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By Dodi Safari

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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 has been conducted in recent years. However, summary data of carriage prevalence and serotype distribution from Southeast Asia are limited. This may lead to misconception that S. pneumoniae vaccine-type was not prevalent in the region. Systematic review of pneumococcal carriage and serotype distribution are critically important to provide evidence-based data to inform decision making policy. 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 Southeast Asia. We performed a systematic review and meta-analysis for relevant studies on S. pneumoniae carriage conducted prior to PCV introduction from online journal databases published between January 2001 to December 2019. Pooled prevalence of S. pneumoniae in healthy children under 5 years of age in Southeast Asia was 38.0% (95% CI: 30.4 – 45.5), ranged from 68.0% (95% CI: 61.9 – 74.0) in Cambodia, to 8.4% (95% CI: 5.8 – 10.9) in Singapore. Serotypes 6A/B and 23F were accounted for 21.8% (95% CI: 17.0% - 26.7%) and 15.5% (95%: 11.5% - 19.5%), respectively. Serotype 6A/B and 23F which are included in the current pneumococcal conjugate vaccine were the most common serotypes in Southeast Asia. This information is critically important to inform decision making policy in the region including introduction of pneumococcal vaccine into routine immunization programs.

Abstract A number of pneumococcal carriage studies in children has been conducted in recent years. However, summary data of carriage prevalence and serotype distribution from Southeast Asia are limited. This may lead to misconception that *S. pneumoniae* vaccine-type was not prevalent in the region. Systematic review of pneumococcal carriage and serotype distribution are critically important to provide evidence-based data to inform decision making policy. 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 Southeast Asia. We performed a systematic review and meta-analysis for relevant studies on *S. pneumoniae* carriage conducted prior to PCV introduction from online journal databases published between January 2001 to December 2019. Pooled prevalence of *S. pneumoniae* in healthy children under 5 years of age in Southeast Asia was 38.0% (95% CI: 30.4 – 45.5), ranged from 68.0% (95% CI: 61.9 – 74.0) in Cambodia, to 8.4% (95% CI: 5.8 – 10.9) in Singapore. Serotypes 6A/B and 23F were accounted for 21.8% (95% CI: 17.0% - 26.7%) and 15.5% (95%: 11.5% - 19.5%), respectively. Serotype 6A/B and 23F which are included in the current pneumococcal conjugate vaccine were the most common serotypes in Southeast Asia. This information is critically important to inform decision making policy in the region including introduction of pneumococcal vaccine into routine immunization programs.

KEYWORDS: *Streptococcus pneumoniae*; pneumococcal carriage; pneumococcal conjugate vaccine

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 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.[7] This was generally higher compared with children in lower-middle income settings, where 6.5% - 69.8% of children carried the bacteria. Results of pooled estimation showed similar results, with a carriage rate of 65% and 48% for children in low income, or lower-middle income, countries, respectively.[7]

Pneumococcal conjugate vaccines (PCVs) are safe and highly effective, and have been in use in high-income countries for decades. The first PCV, PCV7, were introduced in the US in 2000.[8] Since then, global use has rapidly increased, and PCVs are 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 may protect and prevent the transmission of vaccine serotypes in the community, therefore prevent pneumococcal infection in those unvaccinated with most risk of mortality.[12] Furthermore, it has been showed that pneumococcal vaccination significantly reduced pneumococcal infections cases and deaths around the globe.[13–15] The WHO has made clear its position on pneumococcal vaccine in 2012 and recommends countries to introduce PCV 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. Sixty-one of the 156 million new cases of childhood pneumonia each year occurred in SEA. Furthermore, the incidence of pneumonia in children <5 in SEA 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 DPR (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 program. The remaining countries in the region (Thailand, Vietnam, Malaysia, Brunei Darussalam) have not introduced the vaccine.[19] PCV introduction in this region have 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. For example, although Indonesia, is the most populous country in the region with 9% being children <5 years of Indonesia,[20] lack of data on pneumococcal disease burden in the country has likely hampered decisions to introduced pneumococcal vaccine into routine immunization program 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 *S. pneumoniae* included data from 10 SEAR countries. This study analyzed available data up to March to 2012 and the results showed the scarcity of data on serotype prevalence in SEAR.[21] Another pooled data analysis published in 2016 was serotype distribution and pneumococcal conjugate vaccine serotype carriage for East and Southeast Asia.[22] However, this study focused on East Asia region and only included one SEAR country, Thailand, due to lack of data from other SEAR countries at that time.

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 of PCV introduction 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.

Methods

Study Design, Settings and Participants

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 the collection of nasopharyngeal specimens from children under 5 years of age.

Operational Definition

We retrieved research articles from Pubmed, Science Direct and Jstor. The following combination of keywords are 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 Southeast Asia Region (SEAR) and/or the specimen are from Southeast Asian Population; (ii) publication date between 2001 – 2019; (ii) Pharyngeal and nasal specimen; (iii) 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 rate, serotype prevalence and confidence interval estimation; (ii) sterile site specimen; (iii) review article or book/book chapter; (iv) conducted outside Southeast Asia. Research met inclusion and exclusion criteria were then reviewed by three reviewers independently. Multi-centers study or study conducted in more than 1

country and/or more than 1 province were included if individual data to calculate the carriage prevalence in each country and/or province 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 rate; number of isolates (number of *S. pneumoniae* identified); number of serotypes identified (non-typeable isolates were excluded from the meta-analysis). Data extraction forms from all reviewers were then combined into one excel spreadsheet. The reviewers re-checked all discrepancies to check for errors such as 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, number of *S. pneumoniae* identified.

Statistical Method

The overall carriage rate, 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 interval for each variable.

Results

Results of the Literature Search

We identified 147 studies related to nasopharyngeal carriage of *S. pneumoniae* in SEA from several online databases. Eighty-five studies were excluded due to lack of data provided, and 19 studies 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, 31 were excluded after agreement between reviewers due to the lack of data provided to calculate the estimates of prevalence and confidence interval and specimen collected from sterile site. Therefore, 12 studies were included in the systematic review, data extraction and meta-analysis (Figure 1).

The number of subjects in each study varied from less than 50 to more than 4,000 children under 5 years of age. Seventeen of 18 studies were conducted in a healthy population. Only one study was conducted in patient with upper respiratory tract infections (URTI).[25] Eight studies were conducted in children under 5 years of age,[26–33] while the other 3 studies were conducted in both children <5 and adults [34–36] with each group data available. Nine studies collected nasopharyngeal swabs for *S. pneumoniae* identification,[25,34,35,27,28,36,31–33] 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. Three studies performed Polymerase Chain Reaction (PCR) for serotyping of *S. pneumoniae* [27,28,36] and the other 15 performed Quellung reaction using antisera in the Pneumotest Kit by Staten Serum Institute (SSI).[25,34,35,31–33,26,29,30] All studies were conducted prior to PCV10 and/or PCV13 introduction into National Childhood Immunization Program in each country.

We found the prevalence of *S. pneumoniae* carriage were varied across countries in SEA as shown in forest plot (Figure 2). The prevalence of *S. pneumoniae*

in children <5 years of age in SEA ranged from 9.0% to 68.0%. The lowest carriage rate was found in Singapore with 9.0% (44/491) of children <5 years of age carrying *S. pneumoniae*.[29] The highest carriage rate was found in Cambodia with 68.0% (490/721).[35]

Risk Factors

Risk factors analysis (bivariate and/or multivariate analysis) and reported p value and/or Odds Ratio (OR) were reported in 14 studies, while 1 study reported risk factor associated with *S. pneumoniae* carriage with no p value [34] or OR reported and the other 3 studies were not reported risk factors analysis, p value or OR.[25,36,26]

Of the seven studies that reported risk factors associated with carriage, these included age, passive smoking and maternal education. Age was reported to be one of the risk factor in Lombok Indonesia with p value 0.041 [28] and Semarang with OR 7.7 (CI 1.5 - 13.0) for being a child (analysis compared children age 6-60 months and adults age 45 – 70). In the same study conducted in Semarang Indonesia, passive smoking was also significant risk factor to carriage with OR 2.1 (CI,1.4–3.4).[27] A study conducted in Padang, Bandung and Lombok found maternal education (high school and above was significant factor to carriage with OR 0.61 (0.38 - 0.97) p value 0.037 showed a protective effect for mother who graduated high school or higher education.[31]

History of illnesses such URTI and otitis media and underlying conditions such as stunting were also found to be associated with pneumococcal carriage. A multi-center study conducted in Vietnam, Singapore, Thailand, Malaysia and Philippines found that history of otitis media was associated with carriage with OR 1.7-28.4 and p value 0.006 in the multivariate analysis.[29] Furthermore, a multi-center study conducted in Indonesia in the region of Padang, Bandung and Lombok found that URTI was one

of the factors that could increase the odds of carriage with OR 2.57 (1.42 - 4.63) and p value 0.002. In the same study, stunting was also associated with carriage with OR 1.82 (1.08 - 3.05) p value 0.024.[31]

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 (CI, 1.9–4.7).[27] A similar result was found in the multi-center study conducted in Vietnam, Singapore, Thailand, Malaysia and Philippines with OR for day care enrollment 1.6 (1.2 - 2.2) and p value 0.003.[29]

Meta-analysis of Pneumococcal Carriage

We included 18 studies consisting of 11,548 children under 5 years of age in eight counties in SEAR. Random effects meta-analysis showed that the pooled prevalence of *S. pneumoniae* in healthy children under 5 years of age in SEAR was 38.0% (95% CI: 30.4 – 45.5). These studies were substantially heterogeneous with $I^2 = 92.3\%$. The highest rates of carriage were found in Cambodia with prevalence of 68.0% (95% CI: 61.9 – 74.0). Lowest rate was found in Singapore with prevalence of 8.4% (95% CI: 5.8 – 10.9) (Table 1).

Meta-analysis showed the pooled prevalence of serotype 6A/B was 21.8% (95% CI: 17.0% - 26.7%) with the highest rate of 6A found in Singapore with 48.0% (95% CI: 27.4% – 70.2%) and lowest rate of 6A/B was found in Bandung Indonesia with 7.8% (95% CI: 1.0% – 14.7%) (Table 2). This analysis was moderately heterogenous with $I^2 = 31.9\%$. Serotype 23F accounted for 15.5% (95% CI: 11.5% - 19.5%). The highest rate of 23F was found in Vietnam with 27.2% (95% CI: 16.5% - 37.8%) and the lowest rate of 23F found in Philippines with 8.4% (95% CI: 2.6% -

14.3%) (Table 3). Heterogeneity between studies were not present in this analysis with I^2 lower 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 DPR).[25,34,35,27,28,36,31–33,26,29,30] Most of the studies included in the meta-analysis were from Indonesia. Published pneumococcal carriage studies from the rest of the South East Countries (Myanmar, Brunei and East Timor) were not available at the time of data extraction.

We found that overall pneumococcal carriage was relatively high. However, the variation of carriage rates between countries was also high. This could be due to the difference in site of specimen (nasopharyngeal and anterior nasal swabs) collected to evaluate the carriage rate in each study. Such as study conducted in Singapore and Malaysia that detected the *S. pneumoniae* from nasal swabs specimen were among the lowest carriage rates compare to other countries and/or in the same country but used nasopharyngeal swabs specimen instead for detection of *S. pneumoniae*.[29,36] Although several studies showed that the sensitivity of nasal swab was similar with nasopharyngeal swab, detection of *S. pneumoniae* from nasal swab specimen might lower the recovery rate of *S. pneumoniae* in some countries.[37–40]

The different in carriage rates across countries could also be due to the different in transport media used for the swabs collected. Studies that used Amies transport media such as in Malaysia [26] and Indonesia [30] were found to have lower carriage rates compared with studies used STGG as transport media for the specimen

collected.[28,31,35] This finding similar with the finding of study 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.[16,41]

Swabs used for the collection of specimens could also be the reason of variation in carriage rates across studies. Studies that used calcium alginate swabs, Dacron, cotton and rayon tipped-swab [26,27,29,30,34] had lower rates of carriage compared with studies that used flocked swabs.[28,31–33] Similar study found that flocked swab improved the recovery rate and detection of *S. pneumoniae* from nasopharyngeal swabs. Flocked swabs has higher percentage recovery of *S. pneumoniae* (100%), than Dacron swabs (41%) or rayon swabs (7%).[42]

One of the limitations in this systematic-review were lack of data in published studies available for the calculation carriage rate, serotype prevalence, confidence interval estimation, *effect size* (ES) and *standard errors* (SE) in the meta-analysis. Only small number of studies included in the analysis due to this reason. As outlined above, the variation in type of specimen between studies were also a limitation in this study.

Conclusions

This systematic review found that more than one third of children <5 years of age in Southeast Asian countries were colonized with *S. pneumoniae*. Serotype 6A/B and 23F which are included in the current pneumococcal conjugate vaccine were the most common serotypes in Southeast Asia. High carriage rate of *S. pneumoniae* prior to pneumococcal vaccine introduction across countries in Southeast Asia might become an indication of the need for the introduction of pneumococcal vaccine into routine immunization program.

Competing interests

CS is an investigator on a PCV impact project in Mongolia funded by Pfizer. Other authors declare no conflict of interest

Ethical statement

Ethics approval was not required for this study.

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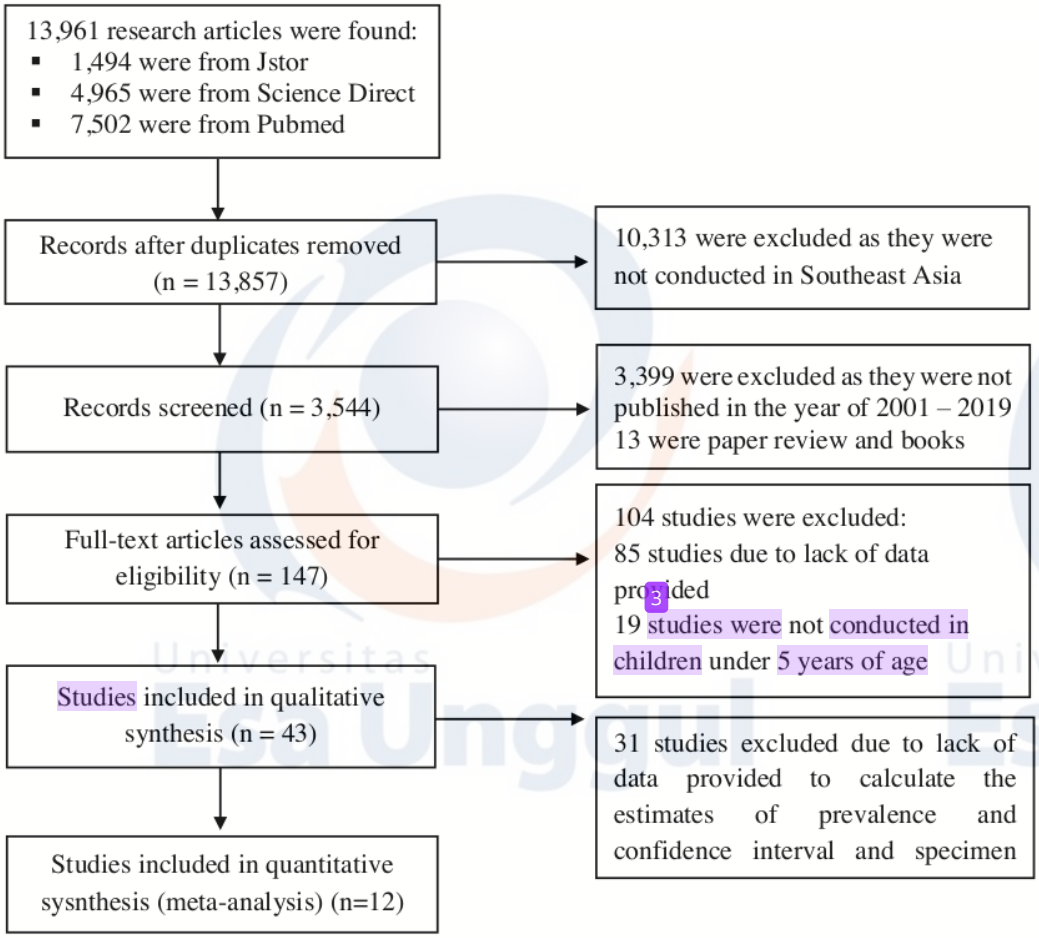

Figure 1. PRISMA Flowchart – Literature Review

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Table 1. Characteristic of Study and Prevalence of *S. pneumoniae* across Southeast Asian Countries

First Author & Year	Country	#Subject	*#S. pneumoniae Identified*	Forest Plot	Carriage Rate (%)	90%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 (Semarang)	243	111		45,7	37,2	54,2
Hadinegoro *et al*, 2016	Indonesia (Lombok)	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
Le *et al*, 2011	Malaysia	47	28		59,6	37,5	81,6
Soewignjo, 2001	Indonesia (Lombok)	484	223		46,1	40,0	52,1
D. Bogaert, 2002	Vietnam	410	84		20,5	16,1	24,9
Fadlyana *et al*, 2018	Indonesia (Bandung)	100	64		64,0	48,3	79,7
Fadlyana *et al*, 2018	Indonesia (Lombok)	101	51		50,5	36,6	64,4
Fadlyana *et al*, 2018	Indonesia (Padang)	101	35		34,7	23,2	46,1
Murad *et al*, 2019	Indonesia (Bandung)	396	106		26,8	21,7	31,9
Satzke *et al*, 2019	Lao DPR	1001	394		39,4	35,5	43,2
Summary		11548	4167		38,0	30,4	45,5

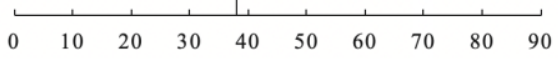

Table 2. Characteristic of Study and Prevalence of Serotype 6AB across Southeast Asian Countries

First Author & Year	Country	#*S. pneumoniae* Identified	6AB	Forest Plot	Carriage Rate (%)	90%CI	
						Lower	Upper
Turner et al, 2012	Thailand	1504	179		11,9	10,2	13,6
Yatim et al, 2012	Malaysia	69	26,91		39,0	24,3	53,7
Farida et al, 2014	Indonesia (Semarang)	111	21		18,9	10,8	27,0
Hadinegoro et al, 2016	Indonesia (Lombok)	557	120		21,5	17,7	25,4
Lee et al, 2001	Vietnam	92	23		25,0	14,8	35,2
Lee et al, 2001	Singapore	41	20		48,8	27,4	70,2
Lee et al, 2001	Thailand	165	38		23,0	15,7	30,4
Lee et al, 2001	Malaysia	58	15		25,9	12,8	39,0
Lee et al, 2001	Philippines	95	18		18,9	10,2	27,7
Soewignjo, 2001	Indonesia (Lombok)	223	61		27,4	20,5	34,2
Fadlyana et al, 2018	Indonesia (Bandung)	64	5		7,8	1,0	14,7
Fadlyana et al, 2019	Indonesia (Lombok)	51	14		27,5	13,1	41,8
Fadlyana et al, 2020	Indonesia (Padang)	35	5		14,3	1,8	26,8
Murad et al, 2019	Indonesia (Bandung)	106	34		32,1	21,3	42,9
Satzke et al, 2019	Lao PDR	394	92		23,4	18,6	28,1
Summary		3565	671,91		21,8	17,0	26,7

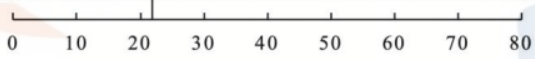

Table 3. Characteristic of Study and Prevalence of Serotype 23F across Southeast Asian Countries

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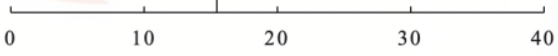
Table 3. Characteristic of Study and Prevalence of Serotype 23F across Southeast Asian Countries

First Author & Year	Country	#Subject	23F	Forest Plot	Carriage Rate (%)	90%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 (Semarang)	111	10		9,0	3,4	14,6
Hadinegoro et al, 2016	Indonesia (Lombok)	557	58		10,4	7,7	13,1
Lee et al, 2001	Vietnam	92	25		27,2	16,5	37,8
Lee et al, 2001	Singapore	41	5		12,2	1,5	22,9
Lee et al, 2001	Thailand	165	41		24,8	17,2	32,5
Lee et al, 2001	Malaysia	58	12		20,7	9,0	32,4
Lee et al, 2001	Philippines	95	8		8,4	2,6	14,3
Soewignjo, 2001	Indonesia (Lombok)	223	51		22,9	16,6	29,1
Fadlyana et al, 2018	Indonesia (Bandung)	64	6		9,4	1,9	16,9
Fadlyana et al, 2019	Indonesia (Lombok)	51	5		9,8	1,2	18,4
Fadlyana et al, 2020	Indonesia (Padang)	35	4		11,4	0,2	22,6
Murad et al, 2019	Indonesia (Bandung)	106	18		17,0	9,1	24,8
Satzke et al, 2019	Lao DPR	394	39		9,9	6,8	13,0
Summary					15,5	11,5	19,5



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