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Review Article

Carriage of *Streptococcus pneumoniae* in children under five years of age prior to pneumococcal vaccine introduction in Southeast Asia: A systematic review and meta-analysis (2001–2019)

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Abstract A number of pneumococcal carriage studies in children have been conducted in recent years. However, summary data of carriage prevalence and serotype distribution from South East Asia Region (SEAR) are limited. This may lead to the misconception that *Streptococcus pneumoniae* vaccine-types are uncommon in the region. Systematic reviews of pneumococcal carriage and the distribution of serotypes are critically important for evidence-based decision-making. We aimed to summarize published data on the serotype prevalence of *S. pneumoniae* carried in the nasopharynx of children under 5 years of age in SEAR. We performed a systematic review and meta-analysis for relevant studies on *S. pneumoniae* carriage conducted prior to PCV program implementation from online journal databases published between January 2001 to December 2019. The pooled prevalence of *S. pneumoniae* in healthy children under 5 years of age in SEAR was 36.0% (95% CI 34.2%–37.8%), and ranged from 68.0% (95% CI: 61.9%–74.0%) in Cambodia to 7.6% (95% CI: 5.7%–9.6%) in Malaysia. Serotypes 6A/B, 23F and 19F were the most common serotypes in children <5 years, accounting for 12.9% (95% CI: 9.4%–16.3%), 9.3% (95% CI: 5.9%–12.8%) and 10.1% (95% CI: 6.6%–13.5%) of isolates, respectively. Vaccine policy makers should take these results into account when making decisions on pneumococcal conjugate vaccine programs implementation. Given the paucity of data,

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collection of more extensive and updated information of *S. pneumoniae* serotype epidemiology in children under five years in SEAR is also very important for future studies.

Introduction

Streptococcus pneumoniae (the pneumococcus) is the most common cause of bacterial pneumonia and meningitis among children and adults worldwide. In 2016, it was estimated that *S. pneumoniae* was the leading cause of lower respiratory infection morbidity and mortality globally, contributing to more than 1 million deaths worldwide.[1] The mortality rate of patients with pneumococcal pneumonia ranges from 10–30%, whereas pneumococcal meningitis mortality rates in adults reach 16–37%.[2] The nasopharynx of children is a common reservoir of *S. pneumoniae*. There are approximately 100 serotypes of *S. pneumoniae* and several of them are highly virulent and can cause invasive pneumococcal disease (IPD) among children.[3–5] Most people colonized with *S. pneumoniae* do not develop invasive disease. However, nasopharyngeal colonization of *S. pneumoniae* is considered a prerequisite of invasive pneumococcal infection.[6] Pneumococcal carriage is common in young children, particularly in low-income settings. A meta-analysis performed from studies conducted around the globe found 20–93% children in low income countries carried pneumococci in their nasopharynx. This was generally higher compared with children in lower-middle income settings, where 6.5–69.8% of children carried the bacteria. Another study on pooled estimation showed similar results, with a carriage prevalence of 65% and 48% for children in low income and lower-middle income countries, respectively.[7]

Pneumococcal conjugate vaccines implementation

Pneumococcal conjugate vaccines (PCVs) are safe and highly effective, and have been in use in high-income countries for decades. The first PCV, PCV7, was introduced in the US in 2000.[8] Since then, global use has rapidly increased, and PCVs have been licensed in over 90 countries.[9] The two current generation vaccines are PCV10 and PCV13. PCV10 covers 10 pneumococcal serotypes of *S. pneumoniae* (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F). PCV13 covers the same serotypes, plus an additional three serotypes (3, 6A and 19A).[10,11] Pneumococcal vaccination provides herd immunity. Vaccinated children are less likely to transmit vaccine serotypes to others in the community, thereby preventing pneumococcal infection in unvaccinated individuals.[12] Pneumococcal vaccination has significantly reduced pneumococcal infections and deaths around the globe.[13–15] In 2012 the WHO made a clear recommendation for countries to introduce pneumococcal vaccine to protect children against *S. pneumoniae* infection.[16] However, there are still countries that have not yet decided to introduce the vaccine into national routine childhood immunization program, including several countries in Southeast Asia.

The population of South East Asia Region (SEAR) accounts for 8.5% of the world's population. Among 156 million annual new cases of childhood pneumonia, 39% occurred in SEAR. The incidence of pneumonia in children <5 years in SEAR is 0.36 episodes per child year, while the world average is 0.26 and the average for developing and developed countries are 0.29 and 0.05, respectively.[17,18] There are 11 countries in SEAR and only four have universal introduction of PCVs: Singapore (PCV13, 2009), Lao PDR (PCV13, 2013), Cambodia (PCV13, 2015) and Myanmar (PCV10, 2016). While Philippines conducted phased introduction of PCV10 and PCV13 in 2013, and Indonesia started the pilot demonstration of PCV13 in several provinces in 2018, the decision has not been made to include the vaccines into routine childhood immunization programs. The remaining countries in the region (Thailand, Vietnam, Malaysia, Brunei Darussalam) have not introduced the vaccine.[19] PCV program implementation in this region has been hampered by several possible reasons such as lack of data of pneumococcal infection, leading to the misconception that *S. pneumoniae* is not a burden to childhood morbidity and mortality in the region. Such as in Indonesia, the most populous country in the region with 9% of total population being children <5 years of age,[20] lack of data on pneumococcal disease burden in the country has likely hampered decisions to introduced pneumococcal vaccine into routine immunization programs for children.

There has been reviews and pooled data analysis for *S. pneumoniae* in SEAR over the years. In 2012, a review on the prevalence of *S. pneumoniae* included data from ten SEAR countries. This study analysed available data up to March 2012 and the results showed the scarcity of data on serotype prevalence in SEAR.[21] Another pooled data analysis published in 2016 included serotype distribution and the proportion of pneumococci that would be potentially prevented by pneumococcal conjugate vaccines for East and Southeast Asia.[22] Currently, there has been recent data available on *S. pneumoniae*, providing more thorough analysis on the carriage, serotype distribution and analysis of risk factors in the region. A number of studies regarding the nasopharyngeal carriage of *S. pneumoniae* in children under 5 years of age has been conducted. However, there is a lack of summary data that provide a pooled estimation of pneumococcal carriage and serotype prevalence prior to PCV program implementation in SEAR. This systematic review will provide analysis on more recent data on *S. pneumoniae* carriage and serotype distribution in the region. This study aimed to summarize nasopharyngeal carriage of *S. pneumoniae* in children under 5 years of age prior to pneumococcal vaccines (PCV10 and PCV13) introduction across countries in

Southeast Asia and describe serotypes prevalence of *S. pneumoniae* that are covered by PCV13.

Study design and operational definition

We performed a systematic review of published literature using the PRISMA 2009 statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[23] on carriage and serotype distribution of *S. pneumoniae* from online journal databases published between January 2001 to December 2019. Research included in this review were studies conducted in Southeast Asia involving children under 5 years of age.

We retrieved research articles from Pubmed, Science Direct and Jstor. The following combination of keywords were used; (*S. pneumoniae* OR pneumoniae OR pneumococcus) AND (pharyngeal OR nasopharyngeal OR oropharyngeal OR nasal OR serotype) AND (carriage OR colonization OR colonisation). We didn't have any language restriction for search terms. Research articles were included based on the following inclusion criteria: (i) Study was conducted in SEAR and/or the specimen were from Southeast Asian Population; (ii) publication date between 2001 and 2019; (iii) Pharyngeal or nasal specimen; (iv) if study conducted in adult and children, only estimations from children were included. Exclusion criteria were (i) Number of events not provided to calculate carriage prevalence, serotype prevalence and confidence interval (CI) estimation; (ii) sterile site specimen; (iii) review article or book/book chapter; (iv) conducted outside Southeast Asia. Research meeting inclusion and exclusion criteria were then reviewed by three reviewers independently. Multicenter studies or studies conducted in more than one country were included if individual data to calculate the carriage prevalence in each country were reported. Studies with participants from different age groups were included if data available for each group.

Variable and data collection

Data collection forms were used to extract the following information: title, authors and year of the study; sample size; carriage prevalence; number of isolates (number of *S. pneumoniae* identified); number of serotypes identified. Data extraction forms from all reviewers were then combined into one Microsoft Excel spreadsheet. The reviewers re-checked all discrepancies to check for errors in data extraction. We used final extracted data for the estimate calculation of carriage prevalence. Extracted data included country, study years, authors, study design, population studied, type of specimen, type of swabs use for collection, transport media, number of subjects and number of *S. pneumoniae* identified.

The overall carriage prevalence, and the prevalence of each serotype, were calculated using available data. Heterogeneity between studies was assessed using the I^2statistic. We used Stata Software version 15.0 to perform meta-analysis (*metaeff*) to calculate *effect size* (ES) and *Standard Errors* (SE).[24] We also performed meta-analysis (*metaan*) to calculate pooled estimation and Confidence intervals (CI) for each variable.

We identified 147 studies related to nasopharyngeal carriage of *S. pneumoniae* in SEAR from several online databases. Among them, 85 studies were excluded due to lack of data provided and a further 19 studies excluded as they were not conducted in children under 5 years of age. Forty-three studies were included in the systematic review and were assessed by three reviewers. Among the 43, 32 were excluded after agreement between reviewers due to specimen collected from sterile site and the lack of data provided to calculate the estimates of prevalence and CI. Therefore, 11 studies were included in meta-analysis (Fig. 1). Among these, one study was a multinational, and was conducted in 11 countries including five countries from SEAR (Table 1). Meta-analysis was conducted per country regardless of study sources. While all these studies were conducted in a period of 19 years, all studies were conducted prior to PCV10 and/or PCV13 introduction into National Childhood Immunization Programs in each respective country.

The number of children under 5 years of age in each study varied from less than 200 to more than 4000 (Table 2). Ten of 11 studies were conducted in a healthy population[25–34] and the other one was conducted in patient with upper respiratory tract infections (URTI).[35] Nine studies were conducted solely in children under 5 years of age,[26,27,29–35] while the other two studies were conducted in both children <5 and adults[25,28] with each group data available. Based on type of specimens collected to identify *S. pneumoniae*, nine studies collected nasopharyngeal swabs[25,33,27,28,30,35,31,34,32] while the other two identified *S. pneumoniae* from nasal swabs.[26,29]

All studies used conventional microbiologic methods (optochin susceptibility and/or bile solubility test) for *S. pneumoniae* identification. Two studies performed Polymerase Chain Reaction (PCR) for serotyping of *S. pneumoniae*[27,33] and the other nine performed Quellung reaction using antisera in the Pneumotest Kit by Staten Serum Institute (SSI).[35,25,28,34,32,26,29–31]

The prevalence of *S. pneumoniae* carriage

Total subjects included in the analysis were 11,501 children <5 years of age. Over one-third of subjects were from Thailand (39.0%),[28,29] followed by Indonesia (22.8%)[27,30,31,33,34] with Lao PDR[32] and Malaysia[26,29] contributing 8.7% and 8.3% respectively. The remaining 19.3% were from Cambodia, Vietnam, Philippines and Singapore combined.[28,29,35] *S. pneumoniae* were identified in 4139 participants. Fixed effects meta-analysis showed that the pooled prevalence of *S. pneumoniae* in healthy children under 5 years of age in SEAR was 36.0% (4139/11,501) with 95% CI 34.2%–37.8% (Table 2).

We found the prevalence of *S. pneumoniae* carriage varied across countries in SEAR as shown in forest plot (Table 2). The prevalence of *S. pneumoniae* in children <5 years of age in SEAR ranged from 7.6% to 68.0%. The highest prevalence of carriage was found in Cambodia with prevalence of 68.0% (95% CI: 61.9–74.0). Lowest prevalence was found in Malaysia with prevalence of 7.6% (95% CI: 5.7–9.6) (Table 2). Heterogeneity between studies was observed in this analysis with $I^2 = 93.5\%$.

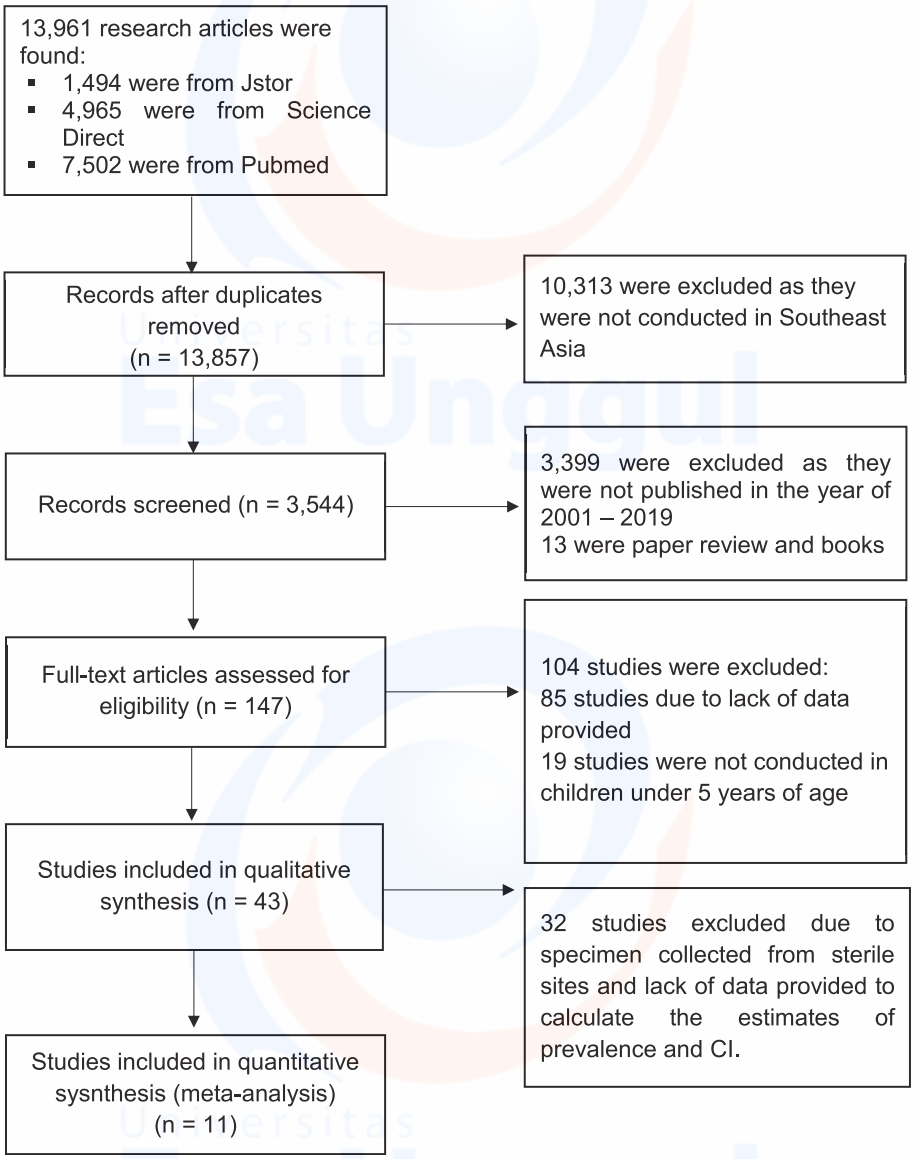


Figure 1. Prisma flowchart - literature review process.

Risk factors

Risk factors analysis (bivariate and/or multivariate analysis) and p value and/or Odds Ratio (OR) were reported in eight studies, while one study reported risk factors associated with *S. pneumoniae* carriage with no p value or OR.[25] The other two studies did not report risk factors analysis, p value or OR.[35,26]

Age was reported to be a factor associated with pneumococcal carriage in three studies.[27,33,34] Exposure to cigarette smoke and having URTI were reported as risk factors in five studies.[25,31–34] Two studies reported recent antimicrobial use as one of the factors associated with carriage as well as living in urban area.[32,34] Other risk factors for carriage (such as season, having otitis media, day care enrolment, weight, height, maternal and paternal education, born by vaginal delivery, poverty and the use of wood as fuel for cooking) were only reported in one study each.[28,29,31,32]

Among studies that reported risk factors age, passive smoking and history of illness (otitis media and URTI) were significantly associated with carriage. Age as a risk factor for pneumococcal carriage were reported in three studies. Age was reported to be one of the risk factor in Lombok Indonesia with p value 0.041[27] and Semarang with OR 7.7 (95% CI 1.5–13.0) for being a child (analysis compared children age 6–60 months and adults age 45–70 years). The same study conducted in Semarang Indonesia, indicated passive smoking was also significant risk factor to carriage with OR 2.1 (95% CI 1.4–3.4).[33] Furthermore, a multi-center study conducted in Vietnam, Singapore, Thailand, Malaysia and Philippines found that history of otitis media was associated with carriage with OR 7.03 (95% CI 1.7–28.4) and p value 0.006 in the multivariate analysis.[29] URTI were

Table 1 Characteristic of study.

First Author & Year	Country	Population	Location	Residence	Type of Specimen	Media Transport	Type of Swabs
Turner et al., 2012	Thailand	Healthy Children and Adult	Camp	Rural	NP	STGG	Dacron
Yatim et al., 2012	Malaysia	Healthy Children <5	Day Care Centers	Urban	Nasal	Amies Transport Media	Cotton Tipped
Farida et al., 2014	Indonesia	Healthy Children <5	Posyandu	Urban	NP	Amies Transport Media	Rayon Tipped
Hadinegoro et al., 2016	Indonesia	Healthy Children <5	Posyandu	Rural	NP	STGG	Flocked
Turner et al., 2015	Cambodia	Healthy Children and Adult	Outpatient Department	Urban	NP	STGG	Flocked Nylon
Lee et al., 2001	Vietnam	Healthy Children <5	Day Care Centers of Outpatient Clinics	Urban	Nasal	Specimen plated immediately onto trypticase soy agar plates	Cotton Tipped
Lee et al., 2001	Singapore						
Lee et al., 2001	Thailand						
Lee et al., 2001	Malaysia						
Lee et al., 2001	Philippines						
Soewignjo et al., 2001	Indonesia	Healthy Children <5	Posyandu	Urban and Rural	NP	Amies Transport Media	Calcium Alginate
D. Bogaert et al., 2002	Vietnam	Children with URTI	Hospital and Clinic	Urban	NP	Not Stated	Not Stated
Dunne et al., 2018	Indonesia	Healthy Children <5	Health Center	Urban and Rural	NP	STGG	Flocked Nylon
Murad et al., 2019	Indonesia	Healthy Children <5	Health Center	Urban and Rural	NP	STGG	Not Stated
Satzke et al., 2019	Lao PDR	Healthy Children <5	Household Visit	Urban and Rural	NP	STGG	Flocked Nylon

found to be one of the factors associated with carriage in Indonesia and Lao PDR with p value 0.001 and < 0.001, respectively.[31,32]

Two studies reported that contact with other children <5 years to be one of the factors associated with carriage. A study conducted in Semarang Indonesia found that contact with toddler(s) at home increased the risk of pneumococcal carriage with OR 3.0 (95% CI, 1.9–4.7).[33] A similar result was shown in Thailand where cohabitation with other children was found to be correlated with carriage with OR 1.4 (95% CI 1.0–1.9).[25] Moreover, a multicenter study conducted in Vietnam, Singapore, Thailand, Malaysia and Philippines found that day care enrolment increased the risk of carriage with OR 1.6 (95% CI 1.2–2.2) and p value 0.003.[29]

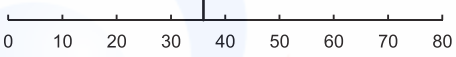
Serotype distribution

We found that serotype 6A/B, 23F, 19F were among the most common serotype reported in SEAR. Meta-analysis showed the pooled prevalence of serotype 6A/B was 12.9% (412/3201) with 95% CI: 9.4%–16.3%. The highest prevalence of 6A found in Malaysia with 39.0% (27/69) with 95% CI: 24.3%–53.7% and lowest prevalence of 6A/B was found in Thailand with 7.9% (119/1504) with 95% CI: 6.5%–9.3% (Table 3).

Serotype 23F accounted for 9.3% (299/3201) with 95% CI: 5.9%–12.8%. The highest prevalence of 23F was found in Vietnam with 32.1% (27/84) with 95% CI: 20.0%–44.3% and the lowest prevalence of 23F found in Indonesia with 5.7% (18/318) with 95% CI: 3.0%–8.3% (Table 4).

Table 2 Prevalence of *S. pneumoniae* across southeast Asian countries.

First Author & Year	Country	#Subject	#Subject Positive *S. pneumoniae*	Forest Plot	Carriage Rate (%)	95%CI	
						Lower	Upper
Turner *et al*, 2012	Thailand	4191	1504		35.9	34.1	37.7
Yatim *et al*, 2012	Malaysia	195	69		35.4	27.0	43.7
Farida *et al*, 2014	Indonesia	243	111		45.7	37.2	54.2
Hadinegoro *et al*, 2016	Indonesia	1200	557		46.4	42.6	50.3
Turner *et al*, 2015	Cambodia	721	490		68.0	61.9	74.0
Lee *et al*, 2001	Vietnam	295	92		31.2	24.8	37.6
Lee *et al*, 2001	Singapore	491	41		8.4	5.8	10.9
Lee *et al*, 2001	Thailand	503	165		32.8	27.8	37.8
Lee *et al*, 2001	Malaysia	762	58		7.6	5.7	9.6
Lee *et al*, 2001	Philippines	307	95		30.9	24.7	37.2
Soewignjo *et al*, 2001	Indonesia	484	223		46.1	40.0	52.1
D. Bogaert *et al*, 2002	Vietnam	410	84		20.5	16.1	24.9
Dunne *et al*, 2018	Indonesia	302	150		49.7	41.7	57.6
Murad *et al*, 2019	Indonesia	396	106		26.8	21.7	31.9
Satzke *et al*, 2019	Lao PDR	1001	394		39.4	35.5	43.2
Summary		11501	4139		36.0	34.2	37.8



Meta-analysis for serotype 19F found the pooled prevalence of serotype 19F was 10.1% (322/3201) with 95% CI: 6.6%—13.5%. The highest prevalence of 19F found in Vietnam with 22.6% (19/84) with 95% CI: 12.4%—32.8% and lowest prevalence of 19F was found in Lao PDR with 5.8% (23/394) with 95% CI: 3.4%—8.2% (Table 5).

Estimate pooled prevalence for serotype 19A was 3.6% (53/1502) with 95% CI: —1.5% - 8.6%. Malaysia has the highest prevalence of 19A with 11.6% (8/69) with 95% CI: 3.6%—19.6%. The lowest prevalence of 19A was found in Indonesia with 1.2% (2/164) with 95% CI: —0.5% - 2.9% (Table 6). Heterogeneity between studies were not present in this analysis with I^2 lower than 10%.

Serotype 3 accounted for 2.1% (20/960) with 95% CI: —4.2% - 8.4%. We found the highest prevalence of serotype 3 was in Indonesia with 4.9% (8/164) with 95% CI: 1.5%—8.3%. Lowest prevalence of serotype 3 was found in Lao DPR with 0.3% (1/394) with 95% CI: —0.2% - 0.8% (Table 7). Heterogeneity between studies were not present in this analysis with I^2lower than 10%.

Discussion

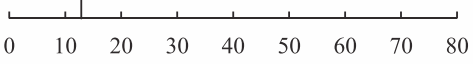
Our systematic review summarized the prevalence of pneumococcal carriage in the community settings of children under <5 years of age across South East Asian countries (Indonesia, Vietnam, Thailand, Singapore, Malaysia, Philippines, Cambodia and Lao PDR).[25,26,33,27—30,35,31,34,32] Over one-third of the subjects analysed in this review were from Thailand. Published pneumococcal carriage studies from the rest of the SEAR (Myanmar, Brunei and East Timor) were not available at the time of data extraction.

While SEAR is one of the most populous regions in the world, studies on pneumococcal carriage are severely lacking in this area. Among those available, published studies included in this review were sparsely scattered over the period of almost two decades. Data for carriage prevalence in several countries, such as Vietnam and Philippines, was only available from 19 years ago. Unfortunately, with so few published studies, we were unable to analyse any changes over time. Importantly, however, although these studies were scattered over a long period of time, all studies were conducted prior to PCV program implementation in each respective country. Therefore, they are still relevant to evaluate *S. pneumoniae* carriage prior to pneumococcal vaccination program implementation in Southeast Asian countries.

We found that overall pneumococcal carriage was relatively high in SEAR. However, the variation of carriage prevalence was also high between countries. This be could due to several factors that may contribute to carriage prevalence such as geographic (urban or rural) and demographic factors (i.e., age, sex, maternal education, household size). However, after comparing studies in the same country with different settings, we found that carriage prevalences were similar between studies conducted exclusively in rural and urban Indonesia and Thailand.[25,27,29,33] This is consistent with findings in systematic reviews conducted in lower-middle income countries that showed no significant difference in carriage prevalence between rural and urban settings.[7] Similar

Table 3 Prevalence of serotype 6A/B across Southeast Asian countries.

First Author & Year	Country	#*S. pneumoniae*	6A/B	Forest Plot	Carriage Rate (%)	95%CI	
						Lower	Upper
Turner *et al*, 2012	Thailand	1504	119		7.9	6.5	9.3
Yatim *et al*, 2012	Malaysia	69	27		39.0	24.3	53.7
Farida *et al*, 2014	Indonesia	111	21		18.9	10.8	27.0
Hadinegoro *et al*, 2016	Indonesia	557	120		21.5	17.7	25.4
D. Bogaert *et al*, 2002	Vietnam	84	14		16.7	7.9	25.4
Dunne *et al*, 2018	Indonesia	164	24		14.6	8.8	20.5
Murad *et al*, 2019	Indonesia	318	35		11.0	7.4	14.7
Satzke *et al*, 2019	Lao PDR	394	52		13.2	9.6	16.8
Summary		3201	412		12.9	9.4	16.3



results were also shown in other countries such as Pakistan and Ethiopia, that concluded there were no significant differences in carriage prevalence between urban and rural.[36,37]

Rather than the study settings itself, the variation in carriage prevalence between studies might be due to other factors such as the difference in methods used during collection that might influence the recovery rate of *S. pneumoniae*. Studies showed variation in type of swabs and transport media used to collect the specimen, and type of specimen itself (Table 1).

Studies conducted in Singapore and Malaysia that detected *S. pneumoniae* from nasal swab specimens were among the lowest carriage prevalence compare to other countries.[26,29] Although several studies showed that the sensitivity of nasal swabs were similar with nasopharyngeal swab, detection of *S. pneumoniae* from nasal swab specimens might lower the recovery rate of *S. pneumoniae* in some countries.[38–41]

The difference in carriage prevalence across countries could also be due to the difference in transport media used for the swabs collected. Studies that used Amies transport medias such as in Malaysia[26] and Indonesia,[30] were found to have lower carriage prevalence compared with studies that used STGG as transport media for the specimen collected.[27,28,31] This is similar with the finding of studies

Table 4 Prevalence of serotype 23F across Southeast Asian countries.

First Author & Year	Country	#*S. pneumoniae*	23F	Forest Plot	Carriage Rate (%)	95%CI	
						Lower	Upper
Turner *et al*, 2012	Thailand	1504	135		9.0	7.5	10.5
Yatim *et al*, 2012	Malaysia	69	13		18.8	8.6	29.0
Farida *et al*, 2014	Indonesia	111	10		9.0	3.4	14.6
Hadinegoro *et al*, 2016	Indonesia	557	58		10.4	7.7	13.1
D. Bogaert *et al*, 2002	Vietnam	84	27		32.1	20.0	44.3
Dunne *et al*, 2018	Indonesia	164	15		9.1	4.5	13.8
Murad *et al*, 2019	Indonesia	318	18		5.7	3.0	8.3
Satzke *et al*, 2019	Lao PDR	394	23		5.8	3.5	8.2
Summary		3201	299		9.3	5.9	12.8

Table 5 Prevalence of serotype 19F across Southeast Asian countries.

First Author & Year	Country	#*S. pneumoniae*	19F	Forest Plot	Carriage Rate (%)	95%CI	
						Lower	Upper
Turner *et al*, 2012	Thailand	1504	169		11.2	9.5	12.9
Yatim *et al*, 2012	Malaysia	69	6		8.7	1.7	15.7
Farida *et al*, 2014	Indonesia	111	9		8.1	2.8	13.4
Hadinegoro *et al*, 2016	Indonesia	557	64		11.5	8.7	14.3
D. Bogaert *et al*, 2002	Vietnam	84	19		22.6	12.4	32.8
Dunne *et al*, 2018	Indonesia	164	13		7.9	3.6	12.2
Murad *et al*, 2019	Indonesia	318	19		6.0	3.3	8.7
Satzke *et al*, 2019	Lao PDR	394	23		5.8	3.4	8.2
Summary		3201	322		10.1	6.6	13.5

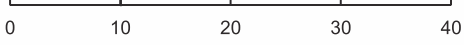


Table 6 Prevalence of serotype 19A across Southeast Asian countries.

First Author & Year	Country	#*S. pneumoniae*	19A	Forest Plot	Carriage Rate (%)	95%CI	
						Lower	Upper
Yatim *et al*, 2012	Malaysia	69	8		11.6	3.6	19.6
Hadinegoro *et al*, 2016	Indonesia	557	24		4.3	2.6	6.0
Dunne *et al*, 2018	Indonesia	164	2		1.2	-0.5	2.9
Murad *et al*, 2019	Indonesia	318	7		2.2	0.6	3.8
Satzke *et al*, 2019	Lao PDR	394	12		3.1	1.4	4.9
Summary		1502	53		3.6	-1.5	8.6

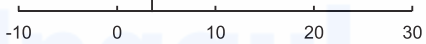
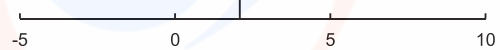


Table 7 Prevalence of serotype 3 across Southeast Asian countries.

First Author & Year	Country	#*S. pneumoniae*	3	Forest Plot	Carriage Rate (%)	95%CI	
						Lower	Upper
D. Bogaert *et al*, 2002	Vietnam	84	1		1.2	-1.1	3.5
Dunne *et al*, 2018	Indonesia	164	8		4.9	1.5	8.3
Murad *et al*, 2019	Indonesia	318	10		3.1	1.2	5.1
Satzke *et al*, 2019	Lao PDR	394	1		0.3	-0.2	0.8
Summary		960	20		2.1	-4.2	8.4



on the validation of media for transportation of *S. pneumoniae* that stated STGG should be adopted for pneumococcal carriage studies due to higher yield and efficacy.[16,42]

Swabs used for the collection of specimens could also be the reason of variation in carriage prevalence across studies. Studies that used calcium alginate swabs, Dacron, cotton and rayon tipped-swabs[25,26,29,30,33] had lower prevalence of carriage compared with studies that used flocked swabs.[27,28,31] Similarly, a study found that flocked swabs improved the recovery rate and detection of *S. pneumoniae* from nasopharyngeal swabs. Flocked swabs have higher percentage recovery of *S. pneumoniae* (100%), than Dacron swabs (41%) or rayon swabs (7%).[43]

It is also important to note that demographic factors and underlying conditions of subjects in each study might also contributed to pneumococcal carriage prevalence. Age was one of the most common risk factors reported. It was reported in a quarter of the studies along with exposure to cigarette smoke and having URTI. This is consistent with other studies that found younger children had more risk to carry *S. pneumoniae* than older children.[44–47] Furthermore, exposure to cigarette smoke and URTI may increase the risk of being colonised with the bacteria. This is consistent with findings from a study conducted in Israel. Children exposed to cigarette smoke had a higher prevalence of pneumococcal carriage than children without exposure to cigarette smoke.[48] Likewise, studies conducted in mother and infants in Africa showed that tobacco smoke exposure was associated with pneumococcal carriage in infants.[49] Furthermore, URTI also correlated with *S. pneumoniae* carriage in children <5 years and increased pneumococcal density.[46,47]

We also analysed the distribution of pneumococcal serotypes. We found that serotype 6A/B, 19F and 23F which are included in the current pneumococcal conjugate vaccine (PCV13) were the most common serotypes identified in SEAR. This is consistent with the findings from other systematic reviews and a surveillance study conducted in Iran that found 6A/B, 19F and 23F were the most common circulating serotypes.[50,51] Moreover, a study conducted in several countries found that serotype 6A/B, 19F and 23F were the highest isolated serotype in Malaysian children and were the most common in African children as well as children in China.[52–54] Consistent with this, a study in Shanghai found serotype 6A/B, 19F and 23F were among the most common serotypes in children <5 years.[55] Among immunocompromised children in Indonesia, and healthy children in India and Serbia, those three serotypes were also the most common.[56–58]

Analysis on other serotypes including serotype 3 and 19A was also performed. Serotype 3 was analysed using data available from studies conducted in Vietnam, Indonesia and Lao PDR.[31,32,34,35] Other countries in SEAR did not detect serotype 3 in *S. pneumoniae* isolates. We found that the prevalence of serotype 3 in children in SEAR was low. Our finding is broadly consistent with results found from systematic-review conducted in mainland China that showed serotype 3 was low in children.[54,59]

Analysis performed for serotype 19A found that the prevalence was relatively low in SEAR. It is important, however, to note that the analysis for 19A were only performed from data available from Malaysia, Indonesia and Lao PDR.[26,27,31,32,34] Data from Thailand, Singapore, Philippines and Cambodia were unable to be included in the analysis as they were reported as serogroup 19. Nevertheless, results in this review were consistent with findings in Brazil, Mexico and Ethiopia that showed serotype 19A were lower in pre-vaccine era than after vaccine was introduced.[60–62] Additionally, findings from several countries in Europe showed that serotype 19A was lower before the introduction of PCV10.[63]

In regard to pneumococcal vaccines, serotype 3 and serotype 19A are additional serotypes included in PCV13 along with serotype 6A. Currently, WHO has not published a position paper recommending a specific PCV-product. Decision on the introduction of either PCV10 or PCV13 is recommended based on local epidemiology.[64,65]

Results on other serotypes were scarcely scattered across studies. Meta-analysis for those serotypes was not able to be performed as very few studies could be included in the analysis for each serotype. There was not enough data to calculate prevalence, CI estimation, *effect size* (ES) and *standard errors* (SE) to provide accurate representation.

It is worth noting that few studies have been conducted to evaluate serotype distribution of *S. pneumoniae* in Southeast Asian countries. Therefore, analysis on such scarce data should be taken with caution. Importantly, however, the serotyping results found in this review are consistent with findings in several other countries across the globe. There are at least 100 serotypes of *S. pneumoniae* and serotype 6A/B, 19F and 23F were among the most common serotype found in children.[50–58]

Apart from the lack of studies on pneumococcal carriage available in SEAR, another limitation in this systematic review was the lack of data in those published studies that were available for the calculation of carriage prevalence, serotype prevalence, CI estimation, ES and SE in the meta-analysis. Due to this reason, only a small group of studies met inclusion criteria and were included in the analysis. This contributed to the high variation (I^2) generated in meta-analysis.

Conclusion

This systematic review found that more than a quarter of children <5 years of age in SEAR were colonized with *S. pneumoniae*. Serotypes 6A/B, 19F and 23F were the most common serotypes found prior to pneumococcal vaccination program implementation into national childhood immunisation programs in Southeast Asian countries. The prevalence of serotype 3 and 19A, two of the three additional serotypes included in PCV13, were relatively low prior to pneumococcal vaccination program implementation in SEAR.

Currently, there are two available pneumococcal conjugate vaccines, PCV10 and PCV13. Decision on the introduction of a specific PCV-product in country and/or region should be based on local epidemiology. Vaccine policy makers should take these results into account when making decisions of pneumococcal conjugate vaccine program implementation. Given the paucity of data, collection of more extensive and updated information of *S. pneumoniae* serotype epidemiology in children under five years in SEAR is also very important for future studies.

Authors' contribution

WODD, DS and CS designed and conceived the study; WODD and IMA performed the analysis; WODD, DS, HA, IMA and CS wrote the manuscript; all the authors read and approved the final manuscript.

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Declaration of competing interest

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