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ABSTRACT

Introduction *Streptococcus pneumoniae* and non-typeable *Haemophilus influenzae* (NTHi) are major otitis media pathogens that densely co-colonise the nasopharynx and infect the middle ear of Australian Aboriginal infants from very early in life. Our co-primary hypotheses are that at 18 months of age infants receiving 10-valent pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV10) compared with those receiving 13-valent pneumococcal conjugate vaccine (PCV13) as a booster at 12 months of age will have higher antibody levels to *Haemophilus influenzae* protein D and that infants receiving PCV13 will have higher antibody levels to PCV13-only serotypes 3, 6A and 19A.

Methods and analyses Our randomised controlled trial will enrol 270 Aboriginal children at 12 months of age to a booster dose of either PHiD-CV10 or PCV13. Children who completed the three-dose primary course schedules of PHiD-CV10 at 2, 4, 6 months of age; PCV13 at 2, 4, 6 months of age; or a combination schedule of PHiD-CV10 at 1, 2, 4 months of age plus PCV13 at 6 months of age are eligible. The co-primary assessor-blinded outcomes when the infants are 18 months of age are as follows: (a) IgG geometric mean concentration (GMC) and proportion with IgG ≥ 100 EU/mL for protein D, and (b) IgG GMC and the proportion with IgG ≥ 0.35 μ g/mL for pneumococcal serotypes 3, 6A and 19A. Secondary immunogenicity comparisons of six primary and booster dose schedules of 10 shared serotypes at 18 months of age, nasopharyngeal

Strengths and limitation of this study

- This study addresses an important health and social issue for Australian Aboriginal and Torres Strait Islander children.
- This study is a randomised controlled trial of two licensed pneumococcal conjugate vaccines (PCVs) given as a booster dose at 12 months of age to children who completed primary course schedules.
- Primary outcomes at 18 months of age are accepted global immunogenicity criteria for licensing and varying PCV schedules.
- Secondary outcomes include 6 monthly nasopharyngeal carriage, standardised assessments of middle ear status, hearing status, developmental milestones and rates of respiratory illness.
- Limitations of the study include limited power for secondary outcomes.

carriage, all forms of otitis media, hearing loss and developmental milestones at 18, 24, 30 and 36 months of age will be reported.

Ethics and dissemination Ethics committees of NT Department of Health, Menzies, WA Department of Health and WA Aboriginal Health approved the study. Results will be presented to communities, at conferences and published in peer-reviewed journals.

Trial registration number NCT01735084.

INTRODUCTION

Background and rationale

Otitis media (OM) is one of the most common childhood infectious diseases of children living in the Northern Territory (NT) of Australia with very high rates reported in infancy.¹ Our surveillance of OM in remote Australian Aboriginal communities shows high rates of disease from weeks after birth throughout early childhood, particularly tympanic membrane perforations (TMPs) in the second year of life.² The mean age of any TMP was 18 months and that of acute otitis media with perforation (AOMwiP) was 8 to <18 months and 21 months for chronic suppurative otitis media (CSOM). The impact of chronic OM in early childhood on hearing loss, developmental milestones, school readiness and academic performance of NT Aboriginal children is not known.

The introduction of 7-valent pneumococcal conjugate vaccine (PCV7) in the NT in 2001 had high uptake (>90%) during infancy³ and resulted in the near elimination of PCV7 types in both nasopharyngeal (NP) carriage and middle ear discharge (ED) among infants.⁴ However, analysis of middle ED from cases of AOMwiP in recipients of PCV7 showed that almost 60% of ED specimens were associated with culture of non-typeable *Haemophilus influenzae* (NTHi), while ~40% were culture-positive for *Streptococcus pneumoniae* (pneumococcus), including 3% having serotypes 3, 6A or 19A.^{5 6} Ten-valent pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV10) and 13-valent pneumococcal conjugate vaccine (PCV13) were licensed in Australia for use in large-scale immunisation programmes in 2009 and 2011, respectively. The NT was the only jurisdiction to include PHiD-CV10 in the childhood immunisation schedule as a 3+1 (2, 4, 6, +18month) schedule for Aboriginal and Torres Strait Islander children from October 2009 to October 2011, when it was replaced by PCV13. PHiD-CV10 has protein D of NTHi (HiD) as the carrier for some serotypes while PCV13 is conjugated to Cross-Reacting Material (CRM₁₉₇)—a variant of diphtheria toxin, and has three additional serotypes (3, 6A and 19A), but not protein D. Evidence of carrier protein D having efficacy for AOM prevention was initially reported from a single randomised control trial (RCT) in which OM was a primary outcome. In that trial of an earlier 11-valent formulation (11PnPD), there was ~55% efficacy for culture-positive pneumococcal vaccine type AOM and 35% efficacy for NTHi AOM following a 3+1 schedule.⁷ This trial also demonstrated a 43% (95% CI: -17 to 72) reduction in the NP carriage of pneumococcal vaccine serotypes and a 43% (95% CI: 1 to 67) reduction in the carriage of *H. influenzae* following the booster dose. Across remote communities in the NT, surveillance of OM, NP carriage and microbiology of ED from children (mean age ~18 months) with AOMwiP or CSOM showed a trend towards less AOM and less NTHi in ED of children who were vaccinated with PHiD-CV10 compared with PCV7 and non-significant differences in clinical or microbiological outcomes in children vaccinated with PCV13.^{2 8 9}

These data provide a strong rationale for rigorous evaluation of these vaccines (PHiD-CV10 vs PCV13) on outcomes during the second and third year of life.

In the present study, eligible participants had been previously enrolled in a trial of pneumococcal conjugate vaccines PHiD-CV10 and PCV13 in sequence or alone trial (PREVIX_COMBO).¹⁰ The trial compared three primary course schedules of PHiD-CV10 at 2, 4, 6 months of age; PCV13 at 2, 4, 6 months of age; or an investigational combination schedule of PHiD-CV10 at 1, 2, 4 months of age plus PCV13 at 6 months. The NT childhood immunisation schedule recommended a booster dose at 18 months of age. However, our surveillance suggested that the booster should perhaps be given earlier, prior to peak incidence of pneumococcal infections at 18 months of age. Our co-primary study hypotheses are that at 18 months of age (a) infants receiving PHiD-CV10 as a booster at 12 months of age will have higher protein D antibody levels compared with those receiving PCV13 as a booster and (b) infants receiving PCV13 as a booster at 12 months of age compared with those receiving PHiD-CV10 as a booster will have higher antibody levels to serotypes 3, 6A and 19A.

Our secondary study hypotheses focus on vaccine-related differences in additional immunogenicity outcomes at 18 months of age, and NP carriage, OM, respiratory illness, hearing loss and developmental delay at 18, 24, 30 and 36 months of age. First, we hypothesise that infants receiving PHiD-CV10 compared with those receiving PCV13 as a booster at 12 months of age will have (i) superior immunogenicity at 18 months of age for common serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F). Second, at each time point 18, 24, 30 and 36 months of age, infants receiving PHiD-CV10 compared with those receiving PCV13 as a booster at 12 months of age will have (ii) less NP carriage of NTHi; (iii) more NP carriage of serotypes 3, 6A and 19A; (iv) less NP carriage of common serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F); (v) less NP carriage of vaccine-related or non-vaccine (replacement) serotypes; (vi) less OM; (vii) less respiratory illness; (viii) less hearing loss and (ix) less developmental delay. Finally, we hypothesise that infants receiving PHiD-CV10 compared with those receiving PCV13 as a booster at 12 months of age will have (x) lower rates of any AOM, any respiratory illness and antibiotic prescription documented in medical records between 12 and 36 months of age.

Explanation for choice of comparators

The WHO recommended the use of either PHiD-CV10 or PCV13 for all infants worldwide in replacement of PCV7 in 2009.¹¹ In the NT, a three-dose primary course plus booster (3+1) of PHiD-CV10 schedule replaced a 3+1 PCV7 plus 23-valent pneumococcal polysaccharide vaccine (23PPV) booster in 2009, with the booster age remaining at 18 months. In July 2011, just 3 months prior to our first randomisation into the primary course PREVIX_COMBO RCT,¹⁰ a 3+0 PCV13 schedule was introduced into the

routine national immunisation programme (NIP), but a 3+1 (2–4–6+18month) PCV13 schedule was recommended specifically for Aboriginal and Torres Strait Islander children in the NT, Queensland and Western Australia. In the NT, this 3+1 PCV13 schedule replaced 3+1 PHiD-CV10 in October 2011. In anticipation that the NT schedule could accommodate a shift in timing of the booster dose, this trial planned to randomise the booster dose at 12 months of age and measure immunogenicity at 18 months of age. While both groups receive an active intervention, the difference in formulation allows for comparisons of outcomes according to presence or absence of specific vaccine components, as well as head-to-head comparisons of shared components.

Objectives

Primary objectives regarding immunogenicity at 18 months of age

To determine (a) whether PHiD-CV10 given at 12 months of age will have superior immunogenicity at 18 months of age for protein D compared with PCV13, and (b) whether PCV13 given at 12 months of age will have superior immunogenicity at 18 months of age for serotypes 3, 6A and 19A compared with PHiD-CV10.

Secondary objectives

Immunogenicity at 18 months of age for 10 shared serotypes

To determine which vaccine given at 12 months of age will have (a) superior immunogenicity at 18 months of age for the serotypes common in both PHiD-CV10 and PCV13 (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F).

NP carriage, OM, hearing loss and developmental outcomes at 18, 24, 30 and 36 months of age

To determine which vaccine given at 12 months of age will have (a) less NP carriage of NTHi at each time point; (b) less NP carriage of serotypes 3, 6A and 19A; (c) less NP carriage for common serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F); (d) less NP carriage of vaccine-related or non-vaccine (replacement) serotypes; (e) less OM at each time point; (f) less hearing loss and (g) less developmental delay when infants are 18, 24, 30 and 36 months of age.

Rates of any AOM, any respiratory illness and antibiotic prescription from 12 to 36 months of age

To determine which vaccine given at 12 months of age will have lower rates of any AOM, any respiratory illness and antibiotic prescription documented in medical records between 12 and 36 months of age.

Immunogenicity of six vaccine groups at 18 months of age

To determine the immunogenicity outcomes in all children in this trial (PREVIX_BOOST) according to previous randomisation to three different primary course schedules of PHiD-CV10 at 2, 4, 6 months of age; PCV13 at 2, 4, 6 months of age; and an investigational combination schedule of PHiD-CV10 at 1, 2, 4 months of age plus PCV13 at 6 months of age in the PREVIX_COMBO

trial.² This creates six primary + booster vaccine schedule comparisons (table 1 or figure 1).

METHODS

Participants, interventions and outcomes

Trial design

The PREVIX_BOOST trial is a primary outcome assessor-blinded, randomised controlled trial with two groups (1:1), to compare the immune responses and clinical outcomes in Aboriginal infants at 18 months of age following PHiD-CV10 (Synflorix, S) or PCV13 (Prevenar13, P) at 12 months of age. The PREVIX_BOOST trial commenced in March 2013. A further grant on Vaccines for Otitis media in Children Entering School (PREVIX_VOICES) allowed additional time points to be included at 24 and 30 months of age and additional outcome measures (audiology and developmental milestones at 12, 18, 24, 30 and 36 months) which commenced in January 2017.

Study setting

Three remote Aboriginal and Torres Strait Islander communities in the NT and a single Western Australian community will participate in PREVIX_BOOST. For pragmatic reasons, the PREVIX_VOICES trial will be restricted to three remote NT communities.

Patient and public involvement

The Council of each community participating in the original PREVIX_COMBO trial was provided with information about this follow-up trial of a booster vaccine, PREVIX_BOOST. Signed agreements of participation from each community Council Chairperson are provided to the Ethics committee. The trial is supported by the Menzies School of Health Research Child Health Division Indigenous Reference Group which provides advice on approaches to engaging communities for trial approval, acceptability of proposed trial methods and approaches to individual and community feedback. The Indigenous Reference Group comprises of Australian Aboriginal community elders, clinicians and nurses. At the completion of the trial, the outcome will be disseminated through appropriate written and oral formats to parents and guardians, and participating communities.

Eligibility criteria

Inclusion criteria

Australian Aboriginal infants previously randomised in the PREVIX_COMBO trial,¹⁰ eligible for NIP routine vaccinations, 11 months and 2 weeks ($11\frac{1}{2}$) to 13 months and 2 weeks ($13\frac{1}{2}$) of age, completed primary PCV vaccination at least 2 months previously, living in a participating remote community, and whose parent or guardian provided signed informed consent, will be eligible to participate in PREVIX_BOOST trial.

Exclusion criteria

Prior adverse reaction to previous pneumococcal conjugate vaccines according to Australian Immunization

Table 1 Schedule of enrolment, intervention and assessments

	Enrolment	Allocation	COMBO					BOOST				
			1	2	3	4	5	6	7	8	9	10
Study visit number		1	1	2	3	4	5	6	7	8	9	10
Age (months)		1	1	2	4	6	7	12	18	24	30	36
Allocation		X						X				
Eligibility screen	X	X						X				
Informed consent	X	X						X				
Interventions												
PHiD-CV10 booster dose following												
		PHiD-CV10 (S)		_	S	S	S		+S			
		PCV13 (P)		_	P	P	P		+S			
		PHiD-CV10 (S) + PCV13 (P)		S	S	S	P		+S			
PCV13 booster dose following												
		PHiD-CV10 (S)		_	S	S	S		+P			
		PCV13 (P)		_	P	P	P		+P			
		PHiD-CV10 (S) + PCV13 (P)		S	S	S	P		+P			
Assessments												
Risk factors												
		Fixed (sex, birthweight, gestational age, maternal education)		X								
		Not fixed (household occupancy, smoke exposure, breastfeeding)		X				X	X	X	X	X
Ear assessment												
		Tympanometry		X	X	X	X	X	X	X	X	X
		Otoscopy			X	X	X	X	X	X	X	X
		Nasopharyngeal swab		X	X	X	X	X	X	X	X	X
		Blood draw (heel prick or venepuncture)		X	X		X		X			
		General health (skin, chest, nose, temp, weight, length)		X	X	X	X	X	X	X	X	X
		Developmental milestone							X	X	X	X
		Audiology							X	X	X	X

*PPP=3 doses of Prevenar at 2, 4 and 6 months of age; *SSS=3 doses of Synflorix at 2, 4 and 6 months of age; SSSP=3 doses of Synflorix at 1, 2 and 4 months and 1 dose of Prevenar at 6 months; +=plus; P=Prevenar; S=Synflorix.

PCV13, 13-valent pneumococcal conjugate vaccine; PHiD-CV10, 10-valent pneumococcal *Haemophilus influenzae* protein D conjugate vaccine.

Handbook¹² or previous booster dose of pneumococcal vaccine.

Interventions and dosing schedules

Infants will be randomly allocated within a study window of 11 months and 2 weeks (11¹/₂) to 13 months and 2 weeks (13¹/₂) of age, in a 1:1 ratio to a booster dose of either:

a. PHiD-CV10 (Synflorix, S)

b. PCV13 (Prevenar13, P)

In combination with the previous PREVIX_COMBO RCT,¹⁰ this allocation created six study arms:

1a.PHiD-CV10 at 2, 4, 6 mo +PHiD-CV10 at 12 months (_SSS+S)

1b.PHiD-CV10 at 2, 4, 6 mo +PCV13 at 12 months (_SSS+P)

2a.PCV13 at 2, 4, 6 mo +PHiD-CV10 at 12 months (_PPP+S)

2b.PCV13 at 2, 4, 6 mo +PCV13 at 12 months (_PPP+P)

3a.PHiD-CV10 at 1, 2, 4 mo plus PCV13 at 6 mo +PHiD-CV at 12 months (SSSP+S)

3b.PHiD-CV10 at 1, 2, 4 mo plus PCV13 at 6 mo +PCV13 at 12 months (SSSP+P)

At the time of study design and planning in 2010, group 2b (_PPP+P) was consistent with the Northern Territory Childhood Immunisation Vaccination Schedule with the exception that the NT schedule recommended the PCV booster be given at 18 months of age.

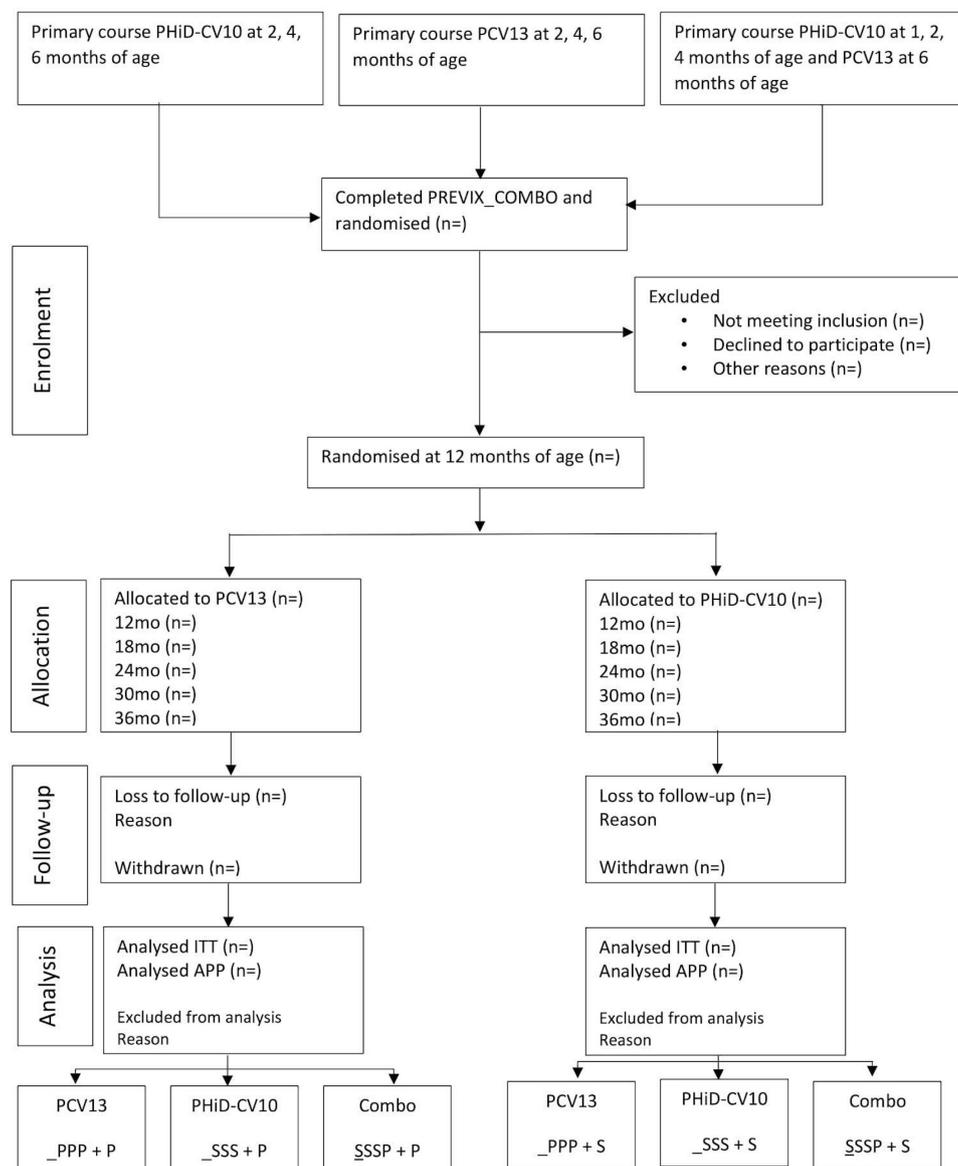


Figure 1 Flow diagram. APP, as per protocol; ITT, intention to treat; PCV13, 13-valent pneumococcal conjugate vaccine; PHiD-CV10, 10-valent pneumococcal *Haemophilus influenzae* protein D conjugate vaccine; _PPP=3 doses of Prevenar at 2, 4 and 6 months of age; _SSS=3 doses of Synflorix at 2, 4 and 6 months of age; SSSP=3 doses of Synflorix at 1, 2 and 4 months and 1 dose of Prevenar at 6 months; +=plus; P=Prevenar; S=Synflorix.

Strategies to improve adherence

Strategies adopted to improve adherence are as previously outlined.¹⁰ Parents will be advised of their baby's scheduled visit dates. Calls will be made in advance to advise parents of scheduled study visit, if they provide a contact phone number. The study will rent vehicles in each community to ensure participants have transport to the health service for all vaccine procedures.

Relevant concomitant care

Clinical trial research nurses will provide all vaccinations according to the current NIP for the indigenous population.¹² There will be no prohibition on concomitant medication; therefore, infants will receive treatment or referral for all concomitant conditions, particularly ear, skin, respiratory and growth problems, according to local guidelines.¹³

Baseline assessment

Demographic data will include age, gender, weight, height, general health history and lifestyle questionnaire. Research nurses will conduct clinical ear assessments, collect NP swabs, use a standardised assessment of developmental milestones and conduct all clinical examinations. A research audiologist will conduct age-appropriate hearing assessments in a sound-proof booth.

OUTCOMES

Primary outcome measure

Immunogenicity

The co-primary outcome measures assessed at 18 months of age (6 months post booster dose) are (a) the IgG geometric mean concentration (GMC) and the

proportion of children with IgG concentration above 100 EU/mL threshold for protein D,¹⁴ and (b) GMC and the proportion of children with IgG concentration above 0.35 µg/mL threshold for serotypes 3, 6A and 19A. The serotype-specific IgG levels will be determined using a modified third-generation ELISA based on WHO recommendations.¹⁵ IgG antibodies to the protein D will be measured by indirect ELISA, with non-lipidated protein D as coating material and expressed in ELISA units (EU/mL) as previously described.¹⁰

Secondary outcome measures

Secondary immunogenicity outcomes

The GMCs of serotype-specific IgG and the proportion of children with IgG above protective threshold of 0.35 µg/mL will be reported for vaccine serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F measured at 18 months of age.

NP carriage and ED microbiology outcomes

The proportion of children with NP carriage of serotype-specific pneumococci and NTHi carriage will be reported at 12, 18, 24, 30 and 36 months of age. NP and ED swab collection, transportation, storage and testing have been described previously.¹⁰ Briefly, NP and ED swabs will be cultured on selective and non-selective media, and semiquantitative colony counts recorded as previously described.^{10 16} Capsular pneumococci will be identified by colony morphology and optochin sensitivity, and serotype determined by the Quellung reaction using serotyping antisera (Statens Serum Institut, Denmark). NTHi will be identified by colony morphology, dependence on X and V growth factors, and lack of reaction with capsular antisera using the Phadebact *Haemophilus* coagglutination test. Other respiratory and otopathogens identified will also be reported, as will antimicrobial sensitivities of major pathogens as previously described.¹⁰ Quantitative PCR will be performed to estimate density of *H. influenzae*, *S. pneumoniae* and *Staphylococcus aureus* in ED swabs and NP swabs collected at 18 months of age.^{17 18}

Clinical outcomes

Otitis media

Standardised ear assessments will be made at 12, 18, 24, 30 and 36 months of age. Video otoscopy and tympanometry will be used as previously described.¹⁰ Diagnoses and management will be determined by research nurses according to Recommendations for Clinical Management of Otitis Media in Aboriginal and Torres Strait Islander Health Populations (2010).¹⁹ The proportion of infants in each allocated group with any OM, otitis media with effusion, acute otitis media without perforation (AOMwoP), AOMwiP, dry perforation (DP) or CSOM at 12, 18, 24, 30 and 36 months of age will be reported. Combined diagnostic categories of any suppurative OM (AOMwoP, AOMwiP plus CSOM) or any tympanic membrane perforation (AOMwiP plus DP plus CSOM) will also be reported.

For additional episodes of OM, data will be extracted from Primary Care Information Systems (PCIS) from birth to 3 years of age. We define AOM as healthcare provider-diagnosed AOM if antibiotic treatment is also prescribed (because antibiotic treatment for all forms of AOM is standard treatment in this population). A new episode of AOM will be defined if at least 2 weeks have elapsed and no AOM confirmed in the interim.

Respiratory illness

The proportion of infants with cough, nasal discharge, wheeze or crackles at 12, 18, 24, 30 and 36 months of age will be reported alone and in combination. Posterior and anterior chest auscultation will be performed, documenting the presence of clear chest, wheeze or crackles. The presence of spontaneous cough or cough on request will also be documented and the quality of cough (wet, dry) established.

For additional episodes of respiratory illness, data will be extracted from Primary Care Information Systems (PCIS) from birth to 3 years of age. We define respiratory illness as all clinician diagnosed cough, cold, runny nose, influenza, bronchiolitis, bronchitis or pneumonia (alone or in combination) if antibiotics were also prescribed or hospitalisation documented. Separate episodes must be 1 week apart or separated by two well days.

Audiology outcomes

The proportion of infants with any hearing loss at 12, 18, 24, 30 and 36 months of age will be reported. Audiological assessments will be conducted by a research audiologist with experience in paediatric audiology and assisted by a trained research assistant or nurse. All assessments will be conducted in sound-proof hearing booths. An Interacoustics paediatric audiometer (PA5) or Otometrics MADSEN Itera II will be used. Visual Reinforcement Observation Audiometry (VROA) in the sound field and Play Audiometry under headphones will also be used to evaluate hearing outcomes. Where possible, air conduction and bone conduction thresholds (both masked and unmasked) will be obtained at octave frequencies of 0.5–4.0 kHz. The pure-tone average will be calculated for air conduction thresholds binaural or monaurally using the three frequencies 0.5, 1.0 and 2.0 kHz. Assessments where only one threshold was recorded will be considered important for inclusion in the analysis. Severity categorisation (hearing impairment) will include 0–15 dB normal, 16–30 dB mild, 31–60 dB moderate, 61–90 dB severe, >90 dB profound. This is consistent with processes used by the primary provider of hearing services in the region (Top End Health Services). Additional audiometric data including that collected prior to appointment of a research audiologist in January 2017 will be sourced retrospectively from Northern Territory Government Hearing Services who assessed children referred from the study.

Developmental milestones

The proportion of infants with any developmental concerns at 12, 18, 24, 30 and 36 months of age will be reported. We will report whether age-appropriate standardised milestones were observed by both mother (carer) and researcher, by neither mother nor researcher, or by either mother or researcher. Standardised developmental milestone questionnaires²⁰ and structured interview questionnaires involving expressive language and phonology (eg, number of words) assessment and quality of life (QoL) relating to OM (eg, communication, social, anxiety, aggression)^{21 22} will be carried out by research nurse with parental assistance to reduce misinterpretation due to cultural and linguistic context.^{23 24} Each time point will have the same questions, in addition to further age-appropriate milestones. Milestones to be reported by observation will be achieved using a two-way approach:

- a. Directly observed by research nurse such as walking, turning in direction of voice when name called; or directly asking child to complete tasks such as identifying objects, anatomical features, saying their name in full and following at least two or more instructions given in a sentence.
- b. Where English is the second language, researcher will ask mother or carer to ask child in their language to complete tasks.

We will also report the proportion of children whose parent or carer has any concern regarding developmental milestones or poor QoL according to these standardised tests.

Sample size

Target sample size for infant enrolment at 12 months of age is 270 participants. Assuming 10% loss to follow-up at 18 months of age, this will provide 240 infants for primary outcome assessments.

Primary immunogenicity outcome

Published studies of PCV13 indicate that proportion above threshold IgG for 6A and 19A could be 37% and 57%²⁵ among PHiD-CV10 group and 87% and 89%, respectively, in the PCV13 group.²⁶ Antibody levels are sustained in adults²⁷; however there are no published studies of immunogenicity outcomes in infants 6 months post vaccination. Similarly, published studies indicate that the proportion of vaccinees with above thresholds IgG for protein D could be 67% to 88%²⁸ in PHiD-CV10 groups. The latter study also demonstrated sustained antibody levels over 1 year. With 270 infants immunised at 12 months of age and 240 (120 per group) with blood drawn at 18 months of age, we will have 99% power to detect these differences for serotypes 6A and 19A, and 97% power to detect the predicted difference in protein D.

Secondary immunogenicity outcomes

Sample size for the six groups of 40 children with primary and booster schedule combinations created by the two consecutive trials will provide 80% power to detect a

conservative difference in serotype-specific pneumococcal GMC of 1.0 µg/mL (SD=1.6). However, for the proportions above protective thresholds for 6A and 19A, the power will be 99% and 90% to detect differences from 37% and 57%²⁵ to 87% and 89%, respectively.

We will be able to combine groups (80 per group) and have over 80% power to detect smaller differences of 0.5 µg/mL (SD=1) in immune correlates for comparisons of the serotypes common to the two vaccines.

Recruitment of participants

In participating communities, parents of participants in PREVIX_COMBO will be asked at the end of the study (infant age 7 months) if they are happy for study staff to contact them again before the child's first birthday to identify if they were interested in participating in the BOOST study. If so, parents and carers will be provided with participant information sheet. Written informed consent will then be obtained from the mother/carer when infant is at eligible age (11¹/₂ to 13¹/₂ months of age).

Assignment of interventions

Allocation

Sequence generation: Allocation to a booster dose of PHiD-CV10 or PCV13 is undertaken by the National Health and Medical Research Council Clinical Trial Centre randomisation service. Minimisation is used and stratified by previous treatment allocated in PREVIX_COMBO¹⁰ and community.

Blinding (masking): Primary outcome assessors (laboratory scientists) will be blinded to the vaccine group allocation. Unblinding a participant's allocated intervention during the trial will be permissible only if requested in writing by the independent Data Safety Monitoring Board (iDSMB) following a unanimous decision by the iDSMB to do so and in accordance with the Terms of Reference.

Data collection methods

Standardised assessment and data collection forms will be used as previously described.¹⁰ Briefly, blood will be collected via heel prick or venepuncture, and volume of whole blood recorded. For the NP swabs, the WHO recommendations are followed.²⁹ For OM, tympanometry and video-otoscopy are performed, and the final diagnosis for each ear is determined by the research nurse for purposes of disease management, according to guidelines.¹⁹

Retention: Participant retention will be promoted through the eligibility criteria (intention of the family and infant to remain in the community) and encouragement at each interaction with study staff.

Data management

Data collection methods have been previously reported.¹⁰ Briefly, field data collected on standardised forms will be returned to the Menzies office and data entered into a MySQL database via a Microsoft Access front end within 1 week of data collection. Microbiology data will

be entered directly onto the same MySQL database. All data will be checked as previously described.¹⁰ Blinded immunology results will be sent in an Excel spreadsheet via email to the senior database manager at Menzies to be linked with the main database at the time of unblinding.

Statistical methods

Analysis principle

The full analysis set will adhere to the principles of intention-to-treat and will comprise all outcome data available at each time point, and the main analysis will compare subjects according to which group they were allocated to. We do not plan to impute any data. Subjects vaccinated within window (11¹/₂ to 13¹/₂ months of age) who complete all study visits and procedures within study windows and for whom complete outcome data are available will be eligible for inclusion in the as-per-protocol analyses.

Demographic characteristics

Baseline characteristics will be provided for each group following the Consolidated Standards of Reporting Trials (CONSORT) guideline,³⁰ using means and SD, for continuous data if assumption of normal distribution is met, otherwise median value and IQR will be reported. Categorical data will be summarised as frequencies and proportions.

Primary immunogenicity outcomes

The primary outcome measures are the pneumococcal serotype-specific IgG GMC and proportion of infants above the threshold IgG concentrations of 0.35 µg/mL and protein D IgG ≥100 EU/mL in each of the two randomised groups at 18 months. Statistical inference will be based on the two-sample t-test, applied to the log-transformed concentrations. Point and two-sided 95% CI estimates will be transformed back and the ratio of GMCs derived. Fisher's exact test will be used to compare the proportions with IgG concentration above thresholds (0.35 and 1 µg/mL for IgG and 100 EU/mL for protein D) and two-sided 95% CI will be reported.

Secondary outcomes

Secondary immunogenicity outcomes

Secondary immunogenicity outcomes will be analysed and reported as for primary immunogenicity outcomes for additional vaccine serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) and non-vaccine serotypes (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F).

Carriage, OM, respiratory assessment and developmental milestone outcomes

The proportion of children with any carriage of pneumococcal serotypes 3, 6A or 19A; any carriage of replacement serotypes; any carriage of NTHi; any OM; any spontaneous cough; or cough on request, any adventitious sounds (crackles or wheeze) on bilateral chest auscultation; any combination of cough, nasal discharge and crackles or wheeze; and any developmental concerns

at 18, 24, 30 and 36 months will be summarised with two-sided 95% CI and reported for each treatment group. Vaccine efficacies for immunogenicity, carriage and any OM will each be calculated as 1 minus the relative risk between vaccine groups with percentages compared with a two-sided Fisher's exact test.

The rate of additional episodes of AOM or bronchiolitis, bronchitis or pneumonia reported in medical records (PCIS and hospitalisations) from birth to age 3 years will be summarised in rates per child years. The effect of vaccine formulation on rates of AOM, bronchiolitis, bronchitis or pneumonia will be assessed using negative binomial regression. The incidence rate ratio and 95% CI will be reported.

Audiology outcomes

Differences in average three-frequency hearing level at each time point will be assessed using a linear mixed model. The mean difference of the two interventions and 95% CI will be reported. Based on the severity categorisation (normal (<15 dB), mild (16–30 dB), moderate (31–60 dB), severe (61–90 dB) and profound (>90 dB) hearing loss), we will report the proportion of children with any hearing loss, mild, moderate, severe or profound hearing impairment at 18, 24, 30 and 36 months of age. These will be reported by ear and by child.

Multivariable analyses

Multivariable analyses will be performed for both primary and secondary endpoints to evaluate variables (eg, overcrowding, breastfeeding and smoking) independently associated with disease endpoints and to assess their potential effect in association between vaccination and disease. For binary, continuous and count outcomes, we will use mixed effect models with the appropriate link function for binomial, Gaussian and negative binomial distributions.

Data monitoring

The independent Data Safety and Monitoring Board that served the PREVIX_COMBO trial agreed to continue to serve the PREVIX_BOOST trial, meeting 6 monthly.¹⁰ As previously described, participant recruitment and retention, protocol deviations and violations, reactogenicity, adverse events and serious adverse events will be reviewed regularly. Aggregate data will be reported, closed sessions held if required and the iDSMB may request interim independent analyses.

Ethics and dissemination

This study has been approved by the following ethics committees: NT Department of Health and Menzies Human Research Ethics Committee (HREC-EC00153), the Government of WA Department of Health (2013:34; 11/2013), and West Australian Aboriginal Health Ethics Committee (WAAHEC 538; 02/2014).

Protocol amendments

All protocol modifications will be reported to the relevant HREC in the NT and in Western Australia. Trial registries will be regularly updated. Investigators, the iDSMB and other stakeholders including participating community health services will be informed of important protocol amendments.

Consent or assent

Who obtains consent: Trained research staff will undertake informed assent and consent. Information will be provided to parents (usually the mother) in written, verbal and pictorial formats, including verbal translation where requested.¹⁰ Signed consent will be required at the time of randomisation, when the infant is between 11¹/₂ and 13¹/₂ months of age, when eligibility criteria will be confirmed. The consent process will include explanations of all elements of consent, according to Good Clinical Practice, the Declaration of Helsinki, NHMRC requirements, and according to local requests to ensure cultural safety (as recommended by the Indigenous Reference Group).

Ancillary studies: Additional consent will be sought from parents or guardians to use participant data and biological specimens for future research relating to OM.

Confidentiality

Personal information will be collected on standardised paper forms. Data will be collected from participants' medical records and by face-to-face interview. As previously described, paper-based and electronic data will be stored in locked cabinets and on a secure password-protected server. Participant ID codes will be used.

Access to data

As previously described for the PREVIX_COMBO trial,¹⁰ this final trial dataset will be under the custody of the trial sponsor, the Menzies School of Health Research.

Ancillary and post-trial care

All participants will have access to ancillary care from their usual healthcare provider (local community health centre). Should the trial show benefit or harm of the any vaccine schedule, recommended vaccination schedules may change accordingly. Compensation for trial participants for trial-related harms is provided through the trial insurance and indemnity by the Menzies School of Health Research.

Dissemination policy

Plans: Trial results will be communicated in aggregate to participant families and their communities in written and oral presentations. Results will be provided for individual communities if requested. Trial results will be published in peer-reviewed international journals, will be presented at relevant national and international conferences, and will be reported to local policy makers (Australian Technical Advisory Group on Immunisation, Therapeutic Goods Administration and the Pharmaceutical Benefits

Advisory Committee) with responsibility for immunisation in Australia. Additional stakeholders including the trial funders (NHMRC and Financial Markets for Children), and vaccine manufacturers, will be informed of the trial findings. Results will be disseminated regardless of the magnitude or direction of effect. There are no publication restrictions.

Authorship eligibility

A publication subcommittee will be appointed to review and classify all proposed publications according to the PREVIX publication guidelines.¹⁰

Committees

The Child Health Division of the Menzies School of Health Research has an Indigenous Reference Group (CHD_IRG), currently chaired by Larrakeyah Elder Bilawarra Lee. The IRG is comprised of Indigenous members with expertise in science, ethics and Indigenous affairs. Role of the CHD_IRG is to review and advise on cultural relevance of research, from inception to implementation. Prof Leach regularly reports to the CHD_IRG and seeks their advice and feedback. CHD_IRG members: *Chair:* B Lee. *Deputy Chair:* Tracy Brand. *Members:* D Bonney, M Mayo, D Campbell, L Murakami-Gold, V McClintic, L Versteegh (*Secretariat*).

Independent Data Safety and Monitoring Board (iDSMB) members: *Chair:* D Isaacs. *Members:* T Nolan, H Gunasekera, P Forder, N Woods, H D'Antoine. An independent study monitor (N Woods) assesses relatedness of adverse events to study intervention.

Data management group: The PI, Prof Leach, is responsible for data quality, security and regulatory requirements. Ms Jemima Beissbarth manages the database, data dictionary and data cleaning. The Menzies Data Management Group led by Mr Steve Buchanan with Mrs Robyn Liddle oversees the long-term storage of the data and holds blinded immunogenicity data.

Collaborators

NHMRC 1046999 and 1120353 grant application investigators: *Chief investigators:* CIs: AJ Leach (PI), K Mulholland, M Santosham, P Torzillo, N Brown, P McIntyre, H Smith-Vaughan, A Balloch, M Chatfield, D Lehmann and M Binks. *Associate investigators:* AIs: A Chang, J Carapetis, PS Morris, V Krause, R Andrews, T Snelling and P Licciardi.

Additional investigators: *PREVIX staff (current or at least 1 year):* *Coordinators:* T Grierson, J Wheeler, N Wilson. *Research nurses:* N Birt, Z Hayes, N Wienert, B Nankervis, K Whykes, S Sprenger, B Arrowsmith, V Coomber, R Sharp. *Laboratory scientists:* D Woltring, J Beissbarth. *Statistician:* V Oguoma. *Admin:* C Gage-Pearson. *Causal staff:* L Bell, N Glasson, M Downie, R Lennox, E Nosworthy.

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Collaborators PREVIX research managers and research nurses (33): Nicole Wilson, Beth Arrowsmith, Tracy Grierson, Carolyn Gage-Pearson (admin), Nicole Weinert, Natalie Bert, Zeina Hayes, Melanie Schwarz, Julie Wheeler, Bronwyn Nankervis, Laura Bell, Jessica Young, Kelly Whykes, Sabine Sprenger, Melisa Downie, Valerie Coomber, Kate Ranford, Rachel Sharp, Elissa Rowe, Jodie Howes, Chantelle Dowling, Claire Haynes, Christine Byrne, Niki Emmett, Sarah Carlisle, Fiona Hildebrand, Kate Dohle, Cathy O'Driscoll, Peta Hamilton, Jesse Abbott. Statisticians: Mark Chatfield, Victor Oguoma. PREVIX audiologists: Dino Hodge, Jennifer Jenson, Janine Pisula, Jana Fogarty, Annette Kaspar. PREVIX laboratory team (16): Jemima Beissbarth, Vanya Hampton, Nerida Liddle, Christopher Wevill, Yuki Ruzsicska, Donna Woltring, Rebecca Cass, Cain Hendy, Shennelle Waters, Shae Tozer, Erin Gargan, Nicole Smitran, Amy Llewellyn, Katrina Lawrence, Jessie Spargo, Kim Hare. Community Researchers: Jeanette Warnir and Georgina Parmbuk (Wadeye), Amanda Turner (Alice Springs), Kaylene Puruntatameri (Wurrumiyanga) Clinic managers and midwives: Tracy Porter & Sharon Overend, Kris O'Connell & Sophie Eakins, Kim Henschke & Maree Daniel, Evelyn Semmens & Amy Richie. M Audiologist student: Belinda Inglis UniMelb Medical Degree Research Program students: Joanna Sen, Jarod Pak, Nashwa Saad CDU MPH student: Leigh Moore Expert advisory group: Allen Cheng, Chris Blyth, Kathy Currie, Michael Binks.

Contributors VMO drafted the manuscript, assisted with statistical analysis plan, revised the manuscript and approved the final version of the manuscript. NW drafted the manuscript, was the Clinical Trial Manager for 5 years and approved the final version of the manuscript. KM and PJT advised on study design, assisted with funding application, participated in investigator meetings, advised on risk management and read the final version of the manuscript. MS advised on study design, assisted with funding application, participated in investigator meetings, advised on risk management, reviewed and approved the final version of the manuscript. PMCI advised on study design, assisted with funding application, participated in investigator meetings, advised on risk management and approved the final version of the manuscript. HS-V advised on study design, assisted with funding application, participated in investigator meetings, advised on laboratory protocols, particularly microbiology, reviewed and approved the final version of the manuscript. AB advised on study design, assisted with funding application, participated in investigator meetings and advised on laboratory protocols, particularly immunogenicity, but was not available to read the final version of the manuscript. MDC advised on study design, assisted with funding application, participated in investigator meetings, assisted with statistical analysis plan, reviewed and approved the final version of the manuscript. DL, MJB and ABC advised on study design, assisted with funding application, reviewed and approved the final version of the manuscript. JC advised on study design, assisted with funding application, reviewed and approved the final version of the manuscript.

VK advised on study design, assisted with funding application, advised on immunisation policy implications and approved the final version of the manuscript. RMA and TS advised on study design, assisted with funding application, reviewed and approved the final version of the manuscript. PL advised on study design, assisted with funding application, reviewed and approved the final version of the manuscript. PSM advised on study design, assisted with funding application, participated in investigator meetings, advised on risk management and provided day-to-day supervision of clinical training, reviewed and approved the final version of the manuscript. AJL (principal investigator, PI) conceived the study, led funding applications, obtained HREC approval and other regulatory approvals, undertook consultations, reporting and has overseen day-to-day management and implementation of the trial, and reviewed and approved the final version of the manuscript.

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Competing interests In the last 5 years, AJL and PM have served on an OM Advisory Board for GSK and have received GSK support for the clinical outreach training program. KM has served on Advisory Boards for GSK who provided in kind support for the Vietnam Pneumococcal trial, of which he is the PI. His group is involved in a collaborative research project with Pfizer on adult pneumonia in Mongolia, and they have received a small grant to support research capacity building in the paediatric hospitals in Ho Chi Minh City, Vietnam. MS has served on the Advisory Board of GSK and Pfizer. He is also co-investigator on projects funded by GSK and Pfizer. ABC serves on an independent data safety monitoring board for two unlicensed GSK vaccines studies currently under evaluation. DL has received support from Pfizer Australia to attend conferences and is an investigator on an investigator-initiated research grant that was funded by Pfizer Australia.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No individual patient data will be available.

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Title:

10-Valent pneumococcal non-typeable H. influenzae protein D conjugate vaccine (PHiD-CV10) versus 13-valent pneumococcal conjugate vaccine (PCV13) as a booster dose to broaden and strengthen protection from otitis media (PREVIX_BOOST) in Australian Aboriginal children: study protocol for a randomised controlled trial.

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