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General health, otitis media, nasopharyngeal carriage and middle ear microbiology in Northern Territory Aboriginal children vaccinated during consecutive periods of 10-valent or 13-valent pneumococcal conjugate vaccines

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ABSTRACT

Objectives: This study aims to monitor the prevalence of suppurative otitis media in remote Indigenous communities after introduction of 13-valent pneumococcal conjugate vaccine (PCV13) in October 2011. We previously reported a decline in suppurative OM following replacement of PCV7 by 10-valent pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV10) in October 2009.
Methods: We continued regular surveillance in remote Indigenous communities between February 2010 and August 2013. This analysis reports the general health, otitis media (OM), nasopharyngeal (NP) carriage and middle ear microbiology in children less than 36 months of age who received a primary course of at least two doses of PHiD-CV10 or PCV13, and not more than one dose of another pneumococcal vaccine.
Results: Mean ages of 511 PHiD-CV10- and 140 PCV13-vaccinated children were 19 and 13 months, respectively. Most children received 3-dose non-mixed PCV schedules. At the time of assessment, general health was poor and prevalence of risk factors was high in both groups: overall, around 14% of children had scabies, 20% had impetigo, 59% had runny nose and 39% had cough. Average household size was 8 persons, and 60% of the mothers smoked. Bilaterally normal middle ears were detected in 10% and 7%, respectively. OM with effusion (OME), almost all bilateral, was diagnosed in 52% and 50%, any suppurative OM (acute OM or any tympanic membrane perforation [TMP]) in 37% and 41%, and TMP in 14% and 12%, respectively. Children in the PCV13 group had significantly less NP carriage of combined *Streptococcus pneumoniae* (Spn) and non-typeable *Haemophilus influenzae* (NTHi) (62% versus 51%) but significantly more polymicrobial (Spn and NTHi) middle ear cultures (12% versus 43%), and significantly less *Staphylococcus aureus*-positive middle ears (40% versus 7%). Although NP carriage of pneumococcal serotype 19A was low in the PCV13 group, serotypes 19F and 23F persist.
Conclusions: The general health, particularly ear health, of little children in remote Australian Indigenous communities remains in crisis. In particular, transition to PCV13 did not show substantial further improvement in ear health. Possible vaccine-related differences in microbiology, including potential beneficial effects of PHiD-CV10 on NTHi infection, need to be further evaluated in randomised trials.

Abbreviations: AOMwiP, acute otitis media with perforation; AOMwoP, acute otitis media without perforation; CI, confidence interval; CSOM, chronic suppurative otitis media; DP, dry perforation; IPD, invasive pneumococcal disease; Mcat, *Moraxella catarrhalis*; mo, month; NT, Northern Territory; NTHi, non-typeable *Haemophilus influenzae*; OM, otitis media; OME, otitis media with effusion; PCV13, 13-valent pneumococcal conjugate vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PHiD-CV10, 10-valent pneumococcal *Haemophilus influenzae* protein D conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine; Prevenar® and Prevenar 13®, trademarks of Pfizer Inc; RD, risk difference; SD, standard deviation; Synflorix®, trademark of the GlaxoSmithKline group of companies; TMP, tympanic membrane perforation

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1. Background

Community based surveillance before [1] and after [2] the introduction of each pneumococcal conjugate vaccine (PCV) has highlighted the poor general health, and particularly high prevalence of otitis media, of Australian Indigenous children living in remote Northern Territory (NT) communities. Throughout this period, among children at a mean age of around 20 months, less than 10% had bilateral aerated (normal) middle ears, ~30% had skin sores or scabies, ~60% had a wet or dry cough, ~50% had a runny nose, and ~30% had abnormal haemoglobin [2]. Although the prevalence of

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Table 1
Pneumococcal vaccines in the childhood vaccination schedule for Northern Territory Indigenous children.

Date commenced	Vaccine	Age (mo)
1 July 2001	PCV7 and PPV23	2, 4, 6 18
1 October 2009[a]	PHiD-CV10	2, 4, 6, 18
1 October 2011	PCV13	2, 4, 6, 18

[a] No other Australian jurisdiction recommended that PHiD-CV10 replace PCV7.

at least one form of otitis media remained high, there has been a steady decline in the prevalence of TMP (either acute otitis media with perforation (AOMwiP), dry perforation (DP), or chronic suppurative otitis media (CSOM)), from 24% in 2001 (pre-PCV) to 17% in children vaccinated with 7-valent PCV (PCV7) to 14% in children vaccinated with 10-valent pneumococcal *Haemophilus influenzae* protein D-conjugate vaccine (PHiD-CV10) [1,2]. *Streptococcus pneumoniae* (Spn, pneumococcus) and non-typeable *H. influenzae* (NTHi) are major pathogens detected by culture [3,4] or PCR [5] in ear discharge of children with TMP. *Staphylococcus aureus* (Sa) is also a common (secondary) pathogen in ear discharge [6], whereas *Moraxella catarrhalis* is rarely cultured or detected by PCR [5]. PCV7 has greatly reduced vaccine-serotype invasive pneumococcal disease (IPD) and provides indirect protective effects via reduced vaccine type carriage [7]. Replacement by non-vaccine serotypes [8] has limited the extent and persistence of this benefit [9]. The data from a trial of 11-valent pneumococcal protein D-conjugate vaccine (11Pn-PD) [10,11] including tympanocentesis for culture of middle ear fluid showed significant protection against NTHi otitis media (OM) [10]. The re-formulated 10-valent vaccine (with serotype 3 removed) has 8 serotypes conjugated to protein-D. Immunogenicity and animal model studies comparing 11Pn-PD and PHiD-CV10 indicated that similar NTHi protection could be expected [11]. Although Australian regulatory authorities did not approve a license indication for NTHi-OM [12], the NT infant vaccination schedule was changed in 2009 from a combination PCV7/PPV23 to a 3 + 1 PHiD-CV10 schedule. This was followed in 2011 by a national shift to a 3 + 0 PCV13 schedule, plus a booster dose for Indigenous children (see Table 1). Through ongoing surveillance, we observed 12% less suppurative OM (AOMwoP, AOMwiP or CSOM) and 10% more OME in the PHiD-CV10 group compared to PCV7-vaccinated children [2]. This shift from suppurative OM to OME was associated with 27% less middle ear NTHi infection, although there was no difference in NTHi carriage [6]. Our primary hypotheses for this subsequent comparison of PHiD-CV10 with PCV13 cohorts were that in children 6–36 months of age, the prevalence of suppurative OM and NTHi-associated middle ear infection would be lower, and the prevalence of bilateral normal middle ears would be higher in PHiD-CV10 vaccinated children compared to PCV13 vaccinated children. We also report findings from general child health checks that are provided as a service by the research nurses.

2. Methods

2.1. Study design, setting, community recruitment and ethical approval

Since 2001 a total of thirty five remote communities in the NT [8] and one in Western Australia have participated in at least one community-based cross sectional survey of OM and NP carriage. This report includes data from 25 Top End communities participating between February 2010 and August 2013. The study was approved by the Human Research Ethics Committee of the Northern Territory Department of Health and the Menzies School of Health Research (EC00153), and the Western Australian Aboriginal Health Information and Ethics Committee (WAAHIEC). Each community council provided written approval of the study to the ethics committee.

2.2. Participant recruitment and consent

Informed consent was sought from parents of all children less than 6 years of age (regardless of ear health status or history) for their child to have an ear examination, nasal swab, swab of ear discharge if present, and general child health check. Parents or carers were also asked for permission to access the mother's and the child's medical records and complete a lifestyle interview regarding information on likely risk or protective factors for otitis media.

2.3. Inclusion and exclusion criteria

Aboriginal children between 0 and 6 years of age, resident in participating communities, were eligible for surveillance. For this report we limit analysis as described below (Statistical analysis).

2.4. Clinical assessments

2.4.1. Ear examinations and general health assessments

All clinical assessments were made by ear health research nurses with extensive training in the diagnosis and management of OM in this population. Otoscopic findings were recorded on a standardised form. Assessments were made using a tympanometer (Grason Stadler GSI 38), a LumiView (Welch Allyn) with Siegel's speculum for pneumatic otoscopy, and a video-otoscope (Welch Allyn macroview or MedRx video-otoscopes).

2.4.2. General health measures

Common conditions of childhood were recorded at the time of ear assessment by direct observation; the child's skin (head, arms, legs and trunk) was examined for the presence of scabies, tinea, skin sores or other skin condition; presence of nasal discharge (visible at a distance of 1 meter), and any cough (spontaneous or cough on request, either wet or dry). We categorised 'not sure' as absent. Antibiotics and other treatments or referrals were provided to participants according to local guidelines.

2.4.3. Definitions of OM

We categorised middle ear states as follows: (1) normal; (2) otitis media with effusion (OME); (3) acute otitis media without perforation (AOMwoP); (4) AOM with perforation (AOMwiP); (5) dry perforation (DP); and (6) chronic suppurative otitis media (CSOM). The final middle ear diagnosis reflected the child's more severely affected ear (highest category). We based our criteria for diagnosis on recommendations for clinical practice in this population [13]: (i) OME – intact and non-bulging tympanic membrane (TM) and Type B tympanogram; (ii) AOMwoP – any bulging of the TM and Type B tympanogram; (iii) AOMwiP – middle ear discharge observed and TM perforation recently healed or present for less than six weeks or covering less than 2% of the pars tensa of the TM; (iv) dry perforation – TM perforation without any discharge observed; (v) CSOM – middle ear discharge observed and perforation present for longer than six weeks and covering at least 2% of the pars tensa of the TM. We also include combination categories of any suppurative OM (any AOM, AOMwiP or CSOM) and any TMP (any AOMwiP, dry perforation or CSOM). Where duration of discharge was not known, size of perforation was used to distinguish AOMwiP and CSOM. Where otoscopy was not successful, we used the child's tympanometry result and defined the child's status as OME if either ear had a Type B tympanogram. We asked the mother if she thought her child had ear pain that day or during the previous evening. These a priori diagnostic criteria have been applied in all our surveillance and clinical trials conducted in this population since 2001 [1].