

# Factors Associated With Developing Cholesteatoma: A Study of 45,980 Children With Middle Ear Disease

Katrina Spilsbury, PhD; Ian Miller, MRCSI; James B. Semmens, PhD;  
Francis J. Lannigan, MD, FRACS

**Objectives/Hypothesis:** To identify factors associated with the rate of developing cholesteatoma following ventilation tube insertion (VTI).

**Study Design:** A population-based retrospective cohort study.

**Methods:** Administrative health data from all private and public hospitals in Western Australia for children who had at least one VTI from 1980 to 2004 was used to identify subsequent hospital admissions for cholesteatoma. Main outcome measures were time to cholesteatoma (survival) outcomes, including hazard ratios, log-rank tests, and Kaplan-Meier failure functions.

**Results:** There were 45,980 children who underwent at least one VTI from 1980 to 2004 with 460 subsequently developing cholesteatoma. The cumulative percentage of children who developed cholesteatoma within 15 years after one VTI procedure was 0.9% (95% confidence interval [CI], 0.8–1.0), after two VTIs 2.1% (95% CI, 1.6–2.3), after three VTIs 3.8% (95% CI, 2.9–4.8), and after four or more VTIs 5.2% (95% CI, 4.0–6.7). The rate of developing cholesteatoma increased 10% (95% CI, 6–14) for each additional year in age before first VTI. For children who underwent two or more VTIs, the rate of cholesteatoma increased 21% (95% CI, 12–32) with each additional year between VTIs. Adenoid removal was associated with a 27% (95% CI, 11–40) reduction in the rate of developing cholesteatoma.

**Conclusions:** Children with persistent or refractory middle ear disease who required multiple VTIs were at increased risk of cholesteatoma. First ventilation tubes inserted at an early age, subsequent ventilation tubes inserted without delay, and adenoid removal were associated with a reduced rate of cholesteatoma development.

**Key Words:** Ventilation tubes, cholesteatoma, survival analysis, medical record linkage.

*Laryngoscope*, 120:625–630, 2010

## INTRODUCTION

Cholesteatoma is usually defined as acquired if it is associated with a defect of the tympanic membrane. It is generally accepted that the middle ear negative pressure resulting from poor eustachian tube function causes part of the tympanic membrane to form a retraction pocket that allows epidermal ingrowths into the middle ear that can lead to the development of cholesteatoma.<sup>1</sup> Several studies have described individual cases where the cholesteatoma was seen to arise from the site of ventilation tube insertion (VTI), suggestive of an iatrogenic origin.<sup>2–4</sup> Around 1% of children who have ventilation tubes inserted develop a cholesteatoma, and it is more common in children who undergo many VTIs.<sup>2</sup> On the other hand, several correlational studies have shown that there has been no increase in cholesteatoma despite a large increase in the use of ventilation tubes.<sup>5,6</sup>

The relative rarity and long lead phase for cholesteatoma development make prospective studies expensive and time consuming; however, cholesteatoma is suited to retrospective population-based cohort studies that use routinely collected hospital data because a hospital admission is required for treatment. Establishing causal inference through observational studies can be difficult; however, large cohort studies are useful to identify biologically plausible and temporal associations where experimental studies have not yet been performed or are impractical. Western Australia has an ongoing and validated data linkage system that creates links between many state-based health data sets from 1980

From the Centre for Population Health Research, Curtin Health Innovation Research Institute, Curtin University of Technology, Perth (K.S., J.B.S.); the Department of Paediatric Otolaryngology, Princess Margaret Hospital, Subiaco (I.M., F.J.L.); and the School of Medicine, Notre Dame University, Fremantle (F.J.L.), Australia.

Editor's Note: This Manuscript was accepted for publication September 30, 2009.

This project was funded through the Western Australian Safety and Quality of Surgical Care Project by an Australian National Health and Medical Research Council project grant.

Send correspondence to Katrina Spilsbury, BSc, PhD, Centre for Population Health Research, Curtin Health Innovation Research Institute, Curtin University of Technology, GPO Box U1987, Perth Western Australia 6845, Australia. E-mail: katrina.spilsbury@curtin.edu.au

DOI: 10.1002/lary.20765

onward, including all hospital admissions and death registrations.<sup>7</sup>

In Western Australia, 8.4% of all children have at least one VTI before reaching 15 years of age.<sup>8</sup> The aim of this study was to investigate demographic and health-related risk factors associated with developing cholesteatoma in Western Australian children after taking the timing and history of VTI into account. The Western Australian Data Linkage System was used to access hospital morbidity records of all those children who underwent VTI from 1980 to 2004. Survival analyses using Cox models with an extended Markov assumption were used to investigate the association of cholesteatoma with ventilation tube history under a multistate framework.

## MATERIALS AND METHODS

Study data was obtained through the Western Australian Quality and Safety of Surgical Care project<sup>9</sup> from the Western Australia Data Linkage System following approvals from the Western Australian Department of Health and the Curtin University of Technology Human Research Ethics Committee. International Classification of Diseases (ICD) codes were used to perform a deidentified extraction of all hospital morbidity and death records pertaining to all persons who underwent a VTI between January 1, 1980 and December 31, 2004 in Western Australia.

A case was defined as any child born in 1980 or later with a residential postcode in Western Australia who underwent at least one VTI. ICD codes were used to identify subsequent VTIs, adenoidectomies, cholesteatomas, and the diagnoses associated with the first VTI. A cholesteatoma was defined as acquired if first mention occurred at least 6 months after the first VTI. Children with cleft palate were identified by relevant ICD diagnosis and procedure codes for cleft palate repair occurring in any hospital admission record. Age at first VTI was defined in years. The year of first ventilation insertion was grouped into 5-year periods, 1980 to 1984, 1985 to 1989, 1990 to 1994, 1995 to 1999, and 2000 to 2004. Residential location was defined as metropolitan, rural, or remote based on patient postcode at admission for first VTI. Aboriginality was recorded if a patient had indentified as having an Aboriginal or Torres Strait Islander heritage. Hospital of first VTI was classified as being located in the only major metropolitan city in Western Australia (Perth) or regional/remote areas and by whether it was a public or private hospital. Ventilation tube history was classified as having had one, two, three, or four or more VTI procedures during follow-up.

Loss to follow-up was not directly measured in this study but was assumed to be mainly due to interstate migration, estimated to be 5% of the population aged 5 years and over every 5 years. This type of loss to follow-up was considered unlikely to be associated with ventilation tube history or the development of cholesteatoma. Administrative data was complete in all demographic variables of interest for all cases identified in this study.

Survival time was defined as time in years from date of first VTI to either first record of cholesteatoma that was treated at least 6 months after the first VTI, study censor date of December 31, 2004, or date of death if it occurred before the study censor date. The cumulative percentage of cases developing cholesteatoma by ventilation tube history was estimated by the Kaplan-Meier failure function. Log-rank tests were used to assess equality of survivorship functions.

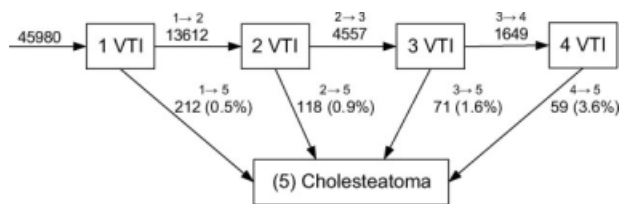


Fig. 1. Multistate structure used to define the relationship between ventilation tube insertion (VTI) and cholesteatoma. The numbers of children who made transitions through the VTI states are shown as is the percentage of children who subsequently developed cholesteatoma while in that state.

Multivariate survival analysis was complicated by ventilation tube history and adenoidectomy, both considered as internal time-varying variables. Interpretation can be problematic because internal time-dependent variables require the survival of the individual to exist, and thus the observed value may carry information about the time to failure or informative censoring. It can also be difficult to establish whether an internal time-varying covariate is a confounder, mediating variable, or both, which can lead to bias and misinterpretation of hazard values. To minimize these problems, we considered the association between potential risk factors and the development of cholesteatoma under a multistate modeling structure using Cox (proportional hazards) models under an extended Markov assumption.

Four transient states and one absorbing state were defined (Fig. 1). All individuals entered the study in state 1 (having had one VTI). If an individual underwent a subsequent VTI they moved into state 2, and so on. An individual moved to the absorbing state if a hospital admission with a diagnosis of cholesteatoma was identified. Data was organized in the counting process format for right-censored survival data whereby the number and types of states that an individual experiences was represented by a separate row in the dataset, and the entry and exit time into each transition state recorded. End-of-study censoring was assumed to be independent of the disease process.

The final Cox model used time in years from first VTI as the analysis time. Ventilation tube history and adenoidectomy (transitions through states) were entered as time-dependent covariates, whereas time of entry into each VTI state (extended Markov assumption) was entered as a time-independent variable. Potential predictors and confounders, age at first ventilation tube (entered as continuous variable), sex, Aboriginality, hospital, and residential location were also tested for importance. Cleft palate was entered into the model as an interaction term with ventilation tube history. Only transitions to the state of cholesteatoma were of interest, and transitions through VTI states were censored.

Tests for violation of the proportional hazards assumption were performed using Schoenfeld residuals. Likelihood ratio tests were used to include or exclude covariates from the adjusted model and to identify any potential plausible interaction terms at the 5% level. Chi-square, rank sum, and *t* tests were also used to test equality in proportions, medians, and means where appropriate. All data management and statistical analyses were performed using Stata version 10 (Stata Corp., College Station, TX).

## RESULTS

There were 46,095 children who had at least one VTI in a Western Australian hospital and were born in 1980 or later. One hundred and fifteen (0.2%) were excluded because their postcode indicated an interstate

TABLE I.  
Summary Characteristics of the 45,980 Children Who Underwent At Least One VTI in Western Australia  
From 1980–2004 By Cholesteatoma Status.

	No Cholesteatoma		Cholesteatoma		Rank Sum P Value
	Median	IQR	Median	IQR	
Age at first VTI, yr	3	1–5	3	1–5	.718
Age at cholesteatoma, yr	—	—	8	6–12	
	No.	%	No.	%	Log-Rank P Value
Number of VTI procedures					
One	32,147	99.3	212	0.7	
Two	8,925	98.7	118	1.3	<.001*
Three	2,858	97.6	71	2.4	
Four or more	1,590	96.4	59	3.6	
Adenoid surgery					
No	27,250	98.9	290	1.1	
Adenoidectomy	8,291	98.8	97	1.2	.009*
Adenotonsillectomy	9,979	99.3	73	0.7	
Sex					
Male	27,086	99.0	280	1.0	.565
Female	18,434	99.0	180	1.0	
Cleft palate					
No	44,877	99.0	431	1.0	<.001*
Yes	643	95.7	29	4.3	
Aboriginal and/or TSI					
No	43,608	99.0	437	1.0	.213
Yes	1,912	98.8	23	1.2	
Residential location					
Metropolitan	35,951	99.1	336	0.9	
Rural	6,746	98.6	96	1.4	.002*
Remote	2,823	99.0	28	1.0	
Type of hospital at 1st VTI					
Public (metro)	18,999	98.6	222	1.2	
Private (metro)	21,133	99.1	195	0.9	.138
Public (country)	4,116	99.1	37	0.9	
Private (country)	1,272	99.5	6	0.5	
Year of 1st VTI					
1980–1984	1,839	98.5	29	1.6	
1985–1989	7,422	98.2	138	1.8	
1990–1994	11,281	98.6	162	1.4	.117
1995–1999	12,814	99.2	107	0.8	
2000–2004	12,164	99.8	24	0.2	

\* $P < .05$ .

VTI = ventilation tube insertion; IQR = interquartile range; TSI = Torres Strait Islander.

or offshore island residence, leaving 45,980 children. A diagnosis of chronic nonsuppurative otitis media was documented in 19,119 (41.6%) children at time of first VTI. A diagnosis of acute nonsuppurative otitis media was present in 387 (0.5%), acute suppurative otitis media in 68 (0.2%), and chronic suppurative otitis media in 158 (0.3%) of cases. The remaining 26,249 (57.1%) cases had unspecified otitis media or other diagnoses recorded.

After excluding the 25 cases of cholesteatoma that occurred within 6 months following the first VTI, there remained 460 (1%) cases admitted to hospital with a diagnosis of cholesteatoma following ventilation tube surgery (Table I). The median follow-up time for the cohort from first VTI to date of censor, death, or cholesteatoma was 9.1 years (interquartile range [IQR], 4.5–13.8 years). Total follow-up time was 433,910 person-years. The median age at first VTI was 3 years (IQR, 1–

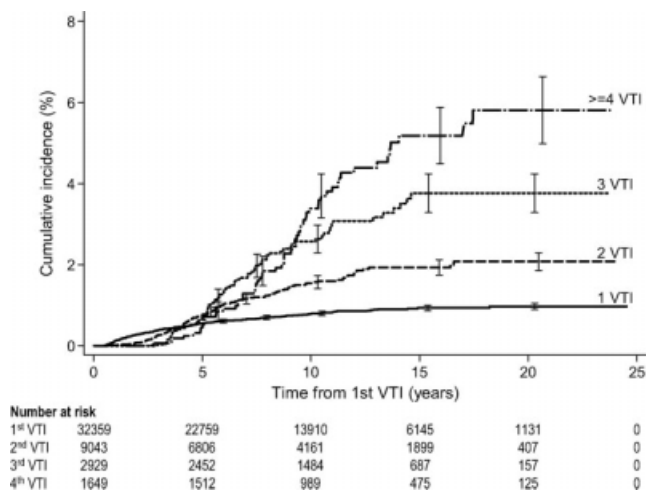


Fig. 2. Cumulative incidence of cholesteatoma (Kaplan-Meier failure function as a percentage) by total number of ventilation tube insertions (VTI) performed by end of follow-up. The numbers remaining at risk at selected time points are indicated. Selected standard errors are indicated by error bars.

5 years) and at admission with cholesteatoma was 8 years (IQR, 6–12 years).

Univariate survival analysis showed that increasing number of VTIs was associated with increased incidence of cholesteatoma (Table I and Fig. 2). The cumulative percentage of children who had only one VTI and who went on to develop cholesteatoma within 15 years after their procedure was 0.9% (95% confidence interval [CI], 0.8–1.0), whereas 2.1% (95% CI, 1.6–2.3) of children who had two VTIs, 3.8% (95% CI, 2.9–4.8) of children who had three VTIs, and 5.2% (95% CI, 4.0–6.7) of children who had four or more VTIs went on to develop cholesteatoma within 15 years of the first procedure. Log-rank tests also indicated that adenoidectomy, cleft palate status, and residential location were all associated with the development of cholesteatoma (Table I). Sex, Aboriginality, type of hospital, diagnosis associated with, and year of first VTI were not associated with cholesteatoma development; however, the paucity of cholesteatoma occurring in some of the smaller groups reduced the power to detect statistically significant differences.

It was observed after adjusting for relevant predictors in a Cox model that increasing numbers of VTIs remained associated with an increased rate of cholesteatoma (Table II). For example, the relative rate of developing a cholesteatoma for a child who had just undergone a fourth VTI was 5.6 times (95% CI, 3.5–9.0) that of a child who had just had their first VTI. This pattern was not observed among children with cleft palate. The relative rate of developing cholesteatoma in children with cleft palate having undergone their fourth VTI was no different (hazard ratio, 1.2; 95% CI, 0.3–4.5) from children with cleft palate having had one VTI.

Increasing age at first VTI was associated with an increased risk of cholesteatoma. The rate of developing cholesteatoma increased 10% (95% CI, 6–14) for each additional year of age before first VTI. For example, the

relative rate of developing a cholesteatoma for a child who had a first VTI at age 6 years was 1.3 (95% CI, 1.2–1.5) times higher compared to a child who had first VTI at 3 years of age.

Increasing time in years since last VTI was associated with an increased risk of cholesteatoma. For instance, the rate of developing cholesteatoma was 21% (95% CI, 12–32) higher for a child who had a second VTI 2 years after their first VTI compared to a child of the same age who had a second VTI only 1 year after their first.

Following adenoidectomy, the rate of cholesteatoma development dropped 27% for all children and after taking other covariates into account. Living in a rural area was associated with a 43% increased rate of cholesteatoma, whereas calendar year of first VTI, sex, type of hospital, diagnosis at first VTI, and Aboriginality were not associated with the rate of cholesteatoma development in the adjusted Cox model.

The average time in years from last VTI to the development of cholesteatoma was 3.8 years, and this did not differ by ventilation tube history (*t* test, *P* = .586). Fifty percent of cholesteatomas were detected by 3 years following last VTI, and 85% were detected by around 7 years (Table III).

## DISCUSSION

Cholesteatoma occurred in 1% of the 45,980 children who underwent VTIs in this large retrospective study spanning 24 years. The risk of developing cholesteatoma increased almost six fold after four or more

TABLE II.  
Results of the Cox Model Estimating the Relative Rate (Hazard Ratio) of Developing Cholesteatoma By Covariates.

Variables	HR	95% CI	<i>P</i> Value
Children without cleft palate*			
2nd vs. 1st VTI	1.80	1.35–2.40	<.001
3rd vs. 1st VTI	3.33	2.22–4.99	<.001
4th vs. 1st VTI	5.60	3.48–9.01	<.001
Children with cleft palate*			
2nd vs. 1st VTI	1.08	0.44–2.63	.871
3rd vs. 1st VTI	1.01	0.34–3.01	.986
4th vs. 1st VTI	1.15	0.30–4.47	.841
Age at first VTI	1.10	1.06–1.14	<.001
Time of entry into current VTI state	1.21	1.12–1.32	<.001
Adenoid surgery <sup>†</sup>	0.73	0.69–0.89	.002
Residence at time of 1st VTI			
Metropolitan	1.0	—	—
Rural	1.43	1.14–1.79	.002
Remote	0.94	0.64–1.39	.770

\*Cleft palate status was entered as an interaction term with the time-varying covariate VTI state.

<sup>†</sup>Adenoid surgery was entered in the model as a time-varying covariate.

HR = hazard ratio; CI = confidence interval; VTI = ventilation tube insertion.

TABLE III.  
Cumulative Number and Percentage of Cholesteatoma Cases Identified At Different Times Following Last VTI.

Cumulative Cases of Cholesteatoma Identified, No. (%)					
1 Yr	3 Yr	5 Yr	7 Yr	10 Yr	Total
59 (13)	238 (52)	343 (75)	391 (85)	433 (94)	460

VTI = ventilation tube insertion.

VTIs in children without cleft palate but not in those with cleft palate. On average, cholesteatoma developed within 3 years of last VTI. Older age at first VTI and increasing time between ventilation tubes insertions were associated with increased rate of cholesteatoma development, whereas adenoidectomy was protective against cholesteatoma. Children living in rural areas also had an increased risk of cholesteatoma.

Limitations of this study include the inability to determine whether ventilation tubes were inserted bilaterally or unilaterally, or which ear had formed the cholesteatoma. Anecdotally, ventilation tubes are mostly placed in both ears in Western Australia, but we can not conclude that every cholesteatoma identified in this study occurred in ears that had previous ventilation tubes. We were also unable to distinguish between congenital cholesteatoma, which occur behind an intact tympanic membrane, and those formed in association with retraction pockets or iatrogenic injury using ICD codes. We attempted to limit the inclusion of congenital cholesteatoma by excluding the 25 cases that were diagnosed within 6 months of first VTI. The inability to distinguish between the type of ventilation tubes used and how long they remained in place was another limitation of the study, as was the inability to determine the severity of the underlying ear disease.

The relative rarity of cholesteatoma and length of follow-up time required makes prospective studies expensive and time consuming. Most larger studies on cholesteatoma and ventilation tubes have involved either institution-based retrospective studies,<sup>2,10</sup> case-control studies,<sup>11</sup> or studies using aggregated data.<sup>6,12</sup> The main advantage of this study was that the large unselected population of almost 46,000 children followed up from birth allows for a wide generalizability of the study results. Using the power of data linkage we were able to identify the surgical history of each individual irrespective of where or when it was performed.<sup>9</sup> By taking the timing of VTIs, adenoid surgery, and cholesteatoma diagnosis into account, additional insights into the relationship between cholesteatoma and ventilation tube history were available.

Increasing risk of cholesteatoma was strongly associated with increased number of ventilation tube procedures in this study. This has been reported previously as evidence of the iatrogenic nature of ventilation tubes<sup>2</sup>; however, we observed that children who had VTIs in quick succession appear to be protected against cholesteatoma compared to those who had the same number of ventilation tubes but had a longer time peri-

ods between them. This suggests that timely treatment with ventilation tubes may reduce exposure to negative ear pressure and subsequently reduce the long-term risk of cholesteatoma. In addition, the lack of association of number of ventilation tubes and risk of cholesteatoma in children with cleft palate suggests that it is the chronic eustachian tube dysfunction that leads to cholesteatoma in most cases rather than ventilation tube placement itself. However, a prospective study is needed to confirm if a causal relationship between the timing of VTI tubes and development of cholesteatoma exists.

The rate of cholesteatoma increased with increasing age at first VTI, regardless of the diagnosis associated with the first VTI. As chronic otitis media is generally present in the first years of life and as early as 3 months of age,<sup>13</sup> children undergoing their first VTI when older may have had increased exposure time to the negative pressure associated with chronic nonsuppurative otitis media and potential retraction pocket formation than children treated at a younger age. The protective effect of early ventilation tubes found in this study is in contrast to an earlier study that found the incidence of cholesteatoma was highest in younger children.<sup>2</sup>

Removal of large adenoids is thought to improve eustachian tube function, thereby reducing exposure to negative pressure in the middle ear. Our observation of a reduced risk of cholesteatoma for all children following adenoidectomy supports this hypothesis; however, the nature of the regression modeling process used means that we cannot determine whether the effect of adenoidectomy is mediated through reducing the need for further ventilation tubes or whether it has a direct association with cholesteatoma development itself.

We found no evidence that risk of cholesteatoma was greatly increased in Aboriginal children despite documented higher incidence of otitis media with effusion.<sup>14</sup> However, this study was only sufficiently powered to detect a large difference in Aboriginal children, and further studies are needed to confirm this result. Cholesteatoma occurred more often in children from rural areas of Western Australia but not in children from remote areas. It is not clear why these differences exist; however, previous studies have shown that the type of ventilation tube used, its duration in situ, and surgeon experience may influence cholesteatoma development,<sup>2,3</sup> and perhaps variations in care could explain some of this difference. Alternatively, issues regarding access to care, for example, waiting lists in the public hospitals or the distances to health services for rural patients, may have also played a role. More detailed research in this area is required.

## CONCLUSION

This retrospective population-based study used hospital morbidity and mortality data to conduct a survival analysis investigating the association between sociodemographic and clinical factors and the rate of developing cholesteatoma in children with middle ear disease. An increased risk of cholesteatoma was observed in children with cleft palate, in children with adenoids, and in

children who underwent multiple VTIs. The inability to identify the type of ventilation tube inserted and the severity of the underlying ear disease was a major study limitation. However, our results support the theory that a major contributor to the development of cholesteatoma is continuing negative middle ear pressure from untreated and/or refractory middle ear disease.

### Acknowledgments

The authors thank the staff of the Data Linkage Branch for access to the WA Data Linkage System and for their assistance in obtaining the data, the WA Health Data Custodians for access to the core health datasets, and the Western Australian Department of Health. We also thank the anonymous reviewers for their helpful comments.

### BIBLIOGRAPHY

1. Bluestone CD, Cantekin EI, Beery QC, Stool SE. Function of the Eustachian tube related to surgical management of acquired aural cholesteatoma in children. *Laryngoscope* 1978;88:1155–1164.
2. Golz A, Goldenberg D, Netzer A, et al. Cholesteatomas associated with ventilation tube insertion. *Arch Otolaryngol Head Neck Surg* 1999;125:754–757.
3. Al Anazy FH. Iatrogenic cholesteatoma in children with OME in a training program. *Int J Pediatr Otorhinolaryngol* 2006;70:1683–1686.
4. Herdman R, Wright JL. Grommets and cholesteatoma in children. *J Laryngol Otol* 1988;102:1000–1002.
5. Padgham N, Mills R, Christmas H. Has the increasing use of grommets influenced the frequency of surgery for cholesteatoma? *J Laryngol Otol* 1989;103:1034–1035.
6. Rakover Y, Keywan K, Rosen G. Comparison of the incidence of cholesteatoma surgery before and after using ventilation tubes for secretory otitis media. *Int J Pediatr Otorhinolaryngol* 2000;56:41–44.
7. Holman CD, Bass AJ, Rouse IL, Hobbs MS. Population-based linkage of health records in Western Australia: development of a health services research linked database. *Aust N Z J Public Health* 1999;23:453–459.
8. Spilsbury K, Kadhim AL, Semmens JB, Lannigan FJ. Decreasing rates of middle ear surgery in Western Australian children. *Arch Otolaryngol Head Neck Surg* 2006;132:1216–1220.
9. Semmens JB, Lawrence-Brown MM, Fletcher DR, Rouse IL, Holman CD. The Quality of Surgical Care Project: a model to evaluate surgical outcomes in Western Australia using population-based record linkage. *Aust N Z J Surg* 1998;68:397–403.
10. Van Heerbeek N, De Saar GM, Mulder JJ. Long-term ventilation tubes: results of 726 insertions. *Clin Otolaryngol Allied Sci* 2002;27:378–383.
11. Kempainen HO, Puhakka HJ, Laippala PJ, Sipila MM, Manninen MP, Karma PH. Epidemiology and aetiology of middle ear cholesteatoma. *Acta Otolaryngol* 1999;119:568–572.
12. Roland NJ, Phillips DE, Rogers JH, Singh SD. The use of ventilation tubes and the incidence of cholesteatoma surgery in the paediatric population of Liverpool. *Clin Otolaryngol Allied Sci* 1992;17:437–439.
13. Boswell JB, Nienhuys TG. Onset of otitis media in the first eight weeks of life in aboriginal and non-aboriginal Australian infants. *Ann Otol Rhinol Laryngol* 1995;104:542–549.
14. Boswell JB, Nienhuys TG. Patterns of persistent otitis media in the first year of life in aboriginal and non-aboriginal infants. *Ann Otol Rhinol Laryngol* 1996;105:893–900.