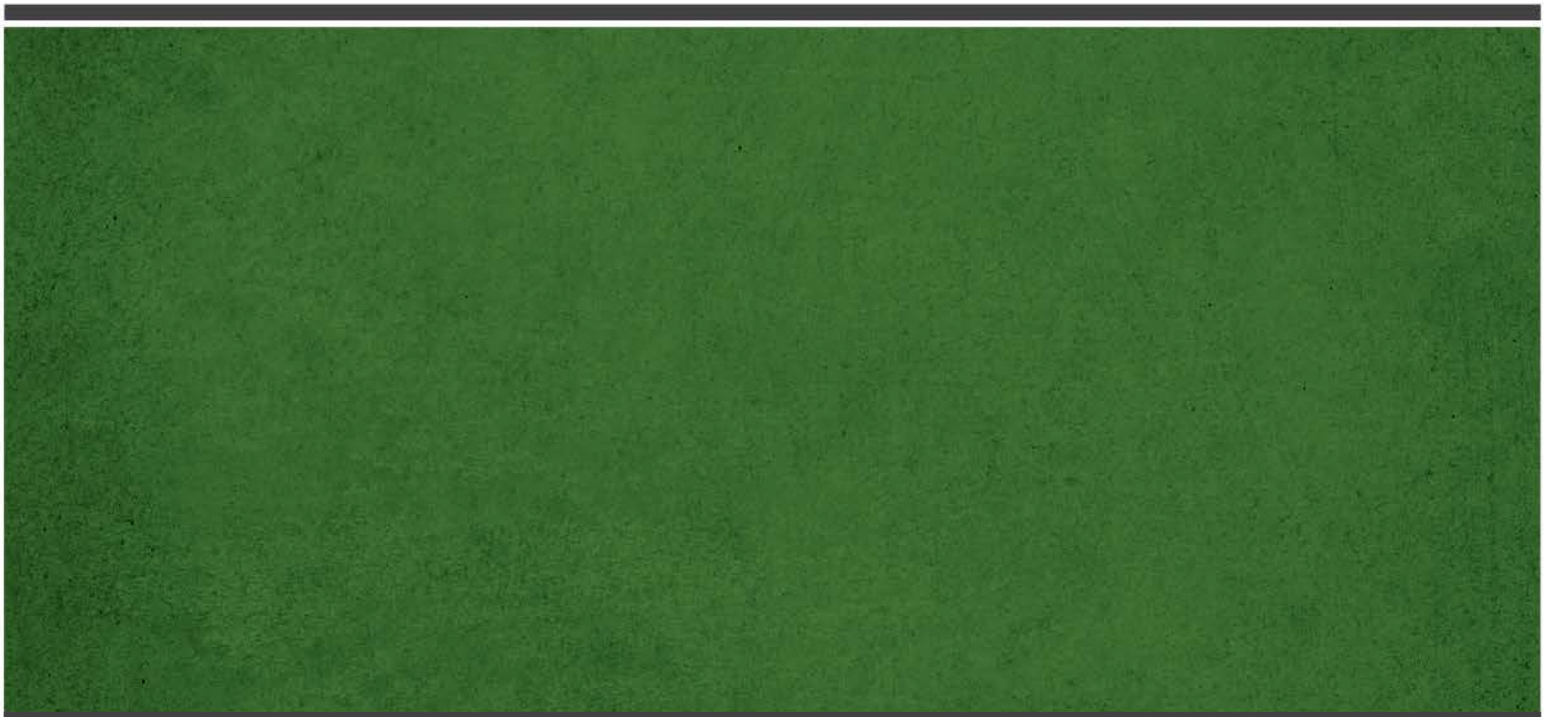
An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Interim guidance on the use of pneumococcal 15-valent conjugate vaccine (PNEU-C-15) in pediatric populations



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Preamble

The National Advisory Committee on Immunization (NACI) is an External Advisory Body that provides the Public Health Agency of Canada (PHAC) with independent, ongoing, and timely medical, scientific, and public health advice in response to questions from PHAC relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence-based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include economics, ethics, equity, feasibility, and acceptability. Not all NACI statements will require in-depth analyses of all programmatic factors. While systematic consideration of programmatic factors will be conducted using evidence-informed tools to identify distinct issues that could impact decision-making for recommendation development, only distinct issues identified as being specific to the vaccine or vaccine-preventable disease will be included.

This statement contains NACI's independent advice and recommendations, which are based upon the best current available scientific knowledge. This document is being disseminated for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monograph. Recommendations for use and other information set out herein may differ from that set out in the product monographs of the Canadian manufacturers of the vaccines. Manufacturer(s) have sought approval of the vaccines and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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I. Background

On November 16, 2021, Health Canada authorized the use of a pneumococcal conjugate 15-valent vaccine, PNEU-C-15 (Vaxneuvance®)[1], for adults 18 years of age and older. An age extension for the use of PNEU-C-15 in the pediatric population was authorized on July 8, 2022, under a priority review. This vaccine provides additional protection against two serotypes (22F and 33F) compared to the currently authorized pneumococcal conjugate 13-valent vaccine, PNEU-C-13 (Prevnar 13®). PNEU-C-15 is currently indicated for active immunization of infants, children and adolescents from 6 weeks through 17 years of age (prior to the 18th birthday) and adults 18 years of age and older for the prevention of invasive pneumococcal disease (IPD), including sepsis, meningitis, complicated pneumonia with or without empyema and bacteremia) caused by *Streptococcus pneumoniae* serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F).

In Canada, current routine immunization programs for healthy infants include the use of pneumococcal conjugate (PNEU-C) vaccines provided either using a 3-dose schedule (at 2 months, 4 months, and 12 months of age) or a 4 dose schedule (at 2 months, 4 months and 6 months followed by a booster dose at 12 to 15 months of age). The routine immunization schedule for healthy low-risk children in the province of Quebec is a mixed schedule that includes the use of PNEU-C-10 at 2 and 4 months of age and the use of PNEU-C-13 at 12 months of age[8]. For children at high risk, there is an additional dose of PNEU-C-10 at 6 months of age.

Among infants at high risk of IPD due to an underlying medical condition, the current routine immunization programs in all provinces and territories include receipt of PNEU-C vaccine in a 4 dose schedule (at 2 months, 4 months and 6 months followed by a booster dose at 12 to 15 months of age) as well as one dose of PNEU-P-23 vaccine at 24 months of age, at least 8 weeks after the last PNEU-C-13 vaccine dose[9]. Children and adolescents at highest risk of IPD should also receive 1 booster dose of PNEU-P-23 vaccine[9].

In 2019, based on the childhood National Immunization Coverage Survey (cNICS), it was estimated that 84.4% of 2-year-old children in Canada had 3 or 4 doses of the pneumococcal vaccine[10]. The current national vaccination coverage goal by 2025 is to have 95% of 2-year-old children immunized with 3 or 4 doses of the recommended pneumococcal vaccine(s)[11]. Some but not all jurisdictions have already achieved the target.

II. Statement objective

The primary objective of this Interim Guidance is to review evidence on the safety and immunogenicity of PNEU-C-15 in the pediatric age group and to develop interim recommendations on its interchangeability with PNEU-C-13 for use in routine pediatric schedules as well as for children at high risk of IPD[2].

III. Methods

NACI reviewed key questions raised in consultation with the Canadian Immunization Committee and the Pneumococcal Working Group (PWG). These included the need for evidence pertaining to the burden of disease to be prevented in the target population(s), the safety, immunogenicity, efficacy, and effectiveness of the vaccine(s), vaccine schedules, and other aspects of the overall pediatric pneumococcal vaccine immunization strategy. A rapid evidence synthesis of clinical trials was performed by the NACI Secretariat and reviewed by the PWG on September 28, 2022.

NACI reviewed this evidence on October 3rd, 2022. The description of relevant considerations, rationale for specific decisions, and knowledge gaps are further described in the text. NACI voted on the interim recommendations on the use of PNEU-C-15 in pediatric populations on October 4th, 2022, and recommendations were approved on December 12, 2022.

For additional information and NACI's current recommendations on the use of pneumococcal vaccines in children, please refer to the Pneumococcal vaccine chapter in the Canadian Immunization Guide (CIG).

Further information on NACI's process and procedures is available elsewhere[3,4].

IV. Vaccine

In Canada, four preparations, PNEU-C-10 (Synflorix™)[5], PNEU-C-13 (PREVNAR®13)[6], PNEU-C-15 (Vaxneuvance®)[1], and PNEU-P-23 (Pneumovax®23)[7] of pneumococcal vaccine are currently authorized for use in persons less than 18 years of age (Table 1). All vaccines are indicated for the prevention of IPD caused by S. pneumoniae vaccine-contained serotypes.

Table 1: Comparison of vaccines authorized for use in persons less than 18 years of age in Canada

	SYNFLORIX™ (PNEU-C-10)[5]	**PREVNAR® 13 (PNEU-C-13)[6]**	**VAXNEUVANCE® (PNEU-C-15)[1]**	**PNEUMOVAX® 23 (PNEU-P-23)[7]**
Manufacturer	GSK	Pfizer	Merck	Merck
Date of initial authorization in Canada	December 11, 2008	December 21, 2009	November 16, 2021 (adults) July 8, 2022 (pediatric)	December 23, 1983
Indication	Indicated for the protection against diseases caused by *S. pneumoniae* vaccine-contained serotypes in infants and children from 6 weeks up to 5 years of age.	Indicated for the protection against IPD (all age groups) and AOM (6 weeks to 5 years of age) caused by *S. pneumoniae* vaccine-contained serotypes in infants and children from 6 weeks to less than 18 years of age.	Indicated for the protection against IPD caused by *S. pneumoniae* vaccine-contained serotypes in infants and children from 6 weeks to less than 18 years of age.	Indicated for the protection against IPD caused by *S. pneumoniae* vaccine-contained serotypes in children from 2 to less than 18 years of age at high risk of IPD.

	SYNFLORIX™ (PNEU-C-10)[5]	**PREVNAR® 13 (PNEU-C-13)[6]**	**VAXNEUVANCE® (PNEU-C-15)[1]**	**PNEUMOVAX® 23 (PNEU-P-23)[7]**
Type of vaccine	Conjugate	Conjugate	Conjugate	Polysaccharide
Composition/ Carrier protein /adjuvant	1 mcg of each saccharide for *S. pneumoniae* serotypes 1, 5, 6B, 7F, 9V, 14 and 23F, and 3 mcg of saccharide for serotype 4, 18C and 19F. Non-Typeable Haemophilus influenza (NTHi) protein D, diphtheria, and tetanus toxoid carrier protein. Aluminium (as aluminium phosphate), sodium chloride and water for injections.	2.2 mcg of each saccharide for *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F and 23F, 4.4 mcg of saccharide for serotype 6B. 34 mcg total concentration of non-toxic variant of diphtheria toxin CRM_{197} carrier protein (individually conjugated). 125 mcg aluminum as aluminum phosphate adjuvant 4.25 mg sodium chloride, 100 mcg polysorbate 80, 295 mcg succinic acid and water for injection.	2.0 mcg each of polysaccharide serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F and 4.0 mcg of polysaccharide serotype 6B. 30 mcg total concentration of non-toxic variant diphtheria toxin CRM_{197} carrier protein. 125 mcg of aluminum (as aluminum phosphate adjuvant). 1.55 mg L-histidine, 1 mg of polysorbate 20, 4.5 mg sodium chloride and water for injection.	25 mcg each capsular polysaccharide serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23Fand 33F. No adjuvant Sodium chloride 0.9 % w/w, phenol 0.25% w/w, (preservative) and water for injection to volume.
Route of administration	Intramuscular injection	Intramuscular injection	Intramuscular injection	Intramuscular or subcutaneous injection
Contraindications	Known hypersensitivity to any component of the vaccine.	Known hypersensitivity to any component of the vaccine, including diphtheria toxoid.	History of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine or any diphtheria toxoid-containing vaccine.	Known hypersensitivity (e.g., anaphylaxis) to any component of the vaccine.
Storage Requirements	Single-dose prefilled syringe. Refrigerate at 2°C to 8°C. Do not freeze. Store in original package.	Single-dose prefilled syringe. Refrigerate at 2°C to 8°C. Do not freeze. Store in original package.	Single-dose prefilled syringe. Refrigerate at 2°C to 8°C. Do not freeze. Protect from light. Administer as soon as possible after being removed from the refrigerator.	Multi-dose vial. Refrigerate at 2°C to 8°C. Discard opened vial after 48 hours.

V. Evidence summary

V.1 Burden of Disease

IPD became nationally notifiable in 2000; before this time, only cases of pneumococcal meningitis were notifiable nationally. With the implementation of routine childhood pneumococcal immunization with PNEU-C-7 vaccine between 2002 and 2006, and PNEU-C-13 vaccine between 2010 and 2012, IPD incidence among children less than two years of age has decreased substantially from a peak of 73.0 cases per 100,000 population in 2003 to an average of 16.2 cases per 100,000 population between 2015 and 2019[12].

Based on the data reported to Canadian Notifiable Disease Surveillance System (CNDSS), IPD due to PNEU-C-13 serotypes decreased in all pediatric age groups between 2011 and 2020[13]. During this period, the decrease ranged from approximately 42% in the 2- to 4- year-old age group to approximately 20% in other age groups. IPD due to serotype 3 deceased from 6.8% in 2011 to 4.9% on 2020 among children less than 2 years old, while it increased from 11.1% in 2011 to 15.8% in 2020 among children 2 to 4 years old. At the same time, IPD cases due to the two additional serotypes 22F and 33F included in the newly authorized PNEU-C-15 vaccine increased from 7.9% to 15.9% in the less than 2 year old age group, and from 11.8% to 18.4% in the 2 to 4 year old age group[13].

The proportion of serotypes 22F and 33F in children 0 to 4 years of age increased from 9.6% in 2011 to 16.7% in 2020. In the 5 to 17 year-old age group, the proportion of these serotypes increased from 5.4% in 2011 to 20.2% in 2019, before decreasing back to 5.0% in 2020. The proportion of serotype 3 in children 0 to 4 years old stayed relatively stable (8.7% in 2011, 8.3% in 2020) and for those 5 to 17 years old, it increased from 6.7% in 2011 to 20.0% in 2020. Data for 2020 may not be reflective of the actual trend as the COVID-19 pandemic may have impacted disease incidence in all age groups.

Serotype 22F was more commonly (11.7%) reported in 2020 among IPD cases in children less than 5 years of age than serotype 33F (5.0%). In 2020, serotypes 3, 22F, 10A, 19A and 15B/C were the most common causes of pediatric IPD, representing approximately half of the cases. Serotype 3 alone caused 11.3% of all pediatric IPD cases in 2020, it was least prevalent (4.9%) in the less than 2 year old age group.

V.2 Evidence on Safety, Immunogenicity, and Efficacy of PNEU-C-15 in Pediatric Populations

NACI reviewed the evidence on safety, and immunogenicity of PNEU-C-15 vaccine from eight Phase 2/3 clinical trials[15–22] which included a range of pediatric populations and which used different vaccine schedules (Table 2). An additional trial, V114-022[23], provided immunogenicity and safety data following the immunization of hematopoietic stem cell transplant (HSCT) recipients.

Since there are currently no efficacy or effectiveness data available for PNEU-C-15 vaccine for any pediatric indication, the basis for regulatory authorization was the demonstration of

comparable safety and immunogenicity (non-inferiority for serotypes common to PNEU-C-13 and superiority for two additional serotypes) in relation to PNEU-C-13 vaccine.

Table 2. Summary of PNEU-C-15 Clinical Trials

Study	Population	Treatments (planned number of participants per group)	Dosing Schedule	Primary Immunogenicity Evaluation
V114-008[15] Lot consistency (Phase 2)	Healthy infants (42 to 90 days of age)	PNEU-C-15, Lot 1 (N=350), PNEU-C-15, Lot 2 (N=350), PNEU-C-13 (N=350)	3 + 1 (2, 4, 6 and 12 to 15 months of age)	Proportion with IgG ≥0.35 µg/mL for 13 shared serotypes at 30 days PD3 IgG GMC at 30 days PD3
V114-029[20] Pivotal	Healthy term and preterm infants (42 to 90 days of age)	PNEU-C-15 (N=860), PNEU-C-13 (N=860) *concomitant administration with routinely administered pediatric vaccines	3 + 1 (2, 4, 6 and 12 to 15 months of age)	IgG response rates at 30 days PD3 IgG GMC at 30 days PD3 IgG GMC at 30 days PD4
V114-031[22] Safety	Healthy term and preterm infants (42 to 90 days of age)	PNEU-C-15 (N=2000), PNEU-C-13 (N=400)	3 + 1 (2, 4, 6 and 12 to 15 months of age)	None
V114-024[17] Catch-up	Healthy infants, children, and adolescents (7 months to 17 years of age)	PNEU-C-15 (N=300), PNEU-C-13 (N=300)	7 to 11 months of age (day 1, week 4 and week 12), 12 to 23 months of age (day 1 and week 8), 2 to 17 years of age (day 1)	IgG GMC at 30 days following the last dose
V114-027[19] Interchangeability	Healthy term and preterm infants (42 to 90 days of age)	P/P/P/P (N=180), P/P/P/V (N=180), P/P/V/V (N=180), P/V/V/V (N=180), V/V/V/V (N=180)	3 + 1 (2, 4, 6 and 12 to 15 months of age)	IgG GMC for the 13 shared serotypes at 30 days PD4 (group 2, group 3, group 4 vs. group 1)
V114-023[16] Sickle Cell	Children with sickle cell disease (5 to 17 years of age)	PNEU-C-15 (N=69), PNEU-C-13 (N=33)	Single dose (day 1)	IgG GMC at Day 30
V114-030[21] HIV	Children with HIV (6 to 17 years of age)	PNEU-C-15 (N=203), PNEU-C-13 (N=204)	Single dose (day 1) followed by a single dose of PNEU-P-23 (week 8)	IgG GMC at Day 30

Study	Population	Treatments (planned number of participants per group)	Dosing Schedule	Primary Immunogenicity Evaluation
V114-025[18] EU 2+1 regimen pivotal trial	Healthy term and preterm infants (2 to 15 months)	PNEU-C-15 (N=591), PNEU-C-13 (N=593) with Infanrix4 + Rotarix	2 or 3 + 1 (preterm infants) (2 or 2&3, 4, and 11 to 15 months)	IgG response rates at 30 days post toddler dose IgG GMC at 30 days post toddler dose
V114-022[23] Stem cell transplant recipients	Adults and children (3 to <18 years of age) who are HSCT recipients	PNEU-C-15 (N=139), PNEU-C-13 (N=138)	3 + 1 (day 1, 30 and 60, and 12 months after HSCT)	IgG GMC at 30 days following dose 3

Abbreviations: V=PNEU-C-15; P=PNEU-C-13; HSCT= hematopoietic stem cell transplant; GMC= geometric mean antibody concentration; IgG=immunoglobulin G; PD3/4=post dose 3 or 4

V.2.1 Immunogenicity Summary

NACI reviewed the available evidence on immunogenicity of PNEU-C-15 in mixed PNEU-C-15 and PNEU-C-13 regimens (pertaining to routine immunization programs for infants and children without IPD risk factors) as well as evidence on immunogenicity of PNEU-C-15 in high-risk pediatric populations. Additional details on immunogenicity findings that were reported in PNEU-C-15 clinical trials in pediatric populations are provided in Appendix A.

Immunogenicity of PNEU-C-15 in mixed PNEU-C-15 and PNEU-C-13 regimens

To address the policy question of PNEU-C-15 interchangeability with PNEU-C-13, NACI reviewed the evidence on immunogenicity in the mixed PNEU-C-15 and PNEU-C-13 regimen (interchangeability trial, V114-027[19]). Overall, available evidence suggests that the vaccines had comparable immune responses for the 13 shared serotypes. The immune response to the two additional serotypes (22F, 33F) and for serotypes 3 was higher after PNEU-C-15 compared to PNEU-C-13. In one study, V114-029 immune responses to serotypes 22F, 33F and 3 were superior following PNEU-C-15 compared to PNEU-C-13 (Appendix A).

In the V114-027 trial, 900 healthy participants 40 to 90 days of age were randomized to one of five groups (n=180 per group) to receive a complete four dose series with PNEU-C-13, PNEU-C-15 or mixed regimen initiated with one, two or three doses of PNEU-C-13 and continued with PNEU-C-15.

When assessed by serotype-specific IgG GMCs and IgG GMC ratios, a mixed regimen of PNEU-C-15 and PNEU-C-13 30 days after dose 4 (administered at approximately 12 to 15 months of age) elicited generally comparable immune responses to a complete 4-dose regimen of PNEU-C-13 for the 13 shared serotypes.

At 30 days following the receipt of the third dose, serotype-specific immune responses for the 13 shared serotypes were generally comparable across intervention groups as assessed by the proportions of participants meeting the pre-specified IgG seroresponse threshold value of ≥0.35

µg/mL and IgG GMCs. In contrast, serotype-specific immune responses for unique serotypes 22F and 33F were higher in PNEU-C-15 vaccine recipients. Immune responses for serotype 33F increased incrementally with additional PNEU-C-15 doses received in the infant series (as assessed by response rates and IgG GMCs) while they remained unchanged for serotype 22F.

Immunogenicity of PNEU-C-15 in pediatric populations at high-risk of IPD

To address the policy question of PNEU-C-15 interchangeability with the currently recommended PNEU-C-13 for children at increased risk of IPD, NACI reviewed the evidence of immunogenicity data from two studies. Overall, in high-risk populations, PNEU-C-15 had comparable immunogenicity to PNEU-C-13 for shared serotypes.

In the V114-23[16] and V114-030[21] trials children 5-17 years old living with sickle cell disease and children 6-17 years old living with HIV, respectively, were randomized to receive either PNEU-C-15 or PNEU-C-13 and PNEU-C-15+PNEU-P-23 or PNEU-C-13+PNEU-P-23. When assessed by serotype-specific IgG GMC and OPA GMT at 30 days post vaccination, immune responses were generally similar between the intervention and comparator groups for the shared serotypes and higher for the PNEU-C-15 unique serotypes, 22F and 33F. At 30 days following the administration of PNEU-P-23 in V114-030, IgG GMC and OPA GMTs were numerically similar for all 13 shared and the two unique serotypes.

V.2.2 Safety Summary

In all studies, the evidence on safety showed that PNEU-C-15 is safe in healthy children and in select special populations. Safety following immunization with PNEU-C-15 vaccine was measured in all Phase 2/3 clinical trials that included healthy children15,17–20,22 (six studies), children with sickle cell disease16 (one study) and HIV infection21 (one study). The measured safety endpoints included the proportion of participants with solicited local and systemic adverse events (AEs) 1-14 days post vaccination, maximum body temperature measurements (1–7 days post vaccination) and serious adverse events (SAEs), up to 6 months following vaccination.

In the pivotal study[18], in which PNEU-C-15 was administered as a 3-dose series (V114-025), the safety profile was found to be generally comparable to PNEU-C-13[18] (Table 9, Appendix A). An integrated safety analysis[1] was conducted for healthy infants (studies 025[18], 027[19], 029[20] and 031[22]) in the final safety database including 3,592 participants receiving at least one dose of PNEU-C-15 and 2,062 receiving at least one dose of PNEU-C-13.

The proportions of participants with local and systemic AEs (solicited and unsolicited) after each dose in the primary series, after the toddler booster dose, and after any dose were generally comparable in both intervention groups. In infants, the most frequently reported AEs following each dose were irritability (45.7%), somnolence (21.8%), injection-site pain (21%), decreased appetite (19.4%) and other injection-site reactions (erythema, swelling, induration; all less than 22%) (Table 10, Appendix A). The majority of participants who received PNEU-C-15 reported maximum body temperature measurements of less than 38.0 °C, with a temperature distribution that was comparable between intervention groups. Of the participants with a maximum body temperature higher than 38.0 °C, the majority had a maximum body temperature below 39.0 °C.

SAEs were reported for up to 5.5% of participants following each dose of PNEU-C-15 and up to 4.7% of participants following each dose of PNEU-C-13. While the majority of SAEs were deemed to be not vaccine-related, there were three vaccine-related SAEs reported in 2 participants in the PNEU-C-15 group and 1 participant in the PNEU-C-13 group (all were pyrexia requiring hospitalization). There were 4 deaths reported among study participants, of which none were considered to be related to the study interventions. The safety profile of mixed dosing regimens with PNEU-C-15 was comparable to complete PNEU-C-13 and PNEU-C-15.

In children with sickle cell disease or living with HIV infection[16,21], the safety profile was generally consistent with the safety profile in healthy children.

V.3 Evidence on Concurrent Administration of PNEU-C-15 With Other Routinely Administered Pediatric Vaccines

Concurrent administration of PNEU-C-15 with other routinely administered pediatric vaccines was assessed in three clinical trials (protocols 025[18], 027[19] and 029[20]) involving over 1,700 infants and toddlers[18–20]. In addition to PNEU-C-15, study participants also received diphtheria, tetanus, pertussis, poliomyelitis (serotypes 1, 2 and 3), hepatitis A, hepatitis B, *Haemophilus influenzae* type b, measles, mumps, rubella, varicella, and rotavirus vaccine, either as monovalent or combination vaccines within the primary infant series or with the toddler booster dose.

Immune responses to all antigens provided concomitantly with PNEU-C-15 met non-inferiority criteria as assessed by the individual antigen-specific response rates (for the combination and monovalent vaccines) or GMT (rotavirus vaccine) at 30 days following vaccine administration. Overall, all studies reviewed by NACI showed that PNEU-C-15 can be administered concurrently with other routine pediatric vaccines.

VI. Recommendation

Following the review of key evidence summarized above, NACI makes the following interim recommendation for public health program level decision-making.

Please see Table 3 for a more detailed explanation of strength of NACI recommendations and grade of the body of evidence.

NACI recommends that PNEU-C-15 vaccine may be used interchangeably with PNEU-C-13 vaccine in children less than 18 years of age. A pneumococcal vaccine series may be started or completed with either vaccine. (Discretionary NACI recommendation)

Summary of evidence, rationale, and additional considerations

- There are currently no data on efficacy or effectiveness that would allow a comparative assessment of clinical outcomes of vaccination with PNEU-C-15 versus PNEU-C-13.
- In immunogenicity studies, PNEU-C-15 has shown to have comparable immune responses to PNEU-C-13 for shared serotypes and higher immune responses for unique serotypes as measured by seroresponse rates, total antibody levels, and functional antibody levels.

- PNEU-C-15 has been shown to have comparable safety profile to PNEU-C-13 when given as a single vaccine type series, when used in mixed PNEU-C-15/PNEU-C-13 schedules and when concurrently administered with other routine pediatric vaccines.
- PNEU-C-15 has the potential to prevent up to about 20% more cases of IPD in children 4 years of age and younger based on CNDSS epidemiology data.
- Introduction of PNEU-C-15 programs into routine schedules may provide additional benefit through direct effects on non-invasive pneumococcal infections (e.g., acute otitis media [AOM], community acquired pneumonia [CAP]). In addition, further indirect benefits of broadened protection could be expected in adults over time, as suggested by the reduction of IPD burden in older adults following the introduction of routine PNEU-C pediatric programs.
- Although NACI has not conducted any cost-effectiveness analysis, if product costs were equivalent, then PNEU-C-15 could potentially provide greater health gains and lead to reduced healthcare utilization compared to PNEU-C-13 due to the protection anticipated from two additional serotypes.
- NACI's recommendations for the use of PNEU-P-23 in combination with PNEU-C-13 or PNEU-C-15 for high-risk children remain unchanged.

Table 3. Strength of NACI recommendations

Strength of NACI Recommendation based on factors not isolated to strength of evidence (e.g., public health need)	**STRONG**	**DISCRETIONARY**
Wording	"should/should not be offered"	"may/may not be offered"
Rationale	Known/anticipated advantages outweigh known/anticipated disadvantages ("should"), OR Known/Anticipated disadvantages outweigh known/anticipated advantages ("should not")	Known/anticipated advantages are closely balanced with known/anticipated disadvantages, OR uncertainty in the evidence of advantages and disadvantages exists
Implication	A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.	A discretionary recommendation may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

VII. Programmatic considerations table

Additional information on PNEU-C-15 is contained within the product monograph available through Health Canada's Drug Product Database (DPD).

Table 4. Summary of PNEU-C-15 knowns and unknowns for use in pediatric population

	Knowns	Unknowns
Benefits	• Immune responses for PNEU-C-15 were comparable /non-inferior to PNEU-C-13 for all shared STs • Higher immune response for non-shared STs and for serotype 3 • Non-inferiority of PNEU-C-15 when concurrently administered with other routine childhood vaccines and in a mixed schedules with PNEU-C-13 • Comparable safety profile for PNEU-C-15 vs. PNEU-C-13	• No efficacy/effectiveness data on PNEU-C-15 to assess clinical outcomes. • No data on the clinical significance of higher/lower serotype-specific immune responses including for serotype 3 and unique PNEU-C-15 non PNEU-C- 13 serotypes. • No data on vaccine effectiveness or immunogenicity for PNEU-C-15 in immunocompromised children or other special populations not included in the trials • Impact on the epidemiology of overall pneumococcal disease burden in children and adults and effect on serotype switching • Cost-effectiveness of the use of PNEU-C-15 vs. PNEU-C-13 was not evaluated for this statement/recommendation.
Risks	• Serotype-specific variability with observed lower GMCs for some serotypes in PNEU-C-15 vs. PNEU-C-13	• Potential rare and very rare adverse events specific to PNEU-C-15

In general, vaccines with increased number of antigens will likely broaden protection not only in terms of IPD, but also non-invasive pneumococcal disease which may include AOM, CAP and other pneumococcal infections. For example, in one European study[14], among children aged 6–36 months with clinically diagnosed AOM, 8% of infections were caused by PNEU-C-15 unique serotypes.

Given the significant number of AOM and CAP infections, even small percent reductions in cases have the potential to significantly reduce the overall pneumococcal disease burden. In addition, further indirect benefits of broadened protection could be expected over time in adults, as suggested by the reduction of IPD burden in older adults following the introduction of previous routine PNEU-C pediatric programs.

VIII. Research priorities

- Determining the direct (children) and indirect (adults) impact of PNEU-C-15 programs on the burden of disease (AOM, pneumonia, IPD) in individuals with and without risk factors for invasive disease in the context of different vaccines and vaccine schedules used in Canada.
- Determining the vaccine effectiveness of PNEU-C-15 in healthy and in immunocompromised pediatric population.
- Determining the duration of immunity for PNEU-C-15 only and in mixed schedule programs.
- Assessing the cost effectiveness of PNEU-C-15 in pediatric population.

List of abbreviations

AEFI	Adverse event following immunization
AOM	Acute otitis media
CAP	Community acquired pneumonia
CI	Confidence interval
CIC	Canadian Immunization Committee
GMC	Geometric mean concentration
HIV	Human Immunodeficiency Virus
IgG	**I**mmunoglobulin G
IPD	Invasive pneumococcal disease
NACI	National Advisory Committee on Immunization
NOC	Notice of Compliance
PHAC	Public Health Agency of Canada
PNEU-C-13	13-valent conjugate pneumococcal vaccine
PNEU-C-15	15-valent conjugate pneumococcal vaccine
PWG	Pneumococcal working group
ST	Serotype

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Appendix A: Immunogenicity of PNEU-C-15 in pediatric populations

Immunogenicity following immunization with PNEU-C-15 was reported in seven Phase 2/3 clinical trials that included healthy children (five studies[15,17–20]), children with sickle cell disease (one study[16]) and HIV infection (one study[21]). The measured outcomes included serotype-specific immunoglobulin G (IgG) responses (reported as the proportion of study participants meeting the IgG threshold value of ≥0.35 µg/mL), geometric mean concentrations (GMC) and opsonophagocytic activity (OPA) geometric mean titres (GMT) at 30 days after dose administration.

In the pivotal double-blind clinical trial V114-025[18], immunogenicity was measured in healthy infants aged 2 to 15 months who were vaccinated with PNEU-C-13 (n=591) or PNEU-C-15 (n=588) at 2, 4 and 11–15 months of age. One month following dose 3, non-inferior seroresponse (based on the lower bound of the 95% CI for the percentage point difference being greater than -10 points) was observed for all 13 shared serotypes, and higher immune responses were observed for the two PNEU-C-15 unique serotypes (Table 5, Appendix A).

Similarly, at one month post dose 3, IgG GMC values were found to be non-inferior (based on the lower bound of the 2-sided 95% CI for the GMC ratio being >0.5) for all 13 shared serotypes and superior for the PNEU-C-15 unique serotypes (Table 6, Appendix A). Of note, although numerically similar, all observed GMC values were generally lower for PNEU-C-15 compared to PNEU-C-13, except for ST3. When assessed by OPA GMT, functional antibodies were found to be generally comparable for all shared serotypes.

In another pivotal double-blind clinical trial (V114-029[20]) immunogenicity was assessed in over 1,700 healthy infants 6 to 12 weeks of age using a four dose schedule (vaccine provided at 2, 4, 6 and 12-15 months of age). One month following dose 4, seroresponse rates after PNEU-C-15 administration were found to be non-inferior for all 13 shared serotypes and superior for the two unique types compared to PNEU-C-13 (Table 7, Appendix A).

In the V114-029 trial, measurement of serotype-specific IgG GMC at 30 days following the 3 dose primary series also demonstrated non-inferiority to PNEU-C-13 for the majority of serotypes, with a response to only one serotype (6A) not meeting the non-inferiority criteria by a small margin (the lower bound of the 2-sided 95% CI for the GMC ratio being 0.48) (Table 8, Appendix A). In addition, 30 days following both dose 3 and dose 4, superiority was demonstrated for the two PNEU-C-15 unique serotypes as well as ST3. Serotype-specific OPA GMT at 30 days following the 3 dose primary series and toddler booster dose were reported to be numerically similar to PNEU-C-13 for the shared serotypes and higher for the unique serotypes.

Clinical trial data on PNEU-C-15 in children

Table 5. Comparison of PNEU-C-13 vs PNEU-C-15 seroresponse rates at 30 days following dose 3 according to serotype (V114-025)

Serotype	Observed Response, %		% Difference (95% CI*)
	PNEU-C-15 (N=588)	PNEU-C-13 (N=591)	(PNEU-C-15 vs. PNEU-C-13)
1	97	99	-2.8 (-4.7 to -1.3)
3	92	84	8.2 (4.4 to 12.2)
4	96	98	-2.2 (-4.5 to -0.1)
5	99	100	-0.9 (-2.2 to -0.2)
6A	99	99	-0.4 (-1.9 to 1.1)
6B	97	99	-1.7 (-3.5 to -0.1)
7F	100	100	0.0 (-0.0 to 0.9)
9V	99	100	-1.1 (-2.4 to -0.4)
14	100	100	-0.2 (-1.0 to 0.5)
18C	99	99	-0.4 (-1.8 to 0.9)
19A	99	100	-0.9 (-2.2 to -0.2)
19F	100	100	-0.4 (-1.3 to 0.3)
23F	97	97	-0.5 (-2.7 to 1.5)
22F	100	6	93.8 (91.5 to 95.6)
33F	99	4	94.9 (92.7 to 96.5)

*p-value for all GMC ratios <0.001.
Abbreviations: CI=confidence interval; N=Number of participants randomized and vaccinated

Table 6. Comparison of serotype-specific IgG GMCs at 30 days following dose 3 (V114-025)

Serotype	IgG GMC		GMC Ratio (95% CI)*
	PNEU-C-15 (N=588)	PNEU-C-13 (N=591)	(PNEU-C-15 vs. PNEU-C-13)
1	1.3	2.1	0.62 (0.57 to 0.68)
3	0.8	0.7	1.28 (1.17 to 1.39)
4	1.3	1.7	0.75 (0.68 to 0.82)
5	2.0	3.1	0.64 (0.59 to 0.70)
6A	3.1	4.6	0.68 (0.61 to 0.76)
6B	4.2	4.4	0.95 (0.85 to 0.76)
7F	3.1	3.9	0.79 (0.72 to 0.85)
9V	2.1	3.0	0.72 (0.66 to 0.78)
14	5.3	7.0	0.75 (0.67 to 0.83)
18C	1.9	2.2	0.88 (0.80 to 0.95)
19A	4.7	5.7	0.83 (0.75 to 0.91)
19F	4.1	4.6	0.88 (0.80 to 0.97)
23F	1.5	1.8	0.87 (0.79 to 0.97)
22F	6	--	71.19 (65.16 to 79.10)
33F	3.4	--	46.58 (42.19 to 51.42)

*p-value for all GMC ratios <0.001.
Abbreviations: CI=confidence interval; GMC=geometric mean concentration (mcg/mL); IgG=immunoglobulin G; N=Number of participants randomized and vaccinated

Table 7. Comparison of PNEU-C-13 vs PNEU-C-15 seroresponse rates at 30 days following dose 3 according to serotype (V114-029)

Serotype	Observed Response, %		% Difference (95% CI)
	PNEU-C-15 (N=858)	PNEU-C-13 (N=856)	(PNEU-C-15 vs. PNEU-C-13)
1	95.7	99.1	-3.4 (-5.2 to -1.8)
3	94.7	79.2	15.6 (12.1 to 19.2)
4	96.4	98.6	-2.2 (-4.0 to –0.6)
5	95.3	97.4	-2.1 (-4.2 to -0.2)
6A	93.7	98.6	-4.9 (-7.1 to –3.0)
6B	88.6	92.0	-3.4 (-6.6 to –0.3)
7F	99.0	99.8	-0.8 (-1.9 to –0.1)
9V	97.1	98.2	-1.0 (-2.8 to 0.6)
14	97.9	97.9	-0.0 (-1.6 to 1.6)
18C	97.4	98.3	-0.9 (-2.6 to 0.7)
19A	97.9	99.7	-1.8 (-3.2 to -0.8)
19F	99.0	100.0	-1.0 (-2.1 to –0.4)
23F	91.5	91.8	-0.3 (-3.2 to 2.7)
22F	98.6	--	6.7 (4.6 to 9.2)
33F	87.3	--	-4.5 (-7.8 to –1.3)

Abbreviations: CI= confidence interval; N= Number of participants randomized and vaccinated

Table 8. Comparison of serotype-specific IgG GMCs at 30 days following dose 4 (V114-029)

Serotype	PNEU-C-15 (N=858)		PNEU-C-13 (N=856)		GMC Ratio[a] (PNEU-C-15 / PNEU-C-13) (95% CI)
	n	GMC	n	GMC	
13 shared[b]					
1	715	1.35	685	2.03	0.66 (0.62 to 0.72)
3	712	0.96	686	0.71	1.35 (1.25 to 1.46)
4	713	1.23	682	1.60	0.77 (0.71 to 0.84)
5	713	2.49	682	3.95	0.63 (0.58 to 0.69)
6A	713	3.70	682	6.21	0.60 (0.54 to 0.65)
6B	712	4.76	682	6.43	0.74 (0.67 to 0.81)
7F	714	3.42	686	4.85	0.70 (0.65 to 0.77)
9V	716	2.40	686	3.29	0.73 (0.67 to 0.80)
14	716	5.61	685	6.95	0.81 (0.73 to 0.89)
18C	713	2.62	684	3.08	0.85 (0.78 to 0.93)
19A	715	4.10	685	5.53	0.74 (0.68 to 0.80)
19F	715	3.55	685	4.47	0.79 (0.74 to 0.86)
23F	713	2.04	683	3.32	0.61 (0.56 to 0.68)
2 unique to PNEU-C-15					
22F	714	7.52	‡	‡	4.69 (4.30 to 5.11)
33F	714	4.15	‡	‡	2.59 (2.36 to 2.83)

[a]GMC ratio and CI are calculated using the t-distribution with the variance estimate from a ST-specific linear model utilizing the natural log-transformed antibody concentrations as the response and a single term for vaccination group.

[b]A conclusion of non-inferiority is based on the lower bound of the 2-sided 95% CI for the GMC ratio (PNEU-C-15 / PNEU-C-13) being >0.5.

‡A conclusion of non-inferiority of PNEU-C-15 to PNEU-C-13 is based on the comparison of the GMC for the 2 additional STs to the lowest responding PNEU-C-13 ST (ST4), excluding ST3.

Abbreviations: CI=confidence interval; GMC=geometric mean concentration (mcg/mL); IgG=immunoglobulin G; N=Number of participants randomized and vaccinated; n=number of participants contributing to the analysis; ST=serotype

Table 9. Comparison of seroresponse rates following the use of different schedules using PNEU-C-13 and/or PNEU-C-15 at 30 days after dose 3 (V114-027)

All randomized participants who were compliant with the protocol, got scheduled dosing of PNEU-C-15 or PNEU-C-13, had IgG concentration ≥0.35µg/mL data available for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F, 22F or 33F in Groups 1, 2, 3, 4 or 5 at 30 Days post Vaccination 3.

Arm/Group Title		Group 1: PNEU-C-13-PNEU-C-13-PNEU-C-13-PNEU-C-13	Group 2: PNEU-C-13-PNEU-C-13-PNEU-C-13-PNEU-C-15	Group 3: PNEU-C-13-PNEU-C-13-PNEU-C-15-PNEU-C-15	Group 4: PNEU-C-13-PNEU-C-15-PNEU-C-15-PNEU-C-15	Group 5: PNEU-C-15-PNEU-C-15-PNEU-C-15-PNEU-C-15
Overall Number of Participants Analyzed		179	181	178	179	179
ST1	Number Analyzed	142 participants	142 participants	129 participants	138 participants	148 participants
	% of participants	97.9	100	99.2	97.8	96.6
	(95% CI)	(94.0 to 99.6)	(97.4 to 100.0)	(95.8 to 100.0)	(93.8 to 99.5)	(92.3 to 98.9)
ST3	Number Analyzed	142 participants	142 participants	129 participants	138 participants	147 participants
	% of participants	73.2	73.9	79.1	81.9	93.9
	(95% CI)	(65.2 to 80.3)	(65.9 to 80.9)	(71.0 to 85.7)	(74.4 to 87.9)	(88.7 to 97.2)
ST4	Number Analyzed	141 participants	139 participants	128 participants	137 participants	147 participants
	% of participants	97.9	98.6	93	94.2	96.6
	(95% CI)	(93.9 to 99.6)	(94.9 to 99.8)	(87.1 to 96.7)	(88.8 to 97.4)	(92.2 to 98.9)
ST5	Number Analyzed	141 participants	141 participants	128 participants	138 participants	148 participants
	% of participants	97.9	99.3	97.7	97.1	98
	(95% CI)	(93.9 to 99.6)	(96.1 to 100.0)	(93.3 to 99.5)	(92.7 to 99.2)	(94.2 to 99.6)
ST6A	Number Analyzed	140 participants	140 participants	128 participants	138 participants	148 participants
	% of participants	99.3	99.3	99.2	97.1	98.6
	(95% CI)	(96.1 to 100.0)	(96.1 to 100.0)	(95.7 to 100.0)	(92.7 to 99.2)	(95.2 to 99.8)
ST6B	Number Analyzed	138 participants	140 participants	127 participants	138 participants	147 participants
	% of participants	91.3	94.3	96.1	95.7	95.2
	(95% CI)	(85.3 to 95.4)	(89.1 to 97.5)	(91.1 to 98.7)	(90.8 to 98.4)	(90.4 to 98.1)
ST7F	Number Analyzed	142 participants	142 participants	129 participants	138 participants	148 participants
	% of participants	100	100	100	100	100
	(95% CI)	(97.4 to 100.0)	(97.4 to 100)	(97.2 to 100.0)	(97.4 to 100.0)	(97.5 to 100.0)
ST9V	Number Analyzed	143 participants	142 participants	128 participants	138 participants	148 participants
		96.5	96.5	96.1	95.7	98.6

	% of participants (95% CI)	(92.0 to 98.9)	(92.0 to 98.8)	(91.1 to 98.7)	(90.8 to 98.4)	(95.2 to 99.8)
ST14	Number Analyzed	142 participants	142 participants	128 participants	138 participants	148 participants
	% of participants	98.6	98.6	96.9	100	98.6
	(95% CI)	(95.0 to 99.8)	(95.0 to 99.8)	(92.2 to 99.1)	(97.4 to 100.0)	(95.2 to 99.8)
ST18C	Number Analyzed	142 participants	142 participants	129 participants	138 participants	148 participants
	% of participants	95.8	100	99.2	97.8	98
	(95% CI)	(91.0 to 98.4)	(97.4 to 100.0)	(95.8 to 100.0)	(93.8 to 99.5)	(94.2 to 99.6)
ST19A	Number Analyzed	143 participants	142 participants	129 participants	138 participants	148 participants
	% of participants	99.3	100	98.4	97.1	97.3
	(95% CI)	(96.2 to 100.0)	(97.4 to 100.0)	(94.5 to 99.8)	(92.7 to 99.2)	(93.2 to 99.3)
ST19F	Number Analyzed	143 participants	142 participants	128 participants	138 participants	148 participants
	% of participants	99.3	99.3	99.2	100	100
	(95% CI)	(96.2 to 100.0)	(96.1 to 100.0)	(95.7 to 100.0)	(97.4 to 100.0)	(97.5 to 100.0)
ST23F	Number Analyzed	140 participants	140 participants	128 participants	135 participants	147 participants
	% of participants	91.4	97.9	90.6	92.6	94.6
	(95% CI)	(85.5 to 95.5)	(93.9 to 99.6)	(84.2 to 95.1)	(86.8 to 96.4)	(89.6 to 97.6)
ST22F	Number Analyzed	138 participants	140 participants	128 participants	137 participants	148 participants
	% of participants	2.9	1.4	93.8	99.3	98.6
	(95% CI)	(0.8 to 7.3)	(0.2 to 5.1)	(88.1 to 97.3)	(96.0 to 100.0)	(95.2 to 99.8)
ST33F	Number Analyzed	141 participants	139 participants	127 participants	137 participants	148 participants
	% of participants	2.1	2.2	39.4	75.9	93.2
	(95% CI)	(0.4 to 6.1)	(0.4 to 6.2)	(30.8 to 48.4)	(67.9 to 82.8)	(87.9 to 96.7)

Abbreviations: CI=confidence interval; ST=serotype

Table 10. Comparison of IgG GMC following the use of different schedules using PNEU-C-13 and/or PNEU-C-15 at 30 days after dose 4 (V114-027)

All randomized participants who were compliant with the protocol, got scheduled dosing of V114 or Prevnar 13™ and had IgG GMC data for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F or 23F in Groups 1, 2, 3, 4 or 5 at 30 Days post Vaccination 4. 13 IgG serotypes in Groups 2, 3, 4 were compared to Group 1 as a protocol-specified primary outcome analysis; 13 IgG serotypes in Group 5 were compared to Group 1 as a separate protocol-specified secondary outcome analysis and reported later.

Arm/Group Title		Group 1: Prevnar 13™-Prevnar 13™-Prevnar 13™-Prevnar 13™	Group 2: Prevnar 13™-Prevnar 13™-Prevnar 13™-V114	Group 3: Prevnar 13™-Prevnar 13™-V114-V114	Group 4: Prevnar 13™-V114-V114-V114
Overall Number of Participants Analyzed		179	181	178	179
ST1	Number Analyzed	147 participants	151 participants	128 participants	139 participants
	µg/mL (95% CI)	2.02	1.69	1.89	1.68
		(1.78 to 2.30)	(1.48 to 1.93)	(1.63 to 2.18)	(1.48 to 1.91)
ST3	Number Analyzed	148 participants	151 participants	128 participants	139 participants
	µg/mL (95% CI)	0.72	0.77	0.68	0.73
		(0.64 to 0.82)	(0.68 to 0.87)	(0.61 to 0.77)	(0.66 to 0.82)
ST4	Number Analyzed	146 participants	151 participants	128 participants	139 participants
	µg/mL (95% CI)	1.51	1.33	1.27	1.23
		(1.30 to 1.76)	(1.14 to 1.56)	(1.10 to 1.46)	(1.08 to 1.41)
ST5	Number Analyzed	147 participants	151 participants	128 participants	138 participants
	µg/mL (95% CI)	3.66	3.39	3.82	2.9
		(3.18 to 4.20)	(2.91 to 3.94)	(3.23 to 4.51)	(2.50 to 3.38)
ST6A	Number Analyzed	146 participants	151 participants	128 participants	139 participants
	µg/mL (95% CI)	6.42	7.16	7.16	5.17
		(5.56 to 7.42)	(6.30 to 8.15)	(6.17 to 8.30)	(4.43 to 6.03)
ST6B	Number Analyzed	146 participants	151 participants	128 participants	139 participants
	µg/mL (95% CI)	6.15	7.58	6.64	6.62
		(5.36 to 7.07)	(6.61 to 8.68)	(5.73 to 7.69)	(5.75 to 7.62)
ST7F	Number Analyzed	146 participants	151 participants	128 participants	139 participants
	µg/mL (95% CI)	5.1	5.69	5.06	3.98
		(4.43 to 5.88)	(4.93 to 6.56)	(4.33 to 5.92)	(3.47 to 4.57)
ST9V	Number Analyzed	147 participants	151 participants	128 participants	139 participants
	µg/mL (95% CI)	2.93	2.76	2.57	2.46
		(2.56 to 3.34)	(2.41 to 3.16)	(2.22 to 2.97)	(2.19 to 2.78)
ST14	Number Analyzed	146 participants	151 participants	128 participants	139 participants

	µg/mL (95% CI)	7.62	10.59	10.91	7.87
		(6.55 to 8.86)	(9.01 to 12.44)	(9.29 to 12.81)	(6.77 to 9.16)
ST18C	Number Analyzed	147 participants	151 participants	128 participants	139 participants
	µg/mL (95% CI)	2.57	3.88	3.7	2.76
		(2.21 to 2.99)	(3.38 to 4.45)	(3.20 to 4.29)	(2.42 to 3.15)
ST19A	Number Analyzed	148 participants	151 participants	128 participants	139 participants
	µg/mL (95% CI)	5.92	5.52	5.2	4.95
		(5.15 to 6.80)	(4.88 to 6.25)	(4.42 to 6.12)	(4.27 to 5.73)
ST19F	Number Analyzed	148 participants	151 participants	128 participants	139 participants
	µg/mL (95% CI)	4.78	4.88	5.02	4.6
		(4.22 to 5.42)	(4.33 to 5.51)	(4.40 to 5.73)	(4.00 to 5.28)
ST23F	Number Analyzed	146 participants	150 participants	127 participants	138 participants
	µg/mL (95% CI)	2.89	2.72	2.29	2.22
		(2.42 to 3.44)	(2.33 to 3.18)	(1.93 to 2.70)	(1.92 to 2.56)

Abbreviations: CI=confidence interval; ST=serotype

Table 11. Comparison of AEs reported in infants (V114-025)

	Adverse Events (AEs), n(%)	
	PNEU-C-15 (N=587)	**PNEU-C-13 (N=591)**
One or more AE	555 (94.5)	550 (93.1)
Injection-Site	427 (72.7)	398 (67.3)
Systemic	536 (91.3)	526 (89.0)
Vaccine-Related AEs	535 (91.1)	525 (88.8)
Injection-Site	427 (72.7)	398 (67.3)
Systemic	483 (82.3)	461 (78.0)
Serious AEs	57 (9.7)	70 (11.8)
Serious Vaccine-Related	0 (0.0)	1 (0.2)
Deaths	0 (0.0)	0 (0.0)
Vaccine Discontinuation Due to an AE	0 (0.0)	0 (0.0)
Injection Site Pain	238 (40.5)	173 (29.3)
Decreased Appetite	199 (33.9)	198 (33.5)
Irritability	421 (71.7)	392 (66.3)
Somnolence	271 (46.2)	247 (41.8)
Urticaria	22 (3.7)	23 (3.9)

Abbreviations: AE=adverse event; N=Number of participants randomized and vaccinated; n=number of participants contributing to the analysis

Table 12. Percentage of participants with solicited local and systemic adverse reactions within 14 days post vaccination in infants receiving a primary series (protocols 025, 027, 029 and 031)

Dose	Dose 1		Dose 2		Dose 3	
	PNEU-C-15 (%) N=3,589	PNEU-C-13 (%) N=2,058	PNEU-C-15 (%) N=3,589	PNEU-C-13 (%) N=2,058	PNEU-C-15 (%) N=3,589	PNEU-C-13 (%) N=2,058
Local reactions[a]						
Pain	27.1	24.1	19.8	18.0	19.1	18.8
Erythema	17.1	14.1	20.0	20.8	17.0	19.1
Swelling	13.7	11.6	11.6	10.7	9.9	9.3
Induration	12.6	13.5	12.6	15.9	11.4	13.1
Systemic reactions[b]						
Decreased appetite	17.0	15.9	15.4	14.0	13.9	14.3
Irritability	55.1	53.2	50.7	47.3	47.0	43.7
Somnolence	40.7	41.3	27.5	27.8	22.8	24.1
Urticaria	1.1	1.5	1.4	1.6	1.6	1.8
Elevated body temperature[c d]						
≥38.0 C and <39.0 C	43.4	42.0	39.3	39.6	35.7	37.4
≥39.0 C and <40.0 C	2.2	2.6	3.4	4.6	3.5	3.1
≥40.0 C	0.2	0.0	0.3	0.4	0.5	0.2

[a]Full term infants in Protocol 025 received Dose 1 and Dose 2 as part of a 2-dose primary series. Preterm infants in Protocol 025 received Dose 1, Dose 2, and Dose 3 as part of a 3-dose primary series.
[b]Solicited on Day 1 through Day 14 postvaccination following each dose.
[c]Solicited on Day 1 through Day 7 postvaccination following each dose.
[d]Percentages reflect the number of participants with temperature data based on a rectal equivalent temperature.
Abbreviations: N=Number of participants vaccinated