In Malaysia, various aspects of the epidemiology of pneumococcal carriage and disease remain largely unclear due to the lack of supporting data. Although a number of relevant studies have been documented, their individual discrete findings are not sufficient to inform experts on pneumococcal epidemiology at a national level. Therefore, in this review we aim to bring together and systematically evaluate the key information regarding pneumococcal disease epidemiology in Malaysia and provide a comprehensive overview of the data. Major aspects discussed include pneumococcal carriage, disease incidence and prevalence, age factors, invasiveness of pneumococci, serotypes, molecular epidemiology and antibiotic susceptibility. Penicillin resistance is increasingly prevalent and studies suggest that the majority of pneumococcal serotypes causing pneumococcal disease in Malaysia are covered by currently available conjugate vaccines. Continued surveillance is needed to provide a better understanding of pneumococcal epidemiology in Malaysia.

**Streptococcus pneumoniae** is a major human pathogen causing various life-threatening diseases such as pneumonia, sepsis and meningitis [1]. This pathogen poses persistent threats to the community worldwide, especially to young children and elderly adults from both industrialized and developing countries. Pneumococcal disease is the leading cause of vaccine-preventable deaths in children <5 years old [2].

In 2010, diseases of the respiratory system were the primary cause of hospitalizations of infectious-cause among the Ministry of Health (MoH) hospitals in Malaysia [3]. Of utmost concern is that pneumonia was the fourth leading cause of death in MoH hospitals. In a separate report, *S. pneumoniae* was ranked at 25th among a total of 99 significant bacterial pathogens encountered in 15 hospitals, marking an incidence rate of 75.4 per 100,000 patients for *S. pneumoniae* [4].

Pneumococcal conjugate vaccines (PCV) have been developed against serotypes 7, 10 and 13, which cause the majority of invasive pneumococcal disease (IPD) in the USA and other Western countries, and these vaccines are now widely used in many high-, middle- and low-income countries worldwide. No PCV is currently included in the Malaysian pediatric immunization schedule, although licensure for PCV7 was gained in 2006. Malaysian epidemiological data, including serotype-specific disease estimates, are important in order to develop appropriate vaccine policy for the country.

However, in common with a number of other southeast Asian countries [5], information on pneumococcal diseases among the Malaysian population is especially scarce and only a limited number of related studies have been reported throughout the years. The use of data for meaningful comparative analysis is further complicated by the unmatched study designs adopted by individual research groups. The subject population recruited in the respective studies were relatively imbalanced in terms of their geographical and demographical distributions. Data on pneumococcal epidemiology are indeed completely absent for several states. In this review, we aim to provide a comprehensive view on the epidemiology of pneumococcal diseases in Malaysia based on the available literature.

**Literature review methodology**

To provide an overview of the trend and characteristics of pneumococcal disease in Malaysia,
we searched the current literature for studies regarding prevalence, serotype and genotype distribution, antibiotic susceptibility, age factors and clinical sites of infection of pneumococcal colonization and disease. The MEDLINE (Ovid) database was used to identify relevant studies and review articles. Studies describing various aspects of pneumococcal disease among the Malaysian population were included. The search was carried out in English and was limited to studies published in English. Search terms included: Streptococcus pneumoniae, pneumococcus, pneumococcal infection, penicillin resistance, antibiotic susceptibility, PCV, Malaysia, Malaysian, South East Asia, Serotype, multilocus sequence typing (MLST), clones, pneumonia, meningitis, bacteremia, respiratory infections, otitis media (OM), separated by binary operators ‘OR’ or ‘AND’. Search terms were used in text, title or abstract. Manual searching of the reference lists of identified publications was also carried out. Fourteen studies regarding the epidemiology of carried or disease-causing pneumococci performed between 1984 and 2009 in Malaysia (including both peninsular Malaysia and East Malaysia) were identified for inclusion in this review (Table 1). The percentage of S. pneumoniae reported throughout this review denotes the proportion of pneumococci among other bacteria detected from the respective studies (if applicable) unless otherwise stated. The majority of the studies (n = 10) identified were based in or partly involved the densely populated urban areas in Kuala Lumpur (capital city of Malaysia) and Selangor, which also included two country-wide surveillance studies. Others involved subject populations from urban or suburban areas resided within the states of Kelantan, Perak, Penang, Negeri Sembilan, Johor Bharu, Pahang, Perlis and Terengganu of Peninsular Malaysia, and both Sabah and Sarawak of East Malaysia. All studies involved multiethnic and socioeconomic groups, although region-specific differences in the actual distribution of these factors do occur.

Pneumococcal carriage in young children
S. pneumoniae constitutes part of the complex normal flora in the human upper respiratory tract. Colonization by pneumococci begins as early as hours after birth and peaks around the age of 3 years [6]. Colonization by the homologous strain, especially in the nasopharyngeal (NP) and other respiratory sites, is valuable as the indicator predicting the potential risk of infection [7]. Carriage of pneumococci is asymptomatic and is known to precede disease manifestations [6]. Symptomatic diseases will ensue upon breaching of host immunological barriers into various sterile sites leading to serious and potentially life-threatening infections [8–10].

Asymptomatic colonization
Unfortunately, data on asymptomatic pneumococcal colonization among the Malaysian population is largely absent. To our knowledge, only one such study has been undertaken. Malik et al. investigated the prevalence of pneumococcal colonization among children <6 years of age in Kota Bharu, Kelantan [11]. NP swabs were obtained by inserting the cotton-tipped applicator into the posterior nasopharynx of the subject and rotated for approximately 30 s before removing the swab and inoculating onto blood agar plate instantaneously, followed by incubation at 37°C under 3–12% CO₂ for 24–48 h. Pneumococci were detected from NP swabs of 10.1% (36 out of 355) of the children. Participants included healthy children, children with developmental delay, and children presenting with respiratory infection or diarrhea on the day of sampling. Acquisition of carriage pneumococci as early as ≤24 months old was determined in the study [11].

Pneumococcal colonization in children with acute respiratory infections
Pneumococci were isolated from 17.1% (250 out of 1466) of the NP aspirates obtained from children <5 years old in a national hospital-based acute respiratory infections (ARI) study [12]. The NP aspirates were collected using a mucus extractor and the specimens were inoculated directly onto Ox blood agar with gentamicin. Identification tests were carried out after overnight incubation at 37°C. This particular study is of interest because pneumococcal-childhood ARI is rarely reported in Malaysia. However, since the upper and lower respiratory tract infections were not differentiated among the ARI children, we consider that the pneumococci collected from NP aspirates best reflect pneumococcal carriage in children with respiratory tract infections as opposed to being regarded as etiological agents responsible for ARI. Therefore, the actual role of S. pneumoniae in causing lower respiratory tract infection could not be determined from this study. This shortcoming in study design can be improved by collecting specimens from the lower respiratory tract to provide insight into the role of S. pneumoniae in cases of lower respiratory tract infections in the future.

Based on the NP aspirates/swab collection and immediate culture methodology described in these two studies, the carriage rates reported are likely to reflect the true carriage rates among the subject community recruited, assuming that appropriate diagnostic microbiology techniques were employed; however, the small study sizes mean that findings cannot be taken as representative of other communities in Malaysia. Carriage of pneumococci among Malaysian children was significantly lower than the >48% reported in the neighboring countries, Vietnam and Indonesia [13,14], which broadly share similar socioeconomic status with Malaysia; this suggests that the carriage rates in Malaysia may resemble those reported for other East Asian countries such as Korea and Taiwan that showed low pneumococcal carriage rates (14%) [15,16]. By contrast, high carriage rates of over 65 and 90% have been reported in Australian aboriginal children [17,18] and Gambian children [19], respectively. Globally, pneumococcal carriage among young children has been reported to vary greatly between 2 and 86%. This large variation is probably complicated by differences in study design, study population, sampling methods, sample storage and culture conditions and other underlying factors such as age, socioeconomic status, pre-existing clinical conditions, immune system functionality, overcrowding especially during the first year of life, and co-colonization with other respiratory tract flora [6,20–22]. Among Malaysian children, nutritional status appeared to be an important factor affecting the rate of colonization in one study (p = 0.07) [11]. The nutritional status was assessed based on...
Table 1. Summary of studies included in this review.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study period</th>
<th>Subject population (location)</th>
<th>Age group</th>
<th>Sample type</th>
<th>Pneumococci isolated†</th>
<th>Antibiotic profiles</th>
<th>NS (%)‡</th>
<th>Isolates serotyped (n)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheong et al. (1988)</td>
<td>September 1984 to August 1985</td>
<td>Acute respiratory infections (three hospitals§)</td>
<td>1 month to 5 years</td>
<td>NPA</td>
<td>250/-/1466</td>
<td>Penicillin, Cephaloridin, Erythromycin, Tetracycline, Lincomycin</td>
<td>2.0</td>
<td>92</td>
<td>[12]</td>
</tr>
<tr>
<td>Choo et al. (1990)</td>
<td>1985–1987</td>
<td>Pyogenic meningitis (Kelantan)</td>
<td>Children</td>
<td>CSF</td>
<td>13/58</td>
<td>Penicillin, Chloramphenicol</td>
<td>0.0</td>
<td>Nil</td>
<td>[38]</td>
</tr>
<tr>
<td>Hussain et al. (1998)</td>
<td>1 January 1995 to 31 December 1995</td>
<td>Meningitis patients (from five centers¶)</td>
<td>≤12 years</td>
<td>CSF</td>
<td>8/58/435</td>
<td>Nil</td>
<td></td>
<td>Nil</td>
<td>[37]</td>
</tr>
<tr>
<td>Rohani et al. (1999)</td>
<td>Between 1996 and 1997</td>
<td>Pneumococcal isolates referred from hospitals throughout the country</td>
<td>All</td>
<td>Blood, sputum, NPA, other</td>
<td>92</td>
<td>Penicillin, Azithromycin, Co-amoxiclav, Cefaclor, Cefuroxime, Ceftriaxone</td>
<td>10.9</td>
<td>Nil</td>
<td>[68]</td>
</tr>
<tr>
<td>Hooi et al. (2001)</td>
<td>1 November 1999 to 16 August 2000</td>
<td>CAP patients (Penang hospital)</td>
<td>≥12 years</td>
<td>Blood, sputum, urine</td>
<td>3/42/98</td>
<td>Nil</td>
<td></td>
<td>Nil</td>
<td>[29]</td>
</tr>
<tr>
<td>Desa et al. (2003)</td>
<td>March 1999 to July 2000</td>
<td>Patients (UMMC)</td>
<td>All</td>
<td>Sputum, blood, CSF, other</td>
<td>100</td>
<td>Penicillin, Ceftriaxone</td>
<td>31.0</td>
<td>50</td>
<td>[54]</td>
</tr>
<tr>
<td>Lim et al. (2007)</td>
<td>May 1999 to August 2004</td>
<td>Children with IPD (UMMC)</td>
<td>&lt;14 years</td>
<td>Blood, CSF, BAL, PF</td>
<td>50</td>
<td>Penicillin (49 isolates only)</td>
<td>61.2</td>
<td>Nil</td>
<td>[24]</td>
</tr>
</tbody>
</table>

†Standalone figure denotes the number of pneumococci isolated; figure ‘A/B’ denotes A pneumococci isolated over B bacterial isolates obtained; figure ‘A/B/C’ denotes A pneumococci isolated over B bacterial isolates obtained among C patients/specimens. '-' denotes data not available.
‡Percentage of nonsusceptible strains (intermediate and resistant).
§Kuala Lumpur General Hospital, Ipoh General Hospital and Kota Bharu General Hospital.
¶Pediatric Institute, Hospital Kuala Lumpur; Kota Bahru Hospital, Kelantan; Hospital Sultanah Aminah, Johor; Hospital Alor Setar, Kedah; and Hospital Kuching, Sarawak.
#Hospital Pulau Penang, Hospital Kota Bharu, Hospital Kuala Lumpur, Hospital Sultan Aminah, Hospital Queen Elizabeth, UMMC.
††Tested but not interpreted as no MIC breakpoint recommended by NCCLS.
‡‡Hospital Queen Elizabeth, Hospital Selangor, Hospital Tunku Jaafar, Hospital Sungai Buloh, Hospital Sultanah Aminah, Hospital Sultanah Nur Zaharah, Hospital Tunku Bahiyah, Hospital Tengku Ampuan Rahimah, Hospital Kuala Lumpur, Hospital Raja Perempuan Zainab II, Hospital Ampang, Hospital Umum Sarawak, Hospital Pulau Pinang, Hospital Raja Permaisuri, Hospital Tengku Ampuan Azlan, UMMC.
§§Penicillin (oral) breakpoint (susceptible: ≤0.06 µg/ml; intermediate: 0.12–1.0 µg/ml; resistant: ≥2.0 µg/ml).
BAL: Bronchoalveolar lavage; CAP: Community-acquired pneumonia; CSF: Cerebrospinal fluid; IPD: Invasive pneumococcal disease; NCCLS: National Committee for Clinical Laboratory Standards; NP: Nasopharyngeal; NPA: Nasopharyngeal aspirate; PF: Pleural fluid; UMMC: University Malaya Medical Center.
a modified Wellcome classification of protein-energy malnutrition by a pediatrician. The authors reasoned that nutritional insufficiency could have affected the quantity and quality of secretory IgA involved in regulating and protecting the mucosal lining of the respiratory tract. This has probably contributed to the higher S. pneumoniae colonization rates among the poorly nourished children, rendering them at increased risk of pneumococcal infection. However, factors such as gender, ethnic group (Malay, Chinese, Indian or others), venue of enrolment (school, clinic or hospital ward), number of siblings, and location of home (urban or rural) did not significantly influence the rate of colonization in children in this study.

Incidence & prevalence of pneumococcal diseases in Malaysia

Pneumococcal pneumonia

The WHO estimates that in the Asia Pacific region alone, 49 out of 98 cases of pneumonia deaths in children are attributed to pneumococcal pneumonia [23]. In Malaysia, 4% of the 7000 deaths among children <5 years old were estimated as due to pneumococci, which translates into an incidence of overall pneumonia deaths of 10.2 out of 10,000 children aged under 5 years [23]. Pneumonia is the most common pneumococcal disease in Malaysia [4,24,25]. However, S. pneumoniae was not the bacteriological cause of nosocomial infections such as sepsis, pneumonia and bacteremia, which have been reported in high numbers [26,27].

The percentage of S. pneumoniae reported among adult patients aged ≥12 years with community-acquired pneumonia (CAP) at a major urban-serving hospital in Kuala Lumpur was seven out of 53 (13.2%) [28]. Klebsiella pneumoniae (24.5%; 13 out of 53) and Haemophilus influenzae (seven out of 53; 13.2%) were two equally important pathogens identified in the study. Contrary to these findings, two surveillance studies [29-30] conducted in the state of Penang (located ~330 km north of Kuala Lumpur) and one from Serembang, Negeri Sembilan (~40 km southern of Kuala Lumpur) [31] examining CAP patients of ≥12 years old concordantly reported very low percentages (7.1%, three out of 42 and 1.5%, one out of 68, respectively) of pneumococci among other bacteria detected. The latter had not detected any pneumococci from the study. The study by Chin et al. did suggest a low prevalence of pneumococci, although only sputum samples were being used [30]. By contrast, K. pneumoniae, Mycobacterium tuberculosis, Pseudomonas aeruginosa and Staphylococcus aureus were the most common in Penang and Negeri Sembilan. These findings suggest that pneumococci might not be the major etiological agent

### Table 1. Summary of studies included in this review (cont.)

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study period</th>
<th>Subject population (location)</th>
<th>Age group</th>
<th>Sample type</th>
<th>Pneumococci isolated</th>
<th>Antibiotic profiles</th>
<th>% NS</th>
<th>Isolates serotyped (n)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erleena Nur et al. (2008)</td>
<td>2001–2005</td>
<td>Bacterial meningitis patients (UMMC)</td>
<td>All</td>
<td>CSF</td>
<td>11/47</td>
<td>Penicillin Ceftriaxone</td>
<td>0.0</td>
<td>Nil</td>
<td>[36]</td>
</tr>
<tr>
<td>Yasin et al. (2011)</td>
<td>January 2008 to December 2009</td>
<td>Pneumococcal isolates referred from hospitals throughout the country</td>
<td>All</td>
<td>Blood, CSF, sputum, pus, eye, ear and other</td>
<td>510</td>
<td>(433 viable for further tests)</td>
<td>Penicillin‡‡ Ceftriaxone Cefotaxime Levofloxacin Clindamycin Erythromycin Tetracycline Vancomycin Cotrimoxazole</td>
<td>33.9</td>
<td>433</td>
</tr>
</tbody>
</table>

1Standalone figure denotes the number of pneumococci isolated; figure ‘A/B’ denotes A pneumococci isolated over B bacterial isolates obtained among C patients/specimens. ‘-’ denotes data not available.

2Percentage of nonsusceptible strains (intermediate and resistant).

3Kuala Lumpur General Hospital, Ipoh General Hospital and Kota Bharu General Hospital.

4Pediatric Institute, Hospital Kuala Lumpur; Kota Bahru Hospital, Kelantan; Hospital Sultanah Aminah, Johor; Hospital Alor Setar, Kedah; and Hospital Kuching, Sarawak.

5Hospital Pulau Penang, Hospital Kota Bharu, Hospital Kuala Lumpur, Hospital Sultan Aminah, Johor; Hospital Alor Setar, Kedah; and Hospital Kuching, Sarawak.

6Hospital Pulau Penang, Hospital Kota Bharu, Hospital Kuala Lumpur, Hospital Sultan Aminah, Hospital Queen Elizabeth, UMMC.

7Tested but not interpreted as no MIC breakpoint recommended by NCCLS.

8Hospital Queen Elizabeth, Hospital Selayang, Hospital Tunku Jaafar, Hospital Sungai Buloh, Hospital Sultanah Aminah, Hospital Sultanah Nur Zahirah, Hospital Tunku Bahiyah, Hospital Tengki Ampuan Rahimah, Hospital Kuala Lumpur, Hospital Raja Perempuan Zainab II, Hospital Ampang, Hospital Umum Sarawak, Hospital Pulau Pinang, Hospital Raja Permaisuri, Hospital Tengku Ampuan Afzan, UMMC.

9Penicillin (oral) breakpoint (susceptible: ≤0.06 µg/ml; intermediate: 0.12–1.0 µg/ml; resistant: ≥2.0 µg/ml).

10BAL: Bronchoalveolar lavage; CAP: Community-acquired pneumonia; CSF: Cerebrospinal fluid; IPD: Invasive pneumococcal disease; NCCLS: National Committee for Clinical Laboratory Standards; NP: Nasopharyngeal; NPA: Nasopharyngeal aspirate; PF: Pleural fluid; UMMC: University Malaya Medical Center.
causing CAP in Penang. A similar trend in the northern part of Peninsular Malaysia, as well as the states southern to Kuala Lumpur, is suggested. On the other hand, *S. pneumoniae* is a significant CAP pathogen in Kuala Lumpur and potentially in the nearby Klang Valley areas. Hence, regional variation could be the possible explanation for the observed differences. In addition, both studies in Penang revealed that *S. pneumoniae* and *H. influenzae* did not undergo significant overall change in CAP incidence over the 7-year period [29,30]. Hence, we suggest that despite only being present at minimal levels, *S. pneumoniae* as well as *H. influenzae* might not just exist as transient pathogens but rather persist in the population. However, an important point to note is that all three studies mentioned above were representative for individuals ≥12 years old. Children, especially those ≤5 years old who are the major group frequently affected by pneumococcal diseases [32–35], were not investigated in these studies and the pneumococcal distribution in this group may differ considerably from adults. Therefore, we suggest that younger children should be sampled in future studies and also that any such studies should involve more states throughout Malaysia in order to provide representative data.

**Pneumococcal meningitis**

Bacterial meningitis represents a serious health threat worldwide; the prevalence of pneumococcal meningitis among the Malaysian population has been reported by three research groups. A 5-year retrospective study at University Malaya Medical Center (UMMC) examining patients of all age groups identified *S. pneumoniae* as the major causative agent in bacterial meningitis (11 out of 47; 23.4%) [36]. Together with *H. influenzae* and *Escherichia coli*, they accounted for approximately half of all cases. Likewise, *S. pneumoniae* was ranked as one of the leading pathogens (eight out of 58; 13.8%) following *H. influenzae* type b (Hib) (28 out of 58; 48.3%) in childhood meningitis cases (<12 years of age) in a five-hospital-based study [37]. An incidence rate of 76.7 per 100,000 per year had been estimated among children <5 years old [37]. A similar pattern of domination by *H. influenzae* and *S. pneumoniae* was observed among children with pyogenic meningitis in Kelantan, where half of the total cases were attributed to *H. influenzae* (29 out of 58; 50.0%) followed by *S. pneumoniae* (13 out of 58; 22.4%) [38]. As Hussain et al. reported opposition from the local population stemming from an apprehensive fear of the lumbar puncture procedure and side effects [37], it is our belief that the actual prevalence of pneumococcal meningitis as well as other bacteria-related cases might not have been accurately estimated. Overall, the role of *S. pneumoniae* among the Malaysian population is of great importance. Due to the distant study sites and the year’s separation between these studies, the temporal trend in pneumococcal meningitis among the Malaysian population could not be evaluated, but certainly *S. pneumoniae* has a very important role in childhood meningitis, and hence more studies should focus on this manifestation of pneumococcal disease.

On the other hand, local data on ARI and bacteremia are extremely limited. It was estimated that out of the approximate 4000 cases of childhood ARI, the mortality rate could reach up to 5%; 15–20 deaths are estimated per 750 cases of pneumococcal bacteremia [39].

**Pneumococcal OM**

OM is a frequent cause of childhood infections worldwide. In the Asia-Pacific region, the prevalence of OM was highest in children aged 2–5 years compared with other age groups. For children of school-age, the rate varied considerably between countries from 3.3 to 12.2% [40]. *S. pneumoniae* and *H. influenzae* were the most important etiological agents causing acute OM (AOM) throughout the Asia-Pacific region [40]. In Malaysia, approximately 500,000 cases of pneumococcal OM in children <2 years of age are estimated annually and approximately 5% of the cases progress into chronic otorrhea [39]. The prevalence of OM with effusion, a condition characterized by presence of persistent middle ear effusion without signs or symptoms of acute inflammation after a prior AOM episode [41], was 13.8% among kindergarten children aged 5–6 years with higher prevalence in urban compared with rural areas [42]. Among the school-age children between 7 and 12 years old, the prevalence was comparatively lower at 7.3% [43].

**Pneumococcal infections: age factors & ability to cause invasive pneumococcal disease**

In general, children aged less than 5 years and older adults are recognized as the most frequently infected groups. Studies conducted elsewhere in western countries [44–45], Asia [46–49], and in neighboring countries from Southeast Asia (SEA) [44–49] have all noted the increasing rate of pneumococcal carriage or diseases among younger children. In Malaysia, a similar situation was observed. By definition, IPD refers to the isolation of pneumococcus from a normally sterile site including blood, cerebrospinal fluid (CSF) and other bodily fluids. The clinical criteria for IPD were defined in the study by the clinical course of disease, laboratory isolation of pneumococcus and/or supporting diagnostic procedures such as radiographic confirmation in the case of pneumonia. As noted by Lim et al. [24], the majority of the IPD cases among children <14 years old admitted to UMMC in the period 1999–2004 were due to pneumonia (82%; definite and probable 16 and 66%, respectively). Remarkably, nearly all (92.7%) of these cases occurred among children ≤5 years of age, and a large proportion of these cases (84.2%) were in children aged <2 years. Overall, children <2 years constituted 76% of the total IPD cases among children <14 years old. Cases of definite bacteremia without focus and meningitis were significantly less common than pneumonia.

In another study, the largest proportion (31.1%) of the 273 clinical pneumococci isolated from patients of all ages and multiple sites were from children aged 0–10 years [4]. Among this age group, 64.7% (55 out of 85) were from younger children aged ≤2 years. Overall, those aged ≤2 years contributed 20.1% (55 out of 273) of the total pneumococcal isolates obtained. Moreover, the majority of the invasive isolates (46.7%) were also reported from the 0–10 year age group; approximately twice the percentage among older adults aged ≥51 years (20%). A more recent study by the same group similarly reported that 21% of pneumococcal
isolates were from children <2 years old, half of which were from invasive cases [25]. These findings strongly indicate that approximately one fifth of patients hospitalized due to pneumococcal infections are children <2 years old, the primary pneumococcal vaccination target group. Also of note is that the elderly (≥50 years old) were the second most commonly infected group; approximately 50% of the hospitalized cases were invasive. As these data are drawn from multicenter and multistate studies, we believe these estimates better reflect the true situation with regards to pneumococcal disease in Malaysia.

Our recent single-center study reported 14.6% of pneumococci isolated in our laboratory were from children ≤2 years of age [52]. However, only 22.7% of these isolates were from invasive sites. Beside this, 33.8% of the total isolates were from older adults (≥50 years old), which was comparatively higher than those reported by Rohani’s group. These observed differences are most probably due to the small sampling site from one hospital and hence the outcome is thought to reflect only hospitalized cases from the local community served by UMMC and is not representative of the whole Malaysian population. However, based on these studies, the impact of pneumococcal diseases on populations at the extreme of age in Malaysia is evident.

**Pneumococcal serotypes**

Only a limited number of studies provided information on serotype distribution in Malaysia. Of note, increasing interest in this field has been observed based on the quantity of publications in recent years. Contemporary data on the most recent trend in serotype distributions concluded that 19F, 14, 23F, 6B and 19A were the major serotypes responsible for various invasive and noninvasive pneumococcal diseases in Asia [53]. This rank order is similar in Malaysia, where serotype 19F was the most common serotype detected, irrespective of age groups and sites of isolation (i.e., invasive and noninvasive disease taken together) [12,25,52,54]. Other prevailing serotypes include 23F, 1, 6A, 6B and 19A. Similarly, for children aged ≤5 years, serotype 19F was most frequently encountered followed by 6B [25,52]. Other common childhood serotypes include serotype 6A, 19A and 14, all of which are included in one or more PCV formulations. A similar rank order was observed when only invasive isolates were considered, except for serotype 19F. Of note, no serotype 19F was reported among children ≤5 years old but rather serotype 1 (four out of 20; 20.0%) and 19B (three out of 20; 15.0%) were the most prevalent (although the differences are not significant, most likely due to low sample size) [4]. In addition, serotype 19F was found to be associated with noninvasive sites while serotype 19A was associated with invasive sites [52]. Although less commonly detected in children aged 5 years and younger, serotype 1 was invasive and isolated from IPD cases in the younger children [25].

Postvaccination increases in the prevalence of non-vaccine serotypes (NVT) have drawn much attention in recent years, fuelled by concerns that pneumococcal disease due to NVT would greatly counterbalance and neutralize the effect of PCV [55]. In particular, the emergence of serotype 19A has been reported in many countries including the USA [56,57], France [58,59], The Netherlands [60], China [61] and Taiwan [62]. In Malaysia, the reported prevalence of serotype 19A has fluctuated considerably over time. In the mid 1980s, 5.4% (five out of 92) of pneumococci isolated from NP aspirates of children with ARIs (undifferentiated lower and upper respiratory tract infections) in three hospitals were reported to be serotype 19A [12]. Later, in the 1990s, little or no serotype 19A (only one out of 201 isolates) was reported from both multicenter [4] and single-center studies [54], which included patients of all ages and pneumococci isolated from various sites. Later, two recent studies that have comparable study designs with those conducted in the 1990s reported serotype 19A to make up approximately 5% of total pneumococci [25,52]. Therefore, we speculated that prevalence of serotype 19A may fluctuate among the Malaysian population but that some of this observed fluctuation could be attributed to sampling error. However, natural temporal fluctuation should not be confused with postvaccination effects as none of the pneumococcal vaccines are currently incorporated in the national immunization programme (NIP), and population coverage of these vaccines from private healthcare providers is low. Moreover, invasive strains accounted for 70–75% of serotype 19A infections [25,52] and in children aged under 5 years, the prevalence was approximately 58%. These findings denote that serotype 19A has invasive capability among young children and the total population. The invasive potential of serotype 19A has been reported elsewhere using odds ratios [63], but Malaysian-specific estimates are not able to be made in the absence of comparator carriage data for this serotype.

We attempt to predict the effectiveness of various formulations of PCV among the Malaysian population based on the three most recent serotype surveillance studies [25,52,54]. We defined vaccine types (VT) as pneumococcal serotypes included in the PCV. The PCV7, PCV10 and PCV13 would cover 50.9% (95% CI: 47.1–54.8%), 58.8% (95% CI: 55.0–62.6%) and 66.4% (62.6–70.0%), respectively, of the overall pneumococci reported. However, this overall estimate does not take account of the differential distribution of serotypes in different age groups. Particular attention should be paid to the children ≤5 years old, who are the main group targeted by pneumococcal vaccinations. The average coverage estimated based on data available for children ≤5 years old from two studies [25,52] shows that PCV7, PCV10 and PCV13 coverage increases to 57.9% (95% CI: 50.5–64.9%), 63.5% (95% CI: 56.2–70.2%) and 71.9% (95% CI: 64.9–78.0%), respectively, further emphasizing the potential benefit of PCVs for prevention of pediatric pneumococcal disease in Malaysia. Among this age group, 55.4% (95% CI: 44.7–65.5%), 63.9% (95% CI: 53.1–73.4%) and 73.5% (95% CI: 63.1–81.8%) of the IPD cases could have been prevented by these three PCVs, respectively. It should be noted that the nonimmunized population would also be predicted to benefit from indirect protection as a result of herd immunity following widespread vaccine introduction [64].

**Molecular epidemiology**

Based on the study conducted by Shin et al. [65], ST320 (21.4%) and ST172 (21.4%) were among the predominating serotype 19A clones in ten Asian countries. Unlike Korea (ST320: 81.3%),
Taiwan (ST320: 63.6%) and Saudi Arabia (ST320: 55.6%) where a single clone predominated the pool, no major 19A clone was noted for Malaysia, although ST320 and ST172 were slightly more prevalent than others (ST63, 4458, 3781, 2636, 2855, 4937 and 6003). Four of these nine sequence types (STs) had not previously been reported from other Asian countries [65]. Although no major conclusion can be drawn based on this one small study, the findings suggest the presence of a diverse pool of serotype 19A clones among the local isolates. Together with the observation of high numbers of novel STs in studies performed in the neighboring countries of Thailand [65] and Singapore [66], this indicates the likely existence of more undiscovered STs circulating in the Peninsular Malaysia region; however, care must be taken when interpreting these data, as sampling biases are unknown. Considering the proclivity of serotype 19A to cause IPD among the local population, continued monitoring of the serotype and ST distribution among the Malaysian population is warranted.

Related multilocus sequence typing information is available from the pneumococcal MLST database [101]. At the time of writing, only 35 Malaysian strains had been uploaded to the database, and are summarized in Table 2. Based on the database, serotype 19F is the most common serotype found, followed by serotype 19A and a diverse pool of low prevalence serotypes. It should be noted that this database is not representative, novel STs are more often uploaded than those already present, and the small number of Malaysian strains precludes any meaningful analysis. Surveillance studies conducted by the Rohani research group demonstrated that serotypes 1 and 6B were the most commonly detected serotypes in the past [4]; however, by 2009 the order of prevalence was 19F, 6B, 19A, 1, 6A [25]. More findings are needed to better describe the relationship between serotypes circulating and causing disease in Malaysia as well as the associated STs.

### Antibiotic susceptibility

As reported by most studies reviewed here, β-lactam antibiotics were the main class of antibiotics characterized for susceptibility patterns among the local pneumococcal isolates. Very little information is available on susceptibility of colonizing pneumococci in Malaysia. In a study examining the penicillin susceptibility of colonizing pneumococcal strains among children <6 years old from Kota Bharu, all NP isolates (except one) were susceptible to penicillin [11]. No further data on antibiotic susceptibility patterns in colonizing pneumococci are available, although the study suggests that penicillin-susceptible strains are the predominant colonizing strains.

Malaysia and its close neighbor Singapore were previously observed to have lower rates of pneumococcal penicillin resistance (10–20%) than those reported for other countries in the SEA region [67]. In cases of pneumococcal meningitis, pneumococci isolated from CSF exhibited complete susceptibility to penicillin as reported by two studies [36,38]. These strains were also susceptible to ceftriaxone [36] and chloramphenicol [38]. The data are extremely limited; however, the outcome suggests that pneumococcal meningitis in Malaysia is largely caused by penicillin-susceptible pneumococci.

To evaluate the fluctuations in penicillin susceptibility over 24 years, data reported from six studies were analyzed and compared. Five of the latest surveillance studies [4,25,52,54,68] on patients of all age groups and all clinical sites were included, together with an important study describing valuable information on resistance trends during 1984/85, although only NP isolates from children <5 years of age presenting with ARI were examined [12]. In these studies, penicillin susceptibility was assigned using: E-Test method [4,54,68], disc diffusion method [12] or agar dilution method [52]. Breakpoints were defined according to the Clinical and Laboratory Standards Institute (CLSI; formerly known as NCCLS) guidelines. To allow fair comparison of data, the author used the penicillin (oral) criteria for Yasin et al. [25] in order to apply the same penicillin interpretative range used in other studies (susceptible: ≤0.06 µg/ml; intermediate: 0.12–0.1 µg/ml; resistant: ≥2.0 µg/ml). Penicillin-intermediate (PISP) and resistant strains (PRSP) were referred to collectively as penicillin-nonsusceptible Streptococcus pneumoniae (PNSP). The major trend observed was that pneumococcal susceptibility to penicillin has decreased over the period from 1984 to 2007 (Figure 1) followed by a slight increase by 2008/9. In the mid 1980s, PNSP strains

### Table 2. Serotypes and sequence types reported for Malaysian pneumococci.

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Sequence types (no. of isolates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3797</td>
</tr>
<tr>
<td>14</td>
<td>3782</td>
</tr>
<tr>
<td>19</td>
<td>883</td>
</tr>
<tr>
<td>19A</td>
<td>3781, 6003, 5817, 5818, 5819, 5820, 5821, 5822</td>
</tr>
<tr>
<td>19F</td>
<td>879, 81 (3), 236 (4), 986</td>
</tr>
<tr>
<td>23A</td>
<td>338</td>
</tr>
<tr>
<td>23F</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>3798</td>
</tr>
<tr>
<td>4</td>
<td>3798</td>
</tr>
<tr>
<td>6A</td>
<td>904, 5863, 457</td>
</tr>
<tr>
<td>6A/B</td>
<td>3784</td>
</tr>
<tr>
<td>6B</td>
<td>95, 5865</td>
</tr>
<tr>
<td>6C</td>
<td>5241, 5868 (2)</td>
</tr>
<tr>
<td>9V</td>
<td>4128</td>
</tr>
</tbody>
</table>

*Applicable for sequence types with more than one isolate.
Data taken from [101].
made up less than 5% of those reported. However, the situation continued to change with consistent expansion of PNSP strains in the mid 1990s. By the recent decade beginning in the year 2000, PNSP constituted 30–50% of the Malaysian isolates and PISP represent the dominant portion of PNSP, which remained stable throughout the years. The increasing penicillin resistance trend in Malaysia has also been highlighted from the Asian Network for Surveillance of Resistant Pathogens (ANSORP) studies [69]. The association between penicillin susceptibility and the age of patients was not clear. Desa et al. demonstrated that isolates from children <13 years of age had higher penicillin resistance levels compared with pneumococci isolated from other age groups [54], but no significant association was observed in our previous study [52].

Apart from this, it is interesting to note that PRSP had reduced considerably in childhood IPD in one particular study from approximately 52% (year 2000) to 20% (year 2001) and at the third year to 11% (year 2003), excluding the years 1999 and 2004 as incomplete years [24]. Note that the nearest values were estimated based on the chart presented by the authors as no definite value was stated. A slight concern with the finding is the limitation in term of small sample size (n = 49) and subject population (children <14 years old with IPD), which might not accurately reflect the extent of penicillin resistance among all age groups.

Besides penicillin, the third-generation cephalosporin antibiotic ceftriaxone showed better in vitro anti-pneumococcal activity than penicillin [54]. Just over 81% of pneumococcal isolates included in this study were susceptible to ceftriaxone while only 69% were susceptible to penicillin (Figure 2). Moreover, strains that were nonsusceptible to penicillin (30%) exhibited better susceptibility to ceftriaxone, 65 and 20% of PRSP were ceftriaxone-intermediate and -susceptible, respectively; 72.7% of PISP were ceftriaxone-susceptible; all penicillin-susceptible strains were also ceftriaxone-susceptible. In addition, tetracycline was the least effective against S. pneumoniae [4,12]. Similarly, strains tested against five antibiotics by Cheong et al. showed minimal levels of resistance (≤3.4%) against cephaloridine, erythromycin and lincomycin [12].

Hence, it is clear that the prevalence of PNSP has increased from the mid 1980s to present. The recommended alternatives to penicillin are amoxiclav and ceftriaxone [68]. Continued monitoring is exceptionally important to monitor any changes in antibiotic susceptibility that could have significant impact on the choice of empirical therapy for medical practitioners in Malaysia.

**Antibiotic susceptibility in relation to serotypes**

In settings with a high prevalence of VT, widespread use of PCV7 was predicted to result in reduction of antibiotic resistance; indeed, a US study reported an 81% decrease in the rate of IPD caused by PNSP pneumococci in children aged <2 years [70]. However, a Portuguese study showed that despite resistance being associated with PCV serotypes, no changes in the rates of PNSP were observed and that this could be explained by an expansion of NVT variants of existing clones [71].

In order to understand the potential impact of PCV use on antibiotic resistance in Malaysia, the antibiotic susceptibilities of VT pneumococci should be assessed. Although four studies that reported both antibiotic susceptibility and serotype of Malaysian isolates were identified [12,25,52,68], unfortunately the relationship between antibiotic resistance and serotypes was not presented in three of these studies [12,25,68]. Our previous study showed that PRSP belonged to five serogroup/types 19F, 23F, 34, 6A/B and 9V/N [52], while another group reported that it was serotypes 1, 3, 6B, 7B, 11C, 14,19B, 19F, 22A, 22F, 23B [68]. Penicillin resistance was also noticed in NVT strains [52]. Serotype 19F also accounted for a large proportion of strains (27–58%) exhibiting reduced susceptibility to penicillin followed by 19A and 23F [25,52,54]. Also of note is that nontypable pneumococci were frequently found to be nonsusceptible to this drug (41.7%) [25] but contradicting data have also been reported [52]. Statistical analysis showed that serotype was associated with penicillin susceptibility (p<0.001) and two studies observed that serotype 19F was significantly associated with increased penicillin resistance [52,54]. Most strikingly, all nine invasive isolates (100%) from our previous study were nonsusceptible to penicillin [52]; seven of these isolates were blood
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isolates from children aged under 5 years of age. PNSP strains have been shown to be highly homogenous and were suggested to have originated from a few dominant clones [54]. PNSP also tend to be resistant to other drug groups (erythromycin, trimethoprim–sulfamethoxazole, tetracycline and clindamycin) [25].

Based on the documented data [25,52], PCV7,-10 and -13 include 71.3% (95% CI: 64.3–77.4%), 72.9% (95% CI: 66.0–78.9) and 80.1% (95% CI: 73.7–85.3), respectively, of the PNSP serotypes. The coverage increases to 66.2% (95% CI: 54.3–76.3%), 67.6% (95% CI: 55.9–77.6%) and 79.4% (95% CI: 68.4–87.3%), respectively, for PNSP detected among children aged ≤5 years. Hence, it is speculated that introduction of PCV7 would greatly reduce not only the etiological disease serotypes but also reduce the incidence of PNSP, especially among the younger children in Malaysia.

Conclusion
Knowledge of the prevalence of S. pneumoniae and various aspects of pneumococcal disease patterns provides valuable information in appraising the current situation in Malaysia. From the data reviewed here, it appears that antibiotic-resistant S. pneumoniae, particularly PNSP, has increased during the past decade; however, care must be taken when drawing conclusions from a small number of disparate studies. Treatment outcomes would be significantly complicated by the resistant strains where delays in the length of treatment course would greatly increase the risk of disease progression and hence mortality; such delays also increase the healthcare costs for pneumococcal infections. Pneumococcal resistance against penicillin is determined to be associated with serotype. Among all serotypes detected, the most prevalent serotype, 19F, is associated with high penicillin resistance. Fortunately, serotype 19F, as well as those frequently detected from the local population, is included in all PCV formulations. Based on the estimation that a large proportion of pneumococcal diseases serotypes, especially those causing disease in children ≤5 years old, were covered by PCVs, certainly the Malaysian population would benefit from the utilization of such vaccines. However, no PCV has been incorporated into the Malaysian NIP and the availability is mainly through private healthcare providers, rendering fairly low population coverage. Further worsening the situation is a lack of knowledge among Malaysian parents regarding the importance of pneumococcal vaccination to their children, not accounting those who are not aware of the availability of this vaccine. According to the 2006 Global Pneumococcal Disease Awareness Survey, as many as 69% of Malaysian parents are not aware of pneumococcal diseases and approximately 38% were are not aware of PCV [102].

The data reviewed here suggest that between 47 and 66% of circulating pneumococci and over 69% of PNSP in Malaysia are of serotypes included in existing PCVs; however, the existing data do not allow robust estimates of serotype prevalence or prevalence of antibiotic resistance among VT pneumococci. Implementing any of the three PCV formulations into the NIP would be likely to reduce mortality and morbidity and also reduce the incidence of PNSP directly and indirectly by preventing the spread of resistance to susceptible strains. In light of this, it is important that policy in this area is reviewed. Aljunid et al. has demonstrated that, based on a decision analytical model of a hypothetical birth cohort of 550,000 individuals, PCV7 immunization in infants will be highly cost effective for Malaysia (RM35,196, US$10,261 incremental cost per life-year gained), which is approximately half the cost–effectiveness threshold for public health interventions for Malaysia estimated by the WHO [72]. Hospitalizations due to pneumococcal diseases is speculated to be reduced by 9585 cases for Malaysia estimated by the WHO [72]. Improved data regarding pneumococcal epidemiology are required in order to make the most beneficial and cost effective decision for the country and the region of SEA as a whole.

A lack of precaution in antibiotic prescribing and usage could be one of several factors contributing to the development of
antibiotic resistance in Malaysia. Careful prescribing of antibiotics is thus vital. Moreover, failure of patients to adhere to the antibiotic administration instructions, such as failure to complete a full course of antibiotics once symptoms subside, may result in selection of nonsusceptible clones leading to increases in antibiotic nonsusceptibility, requiring increased dosage of the same drug or changes in antibiotic prescription in the event of chronic or recurrent infections.

It is encouraging that research into various aspects of pneumococcal diseases in Malaysia has been reported since the 1980s. Nevertheless, a number of limitations from the study designs have been highlighted throughout the review; the small sample size, limited or lack of description of the subject population, sampling methods and geographical distribution of the study population have greatly restricted the conclusions that can be drawn. Estimation of the prevalence of pneumococcal serotype, genotype and antibiotic resistance that are required to predict vaccine coverage are available but still largely insufficient. As pneumococcal epidemiology may vary considerably with geographical distribution, we emphasize the importance of coordinated active surveillance studies in different parts of Malaysia, for example through establishment of nationwide or sentinel surveillance networks. Data from states in the northern and eastern states of peninsular Malaysia are much needed, as are data from West Malaysia, which is distinctively situated in Borneo Island and differs in many ways from other parts of peninsular Malaysia and thus has the potential for a different circulating pneumococcal population. Population- or community-based surveillance is rarely performed in Malaysia; new studies should be directed in a coordinated way with improved standardization in study design and reporting to enable comparative analysis for long-term assessment. Collaboration between countries in the region regarding the design and implementation of surveillance studies would facilitate high-quality data collection and analysis. Ethnic, cultural and socioeconomic differences may also contribute to differences in pneumococcal epidemiology and studies to investigate these factors in the multi-ethnic Malaysian population are needed. Currently, cost–effectiveness estimates have been reported only for PCV7; similar data for PCV-10 and -13 based on improved serotype-specific data are now required.

**Expert commentary & five-year view**

This review summarizes various aspects of pneumococcal carriage and disease epidemiology in Malaysia, a developing economy unique with its multi-ethnic and multicultural society. This review has been limited by the lack of, if not inadequate, documentation with regards to the burden and incidence of pneumococcal diseases in Malaysia and the prevalence of this pathogen in the community and hospital settings. Most of the studies reported were considerably small in terms of the sample size, and differed in methods reported for isolate collection and cultivation methodology, study period, subject population and areas of coverage, which altogether affected the reliability and confidence of the outcomes. In many instances estimates for prevalence, incidence and serotype distribution scattered widely. Nonetheless, we have collected the relevant data to provide a Malaysian perspective of pneumococcal epidemiology in the most comprehensive presentation to date. It is critical that standardized methodology and improved reporting are employed if meaningful information to underpin policy for prevention and treatment of pneumococcal disease is to be drawn from future studies in the region. Surveillance of childhood carriage should receive more attention as the most recent study dated back to the 1990s; this is also true for AOM, ARI and other pneumococcal disease-orientated studies (pneumonia, meningitis, bacteremia) in relation to *S. pneumoniae*. As pneumonia was found to be the most frequent cause of pneumococcal-related death in Malaysia, work to better describe the burden and epidemiology of pneumococcal pneumonia should now be a priority.

At the same time, we highlighted the intense efforts by several Malaysian research groups and collaborators concerning their contributions especially in antibiotic susceptibility, sero-epidemiology, and molecular characterization of *S. pneumoniae*, as evident from the increasing reports and the increasing scale of the studies in recent years. There can be no doubt that penicillin-resistant pneumococci are increasingly common among the local population and we speculated that the large underlying intermediate resistant strains signify that a transition to a penicillin-resistant era is beginning. If no strict regulation on antibiotic misuse and education on good antibiotic stewardship is implemented in the next few years this pool of less-susceptible strains will continue to be selected and expanded. Hence, the situation will undoubtedly continue to worsen. Increasing interest in sero-epidemiological study is reasoned to be most likely driven by the encouraging efficacies documented following the global introduction of PCV7 and the newer PCV generations in many countries. However, it is of concern that none of the PCVs are currently incorporated into the routine NIP in Malaysia. The use of PCVs by neighboring countries in SEA, increasing urbanization and increased travel between countries along with other natural fluctuations in prevalence of pneumococcal clones and serotypes, may lead to changes in sero-epidemiology and antibiotic resistance of Malaysian pneumococci in the next 5–10 years. However, no major changes in serotype distribution are expected to stem directly from the very low use of PCV through the private health sectors currently in Malaysia. Even with immediate implementation of PCV into the NIP, the effects would not be expected to be significant for at least the next 2 years.

The data and commentary presented here will be of interest to both researchers and healthcare policy makers in Malaysia and calls for dialogue to develop a strategy to continue and improve epidemiological studies and vaccine policy in Malaysia.

**Financial & competing interests disclosure**

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Key issues

- The evidence base regarding pneumococcal colonization and disease in Malaysia is limited; however, some conclusions can be drawn.
- Pneumococcal carriage among Malaysian children appears to be low (10–20%). Infants as young as ≤24 months of age begin acquisition of *Streptococcus pneumoniae*; the highest prevalence is observed among kindergarten children (5–6 years old), with prevalence decreasing in school-age children.
- In Malaysia, diseases of the respiratory system, particularly pneumonia, are the most common pneumococcal diseases.
- *S. pneumoniae* is one of the major pathogens responsible for pneumonia and meningitis in Malaysia.
- Extreme age groups, especially children ≤5 years old, appear to carry the largest disease burden.
- In general, the common serotypes among the total populations, irrespective of sample sites, are serotype 19F, 23F, 1, 6A, 6B and 19A. The prevailing serotypes among children aged under 5 years of age are 19F, 6B, 6A, 19A and 14. This is also observed in invasive childhood (≤5 years of age) serotypes (except for 19F).
- The estimated PCV7, PCV10 and PCV13 efficacies among children ≤5 years old are 54.8, 60.7 and 72.1%, respectively.
- Penicillin nonsusceptibility has increased over the past 20 years, largely attributed to the intermediate susceptible strains.
- Amoxiclav and ceftriaxone exhibited better anti-pneumococcal activity than penicillin and have been recommended as alternatives to penicillin.

References

Papers of special note have been highlighted as:

- of interest
- of considerable interest


26 Multicenter surveillance describing the recent trend in serotype distributions and multiple association factors.


42 Capeding MR, Sombrero LT, Esperar GA, Monday MU, Taclibon AG. Pneumococcal serotypes among Filipino


53 Single-center surveillance describing the recent trend in serotype distributions and multiple association factors.


- Estimated the potential benefits, including the cost-effectiveness and reduction of hospitalization episodes due to pneumococcal diseases from the routine PCV7 immunization, to children in Malaysia.

**Websites**
