1. Introduction

Otitis media (OM) is one of the most commonly diagnosed infections among children. In the United States, more physician visits and more antibiotic prescriptions are written for OM than for any other infectious disease in childhood [1]. By one year of age, around 60% of children have experienced at least one episode of acute otitis media (AOM) [2]. By the age of 7 years, there are few children who have not had at least one episode of AOM, and around 75% who have had at least three episodes [2]. OM represents a significant economic health burden and adversely affects the quality of life of children and their families [1,3].

AOM is frequently a self-limiting disease although around 50% of children will have a recurrent episode and as many as 26% will have a persisting middle ear effusion 3 months after an AOM episode (otitis media with effusion, OME, also know as serous OM) [4]. Tympanic membrane (TM) perforation is the most common complication of AOM [5]. A persisting discharge through a perforated TM that lasts for 6 weeks or more is known as chronic suppurative otitis media (CSOM). CSOM is a disabling outcome estimated to affect between 65 and 350 million individuals globally, causing hearing loss in around 60% [6]. Mastoiditis is the second most frequent complication of OM after TM perforation [5]. Other serious complications of OM are generally classified as being extra-cranial: including temporary or permanent hearing loss, vestibular dysfunction, facial paralysis, adhesive OM and cholesteatoma, or, intracranial: including brain abscess and sinus thrombosis [4].

AOM is a polymicrobial disease where aetiology is often difficult to establish. The most frequently identified bacterial causes are *Streptococcus pneumoniae* (Spn) and *Haemophilus influenzae* (Hi), followed to a varying degree by *Moraxella catarrhalis*, *Staphylococcus aureus* and *S. pyogenes* [7–10]. Growing antibiotic resistance of Spn and Hi to first line therapies has been documented in many countries within the Asia-Pacific region [11,12]. Prevention of infection through vaccination may have a role in reducing antibiotic use and reducing infections due to resistant bacterial strains.

The global epidemiology of OM is not uniform. In some indigenous populations such as Australian Aborigines, Maori and Pacific Islanders, AOM is characterised by early age of onset, high risk of persistent disease and high risk of subsequent development of CSOM [6,13]. The World Health Organization classifies populations by CSOM prevalence rates among children: A low prevalence is defined as CSOM prevalence between 1% and 2%, high prevalence ("avoidable disease burden that must be addressed") between 2% and 4% and highest prevalence ("urgent attention needed to deal with a massive public health problem") greater than 4% [6]. The global burden of disease due to CSOM lies in Africa, South-East Asia and the Western Pacific [6]. For many countries within the Asia-Pacific, the burden of disease due to OM is not well described and general awareness of the disease amongst physicians may be low. Countries defined as high CSOM prevalence countries include Thailand, the Philippines, Malaysia and Vietnam [6]. Aboriginal Australians are defined as a very high prevalence group [6].

Pneumococcal conjugate vaccines containing polysaccharides from 7 or 11 pneumococcal serotypes have show efficacy in preventing AOM due to pneumococcal vaccine serotypes in efficacy trials [7,14–16]. The Pneumococcal Otitis Efficacy Trial (POET) employed a vaccine using Protein D, a cell-surface protein highly conserved among strains of Hi, as carrier protein. As well as demonstrating a statistically significant protective effect of vaccination on overall AOM disease burden and on AOM caused by vaccine serotype Spn, vaccination also prevented AOM due to *Hi* [7].

Table 1
Prevalence of OM by country.

Year of study	Population/setting	Age (years)	*n*	Examination method	OM Syndrome	Prevalence	Ref.
Australia							
1998–2004	Aboriginal children attending primary school in urban area	4–12 yr	119	O, T, A, AR	OM	42.0%	[24]
					OME	18.5%	
					CSOM	1.7%	
2001	Aboriginal children from 29 remote communities	6–30 mos	709	T, PO	OME	41%	[23]
					AOM	33%	
					CSOM	15%	
					Any suppurative OM	48%	
					Any perforation	24%	
					Any OM 6–18 mos	93%	
					Any OM 18–30 mos	92%	
1997	10 Day care centres	<4 yr	252	T, O	OME	9.6 per child yr (cumulative)	[88]
Indonesia							
2002	Population survey	All ages	–	–	CSOM	5.4%	[32]
Japan	No data						
Malaysia							
1993	Urban and rural kindergartens	5–6 yr	1097	T, O	All OME	13.8%	[57]
					Rural region	9.48%	
					Urban region	17.9%	
2005	Population survey	All ages	7041	T, O, OE	All OME	2.93%	Unpublished SSH and others
					Rural region	3.23%	
					Urban region	2.74%	
New Zealand							
2002–2003	Pacific Island children in NZ	2 yr	1001	ST, PO	OME	25.4%	[64]
					AOM	1.9%	
2008–2009	Retrospective primary care medical records review	<5 yr	19,146	Record review	AOM	30.2% (annual)	[62]
Philippines							
1997–1998	National survey	Children	15,381,796		OM	12.23%	[70]
2004–2005	Community survey	All ages	5953	O	Perforation	5.1%	[70]
1994	Hearing impaired	Children	665	SA	OM	18.34%	[69]
					Otorrhoea	2.2%	
					Inflammation	0.7%	
1994	District survey	School children	320	NS	Chronic OM	3.2%	[6]
Taiwan							
2001	Kindergartens & day care centres	3–6 yr	3013	T, PO	OM	9.8%	[74]
					OME	5.2%	
2006	Retrospective database review	≤12 yr	3,678,982	ICD-9 codes	AOM	64.5/1000	Unpublished PCW
1999	High schools	10–18 yr	8723	Questionnaire	OM (annual)	4.3%	[89]
Thailand							
1993–1995	Primary school	7–9 yr	2184	SA, O, T	Any OM	3.25%	[79]
					AOM	0.69%	
					OME	1.14%	
					Chronic OM	1.74%	
2004–2005	HIV + ve children	1–15 yr	76	0	Any OM	38.1%	[80]
					AOM	3.9%	
					CSOM	38.1%	
					Chronic OM	34.2%	
Vietnam							
1995	Rural and urban	6 mos–10 yr	3300	T, PO	Any OM	6.86%	[85]
					COM	2.1%	
					Sequelae otitidis	4.1%	

ST = (screening) tympanometry; SA = (screening) audiometry; PO = (pneumatic) otoscopy; OE = otoacoustic emission; NS = not specified, AR = acoustic reflectometry.

At present, pneumococcal conjugate vaccines are recommended for use in Australia, New Zealand, and Singapore, and the Western Pacific islands of Micronesia, Niue and Palau (http://apps.who.int/immunization_monitoring/en/globalsummary/ScheduleSelect.cfm). With the availability of vaccines that show efficacy in preventing AOM, baseline data on OM disease burden will be important for countries considering vaccination and for assessing vaccine effects on disease epidemiology.

A panel of ear nose and throat (ENT) experts from countries within the Asia-Pacific region met in February 2010 with the aims

of increasing awareness and understanding of the burden of disease of OM in the region and developing regional management guidelines. The first step in the process and the purpose of this report is to review the available published and unpublished literature describing the burden of disease caused by OM within selected Asia-Pacific countries.

2. Methods

PubMed was searched using the terms "otitis media" AND (Asia OR Philippines OR Indonesia OR Singapore OR Malaysia OR Thailand OR Taiwan OR Vietnam OR Australia OR New Zealand OR Japan). Gateway to Japan Journals (J-East, http://science-links.jp/j-east/) was also searched for English abstracts of relevant articles written in Japanese. Publications were limited to human studies published between 1995 and 2010. English and non-English language literature was assessed for relevance by review of abstracts when available. Citations in published papers were also examined. Only studies in children were reviewed. In order to describe all of the available data in the region, papers were not assessed using quality criteria. Additional unpublished data made available by the expert panel were included.

3. Results

3.1. Studies identified in the literature search

There were 1004 'hits' in the initial PubMed search and 87 were selected after abstract review as being of potential interest. Searches of bibliographies yielded additional publications and datasets. Most studies were observational prevalence studies, retrospective hospital-based reviews of medical records or microbiological evaluations of flora isolated from middle ear fluid (MEF) or otorrhoea.

3.2. OM burden in the Asia-Pacific

Available OM prevalence data are summarised in Table 1. Results from studies that evaluated the bacterial aetiology of AOM and CSOM are given in Tables 2 and 3, respectively.

3.3. Australia

3.3.1. Incidence and prevalence of OM

Few studies retrieved after 1995 evaluated OM prevalence or incidence in the general population. A national report on disease burden in Australia estimated that in 2003, 1,174,267 cases of OM occurred in all age groups, of which the majority (67.6%) were in children 0–14 years of age [17].

A recent report on the economic cost of OM in Australia using US prevalence data and Australian population statistics estimated that in 2008, between 658,006 and 1,615,486 children less than 15 years of age were affected by OM [18]. By the age of 12 months, 73% of Australian children are expected to have experienced at least one OM episode. Indigenous children accounted for 12.8% of cases (the indigenous community comprises approximately 2.5% of the national population). In 2008 temporary hearing loss is likely to have affected more than 354,457 children, 87,655 children were

Table 2
Distribution of frequently isolated bacteria from culture-positive samples in children with AOM, by country.

Year of study	Population/setting	Age	n	Sample source	Spn (%)	Hi (%)	*M. catarrhalis* (%)	*S. aureus* (%)	Spn + Hi	PRSP	Ref.
Australia											
pre-PCV7	Aboriginal	<18 mos	53 ears	First/new AOM with perforation	38% Vaccine or vaccine related 21%	55%	–	19%	28%	–	[90]
2000	Aboriginal children	<8 ys	31	Children with AOM	29%	32%	5%	–	–	–	[22]
2001–2004	Tiwi islands post-PCV7	≤12 ys	73 ears	New TM perforations	64%	84%	8%	–	48%	–	[28]
1996–2001	Tiwi islands pre-PCV7		72 ears		59%	88%	0%	–	47%	–	[28]
Japan											
2002–2004	Retrospective. Recurrent AOM	Children	70	MEF, otorrhoea, NP	35.7%	37.1%	–	15.7%	–	40%	[91]
2000–2005	Hospital ENT Dept	Children	41	–	24.7%	24.7%	12.3%	–	–	–	[92]
2001–2002	Hospital	Infants	85	–	38.6% (PRSP)	34.3%	11.4%	–	–	–	[93]
2001–2002	Hospital ENT Dept. patients with influenza	Children	80	Otorrhoea	13.7%	8.7%	3.7%	–	–	–	[94]
–	14 General practices	Children		–	31.8%	35.8%	1.5%	–	–	42.2%	[95]
2001	Clinics	≤10 ys	123 ears	–	40.8%	30.9%	28.3%	–	–	52.6%	[96]
2004–2005	Clinics	≤10 ys		–	32.7%	30.0%	27.3%	–	–	61.6%	[96]
–	–	3 mos–11 ys	47	–	30.4%	41.1%	–	–	–	–	[97]
1998–1999	Hospital	Children	33	Otorrhoea	33%	21%	–	–	–	65%	[98]
–	–	Children	152	Otorrhoea	13.2%	27.9%	2.5%	19.1	–	44.4%	[99]
Taiwan											
2004	Hospital	<18 ys	96	MEF	32%	26%	–	14%	–	73.3%	[100]
1993–2001	Hospital	4–96 mos	18	Medically refractory AOM[a]	25%	0	0	17%	0%	100%	[101]
1997–1999	Hospital	3 m–14 ys	243	MEF[b]	21.7%	10.2%	–	7.0%	–	95.8%	[78]
Thailand											
–	Hospital	3–59 mos	112	MEF/otorrhoea	47%	37%	11%	–	0.9%	19%	[82]

PRSP – penicillin-resistant *S. pneumoniae*.
[a] AOM requiring emergency myringotomy because of toxicity following second-phase antibiotics.
[b] Persistent AOM failed AB Rx for whom myringotomy was indicated; NP nasopharyngeal sample.

Table 3
Microbiological findings in children with CSOM (or otorrhoea) by country.

Country	Year of study	Population/ setting	Age	*n*	Examination method	Commonly identified bacteria	Antibiotic resistance	Ref.
Indonesia	1989	ENT patients	5–16y	38	Middle ear sample through perforation	60% mixed flora *Peptostreptococcus sp., P. aeruginosa, Bacteroides sp., S. aureus, Prevotella sp.,*	58% of patients had B-lactamase producing bacteria	[31]
Malaysia	1994–1995	CSOM	6 m–78y	382 swabs	Otorrhoea	*P. aeruginosa* 27.2% *S. aureus* 23.6%		[59]
Philippines	2004–2005	Outpatients	Paediatric	16	Otorrhoea	*S. aureus* 52%, *P. aeruginosa* 35%	–[a]	[102]
Thailand	2004–2005	HIV+ve	1–15y	16	Otorrhoea	*P. aeruginosa* 31% *Staphylococcus* sp. 12.5% *Hi* 12.5%	–	[80]
Taiwan	2000–2001	Hospital	Outpatients	161	Otorrhoea	*S. aureus* 43.5% *Pseudomonas* sp. 28.8%	13.7% were MRSA	[103]
Vietnam	2009	Urban	1 m–15y	114	?	*P. aeruginosa* 26% Spn 21% *S. aureus* 22%	93% of Spn	Dr Nguyen

n = number of patients.
[a] Not specified for paediatric samples; m = months; y = years.

likely to have been affected by TM perforation, 237 by mastoiditis and 217 by intracranial complications [18].

The epidemiology of OM is markedly different among Aboriginal and non-Aboriginal Australian children. Repeated studies have shown prevalence rates of severe OM in Aboriginal children that are among the highest reported in the world [19]. Middle ear disease in Aboriginal children may be almost universal [13,20,21].

Compared to non-Aboriginal children, OM in Aboriginal children begins very early in life, is frequently bilateral and is less likely to resolve spontaneously, establishing within the first year of life a pattern of chronic persisting disease [13,20–22]. By the age of 6 months, 14% of children have experienced TM perforation, increasing to 40% by 18 months of age [23]. In a survey of 29 remote communities conducted in 2001, OM was detected in 91% of children between 6 and 30 months of age [23]. Almost one quarter of children (24%) had TM perforation and 15% had CSOM. The results were noted to be essentially unchanged compared to a survey conducted 25 years earlier [23]. High rates of middle ear disease (42%) were also present in Aboriginal school-children children in urban locations, although CSOM rates in this setting were lower (1.7%) (Table 1) [24].

Data extracted from a national cluster survey of GP consultations was used to assess OM presentations and complications in indigenous versus non-indigenous children [25]. Over an 8-year survey period, ear problems were the fourth most frequent problem seen by GPs. The incidence of OM was 9.8 per 100 consultations in indigenous children versus 7.3 per 100 consultations in non-indigenous children. Severe OM including CSOM, COM and TM perforation were more frequent in indigenous children than non-indigenous children (7.9% of OM diagnoses versus 1.7%). Management of OM was similar in both groups of children. In a different study, CSOM was the most common reason Aboriginal children attended a Paediatric Outreach service in Far North Queensland between 2001 and 2006 [26].

3.3.2. *Impact of PCV7 on OM*

Infant vaccination with PCV7 was introduced in 2001 for indigenous and at-risk children, and for all children in 2005. Vaccination has been associated with a significant decrease in hospitalisations due to myringotomy and tympanostomy tube placement in children less than 3 years of age [27]. The decrease has been most marked in children less than one year of age (23% reduction) followed by 1 years olds (16%) and 2 year olds (8%) [27].

One study assessed the effects of PCV7 vaccination on OM prevention in indigenous Australians [28]. No changes in the percentage of children developing AOM, OME, TM perforation or CSOM were observed in vaccinated versus unvaccinated cohorts (Fig. 1). The occurrence of repeated TM perforation was statistically significantly lower in the vaccinated cohort at one time point (Fig. 1). The incidence of AOM in the unvaccinated cohort was 1.87 per person year, versus 2.05 per person year in the cohort who receive PCV7. Spn serotypes were different in the two cohorts, possibly reflecting an effect of vaccination. In the unvaccinated cohort vaccine serotypes including 6B, 23F, and serotypes 19A, 16F and 11A predominated. In the vaccinated cohort, serotypes 19A, 19F and 16Fpredominated. The minimal impact of PCV7 vaccination on the onset and progression of OM in this population was attributed to low serotype coverage by PCV7 and onset of disease before completion of the 3-dose primary vaccination course [28].

3.3.3. *Microbiology of OM*

Studies identified in the review period were all conducted in Aboriginal children with a new TM perforation. In line with reports from other countries (Table 2), Spn and Hi were the most frequently identified aetiological agents in AOM (Table). Co-infection with Spn and Hi was commonly observed, present in 28–48% of children.

Unpublished nasopharyngeal carriage data in non-Aboriginal Australian children with recurrent AOM showed that the

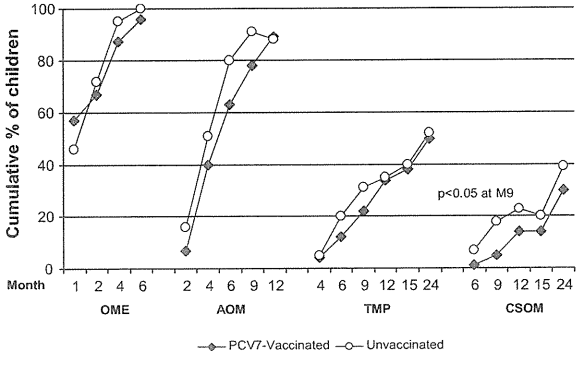


Fig. 1. Cumulative percentage of two cohorts of indigenous children (1996–2001 unvaccinated and 2001–2004 PCV7-vaccinated) with different otitis syndromes over time [28].

microbiological flora of children with recurrent AOM was significantly different from healthy controls [29]. The most commonly isolated bacterium was Hi (non-typable, 54.3%). Carriage of both Spn and Hi was significantly higher in children with recurrent AOM compared to healthy controls ($p = 0.02$ and $p < 0.0001$, respectively). PCV7 serotypes were found in 8–9% of all children whereas PCV7-related serotypes were identified in 53%. Pneumococcal serotypes 19A and 6A were the most frequently isolated serotypes.

3.3.4. Costs of OM

Using published local and international data, the cost of treating uncomplicated OM in children less than 5 years of age in 2008 was estimated between US$166.1 million and US$407.7 million [30]. The bulk of these costs were due to general practitioner visits and medications.

3.4. Indonesia

Three publications and one WHO report were retrieved. Thirty-eight children with CSOM and a history of repeated courses of antibiotics were assessed for microbiological flora via needle insertion through an existing TM perforation [31]. The predominant bacteria making up 106 isolates were similar to reports from other countries (Table 2). A total of 58% of patients harboured beta-lactamase-producing bacteria [31].

In 2007 WHO reported the general population prevalence of CSOM in Indonesia of 5.4%, and an overall prevalence of chronic non-suppurative OM of 3.8% [32].

A descriptive cross-sectional study assessed the prevalence of hearing impairment in children 6–8 years of age with OME between April and July 1998 [33]. The prevalence of hearing impairment in children with OME was 29.2% in 106 ears examined otoscopically, followed by tympanometry and brain evoked response audiometry.

A cross-sectional study with assessed the proportion of type I hypersensitivity reactions in 6–12 year old children with OME, identified by screening 525 primary school students [34]. Of 23 children with OME 78.3% ($n = 18$) had a positive skin prick test compared to 30% (7/23) control children without OME ($p = 0.0015$), suggesting an association between type I hypersensitivity and OME in children.

Between 2008 and 2009, 36 cases of AOM and 324 cases of CSOM were seen at the Cipto Mangunkusumo General Hospital (unpublished Dr Ratna D. Restuti).

3.5. Japan

3.5.1. OM burden

The largest number of studies was identified from Japan. Many were published in Japanese and data were extracted from abstracts in English when available. Data from studies where the age of the investigated cohort was not given in the abstract, and from studies assessing viral to tuberculous AOM aetiologies, were not included.

The outcomes of AOM according to severity of disease and the assessment of different initial treatment regimens were reported in 308 cases of children with AOM [35]. Children with AOM were classified as severe ($n = 277$; 89.9%) or non-severe ($n = 31$; 10.1%) based on symptoms and TM appearance. Children in the severe group were initially managed with amoxicillin whereas children in the non-severe group were managed without antibiotics. The two groups were similar with respect to age and day care attendance. Children with severe disease were more often male (57% versus 36%, $p < 0.05$) and more often colonised with pathogens (77% versus 55%, $p < 0.05$) than children with non-severe disease. Failure of symptoms or TM appearance to improve led to antibiotic changes in 59.9% of the severe group and to the commencement of antibiotics in 51.6% of the non-severe group. Children in the severe group who failed to improve with an initial course of amoxicillin were younger (40.2 months versus 45.8 months, $p < 0.05$), had higher TM severity scores (4.5 versus 4.1, $p < 0.05$), and were more often colonised with penicillin-resistant Spn (PRSP) (33.8% versus 6.5%, $p < 0.01$) than children who responded to amoxicillin. Severe disease occurred more often among males and among children colonised with pathogens. Response to treatment was impaired in young children and in children colonised with pathogens, especially PRSP.

The clinical course of 161 children less than 15 years of age with OME or recurrent AOM was tracked between 1994 and 2000 [36]. Bilateral disease was present in 30% of children. A total of 40% of children improved with medical management, 49% improved after myringotomy, 11% required ventilation tube insertion, and AOM progressed to OME in 2%. Rhino-sinusitis or acute URTI was present in 19% and 36% of children, respectively with OME. Other studies suggest that recurrent infections are caused by bacterial strains or different bacteria than that causing the initial episode [37,38].

In a retrospective hospital survey of children less than 6 years of age with conducted between 1994 and 1997, 259 of 748 patients (35%) with acute pneumonia or bronchitis, had concurrent AOM. Spn was the most commonly isolated bacteria and 83% of Spn isolates were penicillin resistant or had intermediate resistance (PISP) [39].

3.5.2. Economic costs of OM

A recent report on the economic cost of OM in Japan using US prevalence data and Japanese population statistics estimated that in 2006, there were between 351,972 and 746,932 episodes of simple OM, and between 166,396 and 536,456 episodes of complex OM in children below 4 years of age (Table 4) [40]. The medical cost for the treatment of AOM in children below 4 years of age was estimated to be US$1.8 billion.

3.5.3. Microbiology and drug susceptibility of pathogens

As observed in other countries in the region, Spn and Hi, followed *M. catarrhalis* were the most frequently isolated pathogens from children with AOM (Table 2) [41]. Two studies assessed Spn serotypes associated with AOM. The predominant pneumococcal serotype isolated from 175 MEF samples from children less than 10 years of age with AOM in Japan between 2006 and 2007 was 19F (19.4%), followed by serotypes 23F (14.9%), 14 (11.4%), 6B (11.4%), 6A (9.1%), and 3 (9.1%). A total of 26.3% of isolates were PRSP, most often serotypes 19F and 23F [42]. Similar results were observed in between 2005 and 2006 in 856 children less than 6 years of age with AOM. Spn was isolated in 31.7% of

Table 4
OM burden in children younger than 4 years of age in Japan [40].

Age (years)	0	1	2	3	4
Population	1,056,800	1,091,316	1,115,649	1,149,450	1,164,872
No. of AOM episodes: simple	695,140	746,932	517,311	436,570	351,972
No. of AOM episodes: complex	394,421	536,456	273,684	220,915	166,396
Estimated medical cost (million US$)	349	453	490	287	230

cultures, predominantly serotypes 19F (25.9%), 6B (14.9%) and 23F (11.9%). Of these 16.9% were PRSP [43].

Investigation of drug resistance was a common objective of many studies in Japan, triggered by evidence of increasing resistance and evidence that antibiotic resistance is linked to refractory or complicated AOM [44–48].

Drug resistant bacteria were identified in 26% (44 out of 169) bacteria isolated from MEF in children less than 12 years of age with AOM [49]. Drug resistance was linked to younger age and co-infection [49].

In children with AOM, penicillin resistance was detected in 15.6–65% of Spn strains in studies conducted between 1995 and 2007 (Table 2) [50–52]. Drug resistant Hi has also been linked to poor clinical outcomes. Beta-lactamase producing Hi was identified in 14.9% of 209 Hi strain isolated from patients aged 3 to 15 months old, and beta-lactamase negative ampicillin resistant (BLNAR) strains accounted fro 27.2% of strains [53]. In children less than two years of age with AOM, recent macrolide use was linked to isolation of BLNAR Hi [54] and recent penicillin use with PRSP [55].

3.5.4. Complications

Most studies of OM complications were individual case reports. A review of mastoiditis concluded that the most commonly implicated cause was Spn, with an increasing percentage of PRSP isolates over time [56]. In children 2 years of age or younger, acute mastoiditis tended to occur after the first AOM episode.

3.6. Malaysia

Three publications were retrieved. In 1993 a cross-sectional kindergarten-based study assessed the prevalence of OME in 1097 5–6 year-old children [57]. The children were examined otoscopically, followed by tympanometry and assessment of the ipsilateral acoustic reflex to determine the prevalence of OME. Children were recruited from two districts, one urban and one rural. The overall prevalence of OME was 13.8% with a higher prevalence observed in children residing in the urban versus the rural region (Table 1). An increased risk of OME was associated with bottle feeding and higher parental income.

A population based survey conducted in 2005 ($n = 7041$) identified OME in 205 individuals across all ages (prevalence 2.93% 95% CI 2.51; 3.40). Of these, 96 (46.49%) had hearing loss. The prevalence of OME among children 17 years of age and younger was 3.76% (2.33% in those ≤12 years and 1.43% in 13–17 year olds). In a sample of 205 children, the prevalence was SOM was 2.93% (95% CI 2.51; 3.40) [58]. OME prevalence was higher in rural versus urbane settings (Table 1), low income settings (3.05%) versus middle or high income settings (2.81% and 2.77%, respectively), and in individuals with no formal education (36.8% of all case) versus individuals with a tertiary level education (8.52% of all cases).

A study of the microbiology of CSOM examined 382 swabs. In line with data from other countries (Table 3), the most frequently isolated bacteria were *P. aeruginosa* (27.2%) and *S. aureus* (23.6%) [59].

Sixteen patients with complications of OM requiring surgical intervention were identified in a retrospective review of hospital surgical records from 1998 to 2001 [60]. Nine patients had intracranial complications including brain abscess and lateral sinus, while 15 had extracranial complications, of which the most frequent was mastoid abscess (40%) [60]

3.7. New Zealand

A retrospective general-practice based study of OM incidence between 1993 and 1994 showed that OM was the reason for presentation in 1.0% of consultations during the 1-year study period [61]. The incidence of OM was 2.7/1000 person years in children <2 years of age, and was lower in older age groups (2.02–2.04/1000 person years in 2–5 year olds, 0.74–0.81/1000 person years in 6–15 year olds, and 0.09–0.10/1000 person years in >15 year olds) [61].

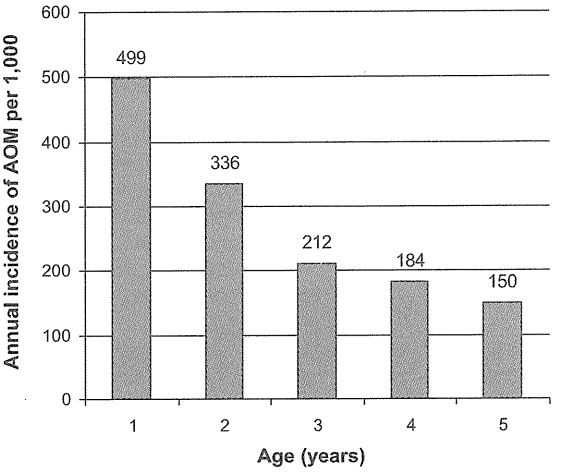


Fig. 2. Incidence of AOM by age in 19,146 <5 year olds derived from retrospective review of medical records from 63 general practices in New Zealand, 2008–2009 [62].

A retrospective survey of AOM presentations in children less than 5 years of age to primary health care physicians was conducted between 2008 and 2009 [62]. In a cohort of 19,146 children, there were 6262 cases of AOM recorded, of which 5225 were new cases (annual incidence 273 per 1000 [95% CI 216; 330]). Annual AOM incidences decreased with age (Fig. 2). A total of 20.3% of children had one or more episodes of AOM during the study period. Recurrent OM was noted in 4% of children. Incidences in Maori (271 per 1000) and Pacific Island (213 per 1000) children were within the same range as non-Maori/Pacific Island children (281 per 1000). Antibiotics were prescribed in 51% of GP consultations for AOM.

National hospital admission and mortality data due to OM were retrospectively searched covering the years 2000 to 2007 [63]. The aetiology of OM was estimated using international data, and Spn and Hi were assumed to account for 72% of OM admissions. The OM hospital admission rate for children less than 5 years of age was 11 per 1000. Admissions for surgical procedures (myringotomy or mastoidectomy) were more frequent than medical admissions (Fig. 3). The highest admission rates were in children between 1 and 2 years of age (Fig. 3). The annual myringotomy rate in children less than 2 years of age was 0.8 per 1000.

3.7.1. OM in Pacific island children

A prospective community-based study of 2-year old Pacific Island children living in New Zealand estimated the prevalence of OME and AOM to be 25.4% and 1.9%, respectively [64]. Most cases of OME (102 out of 118) were bilateral. One child with TM perforation was identified. Risk factors associated with increased OME risk in this population included regular ear discharge, frequent upper respiratory tract infections, snoring and day care attendance [65].

3.7.2. Costs of OM

Costs associated with OM in General Practice and outpatient settings were not available at the time of writing. Using 2006 to 2007 hospital admission data, the estimated annual cost of Spn and

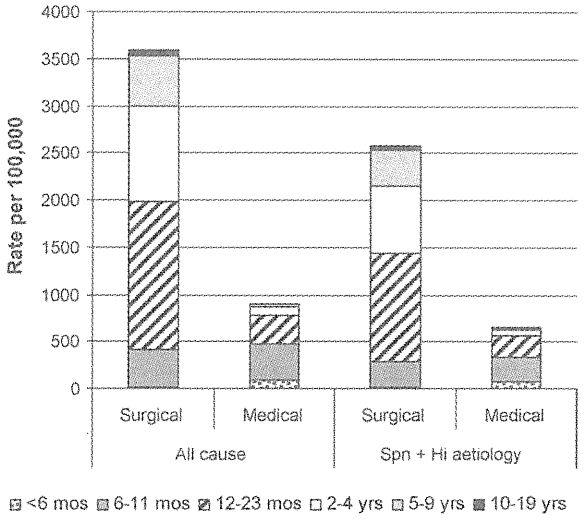


Fig. 3. Annual rate of hospital admissions (medical or surgical) in New Zealand for OM in 2006–2007, by age and estimated aetiology [63].

Hi OM-related hospital episodes for children aged <20 years was US$3.3 million in 2006–2007 [63].

3.7.3. Microbiology of OM

The microbiology of OME was assessed in two studies that assessed bacteria isolated from samples obtained during tympanocentesis and insertion of ventilation tubes [66,67]. Bacteria isolated from 67 children between 11 months and 8 years of age were Hi (45%), *M. catarrhalis* (34%) and Spn (24%) [66]. All Spn and 82% of Hi isolates were amoxicillin sensitive. In a second and later study between 1997 and 1999 (age range of subjects not provided), culture results from 79 MEF samples yielded Hi (59.4%), *M. catarrhalis* (19.0%) and Spn (21.5%) [67]. Amoxicillin resistance was shown in 21.2% of Hi isolates and 41% of Spn isolates (included intermediate resistance).

3.8. Philippines

Philippine OM prevalence data comes largely from surveys of hearing impairment. In a Province-wide Survey conducted in Quezon Province involving 3431 participants, disabling hearing impairment was observed in 20.7%. Wax (70.3%) and middle ear infections (18.8%) were observed to be the most prevalent disorders of the ear in those with hearing impairment [68].

A survey reported by WHO described 3.2% prevalence of chronic OM (2 out of 320 school children) in 1994 [6]. In another study conducted in 1994, the prevalence of OM was 18.34% in 665 Grade 1 to 3 school children in General Santos City with hearing impairment (out of 3121 who underwent screening audiometry) [69]. A national survey of children conducted during the school year between 1997 and 1998 in 15,381,796 children concluded the prevalence of OM was 12.23% [70]. In a study of children participating in a vaccine efficacy study of pneumonia prevention, 22.4% of children with pneumonia had AOM [71]. Between 1993 and 1994, the prevalence of SOM and AOM was estimated to be 45.46% and 54.54%, respectively in 206 children 1 month to 10 years of age with rhinitis (Unpublished – AP Opulencia, TL Jimenez, M. Bautista).

Indirect estimates have been used to estimate national costs of OM. Based on national statistics for population, healthcare budget and wage rates in the Philippines for 2007, it is estimated that 2% of all antibiotic prescriptions are for treatment of OM [72]. With an average cost of US$4.20 to treat each AOM episode, the estimated national cost for paediatric AOM is more than US$126 million. All health costs in the Philippines are borne by the family, where the estimated daily wage ranges between US$2.67 and US$7.85 per day. AOM treatment therefore represents a substantial health burden for families.

The Philippines is classified by WHO as a country with a high prevalence of CSOM [6]. To meet WHO recommendations of 1:100,000 ENT specialists to manage CSOM, 400 additional specialists are required, at an estimated cost of US$ 8.32 M. This amount represented 3% of the Department of Health general appropriations budget for 2007.

3.9. Singapore

Two publications were retrieved. In one study describing the microbiology of CSOM in Singapore, only one of 90 patients was a child and so this study is not discussed further here [73].

A retrospective review of medical records traced presentation and admissions for OM at the KK Women's and Children's Hospital (KKH) in Singapore between 2005 and 2009. The study population was children 12 years of age or less (publication submitted, Dr H Tan). During the observation period, a total of 8124 OM cases were seen at the Children's Emergency Department. Most presentation occurred in children between 3 and 5 years of age (41.48%) and children 2 years of age and under (29.73%) (Fig. 4). Of 8124 cases, 2.1% were admitted to hospital and 14.2% of children underwent myringotomy and tympanostomy tube insertion, 131 children (1.6%) developed serious complications of OM, including adhesive OM (35 children or 0.4%), COM (49, 0.60%), mastoiditis/abscess (12, 0.15%) and cholesteatoma (35, 0.43%).

3.10. Taiwan

3.10.1. Incidence and prevalence of OM

A survey of 3013 3–6 year old children attending kindergartens and day care centres showed that the prevalence of OM was 9.8%, with the highest rates observed between the ages of 3 and 5 years (11.3–12.4%) [74].

A retrospective review of the National Healthcare Insurance reimbursement system of Taiwan was conducted using ICD-9 codes [75–77]. Patients 12 years of age or younger with AOM who received treatment (outpatient or inpatient) during 2006 were assessed. In 2006, 283,084 children sought treatment for AOM (incidence 64.5/1000 based on the 2006 paediatric population estimate from the Annual Beneficiary Statistical Report).The incidence in children aged 5 years or less was 230.5 per 1000, with the highest incidence in 3 to 5 years olds (Fig. 5). The mean age at treatment was 4.7 years (SD 2.8).

3.10.2. Cost of AOM

In 2006 there were 733,546 AOM-related visits in Taiwan, of which 717,263 were outpatient visits and 16,283 AOM-related

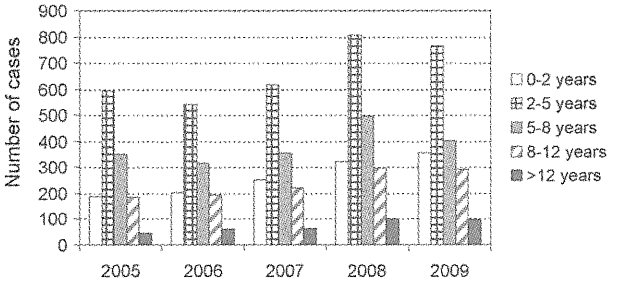


Fig. 4. Age distribution of 8124 patients presenting with OM to a Singapore hospital between 2005 and 2009 (unpublished HKK Tan).

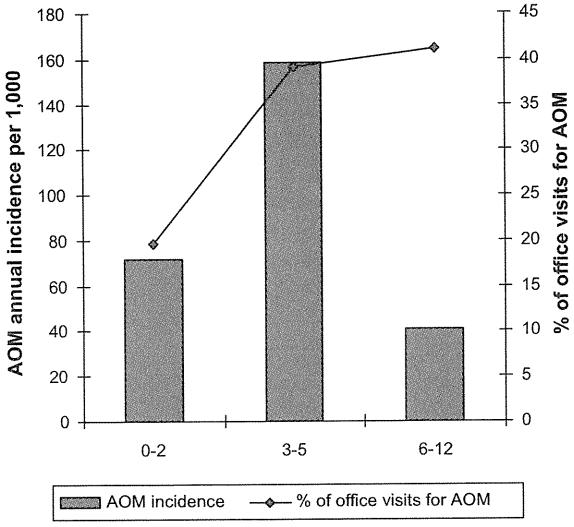


Fig. 5. Annual AOM prevalence and AOM-related outpatient visits and hospital admissions, Singapore [104].

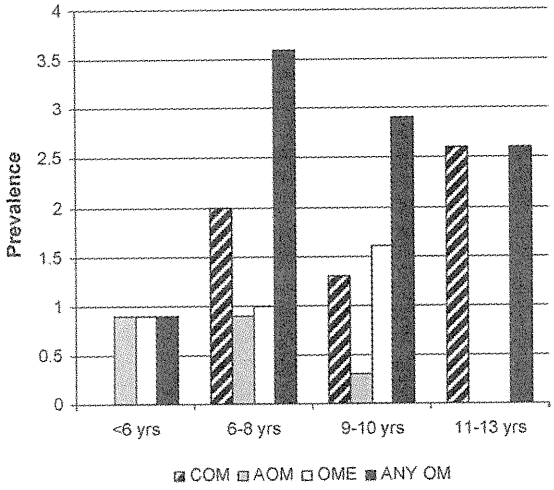


Fig. 6. Prevalence of OM by age in Thailand, 1993–1995 [79].

admissions [75]. The total national AOM-related expenses were more than US$ 17 million. Inpatient costs accounted for 43.1% of the total cost. Antibiotics were administered for a mean of 3.6 days and the mean hospital stay was 4.5 days [75].

3.10.3. Microbiology and complications of OM

Culture results and outcomes were assessed in children with AOM that failed to respond to antibiotic therapy and in whom myringotomy was indicated [78]. Of 243 eligible children, most were less than three years of age (56.8%). MEF samples showed a similar distribution of pathogens as other studies of AOM, with Spn and Hi the most frequently isolated bacteria (Table 2). Penicillin resistance among Spn isolates was extremely high (95.8%). A total of 34 (14%) children developed complications that included recurrent AOM (22 children or 0.9%), ventilation tube insertion (9, 3.7%), hearing impairment (4, 1.6%), mastoiditis or abscess (4, 1.6%), meningitis or sepsis (1, 0.4%), COM (2, 0.8%) [78].

3.11. Thailand

3.11.1. Prevalence of OM

The overall prevalence of OM in 2184 primary school children screened for ear disease through audiometry was 3.25% [79]. The prevalence of AOM, OME and COM was 0.69%, 1.14% and 1.74%, respectively (Fig. 6). Risk factors for ear disease were assessed through questionnaire, but no risk factor, including sex, age, recent upper respiratory tract infection, parental smoking and social status, was identified as significant.

Among 76 HIV positive children aged 1 to 15 years, the prevalence of any OM, AOM and COM was 38.1%, 3.9% and 34.2%, respectively [80]. In otorrhoea samples from those children with CSOM, *P. aeruginosa*, *S. aureus* and Hi were the most frequently isolated bacteria (Table 3).

Children with cleft palate are at high risk for diseases of the middle ear. Among 40 Thai children with cleft palate, 72.5% were found to have OME [81].

3.11.2. Microbiology of OM

A prospective study showed that the major pathogens identified in 112 MEF/otorrhoea samples obtained from 3 to 59 month old children were Spn (46%), Hi (35%) and *M. catarrhalis* (11%) [82]. The most frequently isolated Spn serotype was 19 F (26%) followed by serotypes 14 (22%), 3 (15%), 6 (7%) and 23F (7%). Two children had co-infections.

3.11.3. OM complications

Of 24,321 children and adults with OM identified in a retrospective review of hospital records between 1978 and 1990, 87 (0.36%) suffered intra-cranial complications [83]. Of these 59 (68%) were less 20 years of age and 11 (12.6%) were less than 10 years of age. Meningitis was the most common complication, affecting 49% of patients, followed by brain abscess, sinus thrombosis and perisinus abscess.

In a retrospective review of 107 hospital medical records between 1985 and 2005 in children less than 15 years of age with brain abscess, COM was the predisposing factor in 22.4% of cases, second only to congenital heart disease as the leading cause [84].

3.12. Vietnam

3.12.1. Prevalence of OM

Two articles describing the same cross-sectional community-based prevalence survey were retrieved [85,86]. A total of 3300 children between 6 months and 10 years of age living in a rural or an urban commune in southern Vietnam were assessed in 1995 by otoscopic examination and tympanometry. Overall prevalence of COM was 2.1%, prevalence of sequelae OM was 4.1% and prevalence of SOM was 7.1%. The highest SOM prevalence was observed in children who were 2 years of age (22%). A total of 140 ears were perforated. Ear drum atrophy and retraction were observed more frequently in rural than urban-based children. SOM was significantly more prevalent during the rainy season than during the dry season.

An unpublished survey (Dr NguyenT Hoai An) of 1168 children between 1 and 14 years of age conducted in Hanoi in 2003, showed that the overall prevalence of SOM was 8.9% (Fig. 7). SOM was more prevalent in the cold season than in the hot season (16.09% versus 9.84%, respectively). SOM was also significantly associated with birth weight <2.500 kg (17.82% versus 9.22% in children with birth weight ≥2.500 kg) and bottle feeding (21.62% versus 9.78% in breast fed children).

3.12.2. Hospital data

AOM presentations to Hospital Paediatric No. 2 in Ho Chi Minh city numbered between 3946 and 4903 between 2004 and 2007 (unpublished, Dr Nguyen V Thuc). The number of presenting

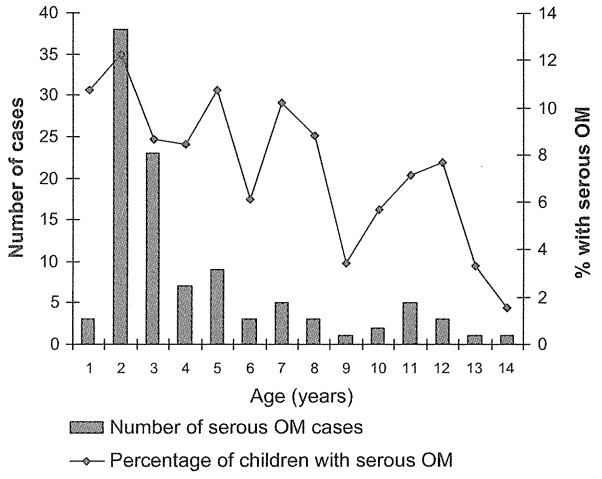


Fig. 7. SOM prevalence by age in 1168 1–14 year olds in Hanoi, 2003 (unpublished, Dr NguyenT Hoai An).

patients admitted to hospital ranged between 131 and 236 each year.

3.12.3. Microbiology of OM

Pathogens and antimicrobial resistance patterns were assessed in 114 children between 1 month and 15 years of age with CSOM in the ENT Hospital in Ho Chi Minh City in 2009 (unpublished, Dr Nguyen MHHon). The most commonly identified pathogens were *P. aeruginosa*, *Spn* and *S. aureus* (Table 3). Resistance of *Spn* isolates to beta-lactams was widespread (93% PRSP) but sensitivity to vancomycin and some quinolones was maintained.

4. Discussion

The available data collated in this review confirms that OM is a common disease of childhood in most Asia Pacific countries, with epidemiological and microbiological features that are with some exceptions, similar to countries outside of the region. Overall however, the disease burden is not well described, highlighting the need for new prospective epidemiological studies to quantify the impacts of OM on children and families. Data from some countries were limited to only small studies, or retrospective studies using medical records. In general comparisons between countries are difficult to make due to differences in study design and methods.

Of the countries we studied, four are classified by WHO as 'High' CSOM prevalence countries (2–4% prevalence): Thailand, Philippines, Malaysia and Vietnam [6]. Australian Aborigines are classified as 'Highest', defined as CSOM prevalence greater than 4% [6]. These rates of CSOM were unable to be verified in the studies reviewed, with the exception of Aboriginal Australians and the Philippines. In a national survey, overall CSOM prevalence in Indonesia was noted to be 5.4% [32], placing Indonesia among WHO-defined 'Highest' prevalence countries.

In non-Aboriginal cohorts of school age children, OM prevalence varied, being as low as 3.25% in Thai children, 12.23% in the Philippines and was higher in HIV positive children (38.1%) in children with HIV. OME in school age children was similarly variable, ranging between 1.14% and 13.8%. In most countries, prevalence/incidence and service utilisation were highest in children between 2 and 5 years of age. Differences in OM prevalence between countries may be due in part to differences in study design, screening methods and definitions of otitis syndromes. The apparently very low rate of ear disease in Thai children needs further confirmation given that this country is rated as a 'High' CSOM prevalence country by WHO.

The burden of OM disease was substantially higher in Pacific Island children living in New Zealand, and was highest in indigenous Australians. In a prospective community-based study the prevalence of OME was also observed to be high in Pacific Island children living in New Zealand [64], but this was not demonstrated in a retrospective review of medical records [62]. Given that clinic attendance rates in Pacific Island children are low [64], it is likely that OM in this group was under-reported using medical record review for case identification. In Aboriginal Australians the percentage of young children (less than 3 years of age) with any OM exceeded 90% and the percentage with any perforation was around 24%. These data confirm the high disease burden in these at-risk groups.

In countries with available data, the annual costs of treating OM are substantial. In countries without national health reimbursement systems such as the Philippines, this economic burden is more likely to rest with families. In developing countries significant investment is needed to provide the medical facilities and staff needed to detect and treat ear disease in children if long term hearing deficits and other sequelae are to be prevented.

Spn and Hi dominated as the primary causes of AOM in all studies, followed by *M. catarrhalis* and *S. aureus*, which is in line with findings in countries outside of the Asia-Pacific region [8]. When tested, PRSP rates varied by country and between studies, but were most frequently isolated in Thailand where in one study 95.8% of Spn isolated from otorrhoea samples were PRSP. These observations are consistent with data from the region [11,12].

Few studies assessed serotype distribution of Spn isolates from MEF. Studies in Japan, Thailand and Australia (post-PCV7) identified serotype 19F as one of the most frequently identified serotypes, followed by serotypes 23F and 6B in Japan, serotype 14 in Thailand [82] and serotypes 19A and 16F in indigenous Australians [28]. Serotype replacement in AOM following universal PCV7 vaccination has been demonstrated in the United States [9,87]. The only study to assess serotype evolution post-PCV7 introduction was a small study in Australia that showed different serotype distribution in a vaccinated cohort [28]. Although too small to be broadly applicable, this study is suggestive that post-PCV7 changes in AOM epidemiology are likely to occur in Australia. We identified no other studies that addressed potential serotype replacement in AOM post PCV7 introduction.

Vaccination with PCV7 significantly reduced the incidence of all-cause AOM by 7.0% in an efficacy trial conducted in the United States. In efficacy trials conducted in the United States and Finland, PCV7 significantly reduced AOM caused by vaccine serotypes by 57–64.7% [14,15]. An 11-valent pneumococcal vaccine conjugated to Protein D showed statistically significant reductions in all-cause AOM (33.6% reduction), AOM due to vaccine serotypes (57.6% reduction) and AOM due to Hi (35.6% reduction) [7]. In Australia, hospitalisations due to myringotomy and tympanostomy tube placement reduced significantly in the years after introduction of PCV7, with the most impact observed in children less than 1 years of age (23% reduction) [27]. Together these data point to potentially important impacts of vaccination on OM prevention. This review indicates that most countries in the Asia Pacific region stand to benefit by introduction of PCVs.

Prospective community-based prevalence studies to assess AOM disease burden are lacking in Indonesia and Singapore, and information on AOM aetiology are lacking in Malaysia, Philippines, Singapore, Vietnam, NZ and in non-Aboriginal Australians. In countries with PCV vaccination policies in place, ongoing assessment of AOM aetiology and serotype would allow evaluation of vaccine impacts and the need for policy changes to move to new vaccines that provide broader coverage. Nevertheless, these types of studies may not reflect research priorities and capacity in individual countries in the region.

5. Conclusion

The available evidence suggests an important burden of disease and economic cost associated with OM in most Asia Pacific countries. Most AOM is caused by Spn and Hi, potentially preventable by vaccination. Large, prospective community-based studies are needed to better assess the disease burden, including evaluation of Spn serotypes implicated in OM. Data from these types of studies will provide an indication of the potential benefits of pneumococcal vaccination in individual countries, and will be important to track vaccine impacts in terms of the incidence and aetiology of OM. AOM prevention through vaccination may also provide a means of reducing antibiotic use and controlling antibiotic-resistant disease in children. This review highlights the need for additional research, and provides a basis on which to build and develop regional guidelines for OM management.

Role of the funding source

This paper originated from meeting presentations and discussions among Asia Pacific ENT experts held on 28 February 2010, Singapore. Funding for this meeting and for medical writing of this paper was provided by an unrestricted educational grant from GlaxoSmithKline (GSK) to the AP ENT Expert Panel. Dr Joanne Wolter received payment for her role in assisting in preparation of the manuscript from GSK. GSK was not involved in the editorial direction of this paper.

Conflict of interest

MM has received institutional support from GSK for travel to scientific meetings. GNL has received support from GSK for travel to scientific meetings, board membership and consultancy fees, and has received payment for lectures and for activities related to her role as the principal investigator in an epidemiological study sponsored by GSK. Institutional grants have been made by GSK for development of educational presentations. SV has received payment for lectures from GSK. NS has received grants from GSK for work unrelated to this manuscript. PCW has received an honorarium from GSK for the work pertaining to this manuscript. SSMH, NY, HKKY, RDR and NTND declare no conflict of interest.

Acknowledgements

The authors thank Dr Nguyen T Hoai An for providing data on serous OM prevalence in Hanoi; Dr Nguyen V Thuc for data on AOM in hospital Peadiatric No 2 in Ho Chi Minh City; Dr Nguyen M HaoHon for pathogens and antimicrobial resistance data in Ho Chi Minh City; Drs AP Opulencia TL Jimenez, M. Bautista from the Philippines for AOM prevalence in children with rhinitis, Dr S.P. Wiertsema from Australia for nasopharyngeal carriage data in Western Australia, and Dr Joanne Wolter for assistance in preparation of the manuscript.

References

[1] J.O. Klein, The burden of otitis media, Vaccine 19 (2000) S2–S8.
[2] D.W. Teele, J.O. Klein, B. Rosner, Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study, J. Infect. Dis. 160 (1989) 83–94.
[3] D. Greenberg, N. Bilenko, Z. Liss, T. Shagan, O. Zamir, R. Dagan, The burden of acute otitis media on the patient and the family, Eur. J. Pediatr. 162 (2003) 576–581.
[4] C.D. Bluestone, Clinical course, complications and sequelae of acute otitis media, Pediatr. Infect. Dis. J. 19 (2000) S37–S46.
[5] T.E. O'Connor, C.F. Perry, F.J. Lannigan, Complications of otitis media in indigenous and non-indigenous children, Med. J. Aust. 191 (2009) S60–S64.
[6] J. Acuin, Chronic Suppurative Otitis Media. Burden of Illness and Management Options, World Health Organization, Geneva, Switzerland, 2004.
[7] R. Prymula, P. Peeters, V. Chrobok, P. Kriz, E. Novakova, E. Kaliskova, et al., Pneumococcal capsular polysaccharides conjugated to protein d for prevention of acute otitis media caused by both *Streptococcus pneumoniae* and non-typable *Haemophilus influenzae*: a randomised double-blind efficacy study, Lancet 367 (2006) 740–748.
[8] E. Leibovitz, M.R. Jacobs, R. Dagan, *Haemophilus influenzae*: a significant pathogen in acute otitis media, Pediatr. Infect. Dis. J. 23 (2004) 1142–1152.
[9] J.R. Casey, M.E. Pichichero, Changes in frequency and pathogens causing acute otitis media in 1995–2003, Pediatr. Infect. Dis. J. 23 (2004) 824–828.
[10] H.M. Massa, A.W. Cripps, D. Lehmann, Otitis media: viruses, bacteria, biofilms and vaccines, Med. J. Aust. 191 (2009) S44–S49.
[11] N.Y. Lee, J.H. Song, S. Kim, K.R. Peck, K.M. Ahn, S.I. Lee, et al., Carriage of antibiotic-resistant pneumococci among Asian children: a multinational surveillance by the Asian Network for Surveillance of Resistant Pathogens (ANSORP), Clin. Infect. Dis. 32 (2001) 1463–1469.
[12] T. Gottlieb, P.J. Collignon, J.M. Robson, J.C. Pearson, J.M. Bell, Prevalence of antimicrobial resistances in *Streptococcus pneumoniae* in Australia, 2005: Report from the Australian Group on Antimicrobial Resistance, Commun. Dis. Intell. 32 (2008) 242–249.
[13] J.B. Boswell, T.G. Nienhuys, Patterns of persistent otitis media in the first year of life in Aboriginal and non-Aboriginal infants, Ann. Otol. Rhinol. Laryngol. 105 (1996) 893–900.
[14] S. Black, H. Shinefield, B. Fireman, E. Lewis, P. Ray, J.R. Hansen, et al., Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group, Pediatr. Infect. Dis. J. 19 (2000) 187–195.
[15] J. Eskola, T. Kilpi, A. Palmu, J. Jokinen, J. Haapakoski, E. Herva, et al., Efficacy of a pneumococcal conjugate vaccine against acute otitis media, N. Engl. J. Med. 344 (2001) 403–409.
[16] T. Kilpi, H. Ahman, J. Jokinen, K.S. Lankinen, A. Palmu, H. Savolainen, et al., Protective efficacy of a second pneumococcal conjugate vaccine against pneumococcal acute otitis media in infants and children: randomized, controlled trial of a 7-valent pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine in 1666 children, Clin. Infect. Dis. 37 (2003) 1155–1164.
[17] S. Begg, T. Vos, B. Barker, C. Stevenson, L. Stanley, A. Lopez, The Burden of Disease and Injury in Australia 2003, Australian Institute of Health and Welfare; PHE 82, Canberra, 2007.
[18] Report by Access Economics Pty Limited for GlaxoSmithKline, The Cost Burden of Otitis Media in Australia, Perth, 2009.
[19] P.S. Morris, A systematic review of clinical research addressing the prevalence, aetiology, diagnosis, prognosis and therapy of otitis media in Australian aboriginal children, J. Paediatr. Child Health 34 (1998) 487–497.
[20] J. Boswell, Presentation of early otitis media in 'top end' Aboriginal infants, Aust. N. Z. J. Public Health 21 (1997) 100–102.
[21] J.B. Boswell, T.G. Nienhuys, Onset of otitis media in the first eight weeks of life in aboriginal and non-Aboriginal Australian infants, Ann. Otol. Rhinol. Laryngol. 104 (1995) 542–549.
[22] K.B. Gibney, P.S. Morris, J.R. Carapetis, S.A. Skull, H.C. Smith-Vaughan, E. Stubbs, et al., The clinical course of acute otitis media in high-risk Australian Aboriginal children: a longitudinal study, BMC Pediatr. 5 (2005) 16.
[23] P.S. Morris, A.J. Leach, P. Silberberg, G. Mellon, C. Wilson, E. Hamilton, et al., Otitis media in young Aboriginal children from remote communities in northern and central Australia: a cross-sectional survey, BMC Pediatr. 5 (2005) 27.
[24] C.J. Williams, H.L. Coates, E.M. Pascoe, Y. Axford, I. Nannup, Middle ear disease in Aboriginal children in Perth: analysis of hearing screening data, 1998-2004, Med. J. Aust. 190 (2009) 598–600.
[25] H. Gunasekera, S. Knox, P. Morris, H. Britt, P. McIntyre, J.C. Craig, The spectrum and management of otitis media in Australian indigenous and nonindigenous children: a national study, Pediatr. Infect. Dis. J. 26 (2007) 689–692.
[26] J. Rothstein, R. Heazlewood, M. Fraser, Health of Aboriginal and Torres Strait Islander children in remote Far North Queensland: findings of the paediatric outreach service, Med. J. Aust. 186 (2007) 519–521.
[27] A. Jardine, R.I. Menzies, S.L. Deeks, M.S. Patel, P.B. McIntyre, The impact of pneumococcal conjugate vaccine on rates of myringotomy with ventilation tube insertion in Australia, Pediatr. Infect. Dis. J. 28 (2009) 761–765.
[28] G.A. Mackenzie, J.R. Carapetis, A.J. Leach, P.S. Morris, Pneumococcal vaccination and otitis media in Australian Aboriginal infants: comparison of two birth cohorts before and after introduction of vaccination, BMC Pediatr. 9 (2009) 14.
[29] S.P. Wiertsema, L. Kirkham, K. Corscadden, E. Mowe, J.M. Bowman, P. Jacoby, et al., Predominance of nontypeable *Haemophilus influenzae* in acute otitis media following introduction of a 3 + 0 pneumococcal conjugate vaccine schedule, Vaccine 29 (32) (2011) 5163–5170.
[30] P.S. Taylor, I. Faeth, M.K. Marks, C.B. Del Mar, S.A. Skull, M.L. Pezzullo, et al., Cost of treating otitis media in Australia, Expert Rev. Pharmacoecon. Outcomes Res. 9 (2009) 133–141.
[31] I. Brook, G. Santosa, Microbiology of chronic suppurative otitis media in children in Surabaya, Indonesia, Int. J. Pediatr. Otorhinolaryngol. 31 (1995) 23–28.
[32] Situation Review and Update on Deafness, Hearing Loss and Intervention Programmes, World Health Organization, Regional Office for South-Easr Asia, New Delhi, 2007.
[33] R. Suwento, H. Hendamin, Prevention of deafness program in Indonesia, Otorhinolaryngol. Indon. Daftar Isi XXX (2000) 28–32.
[34] I. Mayangsari, R. Restuti, N. Irawati, Departmen THT, FKUI/RS Cipto Mangunkusumo Jakarta. Hubungen reaksi hipersensitivitas tipe i pada anak dengan otitis media efusi, Otorhinolaryngol. Indon. Daftar Isi XXXVIII (2008) 1–13.

[35] M. Hotomi, N. Yamanaka, T. Samukawa, M. Suzumot, A. Sakai, J. Shimada, et al., Treatment and outcome of severe and non-severe acute otitis media, Eur. J. Pediatr. 164 (2005) 3–8.
[36] H. Ogawa, Otitis media with effusion: a study of 346 cases in an outpatient clinic, Nippon Jibiinkoka Gakkai Kaiho 105 (2002) 863–872.
[37] N. Yamanaka, M. Hotomi, The current status of infectious diseases in otorhinolaryngology with special emphasis on acute otitis media and treatment strategy for antimicrobial resistant pathogens, Pract. Otol. (Kyoto) 93 (2000) 431–437.
[38] S. Mitsuko, I. Mihoko, T. Shin, O. Kenji, U. Kimiko, Identification of bacterial strain at each episode of recurrent acute otitis media, J. Otolaryngol. Jpn. 103 (2000) 19–23.
[39] E. Hiroko, S. Mitsuko, I. Mihoko, Recent clinical characteristics of prolonged acute lower respiratory tract infection in small children: frequent complications of intractable acute otitis media, Jpn. J. Chemother. 47 (1999) 30–34.
[40] N. Yamanaka, M. Hotomi, R. Sugita, Disease-burden of acute otitis media on children and estimated cost-effectiveness of pneumococcal conjugate vaccine in Japan, J. Pediatr. Infect. Dis. Immunol. 1 (2009) 37–48.
[41] H. Yoshimitsu, Bacteriological studies of otorhinolaryngial infections in our department, Otol. Fukuoka 46 (2000) S177–S179.
[42] M. Hotomi, D.S. Billal, Y. Kamide, K. Kanesada, Y. Uno, F. Kudo, et al., Serotype distribution and penicillin resistance of *Streptococcus pneumoniae* isolates from middle ear fluids of pediatric patients with acute otitis media in Japan, J. Clin. Microbiol. 46 (2008) 3808–3810.
[43] H. Kamiya, T. Kato, T. Togashi, S. Iwata, T. Kurosaki, S. Baba, et al., Epidemiological survey of pneumococcus serotypes in pediatric patients with acute suppurative otitis media, Kansenshogaku Zasshi. 81 (2007) 59–66.
[44] M. Hotomi, K.F.A. Sakai, D.S. Billal, J. Shimada, M. Suzumoto, N. Yamanaka, Antimicrobial resistance in *Haemophilus influenzae* isolated from the nasopharynx among Japanese children with acute otitis media, Acta Otolaryngol. 126 (2006) 130–137.
[45] M. Sawako, N. Takashi, K. Hitoshi, Drug resistance of *Streptococcus pneumoniae* and clinical outcome in children with acute otitis media, Pract. Otol. (Kyoto) 97 (2004) 15–19.
[46] K. Mitsuhiro, K. Shingo, S. Yasuhiko, M. Ichiro, S. Keisuke, K. Hideyuki, Clinical observation of bacterial strain and effect of Cefditoren Pivoxil (CDTR) in acute otitis media, Otol. Jpn. 14 (2004) 668–675.
[47] T. Tomizo, A. Yuko, K. Yutaka, K. Jun'ichi, S. Yoshihiro, T. Minoru, et al., Clinical studies on acute otitis media in children under 10 years of age in Sendai City, Otol. Jpn. 9 (1999) 561–565.
[48] K. Fumiyo, T. Takuya, Current status of therapy for otitis media in our hospital, especially therapy for children affected with intractable otitis media required hospitalization from 1990 to 2000, Otol. Jpn. 12 (2002) 160–165.
[49] S. Kikuta, M. Ushio, Y. Fujimaki, K. Kaga, Factors associated with the presence of drug-resistant bacteria and recurrent acute otitis media in children—a study in a private clinic, Acta Otolaryngol. Suppl. (2007) 5–8.
[50] Y. Uno, Surveillance of susceptibility to antibacterial agents of *Streptococcus pneumoniae* isolated from middle-ear acute otitis media in infants and children, Jpn. J. Chemother. 50 (2002) 854–869.
[51] T. Eiko, T. Emiko, F. Noriko, H. Naomi, M. Reiko, K. Satoshi, et al., Clinical and immunological study of acute purulent otitis media in young children, J. Tokyo Women's Med. Univ. 70 (2000) E74–E79.
[52] U. Yoshifumi, W. Shinsuke, N. Yoshihito, M. Toshiharu, Clinical, epidemiological, and bacteriological study on pneumococcal acute otitis media in infants and children, Jpn. J. Chemother. 47 (1999) 387–395.
[53] Y. Uno, Clinical, epidemiological, and bacteriological study of acute otitis media caused by *Haemophilus influenzae* in infants and children, Jpn. J. Chemother. 49 (2001) 355–362.
[54] K. Tanaka, T. Ichikawa, J. Yano, Acute otitis media due to *Haemophilus influenzae* with antibiotic resistance: experience of a tertiary hospital in Tokyo City, Int. J. Pediatr. Otorhinolaryngol. 73 (2009) 817–819.
[55] K. Tanaka, T. Matsui, T. Tachibana, T. Ichikawa, Y. Imada, J. Yano, Factors associated with acute otitis media in children due to penicillin intermediately resistant *Streptococcus pneumoniae*, Int. J. Pediatr. Otorhinolaryngol. (July) (2009).
[56] A. Yumiko, K. Satoru, I. Yoichi, I. Yukiko, Clinical study of acute mastoiditis in 11 children, Oto-Rhino-Laryngol. Tokyo 43 (2000) 43–48.
[57] A. Saim, L. Saim, S. Saim, B.H. Ruszymah, A. Sani, Prevalence of otitis media with effusion amongst pre-school children in Malaysia, Int. J. Pediatr. Otorhinolaryngol. 41 (1997) 21–28.
[58] Institute for Public Health, Findings of the National Hearing and Ear Disorders Survey, Ministry of Health of Malaysia, 2009, , ISBN: 978-983-3887-62-0.
[59] R. Indudharan, J.A. Haq, S. Aiyar, Antibiotics in chronic suppurative otitis media: a bacteriologic study, Ann. Otol. Rhinol. Laryngol. 108 (1999) 440–445.
[60] Y.T. Long, R. Mahmud, A. Sani, L. Saim, Complications of otitis media requiring surgical intervention, Asian J. Surg. 25 (2002) 170–174.
[61] M.W. Tilyard, S.M. Dovey, S.A. Walker, Otitis media treatment in New Zealand general practice, N. Z. Med. J. 110 (1997) 143–145.
[62] L. Salkeld, K. Matthews, B. Gribben, Otitis media in young children: a continuing health issue in New Zealand – a retrospective study to estimate the incidence of acute otitis media in New Zealand children, in: 12th Asia-Oceania Otolaryngology Head & Neck Congress, Auckland, New Zealand, 2011.
[63] R.J. Milne, S. Vander Hoorn, Burden and cost of hospital admissions for vaccine-preventable paediatric pneumococcal disease and non-typable *Haemophilus influenzae* otitis media in New Zealand, Appl. Health Econ. Health Policy 8 (2010) 281–300.
[64] J.E. Paterson, S. Carter, J. Wallace, Z. Ahmad, N. Garrett, P.A. Silva, Pacific islands families study: the prevalence of chronic middle ear disease in 2-year-old pacific children living in New Zealand, Int. J. Pediatr. Otorhinolaryngol. 70 (2006) 1771–1778.
[65] J.E. Paterson, S. Carter, J. Wallace, Z. Ahmad, N. Garrett, P.A. Silva, Pacific islands families study: risk factors associated with otitis media with effusion among pacific 2-year-old children, Int. J. Pediatr. Otorhinolaryngol. 71 (2007) 1047–1054.
[66] P. Watson, L. Voss, C. Barber, R. Aickin, D. Bremner, D. Lennon, The microbiology of chronic otitis media with effusion in a group of Auckland children, N. Z. Med. J. 109 (1996) 182–184.
[67] D. Ruske, J. Wilson, I. Stewart, Antibiotic resistance and otitis media with effusion in Dunedin, N. Z. Med. J. 112 (1999) 367–368.
[68] N. Martinez, M. Lopez, F. Trinidad, WHO Ear and Hearing Disorders Survey of Quezon Province, 2001.
[69] C. Yabut, J.A. Santos, Prevalence of hearing loss and its various etiologies in primary school aged children in four public schools in General Santos City, in: 4th Asia Pacific Congress on Deafness, Manila, Philippines, 1994.
[70] Prevalence of Hearing Impairment in the Philippines. Department of Education, Culture, and Sports.
[71] M. Lucero, AOM in Filipino children with pneumonia; a nested study within an efficacy trial of pneumoccocal conjugate vaccine, in: International Symposium on Pneumococci and Pneumococcal Diseases, Tel Aviv, Israel, 2010.
[72] C. Navarro-Locsin, Economic cost of otitis media in the Philippines: lessons for a developing country, in: 6th Extraordinary International Symposium on Recent Advances in OM, Seoul, Korea, 2009.
[73] A.H.C. Loy, A.L. Tan, P.K.S. Lu, Microbiology of chronic suppurative otitis media in Singapore, Singapore Med. J. 43 (2002) 296–299.
[74] C.H. Chen, C.J. Lin, Y.H. Hwang, C.J. Ku, Epidemiology of otitis media in Chinese children, Clin. Otolaryngol. Allied Sci. 28 (2003) 442–445.
[75] P.C. Wang, C.J. Chang, C.H. Chang, L.J. Chuang, The economic impacts of acute otitis media in Taiwan, in: ISPOR 12th Annual European Congress, Paris, France, October 24–27, 2009.
[76] P.C. Wang, K.T. Chu, A national survey on the prevalence of pediatric acute otitis media, in: Harold F Schuknecht Society Meeting, Boston, MA, USA, June 11–13, 2006.
[77] P.C. Wang, The impact of AOM in Taiwan: a review of health outcomes, in: The 6th Asian Society for Pediatric Research & 51st Annual Meeting of Taiwan Pediatric Association, Taipei, Taiwan, April 16, 2010.
[78] W.C. Li, N.C. Chiu, C.H. Hsu, K.S. Lee, H.K. Hwang, F.Y. Huang, Pathogens in the middle ear effusion of children with persistent otitis media: implications of drug resistance and complications, J. Microbiol. Immunol. Infect. 34 (2001) 190–194.
[79] S. Chayarpham, J. Stuart, V. Chongsuvivatwong, S. Chinpairoj, A. Lim, A study of the prevalence of and risk factors for ear diseases and hearing loss in primary school children in Hat Yai, Thailand, J. Med. Assoc. Thai. 79 (1996) 468–472.
[80] K. Akkaratham, N. Sonsuwan, P. Oberdorfer, Otitis media among HIV-infected children in Maharaj Nakhon Chiang Mai Hospital, Thailand 2007, Thai. J. Pediatr. 47 (2007) 127–133.
[81] N. Sonsuwan, Y. Sumitsawan, W. Leelakitsup, V. Vaseenon, Otitis media with effusion in cleft palate patients, Thai. J. Otolaryngol. Head Neck Surg. 6 (2005) 110–114.
[82] P. Intakorn, N. Sonsuwan, S. Noknu, G. Moungthong, L. Peruski, J. Pircon, et al., Bacterial aetiology and antibiotic resistance of acute otitis media in young children in Thailand, in: 6th Extraordinary International Symposium on Recent Advances in Otitis Media (ISRAOM), Seoul, Korea, May 6–10, 2009.
[83] J. Kangsanarak, N. Navacharoen, S. Fooanant, K. Ruckphaopunt, Intracranial complications of suppurative otitis media: 13 years' experience, Am. J. Otol. 16 (1995) 104–109.
[84] N. Auvichayapat, P. Auvichayapat, S. Aungwarawong, Brain abscess in infants and children: a retrospective study of 107 patients in northeast Thailand, J. Med. Assoc. Thai. 90 (2007) 1601–1607.
[85] V.H. Balle, M. Tos, H.S. Dang, T.S. Nhan, T. Le, K.P. Tran, et al., Prevalence of chronic otitis media in a randomly selected population from two communes in southern Vietnam, Acta Otolaryngol. Suppl. 543 (2000) 51–53.
[86] H.S. Dang, T.S. Nhan, T. Le, K.P. Tran, T.T. Tran, M.T. Vu, et al., Point prevalence of secretory otitis media in children in southern Vietnam, Ann. Otol. Rhinol. Laryngol. 107 (1998) 406–410.
[87] S.L. Block, J. Hedrick, C.J. Harrison, R. Tyler, A. Smith, R. Findlay, et al., Community-wide vaccination with the heptavalent pneumococcal conjugate significantly alters the microbiology of acute otitis media, Pediatr. Infect. Dis. J. 23 (2004) 829–833.
[88] S.A. Skull, P.S. Morris, A. Yonovitz, R.G. Attewell, V. Krause, A.J. Leach, et al., Middle ear effusion: rate and risk factors in Australian children attending day care, Epidemiol. Infect. 123 (1999) 57–64.
[89] C.F. Chen, K.G. Wu, M.C. Hsu, R.B. Tang, Prevalence and relationship between allergic diseases and infectious diseases, J. Microbiol. Immunol. Infect. 34 (2001) 57–62.
[90] P.S. Morris, A.J. Leach, S. Halpin, G. Mellon, G. Gadil, C. Wigger, et al., An overview of acute otitis media in Australian Aboriginal children living in remote communities, Vaccine 25 (2007) 2389–2393.
[91] S. Motohiro, W. Masaharu, K. Aya, O. Masamichi, Recurrent otitis media in pediatric patients – the effect of tympanostomy tube placement, Otol. Fukuoka 52 (2006) 38–45.
[92] U. Hirotaka, U. Hiroya, M. Hiroshi, Infecting organisms in pediatric acute otitis media and drug susceptibility, Oto-Rhino-Laryngol. Tokyo 48 (2005) 312–319.

[93] H. Kensaku, M. Eiken, S. Takema, T. Hiromi, K. Hiroya, Treatment of acute otitis media caused by penicillin resistant *Streptococcus pneumoniae*, Pract. Otol. (Kyoto) 96 (2003) 509–515.
[94] Y. Hisakazu, S. Mitsuko, E. Hiroko, T. Reiko, K. Toshimitsu, Acute otitis media associated with influenza virus infection, Jpn. J. Chemother. 51 (2003) 419–424.
[95] S. Rin'ya, D. Koichi, N. Masao, N. Takahiko, T. Mikio, W. Hiroshi, et al., A clinicobacteriologic study on clavulanic acid/amoxicillin in pediatric acute otitis media, Jpn. J. Antibiot. 52 (1999) 595–612.
[96] K. Hitome, S. Harumi, Changes in causative bacteria of pediatric acute otitis media, Plact. Oto-Rhino-Laryngol. (Kyoto) 99 (2006) 635–642.
[97] O. Kazunori, Clinical efficacy of Cefzon on acute otitis media in children, Pract. Otol. (Kyoto) 92 (1999) 299–307.
[98] A. Yoshihiro, S. Atsuro, M. Kiyoshi, M. Hiroyuki, H. Tomoyuki, U. Kimiko, Antimicrobial resistance and susceptibility of pathogens causing acute purulent pediatric otitis media, Jpn. J. Chemother. 49 (2001) 606–610.
[99] M. Toshihiro, Y. Eiji, Acute otitis media in pediatric practice, J. Jpn. Pediatr. Soc. 104 (2000) 551–555.
[100] T. Tseng, L. Chen, P.C. Wang, C. Huang, Y. Chen, Clinical report on the bacteriology of acute otitis media in childhood, Fu-Jen J. Med. 5 (2007) 1–8.
[101] A. Shiao, Y. Guo, S. Hsieh, T. Tsai, Bacteriology of medically refractory acute otitis media in children: a 9-year retrospective study, Int. J. Pediatr. Otorhinolaryngol. 68 (2004) 759–765.
[102] P. Ayson, J. Lopez, E. Llanes, Chronic suppurative otitis media: bacteriology and drug sensitivity patterns at the Quirino Memorial Medical Center (2004–2005): a preliminary study, Philipp. J. Otolaryngol. Head Neck Surg. 21 (2006) 20–23.
[103] J. Hwang, C. Chu, T. Liu, Changes in bacteriology of discharging ears, J. Laryngol. Otol. 116 (2002) 686–689.
[104] P.C. Wang, Y. Chang, L.J. Chuang, H. Su, C. Li, Incidence and recurrence of acute otitis media in Taiwan's pediatric population, Clinics 66 (3) (2011) 395–399.

Epidemiol. Infect. (2012), **140**, 1111–1121. © Cambridge University Press 2011
doi:10.1017/S0950268811001592

Incidence of childhood pneumonia and serotype and sequence-type distribution in *Streptococcus pneumoniae* isolates in Japan

J. TANAKA[1]*, N. ISHIWADA[1], A. WADA[2], B. CHANG[2], H. HISHIKI[1], T. KUROSAKI[3,4] AND Y. KOHNO[1]

[1] *Department of Pediatrics, Graduate School of Medicine, Chiba University, Chiba City, Japan*
[2] *Department of Bacteriology, National Institute of Infectious Diseases, Tokyo, Japan*
[3] *Department of Pediatrics, Chiba Municipal Kaihin Hospital, Chiba city, Japan*
[4] *Kurosaki Child Clinic, Chiba City, Japan*

(*Accepted 28 July 2011; first published online 30 August 2011*)

SUMMARY

The 7-valent pneumococcal conjugate vaccine (PCV7) is reported to decrease the incidence of community-acquired pneumonia (CAP) in children. To determine the annual incidence of CAP before the introduction of PCV7, we counted the number of children hospitalized with CAP between 2008 and 2009 in Chiba City, Japan. We investigated serotype and multilocus sequence typing (MLST) for *Streptococcus pneumoniae* isolates in CAP cases. The annual incidence of hospitalized CAP in children aged <5 years was 17·6 episodes/1000 child-years. In 626 episodes, *S. pneumoniae* was dominant in 14·7% and 0·8% of sputum and blood samples, respectively. The most common serotypes were 6B, 23F and 19F. The coverage rates of PCV7 were 66·7% and 80% in sputum samples and blood samples, respectively. MLST analysis revealed 37 sequence types. Furthermore, 54·1% of the sputum isolates and 40% of the blood isolate were related to international multidrug-resistant clones.

Key words: Antibiotic resistance, community-acquired pneumonia, immunization (vaccination), incidence, *Streptococcus pneumoniae* (pneumococcus).

INTRODUCTION

Streptococcus pneumoniae is a frequent aetiological cause of community-acquired pneumonia (CAP) in children. The 7-valent pneumococcal conjugate vaccine (PCV7), introduced in the USA and Europe, has reduced the incidence of invasive pneumococcal disease (IPD) caused by vaccine serotypes (serotypes 4, 6B, 9V, 14, 18C, 19F, 23F) and of carriage of these serotypes [1–4]. Several reports indicate that PCVs are effective against pneumonia [5–7]. Black *et al.* [5] reported that PCV7 reduces the incidence of first episode of clinically diagnosed pneumonia by 6·0%. The rate of all-cause pneumonia hospitalizations in children in the USA aged <2 years decreased by about 35% after the vaccine was licensed [6]. In these studies, bacteraemic pneumococcal pneumonia constituted a minority of the total amount of observed clinical pneumonia. These results indicate that PCV not only prevents invasive pneumococcal pneumonia but also reduces the incidence of all-cause pneumonia. However, little is known about the rate of pneumonia attributable to *S. pneumoniae* and their serotypes.

* Author for correspondence: Dr J. Tanaka, Department of Pediatrics, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba City, Chiba Prefecture, Japan #260-8670. (Email: junko-tanaka@umin.org)

PCV7 was introduced in Japan in February 2010. Surveillance of the population-based incidence of CAP and molecular characterization of isolates causing CAP are fundamental to understanding the impact of PCV7 and to assessing whether the genetic structure of the pneumococcal population changes after implementation of an immunization programme. However population-based studies of CAP in Japanese children are rare.

To estimate bacterial pathogens and to better manage lower respiratory tract infections in children, we examined microbiological specimens of washed sputum according to the Japanese Guidelines for the Management of Respiratory Infectious Diseases [8–13]. Here, we surveyed the incidence of CAP in hospitalized children to obtain baseline data before the introduction of PCV7. We also determined the isolation rate of *S. pneumoniae* in children with CAP using washed sputum and blood samples to estimate the effect of PCV7 on CAP. The isolates were characterized by serotyping and by multilocus sequence typing (MLST).

METHODS

Incidence of CAP and of CAP with pneumococcal bacteraemia in Chiba City

We determined the annual incidence of hospitalized CAP and CAP with pneumococcal bacteraemia in children aged <16 years in Chiba City as follows. We retrospectively counted the total number of patients admitted to 18 hospitals with paediatric wards in and around Chiba City serving the catchment population between 1 April 2008 and 31 March 2009. A questionnaire was sent to 18 hospitals and information was obtained from the clinical records of all of them. We defined CAP as pneumonia that occurred in patients who had not been hospitalized within the past 2 weeks. Acute lower respiratory infection was diagnosed by clinicians at each hospital based on clinical symptoms of one or more of: fever, rapid or difficult breathing, cough and crackle in lung fields on auscultation. Radiographs were taken before admission and the diagnosis of CAP was confirmed by clinicians based on positive radiograph findings at the time of occurrence. Patients with CAP who did not require hospitalization were excluded from this study. The catchment area comprised 944 557 inhabitants, including 140 345 and 42 606 children aged <16 and <5 years, respectively [14].

Rate of *S. pneumoniae* isolated from sputum and blood

We surveyed children who were admitted to six major hospitals in Chiba City. These six hospitals covered 75% of hospitalized children who were diagnosed with CAP within the city during 2005. [15]. Written informed consent was obtained from the parents or guardians of the patients before collecting samples, in accordance with the guidelines of the Institutional Review Board of Chiba University. Demographic and clinical data were collected by paediatricians. Upon admission, blood samples were collected and sputum samples were obtained using a tongue depressor with a light as follows. The tongue was depressed to induce the cough reflex and then sputum was collected using a swab or aspirated into a 1-ml disposable syringe. Sputum samples were washed three times in sterilized saline as described previously [9]. A small portion of washed sputum was homogenized and smeared onto glass slides for Gram staining. Stained smears were judged valid according to Geckler's classification based on the number of leucocytes or alveolar macrophages and squamous or ciliated epithelial cells per low-power field (100x). Smears with Geckler's groups of 4–5 containing >25 leucocytes or macrophages and <25 squamous or ciliated epithelial cells in the low-power microscopic field (100x) were considered adequate. Washed sputum and blood samples were cultured at the microbiology laboratory of each hospital. Pathogens accounting for >50% of the colonies in culture or presenting $>1 \times 10^7$c.f.u./ml of washed sputum were regarded as 'dominant'. *S. pneumoniae* isolates dominant in sputum samples and/or isolates from blood samples were initially stored at −80 °C at each hospital and then sent to Chiba University Hospital and the Department of Bacteriology of the National Institute of Infectious Diseases.

Antimicrobial susceptibility

Antimicrobial susceptibility was tested *in vitro* using broth dilution according to the Clinical and Laboratory Standards Institute guidelines (CLSI M100-S18). Although the CLSI published new breakpoints for penicillin therapy in 2008 (CLSI M100-S18), we used the previously published breakpoints. *S. pneumoniae* was interpreted as susceptible (PSSP), intermediate (PISP), and resistant (PRSP) if the minimum inhibitory concentration (MIC) of penicillin G was ⩽0·06, 0·12–1 and ⩾2 μg/ml, respectively.

Serotyping

Serotypes were determined by the Quellung reaction using antiserum purchased from Statens Serum Institut, Copenhagen, Denmark. We serotyped 6C and 6D using an in-house antiserum and confirmed the results by genetic characterization as described previously [16].

MLST

We performed MLST as described previously [17]. Briefly, internal fragments of each of the seven housekeeping genes, *aroE, gdh, gki, recP, spi, xpt* and *ddl* were amplified by Polymerase chain reaction (PCR) and their sequence types (STs) were determined by reference to the MLST database (http://spneumoniae.mlst.net/). New alleles and allelic profiles were submitted to the database for assignment. The relatedness of isolates and known similar strains in the database were determined by constructing a neighbour-joining tree using the online program, Draw Tree Using Own MLST Data. Relationships among the isolates were determined using eBURST v. 3 software and strains were assigned to clonal complexes (CCs) using the definition of a stringent group, in which all STs share six of seven identical alleles with at least one of the other STs within the group [single-locus variants (SLV)]. We compared STs with those of 43 pneumococcal clones in the Pneumococcal Molecular Epidemiology Network (PMEN; http://www.sph.emory.edu/PMEN/).

Statistical analysis

Data were analysed using PASW Statistics 18 (SPSS Japan Inc., Japan). Associations between underlying diseases and the number of hospitalizations or the results of sputum culture were tested using Fisher's exact test. Correlations between age and isolation rates of pneumococcus and coverage rates of PCV7 were analysed using Pearson's χ^2 test. A P value of $<0{\cdot}05$ was considered statistically significant.

RESULTS

Annual incidence of CAP

During the study period, CAP caused 860 episodes of children being hospitalized. The incidences of CAP in children aged <16 and <5 years were 6·13 and 17·6/1000 child-years, respectively.

Annual incidence of CAP with pneumococcal bacteraemia

Five patients were diagnosed with pneumococcal bacteraemia combined with CAP. The incidences of CAP with pneumococcal bacteraemia in children aged <16 and <5 years were 3·56 and 11·7 episodes/100 000 child-years, respectively.

Isolation of *S. pneumoniae* from sputum and blood culture

A total of 579 children with 626 episodes were admitted to six major hospitals with a diagnosis of CAP. This corresponded to 73% of all CAP episodes occurring in Chiba City during the study period. We obtained sputum and blood samples representing 502 (80·2%) and 544 (86·9%) of the 626 episodes. *S. pneumoniae* was identified and culture-dominant in 175 (27·9%) and 92 (14·7%) sputum samples, respectively. Of five patients with blood samples that were positive for *S. pneumoniae*, one also had a positive sputum culture. The serotypes and STs of the blood and sputum isolates from this patient were identical (serotype 6B, ST90).

Figure 1 shows the age distribution of children with CAP and the results of *S. pneumoniae* identified in sputum and blood cultures. The median age of children with CAP episodes was 1 year. Patients with CAP included 331 (52·9%) children aged <2 years and 230 (36·7%) aged 2–4 years. The median age of children with pneumococcus-positive episodes was also 1 year. *S. pneumoniae* was isolated from the blood of one 2-year-old and four 1-year-old patients. The detection rate of pneumococcus from sputum was the highest in children aged 2–4 years (18·7%), followed by those aged <2 (11·5%) and 5–15 (16·9%) years [statistically not significant, $\chi^2(2)=5{\cdot}92$, $P=0{\cdot}052$].

Of the 579 patients, 215 had one or more underlying diseases, 174 had bronchial asthma, 24 were premature, ten had congenital heart diseases, seven had chromosome anomalies, five had cerebral palsy, and 18 had other diseases. Thirty-seven patients were hospitalized more than once. Multiple hospitalizations were significantly associated with bronchial asthma ($P<0{\cdot}001$), congenital heart disease ($P=0{\cdot}021$) and cerebral palsy ($P=0{\cdot}035$) (Table 1). Underlying diseases and the detection of *S. pneumoniae* from sputum were not significantly related. No one had sequelae with CAP episodes.

Table 1. *Risk of multiple hospitalizations with community-acquired pneumonia based on underlying diseases*

Underlying disease	No. of multiple hospitalizations/ no. with factors (%)	No. of multiple hospitalization/ no. without factors (%)	*P* value*	Relative risk (95% CI)
Bronchial asthma	21/174 (12%)	16/405 (4%)	<0·001	3·06 (1·63–5·71)
Premature birth				
<37 weeks†	3/24 (13%)	34/555 (6%)	0·193	1·07 (0·92–1·25)
<30 weeks	1/8 (13%)	36/571 (6%)	0·412	1·98 (0·31–12·74)
Congenital heart disease	3/10 (30%)	34/569 (6%)	0·021	5·02 (1·85–13·67)
Chromosomal anomaly	1/7 (14%)	36/572 (6%)	0·372	2·27 (0·36–14·32)
Cerebral palsy	2/5 (40%)	35/574 (6%)	0·035	6·56 (2·14–20·12)
Other‡	1/18 (6%)	36/561 (6%)	1·000	0·87 (0·13–5·97)

CI, Confidence interval.
* Fisher's exact test.
† Including preterm birth <30 weeks.
‡ Epilepsy (2), neutropenia (2), achondroplasia (1), acute myeloid leukaemia (during consolidation therapy) (1), bronchiectasis (1), congenital diaphragmatic hernia (1), cretinism (1), gastro-oesophageal reflux disease (1), Kawasaki disease (1), mitochondrial diseases (1), periodic fever syndrome (1), polycystic kidney disease (1), post-cleft lip and palate repair (1), Sotos syndrome (1), tracheal stenosis (1), malnutrition (1).

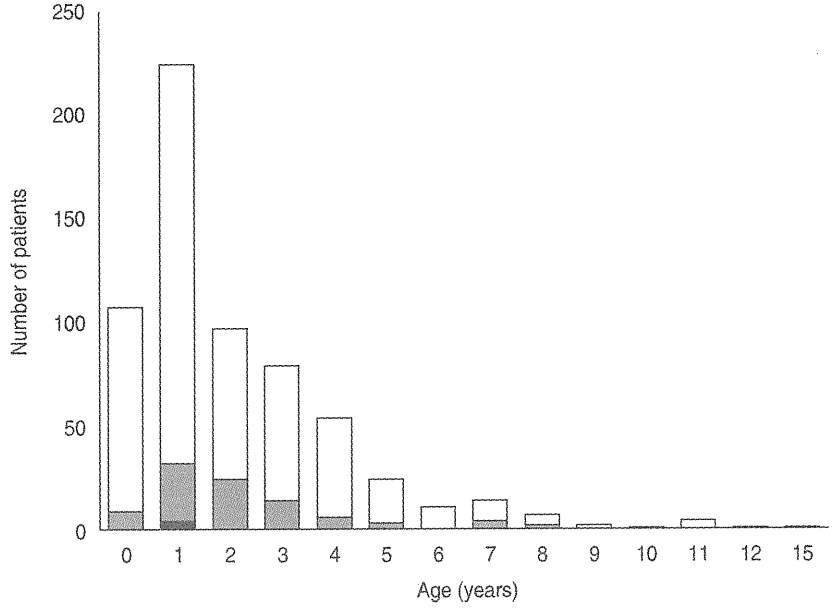


Fig. 1. Age distribution and identification of *Streptococcus pneumoniae* in children hospitalized with community-acquired pneumonia. ▨, *S. pneumoniae* dominantly isolated from sputum; ■, *S. pneumoniae* isolated from blood ($n=626$).

Antimicrobial susceptibility and serotype distribution

Antimicrobial susceptibility and serotypes were tested against 63/92 cultured sputum isolates in which *S. pneumoniae* was the dominant organism and against five blood isolates. Table 2 shows the susceptibility of the *S. pneumoniae* isolates to penicillin G and their serotype distribution. The rates of PISP and PRSP in sputum isolates were 54% and 22%, respectively, and 40% and 40%, respectively, in the blood isolates. Resistance rates in sputum isolates against cefotaxime (MIC $\geqslant 2\,\mu$g/ml), erythromycin (MIC $\geqslant 1\,\mu$g/ml) and clindamycin (MIC $\geqslant 1\,\mu$g/ml) were 4·8%, 92% and 60%, respectively, and 20%, 100% and 60%, respectively, in blood isolates. All isolates were susceptible to meropenem and vancomycin.

Of the 17 identified serotypes, the most frequent in the sputum isolates were 6B (28·6%), 23F (17·5%), and 19F (15·9%) and those in the blood isolates were 6B (60%), 19F (20%), and 19A (20%). Serotype 6C

Table 2. *Serotype distribution and susceptibility of* Streptococcus pneumoniae *isolated from samples obtained from children with community-acquired pneumonia in Japan*

			No. of isolates			
Sample	Coverage rate	Serotype	PSSP	PISP	PRSP	All
Sputum	7-valent (66·7%)	6B	3	9	6	18
		23F		9	2	11
		19F		5	5	10
		14		2		2
		9V	1			1
	10-valent (71·4%)	1	2			2
		7F	1			1
	13-valent (81. 0%)	6A		3	1	4
		3	1			1
		19A	1			1
	Others	6C	1	2		3
		23A		2		2
		35B		2		2
		38	2			2
		15B	1			1
		22F	1			1
		24B	1			1
		Total	15	34	14	63
Blood	7-valent (80%)	6B		2	1	3
		19F			1	1
	13-valent (100%)	19A	1			1
		Total	1	2	2	5

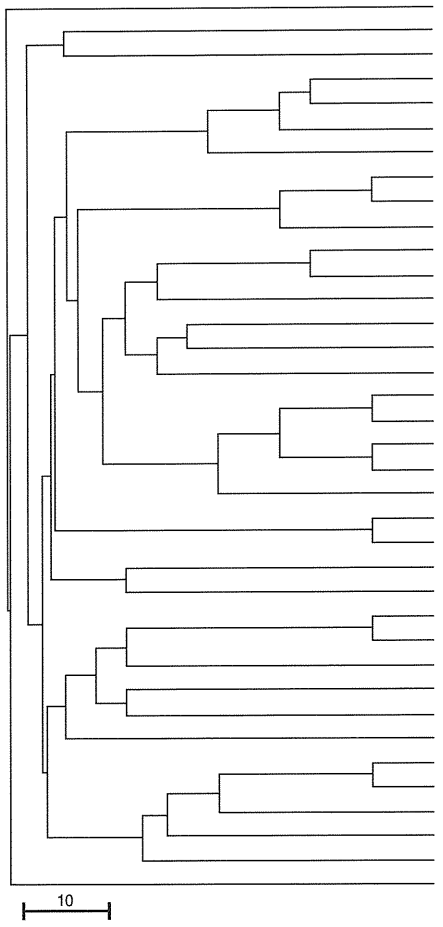
PSSP, Penicillin-susceptible *S. pneumoniae*; PISP, penicillin-intermediate *S. pneumoniae*; PRSP, penicillin-resistant *S. pneumoniae*.

was identified in three sputum isolates. Serotype 6D was not found. The coverage rates of PCV7 were 66·7% and 80·0% in sputum and blood isolates, respectively. The coverage rates in sputum isolates based on age were 65·2%, 73·5% (70·2% in those aged <5 years) and 33·3% in children aged <2, 2–4 and 5–15 years [statistically not significant, $\chi^2(2)=3{\cdot}74$, $p=0{\cdot}154$]. Ten-valent (PCV7 plus additional serotypes 1, 5, 7F), 13-valent (PCV7 plus additional serotypes 1, 3, 5, 6A, 7F. 19A) and investigational 15-valent (PCV7 plus additional serotypes 1, 3, 5, 6A, 7F, 19A, 22F, 33F) PCVs would potentially increase the coverage rates of sputum isolates by 4·7%, 14·3% and 15·8%, respectively. The 13-valent and investigational 15-valent PCVs covered all of the blood isolates.

The serotypes of PSSP in sputum isolates widely varied whereas the 14 PRSP sputum isolates fell into only the following serotypes: 6B (42·9%), 19F (35·7%), 23F (14·3%) and 6A (7·1%). The PISP sputum isolates were represented by eight serotypes with 6B (26·5%), 23F (26·5%), 19F (14·7%) and 6A (8·8%) being the most prevalent. The serotypes of PRSP in blood isolates were also 6B (50%) and 19F (50%), whereas that of PISP isolates was only 6B (100%). The PCV7 and PCV13 coverage rates for PRSP were 92·9% and 100% in sputum, respectively, and 100% in blood isolates.

MLST

MLST was performed on 61/92 sputum isolates in which *S. pneumoniae* was the dominant organism and on five blood isolates. Of the 66 isolates, 37 STs were found including nine new STs (ST5830–5834 and ST5494–5497) with four new alleles. A dendrogram was constructed (Fig. 2) and eBURST analysis revealed six CCs and 25 singletons containing 23 and 43 isolates, respectively. Furthermore, 54·1% and 40% of the sputum and blood isolates had STs identical to 11 international PMEN clones or their SLVs. Eight multidrug-resistant PMEN clones



Sequence Type*	Serotype	Allelic profile*†	No. of isolates	
			Sputum	Blood
ST393	38	10-43-41-18-13-49-6	2	0
ST558	35B	18-12-4-44-14-77-97	2	0
ST433	22F	1-1-4-1-18-58-17	1	0
ST90	6B	5-6-1-2-6-3-4	9	1
ST5830	6B	5-6-1-2-6-1-42	1	0
ST5497	6B	5-6-1-2-**242**-1-271	0	1
ST5834	6B	7-28-1-2-6-1-5	1	0
ST236	19F	15-16-19-15-6-20-26	6	1
ST2993	19F	15-16-4-15-6-20-26	1	0
ST5495	19F	22-16-19-15-6-20-**401**	1	0
ST1437	23F	1-32-6-6-6-1-14	4	0
ST2924	6B	1-5-2-6-6-1-14	1	0
ST855	6A	10-32-19-1-6-14-14	1	0
ST191	7F	8-9-2-1-6-1-17	1	0
ST280	9V	15-17-4-16-6-1-17	1	0
ST180	3	7-15-2-10-6-1-22	1	0
ST2923	6B	2-13-2-5-6-121-29	1	0
ST5831	6B	2-13-2-5-6-124-29	1	0
ST902	6B	2-13-2-5-6-121-121	1	1
ST5494	6B	2-13-2-5-6-121-**400**	1	0
ST5232	6B	2-29-4-1-6-121-121	1	0
ST81	23F	4-4-2-4-4-1-1	1	0
ST282	6A	30-4-2-4-4-1-1	1	0
ST2331	19A	10-16-150-1-17-1-29	1	0
ST2224	6B	7-12-7-1-116-14-29	1	0
ST242	23F	15-29-4-21-30-1-14	5	0
ST3563	23F	15-29-4-21-17-1-14	1	0
ST179	19F	7-14-40-12-1-1-14	1	0
ST199	15B	8-13-14-4-17-4-14	1	0
ST343	14	8-8-4-15-39-12-14	1	0
ST3111	19A	61-60-67-16-10-104-14	0	1
ST338	23A	7-13-8-6-1-6-8	1	0
ST5246	23A	7-13-8-6-1-138-8	1	0
ST5833	6A	7-13-1-6-6-6-121	2	0
ST5496	24B	7-**257**-9-6-25-6-14	1	0
ST5832	6C	7-9-4-16-1-6-384	3	0
ST306	1	12-8-13-5-16-4-20	2	0

Fig. 2. Genetic relatedness, multilocus sequence-typing profile, and serotypes in 37 sequence types of 66 *Streptococcus pneumoniae* isolates from children with community-acquired pneumonia in Japan. Scale bar indicates genetic linkage distance. PMEN, Pneumococcal Molecular Epidemiology Network. * New sequence types and alleles in bold. † In the order: *aroE-gdh-gki-recP-spi-xpt-ddl*.

comprised Spain^{6B}-2, Taiwan^{19F}-14, Taiwan^{23F}-15, Spain^{23F}-1, Utah^{35B}-24, Colombia^{23F}-26, Portugal^{19F}-21, Greece^{6B}-22 and three susceptible PMEN clones comprised Sweden^{1}-28, Netherlands^{15B}-37 and Netherlands^{7F}-39. Isolates related to the eight multidrug-resistant PMEN clones comprised 49·1% and 40% of sputum and blood isolates, respectively. Table 3 shows the numbers and antimicrobial susceptibility of isolates with STs identical to multidrug-resistant PMEN clones or their SLVs. Sputum isolates related to multidrug-resistant PMEN clones comprised 62·5% and 71·4% of PISP and PRSP clones, respectively.

DISCUSSION

The annual incidence of CAP in children aged <5 years who were hospitalized with this condition was 17·6 episodes/1000 child-years and that of CAP with pneumococcal bacteraemia in those aged <5 years was 11·7 episodes/100 000 child-years. In 626 episodes, *S. pneumoniae* was dominant in 14·7% and 0·8% of sputum and blood samples, respectively.

Our findings of the incidence of pneumococcal bacteraemia in children hospitalized with CAP were equivalent to those of our previous survey [15, 18]. The incidence of pneumonia in children aged <5 years that required hospitalization before the introduction of PCV7 in the USA and European countries was 2·25–6·55/1000 child-years [19–21]. The annual incidence of paediatric CAP was higher in the present study than in these reports and similar to that of a study in Germany that included outpatients (13·7–16·9/1000 child-years in children aged <5 years) [22]. The reasons for the variation in incidence

Table 3. *Antimicrobial susceptibility of isolates with sequence types identical to multidrug-resistant PMEN clones or their single locus variants*

Sequence type	Sero-type	Related PMEN clone	No.	MIC_{50} (μg/ml)/(MIC range)								
				PcG	ABPC	CDTR	CTX	MEPM	PAPM	EM	CLDM	VCM
ST90	6B	Spain6B-2 (ST90)	10	1·0 (0·25–2·0)	1·0 (0·25–2·0)	0·50 (0·12–0·50)	0·50 (0·12–0·50)	0·50 (0·50)	0·03 (≤0·008–0·06)	≥8 (≥8)	≥8 (≥8)	0·25 (0·25–0·50)
ST236, ST2993	19F	Taiwan19F-14 (ST236)	8	2·0 (1·0–2·0)	2·0 (1·0–4·0)	0·50 (0·25–2·0)	0·50 (0·25–4·0)	0·25 (0·25)	0·06 (0·03–0·06)	4 (2–≥8)	≤0·12 (≤0·12)	0·25 (0·25–0·50)
ST242, ST3563	23F	Taiwan23F-15 (ST242)	6	1·00 (1·0–2·0)	2·0 (1·00–2·0)	0·50 (0·50–2·0)	0·50 (0·25–2·00)	0·25 (0·12–0·25)	0·03 (0·03–0·06)	≥8 (4–≥8)	≥8 (4–≥8)	0·25 (0·25–0·50)
ST81, ST282	23F 6A	Spain23F-1 (ST81)	2	2·0 (2·0)	2·0 (2·0–4·0)	0·50 (0·50)	0·5 (0·5–1·0)	0·50 (0·50)	0·06 (0·06–0·12)	2 (2–≥8)	≤0·12 (≤0·12–≥8)	0·25 (0·25–0·50)
ST558	35B	Utah35B-24 (ST377)	2	1·0 (1·0)	2·0 (2·0–4·0)	0·25 (0·25–0·50)	0·50 (0·50)	0·25 (0·25)	0·03 (0·03–0·06)	≤0·12 (≤0·12–≥8)	≤0·12 (≤0·12)	0·50 (0·25–0·50)
ST338, ST5246	23A	Colombia23F-26 (ST338)	2	0·25 (0·25–0·5)	0·5 (0·5–1·0)	0·25 (0·25)	0·25 (0·25–0·50)	0·03 (0·03)	≤0·008 (≤0·008)	4 (4)	0·5 (0·5–≥8)	0·25 (0·25–0·50)
ST179	19F	Portugal19F-21 (ST177)	1	1·0	2·0	0·5	0·5	0·03	0·25	≥8	≥8	0·25
ST5830	6B	Greece6B-22 (ST273)	1	1·0	1·0	0·5	0·5	0·06	0·03	≥8	≤0·12	0·5
Other			34	0·12 (≤0·015–2·0)	0·50 (≤0·03–4·0)	0·25 (≤0·03–0·50)	0·25 (≤0·03–0·50)	0·06 (≤0·008–0·25)	≤0·008 (≤0·008–0·06)	≥8 (≤0·12–≥8)	≥8 (≤0·12–≥8)	0·25 (0·25–0·50)

ABPC, Ampicillin; CDTR, cefditoren; CLDM, clindamycin; CTX, cefotaxime; EM, erythromycin; MEPM, meropenem; MIC, minimum inhibitory concentration; PAPM, panipenem; PcG, penicillin G; PMEN, Pneumococcal Molecular Epidemiology Network; VCM, vancomycin.

rates in countries might include differences in access to healthcare, willingness to hospitalize patients and the costs of admission. Free access to any hospital or clinic is guaranteed in Japan, and the costs of almost all medical care for children up to age 6 years in Chiba City are compensated by local government. Thus, most children with CAP in Chiba City, and infants in particular, were treated in hospital.

Another possible reason for the higher incidence is differences in the definition of pneumonia. Pneumonia is usually diagnosed in Japan based on clinical signs and chest radiographic findings confirmed by clinicians, not radiologists. A World Health Organization (WHO) working group developed a method for standardizing the interpretation of chest X-rays of children for epidemiological purposes [23]. Pneumonia was diagnosed by clinicians at each hospital in the present study and included not only WHO-confirmed end-point pneumonia but also other radiographic findings. The incidence of CAP with end-point pneumonia according to WHO standards has yet to be determined.

Identifying the aetiology of childhood CAP is difficult because of the lack of accurate, non-invasive tests. The diagnostic yields of sputum culture are limited by potential contamination from the upper respiratory tract. However, the reliability of microbiological sputum tests can be improved by washing. Bartlett & Finegold [24] showed that washing sputum decreases the number of contaminants by 100- to 1000-fold and does not result in a qualitative and quantitative loss of bacteria recovered in percutaneous transtracheal aspirates. Combining quantitative culture with washing sputum specimens enhances the value of findings. We combine a washing technique with semi-quantitative culture to evaluate pathogenic bacteria [8, 9]. We applied this method with serology to determine the aetiology of CAP in 596 hospitalized children between 1990 and 1991 [25] and identified pathogens in 64·4% of them. Evidence of bacterial, *Mycoplasma pneumoniae* and viral (mostly respiratory syncytial virus) infection was found in 28·8%, 14·9% and 29·9%, respectively, of these children. Two major bacterial pathogens were *Haemophilus influenzae* (19·6%) and *S. pneumonia* (8·6%). The major pathogens defined in this study were consistent with a study of 1700 Japanese paediatric patients with CAP using real-time reverse transcription–PCR [26]. Moreover, the clinical responses to antibiotics administered based on the results of sputum culture are good [10, 11].

Of the 626 episodes in six hospitals examined in the present study, *S. pneumoniae* was identified as the causative pathogen in 96 (15·3%) episodes. Five and 92 were identified from blood and sputum cultures, respectively, including one that tested positive in both cultures. The rate of infection with pneumococcus (15·3%) was similar to that described in a study from Turkey (17·1%) that used washing and quantitative sputum cultures [27], and with a study from Italy (17·8%) that used serological assays with paired sera [28]. However, the findings were relatively lower than those in a study from the USA using pneumolysin-based PCR (44%) [29], even when all *S. pneumoniae* isolates identified in sputum (27·9%) were taken into account. One of the limitations of the present study is the absence of information about previous antibiotic use. The low rate of *S. pneumoniae* detection herein compared with PCR might be related to previous use of antibiotics, which is frequent in Japan.

We could not identify a relationship between underlying disease and the detection of *S. pneumoniae*. However, patients with asthma, congenital heart disease, and cerebral palsy had multiple hospitalizations for CAP. The only vaccines for the prevention of bacterial pneumonia (excluding pertussis) are *H. influenzae* type b and pneumococcal vaccines. Therefore, such patients should be recommended for immunization with these vaccines, both of which are elective in Japan.

The incidence of *S. pneumoniae* that is not susceptible to penicillin has rapidly increased in Japan since around 1990 [30]. The rate of PRSP in the present study was as high as that in previous studies of IPD [18] and acute otitis media (AOM) [31] in Japanese children. The frequency of STs related to multiresistant PMEN clones was also high in the present study. The spread of these clones might be responsible for the high rate of resistant strains developing in Japanese children.

The most prevalent serotype in sputum isolates of children with CAP was 6B, followed by 19F and 23F. The high prevalence of these serotypes was the same as that in a report describing IPD in Japanese children [32]. The overall PCV7 coverage rates in sputum and blood were 66·7% and 80%, respectively. These rates in children aged <5 years were 70·2% and 80%, respectively. PCV7 coverage of bacteraemic pneumonia was equal to that of IPD in the USA and Europe before the introduction of PCVs [33]. However, serotype 14, which is the most common serotype in the USA