

Middle ear abnormalities at age 5 years in relation with early onset otitis media and number of episodes, in the Inuit population of Nunavik, Quebec, Canada

P De Wals^{a,b,c}, JB Lemeur^{a,b}, H Ayukawa^d and JF Proulx^e

^aDepartment of Social and Preventive Medicine, Laval University, Quebec, Canada; ^bDirection des Risques biologiques et de la Santé au Travail, Institut national de Santé publique du Québec, Quebec, Canada; ^cQuebec University Hospital Research Centre, Quebec, Canada; ^dUngava Tulattavik Health Centre, Kuujuaq, Canada; ^ePublic Health Directorate, Nunavik Regional Board of Health and Social Services, Kuujuaq, Canada

ABSTRACT

Otitis media (OM) and their sequelae are a major health issue in the Inuit population of Nunavik, Quebec. Hypotheses of the study were: (i) early onset OM leads to repeated OM; (ii) repeated OM episodes leads to middle ear abnormalities (MEA) at age 5 years, (iii) pneumococcal conjugate vaccines (PCVs) may reduce multiple OM and MEA. Immunisation cards, medical records and audiology screening tests at age 5 years in a sample of 610 children born in 1994–2010 in 3 communities were reviewed. Children were classified into three categories using a score based on audiology screening tests: no abnormality, minor, or major MEA. The average number of OM episodes before age 5 years was 5.0 and 30% had minor and 17% major MEA at age 5 years. Community residency predicted both frequent (≥ 8) OM episodes and MEA. Early onset OM (age < 6 months) was a predictor of frequent OM (RR = 1.71; 95%CI: 1.50–1.95) whereas PCV (≥ 1 dose \geq age 2 months) has no significant effect. Frequent OM episodes were associated with major MEA (RR = 2.16; 95%CI: 1.20–3.85). Although associations were not statistically significant, there was a trend towards a protective effect of PCV administration on frequent OM and minor MEA, but not major MEA. In conclusion, results support an association between early onset OM, frequent OM and MEA that could represent a causal pathway.

ARTICLE HISTORY

Received 12 November 2018
Revised 25 February 2019
Accepted 14 March 2019



KEYWORDS

Pneumococcal conjugate vaccines; Otitis media; audiology deficit; Inuit

Introduction

Otitis media (OM) and their complications constitute a major public health problem in indigenous communities of Northern Canada. This is especially so in the Inuit population, part of which is living in the Nunavik [1], the most northerly region of the province of Quebec. Approximately 90% of Nunavik's population ($n \approx 13,000$ in 2016) is Inuit. The population is scattered in 14 communities dispersed along Hudson Bay and Ungava Bay, with no roads between them or to the south. The 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in 2002; it was replaced by the 10-valent PCV (PCV10) in 2009, and then by the 13-valent PCV (PCV13) in 2011. PCVs are offered, respectively, at age 2, 4, 6 and 12–18 months, and the uptake is high. Since the beginning of the programme, more than 90% of children receive the recommended number of doses [2]. In a recent study among children born in 1994–2010, it was shown that 46% of them had a

middle ear abnormality (MEA, defined as functional and/or anatomical abnormality) at the age 5 audiology screening examination, a minor MEA in 29% and a major one in 17% [3]. The prevalence of minor MEA was reduced in children who had received a pneumococcal conjugate vaccine (PCV) compared to unvaccinated children. No protective effect of PCV, however, was seen for major MEA. In a few studies, it was shown that OM with early onset (i.e. before 6 months of age) was associated with an increased risk of repeated OM during childhood [4,5]. It is reasonable to assume that major and permanent audiology deficiencies are caused by repeated OM episodes during early childhood. In Nunavik, the present analysis was performed to investigate (i) the relationship between early onset OM and repeated episodes during the first 5 years of life, (ii) the relationship between repeated OM episodes and the prevalence of MEAs at 5 years of age and (iii) the impact of PCVs on repeated OM episodes and MEA.

CONTACT P De Wals  philippe.dewals@criucpq.ulaval.ca  Département de Médecine sociale et préventive, Université Laval, CRIUCPQ, 2725, Chemin Ste-Foy, Québec, QC G1V 4G5, Canada

Clinicaltrials.gov registration number: NCT01694329

© 2019 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Methods

Details on health services in the Nunavik region, study population, sources of information, data collection and classification of variables including immunisation status and severity of MEA have been described in a previous publication [3].

Study population

The study targeted children born between 1 January 1994 and 31 December 2010 who were registered by the public health services of Nunavik. Lists of registered children obtained from the two regional hospitals included: the child's name, medical record number, community of residence, gender and date of birth. For logistical and budgetary reasons, the present analysis was restricted to children living in the three largest communities out of 14 in the region: one situated on Ungava bay and two on Hudson bay. Only children with medical records containing information from birth up to their fifth birthday were included in the analysis.

Data collection

The collection of data on outpatient visits was performed for a stratified random sample of births from 1994 to 2005 in the 14 communities, and for all births from 2006 to 2010 in the three selected communities. Medical records were reviewed on-site. Diagnoses reported by nurses or physicians were classified and coded into three broad categories: upper respiratory tract infection, lower respiratory tract infection and OM. Successive OM visits within a 28-day interval were considered as a single episode. Based on the quartile distribution of the number of OM episodes per child, multiple OM was defined as eight or more episodes up to the fifth birthday.

Copies of immunisation cards for all children in the target population were obtained from the primary health care services centres. The information collected included all PCVs received up to the fifth birthday. The 7-valent, 10-valent and 13-valent conjugate vaccines were used successively but no distinction between vaccines was made in the present analysis.

In each school in Nunavik, an audiology screening is performed at least once a year by an audiologist or a trained professional, targeting 5-year-old children in kindergarten classes. Copies of audiology screening tests including otoscopy, tympanometry and audiometry (standardised 500 Hz, 1 kHz, 2 kHz and 4 kHz frequencies) were obtained for children in the target

population. The test closest to the fifth birthday was selected for analysis.

Classification of immunisation status

Children were classified into four groups: (i) those who did not receive any PCV, including children born between 1 January 1994 and 30 April 1997 and not targeted by the PCV programme, and children targeted by the programme who did not receive a dose; (ii) children who received a first dose of PCV before 4 months of age; (iii) children who received a first dose of PCV between 4 and 11 months of age; (iv) children who received a first dose of PCV at or after 12 months of age (mostly those in the PCV7 catch-up programme).

Classification of severity of middle ear abnormalities

Audiology test results were coded according to a classification scheme developed for and tested in a previous study [6]. For each ear and each frequency tested, audiometry results were coded as "Failed" for a response above the threshold of 25 dB at 500 Hz or 20 dB at 1 KHz, 2 KHz and 4 KHz. Tympanometry results were coded as "Normal" (findings reported as normal or a drawing of the tympanogram representing a symmetric hill), as "Minor disorder" (result described as low eardrum mobility, negative pressure, retracted or rigid eardrum or a drawing of the tympanogram representing an eroded hill) or as "Major disorder" (no mobility reported, tympanogram described as flat or a drawing of the tympanogram representing a straight line). Otoscopy results were coded as "Normal" (result reported as normal or good), as "Minor disorder" (eardrum described as retracted, dull or scarred, healed perforation or tympanosclerosis) or as "Major disorder" (including active otitis media, presence of fluid, bulging or perforation of the drum, or presence of a ventilation tube). A score between 0 and 4 was computed for each ear. Each "Failed" frequency of audiogram result accounted for 0.5 points, giving a total between 0 and 2 points for each ear. A minor tympanometry abnormality accounted for 1 point and a major one for 2 points. If the tympanogram was not recorded, otoscopy results were used instead; a minor anomaly at otoscopy accounted for 1 point and a major one for 2 points. A single-ear score ≤ 0.5 was considered as normal, whereas a score between 1 and 2 was considered as a minor abnormality and a score > 2 was considered as a severe abnormality. Children were segmented into three categories according to the worst score in any

ear: no MEA, minor abnormality of one or both ears or major abnormality of one or both ears.

Statistical analyses

Univariate analyses were performed to describe the number of OM episodes before 5 years of age according to gender, season of birth (children born in the fall may be exposed to respiratory viruses at early age), community of residence, early onset AOM (first episode before 6 months of age), immunisation status (no PCV; any PCV, first dose < 4 months; any PCV, first dose 4–11 months; any PCV, first dose \geq 12 months). These explanatory variables or predictors were retained in a multivariate analysis. The prevalence of any or major MEA was analysed according to the same predictors, adding multiple OM but excluding early onset OM (considered as a predictor of multiple OM). Unadjusted and adjusted rate ratios and their confidence intervals were computed using Poisson regression models (for the number of OM episodes) and log-linked binomial regression models (for the existence of MEA) using statistical software R 3.5.0.

The study protocol was approved by the Quebec University Hospital Research Ethics Committee, the Nunavik Public Health Directorate and by Medical Directors of the two regional health centres (Inuulitsivik Health Centre, Puvirnituk, and Ungava Tulattavik Health Centre, Kuujuaq).

Results

A total of 610 children met the eligibility criteria for inclusion in the analysis. The sample represented about 12% of the 5,166 children born in the Nunavik region in the period 1994–2010. The proportion of unvaccinated children was 19% (117/610), 65% (n = 397) received

their first PCV dose before 4 months of age, 7% (n = 42) received the first dose between 4 and 11 months, and 9% (n = 54) at or after 12 months. A total of 4,601 OM visits were recorded representing 3,023 episodes. The great majority of children (91%) had at least one episode (553/610) and 22% of them (136/610) had eight episodes or more, with a maximum of 22. The average number of OM episodes was 5.0 per child. Results of an audiology screening examination were available for 82% of children (n = 503) and the prevalence of any MEA was 47%, 30% for minor (n = 151) and 17% for major anomalies (n = 87).

Among children with audiology screening results, the proportion of children with early OM was 40% (199/503). Of these, 33% were without MEA (87/265), 47% with any MEA (112/238) and 49% (43/87) with major MEA. The proportions of children with multiple OM (\geq 8) were: 16% among children without MEA (41/265), 32% among those with any MEA (76/238) and 40% (35/87) among those with major MEA.

Predictors of multiple OM are shown in Table 1. In univariate analyses, the gender and season of birth were not associated with the number of OM episodes. The community of residence was a significant predictor: 3.9 episodes per child in Community 1; 6.6 in Community 2 and 5.3 in Community 3. There was an association between early onset OM and number of episodes: 6.8 episodes in children with at least 1 OM episode before 6 months of age, and 3.8 episodes among the others. In multivariate analysis, a statistically significant risk of increased incidence of OM was associated with the community of residence and the occurrence of early onset OM (RR: 1.71; 95%CI: 1.50–1.95).

Predictors of any MEA (minor or major) are shown in Table 2. In univariate analyses, season of birth, community of residence, early onset OM and number of episodes were associated with MEA at age 5 years. In

Table 1. Predictors of multiple otitis media episodes (eight or more before fifth birthday) among 610 children born in 1994–2010, living in three selected communities of Nunavik.

Risk factor	Category	Children (n)	Mean/ median episodes (n)	Unadjusted rate ratio (95% CI)		Adjusted rate ratio (95% CI)	
				Value	95% CI	Value	95% CI
Gender	Female	331	4.7/4	Reference		Reference	
	Male	279	5.3/5	1.11	0.97–1.28	1.13	1.00–1.28
Season of birth	Jan–Sep	460	5.0/4	Reference		Excluded	
	Oct–Dec	150	5.0/5	1.00	0.86–1.17		
Community	1	215	3.9/3	Reference		Reference	
	2	192	6.6/6	1.68	1.40–2.02	1.46	1.20–1.77
	3	203	5.3/5	1.35	1.15–1.57	1.17	1.00–1.36
Early onset OM*	No	378	3.8/3	Reference		Reference	
	Yes	232	6.8/6	1.80	1.58–2.04	1.71	1.50–1.95
Immunisation status	No PCV	117	5.4/5	Reference		Reference	
	Any PCV, first dose < 4 months	397	4.7/4	0.86	0.71–1.02	0.91	0.76–1.09
	Any PCV, first dose 4–11 months	42	4.7/4	0.87	0.64–1.16	0.82	0.63–1.06
	Any PCV, first dose \geq 12 months	54	6.3/5	1.16	0.91–1.49	0.94	0.75–1.17

* First episode before 6 months of age

Table 2. Predictors of any middle ear abnormality (MEA) (vs no MEA) at audiology screening test among 503 children born in 1994–2010, living in 3 selected communities of Nunavik.

Risk factor	Category	Children (n)	Any MEA* %	Unadjusted rate ratio (95% CI)		Adjusted rate ratio (95% CI)	
				Value	95% CI	Value	95% CI
Gender	Female	268	46	Reference		Reference	
	Male	235	48	1.04	0.86–1.26	1.03	0.84–1.25
Season of birth	Jan–Sep	370	44	Reference		Reference	
	Oct–Dec	133	56	1.25	1.03–1.51	1.25	1.02–1.54
Community	1	185	35	Reference		Ref	
	2	156	64	1.82	1.45–2.32	1.55	1.15–2.07
	3	162	52	1.47	1.17–1.87	1.41	1.09–1.83
Number of episodes	0–2	138	39	Reference		Reference	
	3–4	117	42	1.09	0.82–1.48	0.99	0.71–1.39
	5–7	129	44	1.14	0.88–1.52	1.03	0.76–1.41
	≥8	119	65	1.67	1.33–2.16	1.39	0.05–1.84
Early onset OM**	No	303	41	Reference			
	Yes	200	56	1.37	1.15–1.63	Excluded	
Immunisation status	No PCV	98	53	Reference		Reference	
	Any PCV, first dose < 4 months	325	42	0.80	0.63–1.05	0.89	0.68–1.16
	Any PCV, first dose 4–11 months	35	56	1.06	0.68–1.53	1.12	0.75–1.66
	Any PCV, first dose ≥12 months	45	67	1.27	0.90–1.73	1.13	0.82–1.54

* Any MEA: one or both ears with a score ≥ 1 (maximum = 4)

** First episode before 6 months of age

multivariate analyses, children born in the fall had a slightly higher risk of MEA compared with those born in other seasons (RR: 1.25; 95%CI: 1.02–1.54) and the community of residence was a significant predictor (Community 2 vs Community 1 RR: 1.55; 95%CI: 1.15–2.07; Community 3 vs Community 1 RR: 1.41; 95%CI: 1.09–1.83). There was a statistically significant trend towards an increased MEA risk associated with multiple OM and a non-statistically significant protective effect of early PCV administration.

Predictors of major MEA are shown in Table 3. The risk associated with multiple OM was significant for major MEA (RR: 2.16; 95%CI: 1.20–3.85) and being male tended to increase the risk of major MEA (RR:

1.48; 95%CI: 0.98–2.20). There was no indication of a protective effect of PCV for major MEA.

Discussion

The relationship between age at the first OM, recurrence of OM episodes, occurrence of chronic OM, complications and the development of permanent anatomical and functional audiology sequelae is complex [7–9]. In this study, we relied on outpatient records mostly from clinical nurses working with indirect medical supervision in remote community health centres. For this reason, all types of OM diagnoses were grouped into one category and this is a major limita-

Table 3. Predictors of major middle ear abnormality (MEA) (vs no or minor MEA only) at audiology screening test among 503 children born in 1994–2010, living in three selected communities of Nunavik.

Risk factor	Category	Children (n)	Major MEA* %	Unadjusted rate ratio (95% CI)		Adjusted rate ratio (95% CI)	
				Value	95% CI	Value	95% CI
Gender	Female	268	14	Reference		Reference	
	Male	235	22	1.55	0.96–2.53	1.48	0.98–2.20
Season of birth	Jan–Sep	370	16	Reference		Reference	
	Oct–Dec	133	20	1.25	1.02–1.54	1.06	0.68–1.65
Community	1	185	16	Reference		Reference	
	2	156	9	0.60	0.30–1.25	0.55	0.28–1.21
	3	162	23	1.41	0.85–2.38	1.19	0.77–1.85
Number of episodes	0–2	138	14	Reference		Reference	
	3–4	117	14	1.00	0.46–2.20	0.98	0.50–1.94
	5–7	129	15	1.05	0.60–2.05	0.86	0.44–1.70
	≥8	119	28	1.96	1.06–3.75	2.16	1.20–3.85
Early onset OM**	No	303	15	Reference		Excluded	
	Yes	200	21	1.35	0.85–2.12		
Immunisation status	No PCV	98	11	Reference		Reference	
	Any PCV, first dose < 4 months	325	20	1.82	0.91–4.15	1.61	0.80–3.25
	Any PCV, first dose 4–11 months	35	19	1.71	0.52–5.12	1.75	0.67–4.81
	Any PCV, first dose ≥12 months	45	14	1.34	0.41–4.03	1.54	0.61–4.03

* Major MEA: one or both ears with a score > 2 (maximum = 4)

** First episode before 6 months of age

tion. The definition of an OM episode was made arbitrarily, based on a predefined interval (less than 28 days) between outpatient visits and not on an individualised interpretation of the patient history. Also, the definition of multiple OM (≥ 8 episodes) was different than in other studies (≥ 4 episodes) [4,5] because of the very high OM frequency in the Inuit population. In the Nunavik region, efforts have been made to standardise audiology screening tests and to train and supervise the personnel who do the screening. In our study, the extraction and coding of outpatients' data was performed by trained medical students under the direct supervision of one of the authors (JBL). The same author was the only person in charge of the classification of all audiology screening tests into categories of severity. Immunisation records in this region are generally of high quality [2].

Another important limitation is the sample size. To analyse the causal pathway between OM with early onset, multiple OM and sequelae, and the possible effect modification of pneumococcal vaccination in terms of the age at administration of the first dose, the number of doses and the type of vaccine would require a very large dataset and the use of stratified analyses, regressions with interaction terms or sophisticated analytical models such as structural equations [10,11]. In this study, we decided to perform two types of multivariate analyses to identify, respectively, predictors of multiple OM and predictors of MEA. To do this, the number of OM episodes was considered as an intermediary variable in the causal pathway starting with early onset OM and ending in sequelae. A multivariate model predicting MEA and including both early onset OM and multiple OM without interaction would have resulted in biased estimates [12]. The sample size was, however, too small to allow precise estimates of interaction terms in regression models.

In a cohort study in Norway, children whose first AOM episode occurred before the age of 9 months were at a significantly higher risk for development of recurrent OM compared to children whose first AOM episode was 10–12 months [4]. In another study in a nation-wide cohort of births in Denmark before PCV introduction, four or more OM episodes before 7 years of age were reported by 64.0% of those who had their OM debut between 0 and 6 months; by 48.2% with debut between 7 and 18 months; and by 28.7% with debut between 19 months and 7 years [5]. The association between early onset and multiple OM was confirmed in our study. It is generally believed that multiple acute OM episodes lead to chronic inflammatory OM which may generate permanent audiology sequelae [13]. We did not find, however, any published

study presenting quantitative evidence to support this. In our study, multiple OM tended to predict the risk of MEA at age 5 years and the association was statistically significant for severe MEA.

In a previous analysis of the same study population but on a larger sample, children vaccinated with any PCV schedule starting at 2 months of age had a lower MEA risk than unvaccinated children or those who received the 7-valent vaccine at later age during the catch-up campaign [3]. However, this apparent protective effect of PCV was not seen for severe MEA. These observations are congruent with results of the present analysis. It may be that the occurrence of acute OM at very young age does predispose to multiple OM caused by diverse bacterial infections and to chronic inflammation leading to sequelae [13]. It may also be well that a PCV schedule starting at the age of 2 months with an interval of 2 months between the three infant doses, as recommended in the Nunavik region, does not substantially modify this pathogenic process, especially for its most severe form. In a randomised trial in the Netherlands, it was shown that one dose of 7-valent pneumococcal conjugate vaccine followed by one dose of 23-valent pneumococcal polysaccharide vaccine in children 1–7 years of age with a history of recurrent OM was not protective and may even increase the risk of further OM episodes [14]. An interesting approach would be an accelerated immunisation schedule consisting of three PCV-10 doses given, respectively at 1, 2 and 4 months of age followed by one PCV-13 dose at 6 months as is currently being tested in the Aboriginal population of Australia [15].

Besides vaccines, unfavourable living conditions predispose to OM and complications [16]. All the data used for this study were extracted from medical records which do not contain information on the household environment such as crowding and smoking, and this is a limitation. However, the number of OM episodes and the prevalence of MEA was the lowest in the most populated Nunavik community with relatively better socioeconomic conditions associated with jobs in governmental agencies and easier accessibility to health care and preventive services in the region. This indicates the need for more comprehensive strategies targeting housing and sanitation, health promotion and uniform accessibility of high-quality health care services.

To conclude, while this study should be interpreted cautiously because of its small sample size, the results support an association between early onset OM, frequent OM and middle ear abnormalities that can be considered consistent with a causal pathway. More

studies on the potential benefits of early PCV administration in populations at high risk of OM should be conducted.

Acknowledgments

The authors thank all the health professionals in Nunavik who participated in data collection.

Disclosure statement

Philippe De Wals received research grants and reimbursements of travel expenses from vaccine manufacturers including the GSK group of companies, Novartis, Pfizer and Sanofi Pasteur.

Funding

This study was funded by the International Polar Year Program of the Government of Canada, administered by the Canadian Institutes for Health Research (Contract # 2008 04 POL – 193340 – CFBA - 56916) and by an investigator-initiated research grant from GlaxoSmithKline Biologicals SA (clinical-trials.gov registration number: NCT01694329). Sponsors were given an opportunity to review a preliminary version of this manuscript but had no role in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, and the preparation, review, and approval of the manuscript; Canadian Institutes for Health Research; GlaxoSmithKline Biologicals.

References

- [1] MacMillan HI, MacMillan AB, Offord DR, et al. Aboriginal health. *CAMJ*. 1996;155:1569–1576.
- [2] Cléophat JE, Le Meur JB, Proulx JF, et al. Uptake of pneumococcal vaccines in the nordic region of Nunavik, province of Quebec, Canada. *Can J Public Health*. 2014;105:e268–e72.
- [3] Le Meur JB, Ayukawa H, Proulx JF, et al. Prevalence of middle ear abnormalities from otitis media in relation with pneumococcal vaccine use in the Inuit population of Nunavik, province of Quebec, Canada. *Vaccine*. 2018;36:5180–5186. Epub 2018 Jul 17.
- [4] Kvaerner KJ, Nafstad P, Hagen JA, et al. Recurrent acute otitis media: the significance of age at onset. *Acta Otolaryngol*. 1997;117:578–584.
- [5] Todberg T, Koch A, Andersson Met al. Incidence of otitis media in a contemporary Danish National Birth Cohort. *PLoS One*. 2014;9:e111732. eCollection 2014.
- [6] Boisvert I Elaboration of a classification and score system for audiology screening data in Inuit children of Nunavik [Master's thesis]. Department of Speech Therapy and Audiology, University of Montreal, 2004.
- [7] Jervis-Bardy J, Sanchez L, Carney AS. Otitis media in indigenous Australian children: review of epidemiology and risk factors. *J Laryngol Otol*. 2014;128(Suppl 1):S16–27.
- [8] Gould JM, Matz PS. Otitis media. *Pediatr Rev*. 2010;31:102–116.
- [9] Zhang Y, Xu M, Zhang J, et al. Risk factors for chronic and recurrent otitis media—a meta-analysis. *PLoS One*. 2014;9:e86397. eCollection 2014.
- [10] Vanderweele TJ. On the distinction between interaction and effect modification. *Epidemiology*. 2009;20:863–871.
- [11] Vanderweele TJ. Invited commentary: structural equation models and epidemiologic analysis. *Am J Epidemiol*. 2012;176:608–612.
- [12] Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiology*. 2009;20:488–495.
- [13] Dagan R, Pelton S, Bakaletz L. Prevention of early episodes of otitis media by pneumococcal vaccines might reduce progression to complex disease. *Lancet Infect Dis*. 2016;16:480–492.
- [14] Veenhoven R, Bogaert D, Uiterwaal C, et al. Effect of conjugate pneumococcal vaccine followed by polysaccharide pneumococcal vaccine on recurrent acute otitis media: a randomised study. *Lancet*. 2003;361(9376):2189–2195.
- [15] Leach AJ, Mulholland EK, Santosham M, et al. Pneumococcal conjugate vaccines PREVenar13 and SynflorIX in sequence or alone in high-risk Indigenous infants (PREV-IX_COMBO): protocol of a randomised controlled trial. *BMJ Open*. 2015;5:e007247.
- [16] O'Connor TE, Perry CF, Lannigan FJ. Complications of otitis media in indigenous and non-indigenous children. *Med J Aust*. 2009;19:S60–4.