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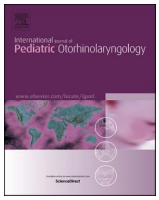

Otitis media at 6-monthly assessments of Australian First Nations children between ages 12–36 months: Findings from two randomised controlled trials of combined pneumococcal conjugate vaccines

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ABSTRACT

Objectives: In remote communities of northern Australia, First Nations children with hearing loss are disproportionately at risk of poor school readiness and performance compared to their peers with no hearing loss. The aim of this trial is to prevent early childhood persisting otitis media (OM), associated hearing loss and developmental delay. To achieve this, we designed a mixed pneumococcal conjugate vaccine (PCV) schedule that could maximise immunogenicity and thereby prevent bacterial otitis media (OM) and a trajectory of educational and social disadvantage.

Methods: In two sequential parallel, open-label, randomised controlled trials, eligible infants were first allocated 1:1:1 to standard or mixed PCV primary schedules at age 28–38 days, then at age 12 months to a booster dose (1:1) of 13-valent PCV, PCV13 (Prevenar13®, +P), or 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugated vaccine, PHiD-CV10 (Synflorix®, +S). Here we report findings of standardised ear assessments conducted six-monthly from age 12–36 months, by booster dose.

Results: From March 2013 to September 2018, 261 children were allocated to booster + P (n = 131) or + S (n = 130). There were no significant differences in prevalence of any OM diagnosis by booster dose or when stratified by primary schedule. We found high, almost identical prevalence of OM in both boost groups at each age (for example 88% of 129 and 91% of 128 children seen, respectively, at primary endpoint age 18 months, difference

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−3% [95% Confidence Interval −11, 5]). At each age prevalence of bilateral OM was 52%–78%, and tympanic membrane perforation was 10%–18%.
Conclusion: Despite optimal pneumococcal immunisation, the high prevalence of OM persists throughout early childhood. Novel approaches to OM prevention are needed, along with improved early identification strategies and evaluation of expanded valency PCVs.

1. Introduction

1.1. Background and objectives

Australian First Nations children living in remote communities continue to experience social and educational disadvantage [1] which can be attributed in part to preventable hearing loss associated with early onset of persistent otitis media (OM). *Streptococcus pneumoniae* (pneumococcus) and non-typeable *Haemophilus influenzae* (NTHi) are dominant pathogens of OM from soon after birth.

The Northern Territory (NT) childhood vaccination schedule replaced 7-valent pneumococcal conjugate vaccine (PCV7) in 2001 with 10-valent pneumococcal *Haemophilus influenzae* protein D conjugate vaccine, Synflorix™ (S, PHiD-CV10) in 2009, then 13-valent PCV, Prevenar13™ (P, PCV13) vaccine in 2011. Routine surveillance found suggestive evidence of less AOM and a lower prevalence of NTHi in ear discharge of PHiD-CV10-vaccinated First Nations children compared to PCV7-vaccinees, and non-significant differences compared to PCV13-vaccinated children [2].

Our objective was to evaluate novel combined PCV schedules to maximise early and longer-term immune protection against both pneumococci and NTHi. We conducted two RCTs in series. The first RCT (PREVIX_COMBO) randomised infants (1:1:1) to standard schedules of either PCV13 or PHiD-CV10 at ages 2-4-6 months, or to a combination 4-dose schedule of PHiD-CV10 at ages 1-2-4 months plus PCV13 at age 6 months [3]. The second RCT (PREVIX_BOOST) randomised these infants (1:1) at age 12 months to a booster of either PCV13 (+P) or PHiD-CV10 (+S) [4]. We have reported co-primary and secondary immunogenicity outcomes, and some clinical and microbiology outcomes to age 18 months [3,4]. Here we report new data on vaccine group differences in all forms of otitis media at ages 12, 18, 24, 30 and 36 months.

2. Methods

Details of PREVIX_COMBO and PREVIX_BOOST protocols have been published [3–6]. Brief methods are described below.

2.1. Study design

The PREVIX_COMBO and PREVIX_BOOST trials were primary outcome assessor-blinded, three-arm (1:1:1) and two-arm (1:1) parallel randomised controlled trials. No changes that affected the primary objectives or outcomes were made after trial commencement.

2.2. Participants

First Nations children were eligible for PREVIX_BOOST if they were 12 months of age, had previously enrolled in the PREVIX_COMBO 3-arm RCT, and were living in one of three remote Aboriginal communities in the NT or a single Western Australian community.

2.3. Randomisation and masking

Sequence generation: After confirming eligibility and obtaining informed consent, research nurses called the 24/7 randomisation service of the National Health and Medical Research Council Clinical Trial Centre to obtain allocation. Stratification by remote community was applied in both trials, and for PREVIX_BOOST, minimisation by PREVIX_COMBO group was applied. This open-label design did not allow for blinding research nurses who were involved in all participant study visits.

2.4. Procedures

2.4.1. Interventions - vaccines

PHiD-CV10 contains 10 pneumococcal serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F and incorporates protein D of NTHi as a carrier protein for eight serotypes. PCV13 contains these ten and additional serotypes 3, 6A, and 19A, but does not incorporate protein D.

2.4.2. Outcomes

2.4.2.1. Risk factor questionnaires at baseline (child age 12 months). Parents or carers were asked standardised questions about number of children in the household, family history of ear disease (“runny ears”), breast feeding, and tobacco and woodfire smoke exposure.

2.4.2.2. Otoscopy and tympanometry. Standardised ear assessments using video otoscopy then tympanometry were made as previously described [5]. Diagnostic categories for each ear and the worse ear at each assessment were ranked according a hierarchy of increasing severity: no otitis media (no OM), otitis media with effusion (OME), acute otitis media without perforation (AOMwoP), dry perforation (DP), acute otitis media with perforation (AOMwiP) or chronic suppurative otitis media (CSOM). Combined diagnostic categories were any OM, any suppurative OM (suppOM; includes AOMwoP, AOMwiP, or CSOM), any tympanic membrane perforation (TMP; includes AOMwiP, DP, or CSOM), and any bilateral OM. We also recorded tympanometric findings separately and according to a hierarchy of increasing severity: type A, C1, C2, and type B. Where otoscopy was only successful in one ear, the diagnosis of the examined ear was used. Where otoscopy was unsuccessful, tympanometry results were used and OME (type B tympanogram) or no OM (type A/C1, or C2) diagnosis allocated. Recommendations for management were made according to local guidelines [7].

2.4.2.3. Concomitant care. All child-visits included a general health check, with management and immunisations according to local guidelines [7,8].

2.5. Analysis and statistical methods

Sample sizes of 425 and 270 were estimated for PREVIX_COMBO and PREVIX_BOOST, respectively [3,4]. Analyses of outcome data available at each time point were according to allocated group. We did not impute any data. All data were analysed using Stata/IC version 15.1 [9]. Baseline characteristics are reported for each PREVIX_BOOST group, using means and standard deviation for continuous data if assumption of normal distribution is met. Categorical data are summarised as frequencies and percentages. For each visit-age, we report the proportion (%) of children with worse ear according to above diagnostic hierarchy. Vaccine group differences in percentages are compared with two-sided 95% Confidence Interval (95%CI).

3. Results

The PREVIX_BOOST trial commenced participant recruitment in March 2013. Additional study visits at 24 and 30 months commenced (in NT communities only) in January 2017. Data collection was completed in September 2018.

3.1. Participant flow

Eligibility: 261 children were randomised to PREVIX_BOOST and allocated 1:1 a booster dose of +P (131) or + S (130) at age 12 months (Fig. 1) [3,4]. At baseline and for each 6-monthly scheduled study visit the numbers of children seen and assessed are given in Fig. 1.

3.2. Baseline characteristics at age 12 months, by vaccine group

Demographics and risk factors for otitis media were similar in both vaccine groups at baseline age 12 months (Table 1).

Of 129 baseline ear assessments in each vaccine group, 114 (88%) and 119 (92%) children in +P and +S groups, respectively had some form of OM; AOMwoP was most common (47% and 50%, respectively), followed by OME (29% and 29%), and TMP (12% children in each group). Bilateral OM was detected in 78% and 78%, which is 88% and 85% of children with OM, respectively (Table 2).

3.3. Post booster dose outcomes at follow-up ages 18, 24, 30, and 36 months, by booster vaccine group

3.3.1. Otoscopy and tympanometry

There were three ear examinations for which otoscopy was missing

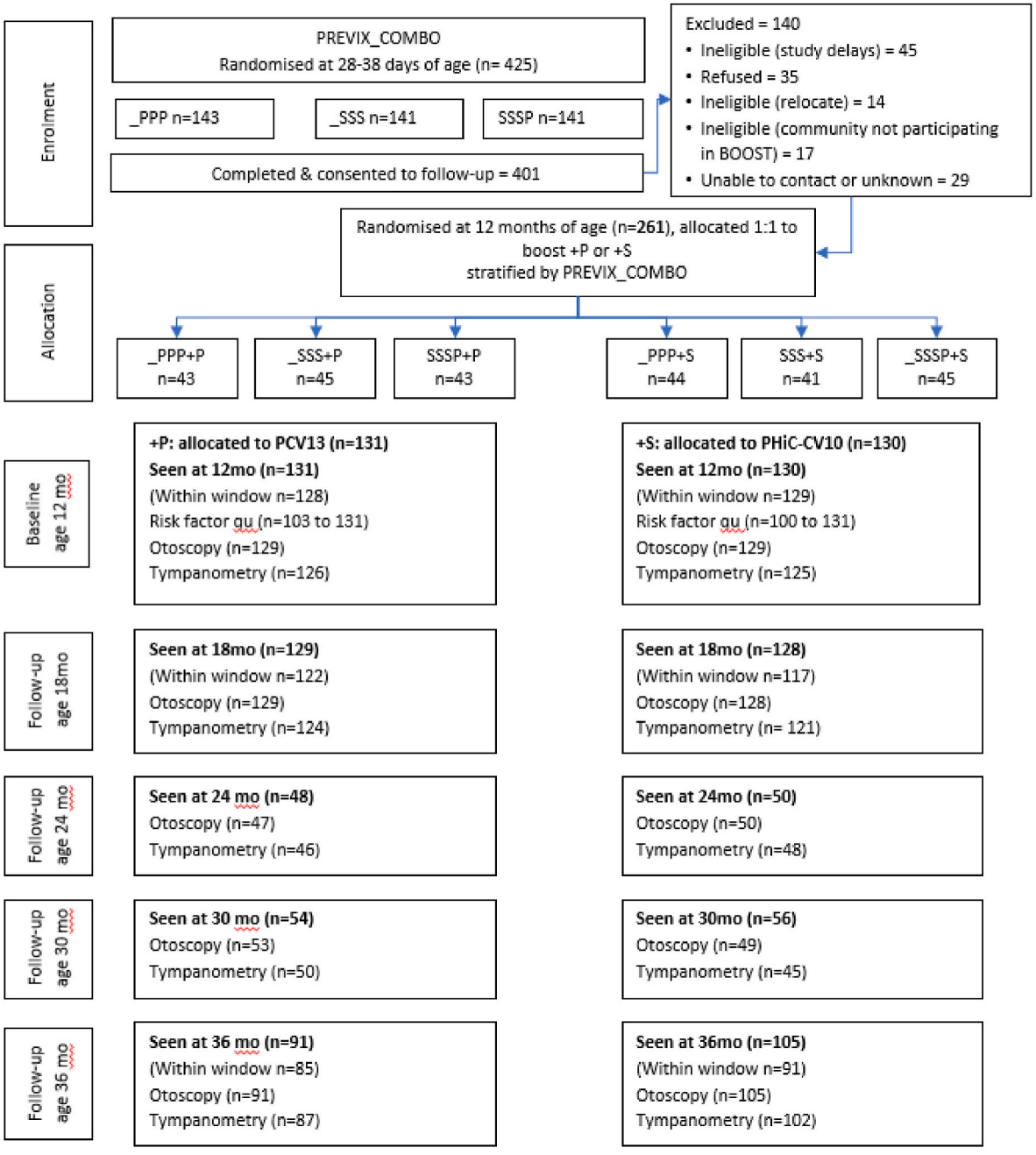

Fig. 1. Participant flow.

Table 1
Baseline characteristics at age 12 months.

BASELINE CHARACTERISTICS	+P	+S
	N = 131	N = 130
Age at randomisation to BOOST (years)	1.02 (0.07)	1.02 (0.05)
Sex male	61/131 (47%)	65/130 (50%)
Gestational age (weeks)	38.14 (1.50)	38.31 (1.58)
Weights at birth (kg)	3.06 (0.47)	3.12 (0.47)
Weight at randomisation (kg)	9.14 (1.07)	9.30 (1.12)
Height at randomisation (cm)	73.8(3.02)	74.0 (3.38)
COMMUNITY		
WURRUMIYANGA/NGUIU	31 (24%)	30 (23%)
WADEYE	51 (39%)	51 (39%)
KUNUNURRA	20 (15%)	18 (14%)
MANINGRIDA	29 (22%)	31 (24%)
Risk factor questionnaire at randomisation	N = 130	N = 129
How many other kids do you have?		
0	1 (1%)	0 (0%)
1	44 (34%)	44 (34%)
2	39 (30%)	34 (26%)
3	26 (20%)	26 (20%)
4	14 (11%)	15 (12%)
5	3 (2%)	5 (4%)
6	1 (1%)	3 (2%)
7	1 (1%)	2 (2%)
How many kids under 5 will live with you and baby?		
0	44 (34%)	41 (32%)
1	45 (35%)	40 (31%)
2	25 (19%)	28 (22%)
3	10 (8%)	11 (9%)
4	2 (2%)	4 (3%)
5	2 (2%)	3 (2%)
6	1 (1%)	2 (2%)
7	1 (1%)	0 (0%)
Response 'yes' to following		
Have any of your other children had runny ears?	23/113 (20%)	21/109 (19%)
Has you baby had any bad runny nose since the last study visit?	58/131 (44%)	52/129 (40%)
Are you breastfeeding?	120/131 (92%)	114/129 (88%)
Are you bottle feeding?	34/130 (26%)	33/129 (26%)
Do you smoke cigarettes?	91/131 (70%)	79/129 (61%)
Did you smoke when you were pregnant?	46/103 (45%)	48/100 (48%)
Does anyone smoke at your house?	35/131 (27%)	35/129 (27%)
Do you cook with or sit near a wood fire?	38/130 (29%)	45/129 (35%)

+P: Prevenar13™ PCV13 13-valent Pneumococcal conjugate vaccine.
+S: Synflorix™ PHiD-CV10 10-valent pneumococcal H. influenzae protein D conjugate vaccine.

and tympanometry was available. All were bilateral type B tympanograms allocated an OME diagnosis. There were no statistically significant differences in any form of OM between + P and +S groups at any age post-booster (Table 2), nor when stratified by primary schedules.

At primary endpoint age 18 months (6 months post booster dose), 129 and 128 children were seen in +P and +S groups, respectively. Of these 113 (88%) children in the +P group and 116 (91%) in the +S group had some form of OM; 37% and 40%, respectively had OME, 36% and 34% had AOMwoP, and 14% and 17% had TMP(s), respectively. Bilateral OM was present in 75% and 73%, which is 85% and 81% children with OM (Table 2, Fig. 2).

At age 24 months, 47 and 50 children were seen in +P and +S groups, and at age 30 months, 53 and 49 were seen, respectively. At each age between 74% and 88% had some form of OM; between 47% and 57% had OME, 9%–22% had AOMwoP, and 8%–18% had TMPs. Bilateral OM was present in 55%–66%, which is 70%–75% children with OM (Table 2, Fig. 2).

At age 36 months, 91 and 105 children were seen in +P and +S groups, respectively. By this age prevalence of bilateral normal ears (no OM) had increased from baseline in both groups (28% and 27%) with correspondingly fewer children having any OM (71% and 73%); OME was the worse ear diagnosis in 41% and 48% children, AOMwoP in 13% and 8%, and TMPs in 17% and 18%, respectively. Bilateral OM was present in 52% and 51%, which is 70% children with OM in each group (Table 2, Fig. 2).

Analysis of each type of OM or any OM stratified by six groups (primary and booster schedules) found no significant differences at primary endpoint 18 months or when all ages were combined.

3.4. Patterns of OM, booster groups combined

3.4.1. Bilateral OM, unilateral OM, and bilateral no OM

For both + P and +S groups and all ages combined, there were 910 assessment visits, including 906 bilateral assessments. Bilateral OM was 78% at age 12 months, then 74%, 61%, 59%, and 52% at each age to 36 months. For each worse ear diagnoses OME, AOMwoP, AOMwiP, and CSOM the contralateral ear was rarely without OM; 28%, 8%, 13%, and 12%, respectively had unilateral OM (data not shown). Bilateral no OM was 10% at 12 months, increasing to 11%, 16%, 25% and 27% at each age to 36 months (Table 2); a total of 98 children had at least one diagnosis of bilateral no OM.

3.4.2. Persistent, recurrent or chronic OM

Sequential 6-monthly ear assessments from age 12 months were successful at all five visits for 62 children (310 assessments); 33 (52%) had OM at all five visits, 53 (86%) had recurrent OM (at least three consecutive 6-monthly assessments with any OM), and no child was without OM. Transitions in OM diagnosis show that OME and AOMwoP persist (55% and 37%) and rarely resolve (18% and 11%, respectively), and that tympanic membrane perforations seldom heal; 2 of 19 (11%) DP cases, 13 of 21 (62%) AOMwiP cases, and 5 of 30 (17%) CSOM cases (Table 3).

3.4.3. CSOM: age of onset, prior OM history and follow-up

Data from both PREVIX trials from age 4–36 months identified 39 children with a diagnosis of CSOM at one or more child-visits (82 diagnoses made). Onset of first detected CSOM was at age 6 or 7 months in 49% these children, 74% by age 12 months. At the visit prior to first detection of CSOM, most children (25/39, 64%) had AOMwiP or AOMwoP. A follow-up visit was available for 41 of the 82 diagnoses of CSOM; 81% had persisting TMP. By comparison, 46% of 35 cases of AOMwiP with follow-up, had persisting TMP(s).

3.4.4. OM history for children with no OM or suppurative OM at age 36 months

Of 196 children seen at 36 months, 54 (27%) had no OM; 52 of these were previously seen at both 12 and 18 months, 22 at 24mo and 22 at 30 months. The proportion of these children with no OM increased with age (14%, 17%, 36%, and 45%) and very few had AOMwiP or CSOM (2%, 8%, 5%, and 0%). By contrast, of 51 (26%) children with suppurative OM at age 36 months, 39 had a prior OM history, only 4 had no OM previously (3%, 0%, 7% and 7% children seen at ages 12, 18, 24 and 30 months) whereas most had suppurative OM (71%, 62%, 36%, and 33%).

4. Discussion 913

Our previous trials [3,4,6], and head-to-head RCTs conducted elsewhere, compare immunogenicity of different PCV schedules or formulations [10,11] and impact on pneumococcal carriage [12], however impact on OM is rarely included. To our knowledge this is the first prospective cohort study of regular scheduled otitis media assessments in First Nations children from age 1–3 years. This study is also the first globally to evaluate otitis media outcomes in a head-to-head PCV trial

Table 2
Otitis Media. Vaccine group prevalence and comparisons (difference, 95%CI, p value) of all forms of otitis media among children seen since 2013 at ages 12, 18, 24, 30, 36 months, according to child's worse ear (*study visits at age 24 and 30 months commenced in 2017).

Visit-age (months) Diagnosis	Total N = 261	+P N = 131		+S N = 130		DIFF % +P - + S	95%CI	p
12		N	%	N	%	+P - + S		
Age-eligible and seen	258 (99%)	129		129				
Not seen	3 (1%)	2	2%	1	1%	1%	−2,3	1
No OM	25 (10%)	15	11%	10	8%	4%	−3,11	0.40
OME	76 (29%)	38	29%	38	29%	0%	−11, 11	1
AOMwoP	125 (48%)	60	47%	65	50%	−4%	−18,8	0.62
DP	3 (1%)	2	2%	1	1%	1%	−2, 3	1
AOMwiP	11 (4%)	5	4%	6	5%	−1%	−6, 4	1
CSOM	18 (7%)	9	7%	9	7%	0%	−6, 6	1
anyOM	233 (89%)	114	88%	119	92%	−4%	−11,3	0.4
Bilateral OM	201 (78%)	100	78%	101	78%	−1%	−11,9	1
TMP	32 (12%)	16	12%	16	12%	0%	−8, 8	1
Suppurative OM	152 (59%)	74	57%	78	60%	−3%	−15, 9	0.70
18								
Age-eligible and seen	257 (98%)	129		128				
Not seen	1 (1%)	1	1%	0	0%	1%	−1, 2	0.32
No OM	28 (11%)	16	12%	12	9%	3%	−5, 11	0.55
OME	99 (39%)	48	37%	51	40%	−3%	−15, 9	0.70
AOMwoP	90 (35%)	47	36%	43	34%	3%	−9, 14	0.70
DP	5 (2%)	4	3%	1	1%	2%	−1, 6	0.37
AOMwiP	20 (8%)	8	6%	12	9%	−3%	−10, 3	0.36
CSOM	15 (6%)	6	5%	9	7%	−2%	−8, 3	0.58
anyOM	229 (88%)	113	88%	116	91%	−3%	−11, 5	0.56
Bilateral OM	191 (74%)	97	75%	94	73%	2%	−9, 12	0.78
TMP	40 (16%)	18	14%	22	17%	−3%	−12, 6	0.50
Suppurative OM	120 (47%)	62	48%	58	45%	3%	−9, 15	0.71
24*								
Age-eligible and seen	97 (37%)	47		50				
Not seen	1 (1%)	1	2%	0	0%	2%	−2, 6	0.49
No OM	16 (16%)	10	21%	6	12%	9%	−5, 24	0.28
OME	53 (55%)	27	57%	26	52%	5%	−14, 25	0.37
AOMwoP	17 (18%)	6	13%	11	22%	−9%	−24, 6	0.29
DP	5 (5%)	2	4%	3	6%	−2%	−10, 7	1
AOMwiP	1 (1%)	0	0%	1	2%	−2%	−6, 2	1
CSOM	5 (5%)	2	4%	3	6%	−2%	−10, 7	1
anyOM	81 (83%)	37	79%	44	88%	−9%	−24, 5	0.28
Bilateral OM	59 (61%)	26	55%	33	66%	−11%	−30, 9	0.30
TMP	11 (11%)	4	8%	7	14%	−6%	−18, 7	0.53
Suppurative OM	27 (28%)	10	21%	17	34%	−13%	−30, 5	0.18
30*								
Age-eligible and seen	102 (39%)	53		49				
Not seen	0	0		0				
No OM	25 (25%)	14	26%	11	22%	4%	−13, 21	0.65
OME	49 (48%)	25	47%	24	49%	−2%	−21, 18	1
AOMwoP	10 (10%)	5	9%	5	10%	−1%	−12, 11	1
DP	10 (10%)	6	11%	4	8%	3%	−8, 15	0.74
AOMwiP	2 (2%)	0	0%	2	4%	−4%	−10, 1	0.23
CSOM	6 (6%)	3	6%	3	6%	0%	−10, 9	1
anyOM	77 (75%)	39	74%	38	78%	−4%	−21, 13	0.65
Bilateral OM	60 (59%)	31	58%	29	59%	−1%	−20, 18	1
TMP	18 (18%)	9	17%	9	18%	−1%	−16, 13	1
Suppurative OM	26 (25%)	14	26%	12	24%	2%	−15, 19	1
36								
Age-eligible and seen	196 (75%)	91		105				
Not seen	2 (1%)	2	2%	0	0%	2%	−1, 5	0.22
No OM	54 (27%)	26	28%	28	27%	2%	−11, 14	0.87
OME	87 (44%)	37	41%	50	48%	−7%	−21, 7	0.39
AOMwoP	20 (10%)	12	13%	8	8%	6%	−3, 14	0.24
DP	16 (8%)	8	9%	8	8%	1%	−7, 9	0.8
AOMwiP	5 (3%)	3	3%	2	2%	1%	−3, 6	0.66
CSOM	14 (7%)	5	5%	9	9%	−3%	−10, 4	0.58
anyOM	142 (72%)	65	71%	77	73%	−2%	−14, 11	0.87
Bilateral OM	101 (52%)	47	52%	54	51%	−2%	−14, 14	1
TMP	35 (18%)	16	17%	19	18%	0%	−11, 10	1
Suppurative OM	51 (26%)	26	29%	25	24%	5%	−8, 17	0.51

+P: Prevenar13™ PCV13 13-valent Pneumococcal conjugate vaccine.
+S: Synflorix™ PHiD-CV10 10-valent pneumococcal H. influenzae protein D conjugate vaccine.
CI: Confidence Interval.
P: p value (2-sided Fisher's exact).
Otitis media diagnosis in child's worse ear according to hierarchy of NoOM, OME, AOMwoP, DP, AOMwiP, CSOM.
NoOM – both ears without OM.
OME - OM with effusion (bilateral or contralateral NoOM).
AOMwoP – acute OM without tympanic membrane perforation (bilateral or contralateral ear with OME or NoOM).

DP - Dry Perforation (bilateral or contralateral ear with AOMwoP, OME, or NoOM).
AOMwiP - acute OM with tympanic membrane perforation (bilateral or contralateral ear with dry perf, AOMwoP, OME, NoOM).
CSOM – chronic suppurative OM (bilateral or contralateral ear with AOMwiP, dry perf, AOMwoP, OME or NoOM).
Combination categories:
anyOM – either ear with some form of OM.
bilateral OM – both ears with some form of OM.
TMP – tympanic membrane perforation, either AOMwiP, DP or CSOM.
Suppurative OM – either AOMwoP, AOMwiP or CSOM.

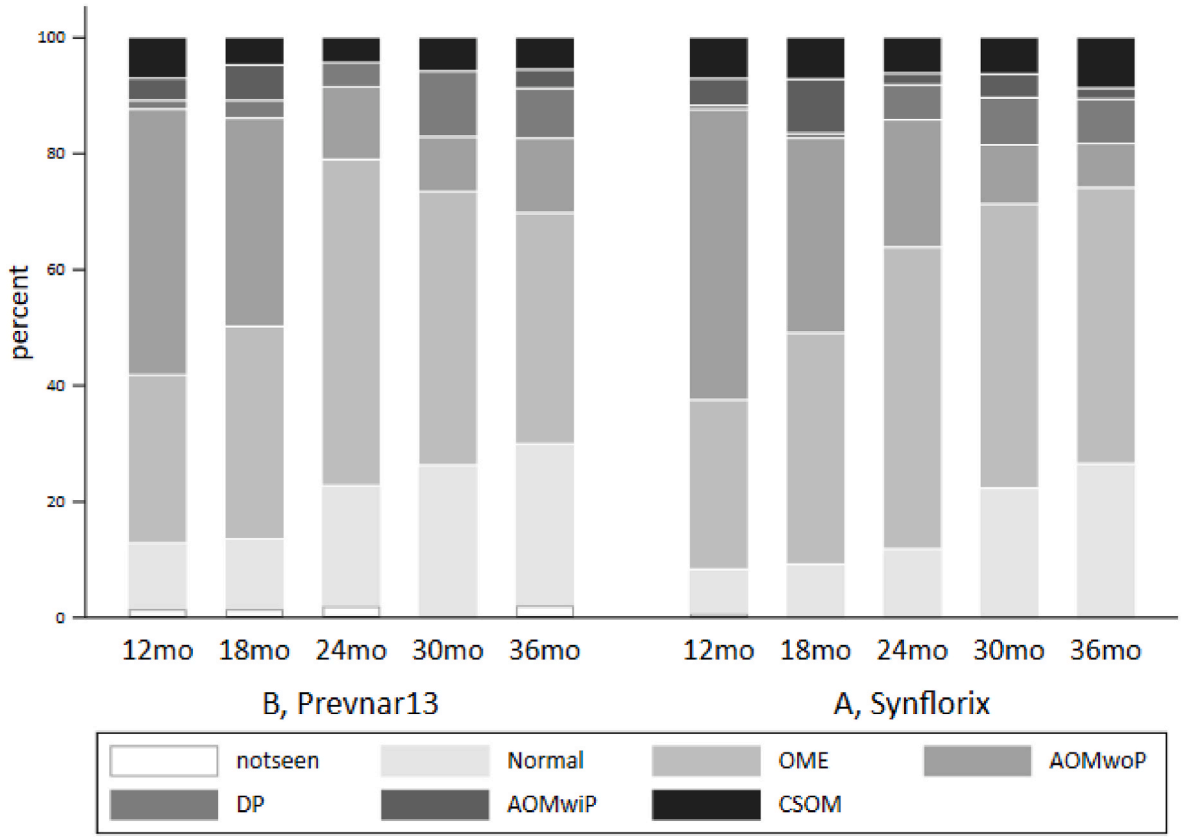

Fig. 2. Otitis media. Proportion of children (%) with worse ear diagnosis at visit-age 12 (Baseline), 18, 24, 30, and 36 months, by vaccine group.

Table 3
Transitions in OM diagnosis at 6-monthly ear assessments.

To:	No OM	OME	AOMwoP	DP	AOMwiP	CSOM	TOTAL
From:							
No OM	26	26	11	0	2	0	61
	43%	43%	18%		3%		
OME	35	107	39	5	5	4	195
	18%	55%	20%	3%	3%	2%	
AOMwoP	20	78	65	2	7	3	175
	11%	45%	37%	1%	4%	2%	
DP	0	2	0	8	2	7	19
		11%		42%	11%	37%	
AOMwiP	2	9	2	2	2	4	21
	10%	43%	10%	10%	10%	19%	
CSOM	1	2	2	8	5	12	30
	3%	7%	7%	27%	17%	40%	
TOTAL	84	220	119	25	23	30	501

Otitis media diagnosis in child's worse ear according to hierarchy of NoOM, OME, AOMwoP, DP, AOMwiP, CSOM.
NoOM – both ears without OM.
OME - OM with effusion (bilateral or contralateral NoOM).
AOMwoP – acute OM without tympanic membrane perforation (bilateral or contralateral ear with OME or NoOM).
DP - Dry Perforation (bilateral or contralateral ear with AOMwoP, OME, or NoOM).
AOMwiP - acute OM with tympanic membrane perforation (bilateral or contralateral ear with dry perf, AOMwoP, OME, NoOM).
CSOM – chronic suppurative OM (bilateral or contralateral ear with AOMwiP, dry perf, AOMwoP, OME or NoOM).

[13]. The primary immunogenicity outcomes and select secondary outcomes of the PREVIX_COMBO and PREVIX_BOOST RCTs have been reported from age 1–18 months [3–5]. The present report to age 36 months identifies ongoing high prevalence of persistent bilateral OM throughout early childhood. There were no differences in OM prevalence between groups at any timepoint, whether stratified by the primary schedule or by the booster vaccine received. Almost 100% follow-up was achieved at primary endpoint age 18 months, but a limitation of our study is the high loss-to-follow-up at age 36 months (30% in the +P group and 20% in the +S group not age-eligible for ear assessments), which has reduced power to detect small differences in prevalence of each type of OM between vaccine groups at that age. It is clear that current pneumococcal vaccines are not useful for preventing all-cause otitis media in this population. Pneumococcal serotype carriage in this population at this time was dominated by non-PCV13 vaccine serotypes (1032/1159, 89%). The most common serotypes (in order) were 16F (15%), 11A, 10A, 7B, 15A, 6C, 35B, 23B, 13, and 15B, accounting for 65% of carriage, with low levels of 22F, 33F, and 12F circulating in the population [6]. PCV20 (licensed in the US for individuals 6 weeks and older) contains seven additional serotypes (8, 10A, 11A, 12F, 15B, 22F, 33F).

As previously reported, in remote NT First Nations communities very few infants or young children are without OM. Early reports from an urban First Nations birth cohort study in Perth, Western Australia has identified 39% of 71 children having evidence of OM at age 2–4 months [14]. In 2014 and 2016 we reported prevalence of OM in First Nations children during PCV7-, PHiD-CV10- and PCV13-eras. At mean age 18 months prevalence of bilateral normal ears (no OM) was <10% and around 15% had TMPs in each PCV era [2,15]. In the present study which spanned 2013 to 2018, at age 18 months the prevalence of no OM was 10% and TMP 16%; 74% children had bilateral OM which is 83% of OM cases. We report TMP as the sum of CSOM, AOMwiP, and DP as definitions vary widely and these conditions fluctuate in young children, with 70% having either CSOM, AOMwiP or DP at follow-up. According to the World Health Organization which has described a 4% prevalence of CSOM as a public health emergency requiring immediate action, we are still in crisis in the NT. We intend to analyse combined data from our studies using data-linkage to better understand the longer-term pathways for First Nations children with and without early onset and chronic OM [16]. Most resources allocated to tackling this crisis have been fly-in/fly-out audiology outreach services or ENT teleotology. At December 2021, there were 3403 Indigenous children and young people on the NT audiology wait list and 1835 on the wait list for ENT teleotology services [17]. Of 2000 audiology services (including assessment of middle ear function, hearing loss and middle ear disease, and recommended clinical care or rehabilitation), only 220 (11%) were provided for children up to age 3 years, and 150 (26%) ENT teleotology services were for children up to age 5 years [17]. Outcomes across all ages were either follow-up (main action) or surgery (mainly myringoplasty and myringotomy), but neither the number of hearing aids fitted nor surgeries conducted was reported [17]. The mean age of hearing aid fitting for First Nations children across Australia is 6 years [18]. Applying the current Guidelines algorithm for referral pathway [8] to infants in our first RCT, PREVIX_COMBO, would result in 71% requiring audiological referral based on OM diagnoses in the first year of life [5] and a 33% ENT referral based on mean hearing level >30 dB in the PREVIX_BOOST study.

The WHO acknowledges the need for ear and hearing care to be integrated into primary health care, achieved through capacity building at this level. However, workforce shortages in NT remote PHC services often dramatically reduce a clinic's healthcare capacity to respond effectively. We recently demonstrated evidence of this impact on ear health services in remote communities (2014–2018); for the youngest age groups (<2 and 2–4 years), we found that 6-monthly ear health check screening programs reached around 75%–80% children, of whom ~50% had a diagnosis of OM. However, appropriate treatment was documented for only 20–30% of OM cases and appropriate follow-up was completed for ~20% cases [19].

We suggest that in this and other regions where access to audiology services for young children is limited and referral pathways to hearing aid and ENT consultations are delayed, PHC services should have a well-resourced ear and hearing health strategy that ensures all children have age-appropriate scheduled ear assessments, findings are documented, medical management is implemented including timely recalls. Children with OM conditions that meet criteria for audiology assessment should receive immediate appropriate management of their communication needs in the home and early childhood centres. A strategy that also includes developmental 'red flag' questions may help prioritise those for timely hearing aid fitting or ENT surgery. A greater presence of Aboriginal or Torres Strait Islander health professionals could help families to gain confidence and feel safe in identifying their child's ear and hearing-related needs [20,21]. Of course, these approaches do not address the fundamental question of how to prevent high rates of ear disease occurring in the first place. Development of novel preventive approaches, an ongoing focus on the social determinants of health, and evaluation of next generation and increased valency pneumococcal conjugate vaccines to prevent otitis media must be priorities.

Ethics approval and consent to participate

Ethical approval has been obtained from Human Research Ethics Committees of the Northern Territory Department of Health and Menzies School of Health Research (NHMRC Reg no: EC00153), the Central Australian HREC (NHMRC Reg no: EC00155) and West Australian Aboriginal Health Ethics Committee (WAAHEC- 377-12/2011). Parents or guardians provided signed informed consent for their infant's participation.

Availability of data/Data sharing

Data collected for the study that underlie the results reported in this Article, including individual participant data and a data dictionary defining each field in the set, will be made available after de-identification. No additional, related documents will be available, and the study protocols have been published. Data will be available up to 3 years after publication of this Article, upon request to the corresponding author. Data will be shared with investigators whose proposed use of the data has been approved by the ethics committees of NT Health, Menzies School of Health Research, WA Department of Health, and WA Aboriginal Health Ethics Committee, and approved by the Menzies' Child Health Division's Australian First Nations Reference Group, for analyses that meet criteria for excellence in research with Aboriginal and Torres Strait Islander people, and with an institutional-signed and investigator signed data sharing research agreement.

Role of funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author and statistician had full access to all the data and AJL had responsibility for the decision to submit for publication. AJL was not paid by any agency to write this article.

Data safety monitoring

The study was overseen by an independent Data Safety and Monitoring Board (iDSMB).

Author contributions

AJL (Principal Investigator, PI) conceived the study, led funding applications, obtained HREC approval and other regulatory approvals,

undertook consultations, reporting and had overseen day to day management and implementation of the trials, managed, had direct access to and verified the reported data, analysed and interpreted the data, created Tables and Figures, wrote the first draft and final version of manuscript. NW managed the trial, participant recruitment and retention, specimen collection, reported to Ethics committees and data safety monitoring board, managed quality of data and read the final version of the manuscript. BA assisted participant recruitment and retention, specimen collection, managed quality of data and read the final version of the manuscript. JB managed microbiology and serology collections, data base and data quality, and read the final version of the manuscript. EKM 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 and read the final version of the manuscript. 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. PM advised on study design, assisted with funding application, participated in investigator meetings, advised on risk management and read the final version of the manuscript. HS-V advised on study design, assisted with funding application, participated in investigator meetings, advised on microbiology protocols, and reviewed the final version of the manuscript. SS advised on study design, assisted with funding application, participated in investigator meetings, advised on laboratory protocols, particularly microbiology, and reviewed the final version of the manuscript. VO participated in investigator meetings, wrote the final statistical analysis plans, had direct access to and verified the reported data, generated Tables and Figures and read the final version of the manuscript. MC advised on study design, assisted with funding application, participated in investigator meetings, wrote the initial statistical analysis plans in the protocols, analysed data, generated Tables and Figures and read the final version of the manuscript. DL advised on study design, assisted with funding application, participated in investigator meetings, advised on Tables and Figures and read the final version of the manuscript. MB advised on study design, assisted with funding application, participated in investigator meetings, advised on Tables and Figures and read the final version of the manuscript. PL advised on laboratory protocols, particularly immunogenicity, and read the final version of the manuscript. RMA advised on study design, assisted with funding application, participated in investigator meetings, advised on Tables and Figures and read the final version of the manuscript. TS advised on study design, assisted with funding application, participated in investigator meetings, advised on Tables and Figures and read the final version of the manuscript. VK advised on study design, assisted with funding application, participated in investigator meetings, advised on Tables and Figures and read the final version of the manuscript. JC advised on study design, assisted with funding application, participated in investigator meetings, advised on Tables and Figures and read the final version of the manuscript. ABC advised on study design, assisted with funding application, participated in investigator meetings, advised on Tables and Figures and read 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, and read the final version of the manuscript.

Trial registration

ClinicalTrials.gov NCT01735084 and NCT01174849.

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Declaration of competing interest

AJL received funds from NHMRC paid to the institution, and GSK provided materials for immunogenicity assays. AJL received funds from Merck Sharp and Dohme for analysis of pneumococcal carriage, payment to institution. **ABC** served as advisor on a Data Safety Monitoring Board for an unlicensed vaccine (GlaxoSmithKline) and an unlicensed monoclonal antibody (AstraZeneca), was an adviser on an unlicensed molecule for chronic cough (Merck); and has multiple project grants and a Centre of Research Excellence relating to various aspects of bronchiectasis in children from the National Health and Medical Research Council. ABC received Royalties or licences as an author of cough and bronchiectasis topics, and Partial reimbursement for airfares as a speaker for European Respiratory Society. All payments were to the institution. **PM** served on a data safety and monitoring board for the Novavax COVID-19 vaccine. **JB** provided a report to MSD Australia.

All other authors (DL, HS-V, MB, MC, PL, PSM, PT) declare no competing interests.

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