followed up with PPSV23 in this study as is recommended for children with SCD, other studies have supported the use of V114 followed by PPSV23 in at-risk populations [68,109].

Children living with HIV are highly vulnerable to IPD compared to healthy children, even on anti-retroviral therapy with undetectable viremia [110–112]. Similar to children with SCD, a sequential vaccination strategy is often recommended for children with HIV, in which vaccination with PCV is followed by vaccination with PPSV23 for broader pneumococcal serotype coverage. The safety and immunogenicity of V114 or PCV13 followed 8 weeks later by PPSV23 was evaluated in 407 children with HIV receiving mono or combination antiretroviral therapies [109]. Administration of V114 followed by PPSV23 was well tolerated in the study. There was a numerically higher proportion of participants who reported vaccine-related AEs in the V114 group (78.3%) compared to the PCV13 group (67.2%). However, the majority of AEs in both groups were of mild-to-moderate intensity and of short duration. The proportions of participants with SAEs were comparable between groups, and no V114-related SAEs or deaths were reported. Immunogenicity to all 13 shared serotypes was induced following V114, and these levels were maintained or increased after PPSV23. Serotypes 22F and 33F were higher

Table 2. Summary of concomitant vaccine immunogenicity assessments from PCV15 studies using 3 + 1 and 2 + 1 vaccination regimens.

		2 + 1 schedule	2 + 1 alternative schedule	3 + 1 schedule	
Antigen	Criteria	Percent difference PCV15-PCV13 (95% CI)			Noninferiority margin - %
Diphtheria toxoid	% ≥0.1 IU/ml	−0.6 (−1.7, 0.4)	0.2 (−0.6, 1.0)	−0.7 (−2.6, 1.1)	−10
Tetanus toxoid	% ≥0.1 IU/ml	−0.4 (−1.3, 0.3)	0.2 (−0.6, 1.0)	0.2 (−0.4, 0.8)	−5
Pertussis-PT	% ≥5 EU/ml	−0.2 (−1.3, 0.9)	0.2 (−0.6, 1.0)	0.5 (−0.7, 1.9)	−10
Pertussis-FHA	% ≥5 EU/ml	−0.2 (−1.0, 0.5)	0.2 (−0.6, 1.0)	−0.3 (−1.3, 0.8)	−10
Pertussis-FIM 2/3	% ≥20 EU/ml		0.2 (−0.8, 1.2)	2.0 (−3.1, 7.1)	−10
Pertussis-PRN	% ≥5 EU/ml	−0.4 (−1.3, 0.3)	0.2 (−0.8, 1.2)	1.8 (−3.2, 6.8)	−10
Poliovirus 1	% with NAb ≥ 1:8 dilution	0.0 (−0.7, 0.7)	0.0 (−0.9, 0.9)	0.0 (−0.7, 0.8)	−5
Poliovirus 2	% with NAb ≥ 1:8 dilution	0.0 (−0.7, 0.7)	0.2 (−0.6, 1.1)	0.0 (−0.6, 0.6)	−5
Poliovirus 3	% with NAb ≥ 1:8 dilution	0.2 (−0.5, 1.1)	0.0 (−0.8, 0.7)	0.0 (−0.6, 0.6)	−5
Hib-PRP	% ≥0.15 ug/ml	0.4 (−1.3, 2.1)	−1.1 (−3.3, 0.9)	−1.4 (−4.3, 1.5)	−10
HBsAg	% ≥10 mIU/ml	−0.8 (−2.0, 0.0)	−0.6 (−2.0, 0.5)	−0.2 (−3.7, 2.0)	−10
Hepatitis A	% ≥10 mIU/ml			0.3 (−1.6, 2.2)	−10
Measles	% ≥225 mIU/ml			−0.2 (−1.8, 1.3)	−5
Mumps	% ≥10 mumps Ab units/ml			−1.7 (−3.8, 0.2)	−5
Rubella	% ≥10 IU/ml			−0.9 (−2.3, 0.5)	−5
Varicella zoster	% ≥5 gpELISA units/ml			−1.3 (−3.2, 0.5)	−10
				Ratio PCV15/PCV13 (95% CI)	
Rotavirus	IgA GMT			0.97 (0.70, 1.34)	>0.5

CI=confidence interval; IU=international unit; EU=endotoxin unit; PT=pertussis toxin; FHA=filamentous hemagglutinin; FIM 2/3=fimbriae types 2 and 3; PRN=pertactin; Nab=neutralizing antibodies; Hib=Haemophilus influenzae type b; PRP=polyribosylribitol phosphate; HBsAg=hepatitis B surface antigen; Ab=antibody; gpELISA=glycoprotein enzyme-linked immunosorbent assay; IgA=immunoglobulin A; GMT=geometric mean titer.

after V114 and maintained or increased after PPSV23, suggesting earlier protective immunogenicity in this population. Overall, these data support the use of V114 in HIV-infected children.

Preterm infants (less than 37 weeks gestation) have up to three times the risk of IPD compared to full-term infants [113]. As an objective in the Phase 3 program, a proportion of healthy infants enrolled in 4 V114 studies were preterm infants, and a subsequent pooled secondary analysis was performed on these data to evaluate safety and tolerability of V114 in this population. A total of 354 preterm infants were vaccinated using a 3 + 1 regimen with either V114 or PCV13. Proportions of participants with AEs, vaccine-related AEs, and SAEs were comparable between groups. Pyrexia occurred in 37.4% of V114 recipients and 47.2% of PCV13 recipients, and only three participants recorded a maximum temperature of >40.0°C after any dose (2 in the V114 group, 1 in the PCV13 group). No V114-related SAEs occurred in preterm infants, and no deaths occurred. As assessed by serotype-specific IgG GMCs and OPA GMTs, V114 induced comparable immune responses to the 13 shared serotypes and higher responses to serotypes 22F and 33F in preterm infants. These data demonstrate the safety, tolerability, and immunogenicity of V114 in preterm infants.

3. Expert opinion

V114 is a valuable modern PCV in the fight to prevent IPD globally. The safety and immunogenicity profiles in infants and children are favorable and will provide broader pneumococcal serotype coverage without increased reactogenicity. V114 is interchangeable with PCV13, can be safely administered with other routine pediatric vaccines, and is well tolerated and immunogenic in several at-risk populations, thereby facilitating a seamless integration into existing pediatric immunization programs. The focus of the Phase 3 program on at-risk populations and the geographic diversity in site selection is a specific strength in the development of V114 and provides confidence in the use of V114 in individuals with a variety of preexisting conditions and backgrounds. The expected added coverage from inclusion of serotypes 22F and 33F will be highly beneficial in most regions globally where these are prominent non-vaccine serotypes causing IPD.

An important consideration for the development of new PCVs is providing broader serotype coverage while also providing robust immunogenicity to all serotypes contained in the vaccine. Some serotypes contained in current PCVs, including 3, 19A, and 19F, remain major causes of disease even in individuals fully vaccinated with a PCV that includes these serotypes. Serotype 3 currently leads in vaccine-type residual disease globally. Therefore, there is caution warranted in projections of new PCV effectiveness based simply on the serotypes contained in the vaccine. The V114 development program aimed at improving immunogenicity to serotype 3 which was successful and resulted in higher vaccine-induced immune responses compared to PCV13 across pediatric and adult populations. This outcome demonstrates that optimization of PCVs for increased immunogenicity against problematic serotypes is possible and adds anticipation to future real-world evidence studies of V114 effectiveness against disease caused by serotype 3. It remains unknown whether a focused approach such as the one used with V114 for serotype 3 could be employed to improve immunogenicity and subsequent vaccine effectiveness against other recalcitrant serotypes such as 19A and 19F. This should remain an important consideration in the development of new PCVs while also engineering for broader coverage. While alternative approaches to pneumococcal vaccine design are currently in development using novel carrier proteins, novel adjuvants, and protein-based or whole-cell platforms, it is unknown whether any of these can improve on the current most widely used approach while also maintaining a favorable safety and tolerability profile.

With the licensure of V114 and more recently PCV20, the global use of PCVs will change and therefore with it the epidemiology of pneumococcal diseases. It is possible that these changes will result in a significant impact on antimicrobial resistance among pneumococci globally as more serotypes are targeted with newer vaccines. There is an associated opportunity within national immunization programs as the options for the prevention of pneumococcal disease are expanded. While all currently licensed pneumococcal vaccines are projected to be cost effective, cost variation between pneumococcal vaccines can affect decision-making at the national level. Cost-effective, broad protection is now available in newer PCVs, while established vaccines such as PPSV23, for children 2 years and older, and PCV10 still offer benefits at a lower price point. Global access to effective pneumococcal vaccines should be a continued priority as the complexity and associated development cost of current generation vaccines change.

In conclusion, it is an exciting time for pneumococcal vaccines and the hope of more complete protection against PD to prevent morbidity and mortality from pneumococcal infections. With a favorable safety and tolerability profile and robust immunogenicity results coupled with broad pneumococcal serotype coverage, V114 is well positioned to advance prevention of pneumococcal disease globally.

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Declaration of interest

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Author contributions

All authors contributed to the conception, design, or planning and/or the interpretation of the results and drafting of the manuscript. All authors critically reviewed or revised the manuscript for important intellectual content, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

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