

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Between 2008 and 2009, 36 cases of AOM and 324 cases of CSOM were seen at the Cipto Mangunkusumo General Hospital (unpublished Dr Ratna D. Restuti).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

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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 for 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

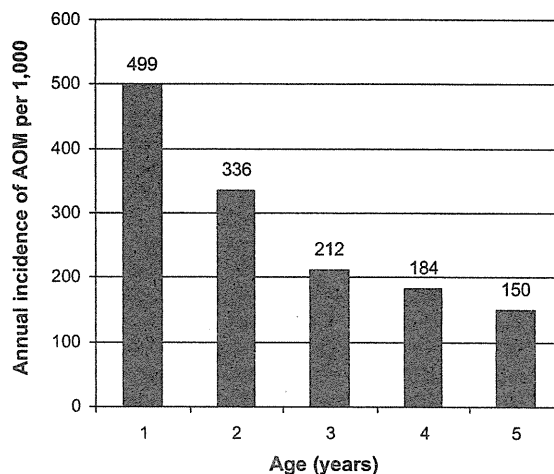


Fig. 2. Incidence of AOM by age in 19,146 <5 year olds derived from retrospective review of medical records from 63 general practices in New Zealand, 2008–2009 [62].

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].

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

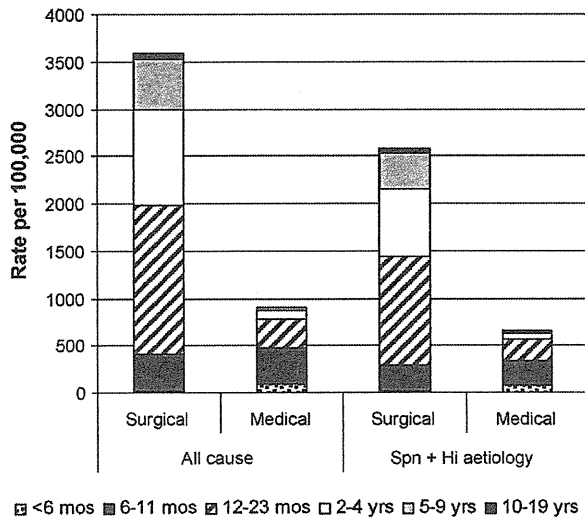


Fig. 3. Annual rate of hospital admissions (medical or surgical) in New Zealand for OM in 2006–2007, by age and estimated aetiology [63].

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

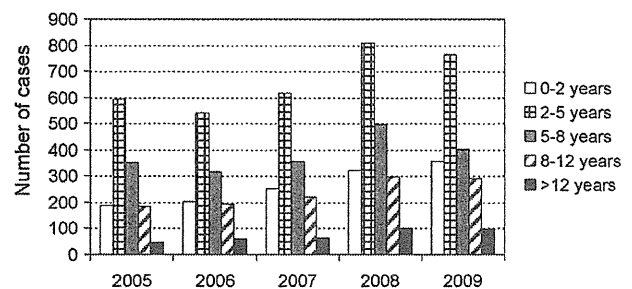


Fig. 4. Age distribution of 8124 patients presenting with OM to a Singapore hospital between 2005 and 2009 (unpublished HKK Tan).

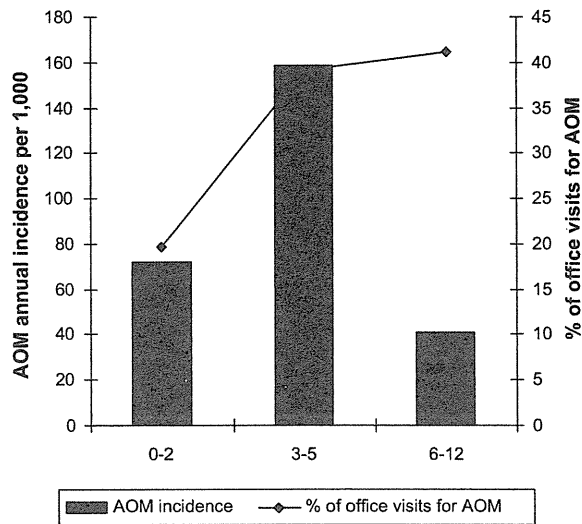


Fig. 5. Annual AOM prevalence and AOM-related outpatient visits and hospital admissions, Singapore [104].

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 9.9%), 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 otorrhea 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/otorrhea 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

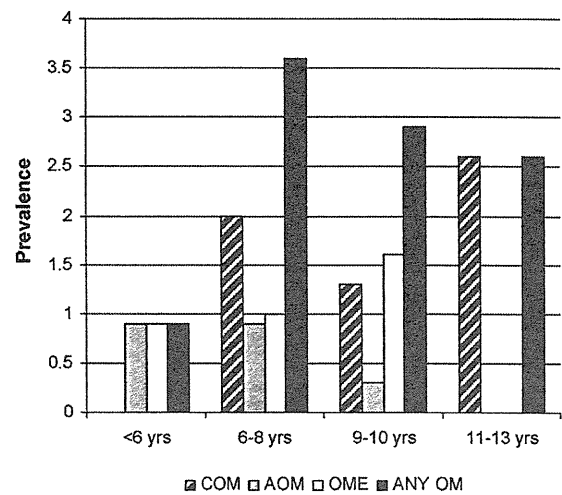


Fig. 6. Prevalence of OM by age in Thailand, 1993-1995 [79].

(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 than 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

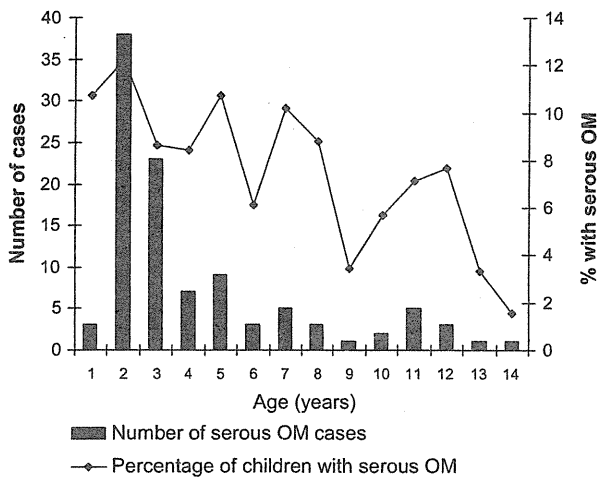


Fig. 7. SOM prevalence by age in 1168 1–14 year olds in Hanoi, 2003 (unpublished, Dr NguyenT Hoai An).

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.

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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.

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

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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.

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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 × 10⁷ 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 <0.05 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, $\chi^2(2)=5.92$, $P=0.052$].

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 ($P<0.001$), congenital heart disease ($P=0.021$) and cerebral palsy ($P=0.035$) (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).

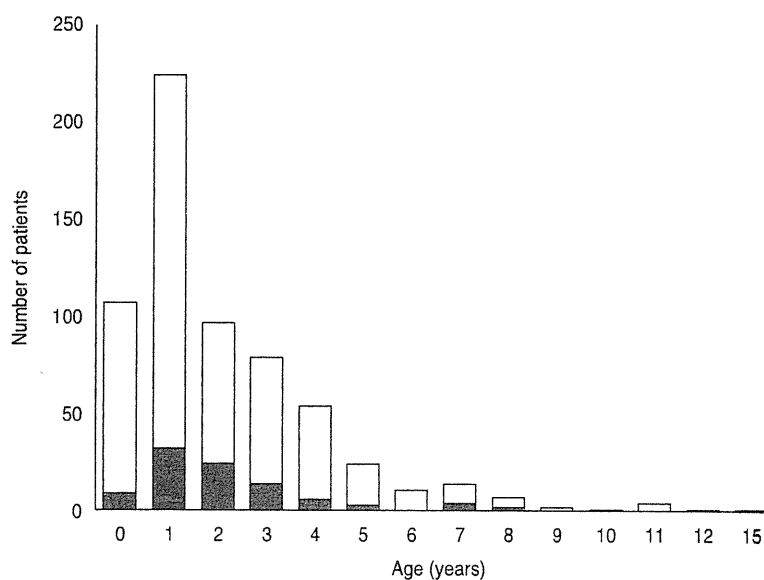


Fig. 1. Age distribution and identification of *Streptococcus pneumoniae* in children hospitalized with community-acquired pneumonia. ■, *S. pneumoniae* dominantly isolated from sputum; ■, *S. pneumoniae* isolated from blood ($n=626$).

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 $\geq 2 \mu\text{g/ml}$), erythromycin (MIC $\geq 1 \mu\text{g/ml}$) and clindamycin (MIC $\geq 1 \mu\text{g/ml}$) 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

Sample	Coverage rate	Serotype	No. of isolates			
			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, $\chi^2(2)=3.74$, $p=0.154$]. 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

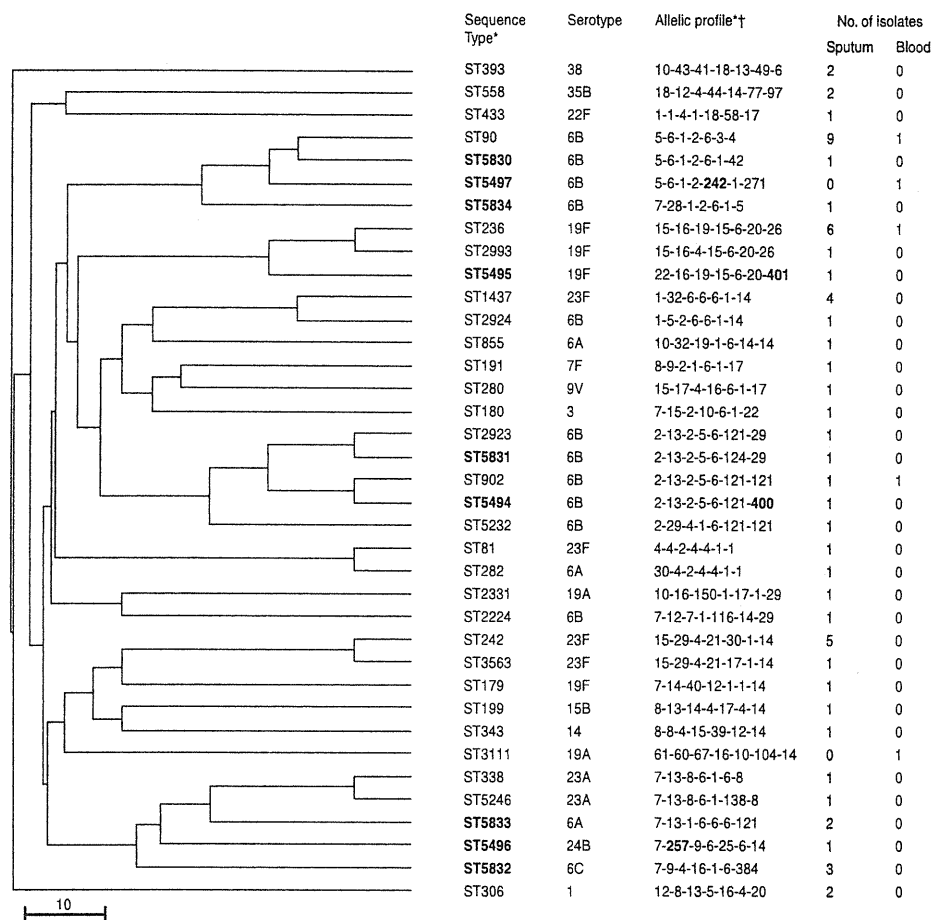


Fig. 2. Genetic relatedness, multilocus sequence-typing profile, and serotypes in 37 sequence types of 66 *Streptococcus pneumoniae* isolates from children with community-acquired pneumonia in Japan. Scale bar indicates genetic linkage distance. PMEN, Pneumococcal Molecular Epidemiology Network. * New 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 Sweden¹-28, 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. pneumoniae* (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 multi-resistant 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

and Europe preceding PCVs [34], and serotype 1, which has been predominant in complicating pneumonia before and after PCVs became available [35], were undetectable in our blood culture. Information about non-bacteraemic pneumonia serotypes is limited. The coverage rates of PCV7 in patients aged <5 years with respiratory infections determined using oropharyngeal swab samples in Vietnam, hypopharyngeal aspirates in China and nasopharyngeal isolates in Switzerland were 88.7% [36], 76.3% [37], and about 70% (<2 years) [38], respectively, with serotype 19F being the most frequent.

PCV7 coverage rates for PRSP were 92.9% and 100% in sputum and blood isolates, respectively. We hope that PCV7 will reduce the incidence of respiratory tract infections, especially those caused by strains that are less susceptible to penicillin.

Serotypes have changed in countries where PCV7 has been introduced as routine immunization and the emergence of serotype 19A with multidrug resistance has become a problem [1, 2, 39–41]. ST199 and ST320 are the major STs found in these countries. Here, we found only serotype 19A *S. pneumoniae* with ST2331. One isolate had ST199 but its serotype was 15B.

The incidence of serotype 6C, which was distinguished from serotype 6A in 2007 [42], also increased after the introduction of PCV7 [43]. Serotype 6C was isolated from <2% of children with IPD and from 9.5% of samples from the nasopharyngeal mucosa of healthy children in Japan [16]. We identified three 6C isolates from sputum (4.8%) with the new sequence type ST5832 in our patients with CAP.

Some limitations of this study should be considered. This study covered only a 1-year period and therefore does not account for annual variations in either the incidence of disease or the detected serotypes. In addition, information about previous antibiotic administration was not available.

PCV7 was introduced as an elective vaccine in Japan in February 2010. New PCVs, especially 13-valent and the investigational 15-valent types, would potentially increase the coverage rate of sputum isolates. Switching to these new PCVs should be considered with the increase of non-vaccine serotype. Continued surveillance to detect changes in the incidence of CAP caused by pneumococci, their antimicrobial resistance, serotypes and genotypes are crucial for evaluating the impact of PCV7 and to effectively prevent pneumococcal infections.

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DECLARATION OF INTEREST

None.

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Incidence of bacterial coinfection with respiratory syncytial virus bronchopulmonary infection in pediatric inpatients

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Abstract Bacterial coinfection occurs in pediatric bronchopulmonary infections caused by respiratory syncytial virus (RSV), but the incidence is uncertain. Our subjects are 188 pediatric inpatients having RSV bronchopulmonary infection in two hospitals in Chiba Prefecture between 2005 and 2007. On admission, antigen detection kits using nasopharyngeal aspirate were performed to detect RSV infection and washed sputum bacterial culture was performed to detect bacterial infection. Of the 188 pediatric inpatients with RSV bronchopulmonary infection, 95 (50.5%) patients were aged less than 1 year, 57 (30.3%) were aged 1–2 years, and 36 (19.1%) were aged 2 years or more. Thirty-six (19.1%) patients were associated with bronchial asthma attacks. Pathogenic bacteria were predominantly isolated from 43.6% of the patients. The three most frequently isolated bacteria were *Haemophilus influenzae* (43.9%), *Streptococcus pneumoniae* (36.6%), and *Moraxella catarrhalis* (29.3%). We found that 38.9% of *H. influenzae* strains were β -lactamase-nonproducing ampicillin-resistant strains. All *S. pneumoniae* strains were penicillin G (PcG) sensitive. However, 21.9% of *S. pneumoniae* strains showed PcG minimum inhibitory concentration values of 2 μ g/ml. RSV bronchopulmonary

infections in hospitalized children are often associated with antimicrobial-resistant bacterial infection in their lower airways. These results indicate that we should be aware of bacterial coinfections in the management of pediatric inpatients with RSV bronchopulmonary infection.

Keywords Respiratory syncytial virus · *Haemophilus influenzae* · *Streptococcus pneumoniae* · Bronchopulmonary infection

Introduction

Respiratory syncytial virus (RSV) is one of the major pathogens in upper and lower respiratory tract infection in children. RSV infections are often associated with bacterial coinfections, which increase the severity of the RSV infection [1–3]. Several papers that have examined the occurrence of bacterial coinfection in children with severe RSV infection requiring pediatric intensive care unit (PICU) admission have found the incidence to be between 17.5 and 44% [4–6]. However, both the incidence of bacterial coinfection with RSV bronchopulmonary infection in pediatric inpatients not requiring PICU admission and the prevalence of antimicrobial-resistant pathogenic bacteria isolated from these patients are poorly understood.

Most pediatric patients with RSV bronchopulmonary infections exhibit wheezing and productive cough. Therefore, sputum can be obtained easily from children with RSV infection, irrespective of age. Unfortunately, the diagnostic yields of sputum culture are limited because of potential contamination from the upper respiratory tract. For this reason, previous studies have considered expectorated sputum washing as a useful means for improving sputum for microbiological examination [7–11].

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