Vaccine 37 (2019) 3159–3166

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Serotype distribution of disease-causing *Streptococcus pneumoniae* in Thailand: A systematic review

Rebecca E. Hocknell [a], David W. Cleary [a,b], Somporn Srifeungfung [c,d], Stuart C. Clarke [a,b,e,*]

[a] Faculty of Medicine and Institute for Life Sciences, University of Southampton, Southampton, United Kingdom
[b] NIHR Southampton Biomedical Research Centre, University Hospital Southampton Foundation NHS Trust, Southampton, United Kingdom
[c] Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand
[d] Faculty of Medicine, Siam University, Thailand
[e] Global Health Research Institute, University of Southampton, Southampton, United Kingdom

ARTICLE INFO

Article history:
Received 26 October 2018
Received in revised form 23 April 2019
Accepted 25 April 2019
Available online 3 May 2019

Keywords:
Invasive pneumococcal disease
IPD
non-IPD
Pneumococcus
Thailand
Pneumococcal conjugate vaccine

ABSTRACT

Background: *Streptococcus pneumoniae* infection is associated with a high morbidity and mortality worldwide. There are currently >98 known serotypes; the most burdensome are covered by current pneumococcal conjugate vaccines (PCVs) such as PCV10 (Synflorix®) and (Prevnar 13®) PCV13. However, at present no PCV is available on the National Expanded Programme of Immunization (EPI) in Thailand.
Methods: Here we report a systematic review of studies regarding pneumococci associated with invasive pneumococcal disease (IPD) and non-IPD in Thailand. The NCBI PubMed database and Google Scholar were used to identify relevant papers published from 1st January 1990 to 21st August 2017. The quantitative analysis was reported as the distribution of serotypes across two age groups, ≤5 and >5 years old, as these were the most commonly reported. Where age was not stated, or data was combined, data were categorised as all ages.
Results: The search returned 15 relevant articles. From these the five most common disease-causing serotypes, in rank order, were 6B, 23F, 14, 19A and 19F. Vaccine coverage would be 55.3% for PCV10 and 69.7% for PCV13. There was insufficient data to draw conclusions regarding non-invasive disease-causing pneumococcal serotypes.
Conclusion: This review demonstrates that the serotypes which were most responsible for disease in Thailand are included in PCV10 and PCV13. Better surveillance data of IPD and non-IPD are required for monitoring vaccine effectiveness if PCV is implemented nationally.

Contents

* Corresponding author at: Infectious Disease Epidemiology Group, Academic Unit of Clinical and Experimental Sciences, Mail point 814, Level C Faculty of Medicine, University of Southampton, University Hospital Southampton Foundation NHS Trust, Southampton SO16 6YD, United Kingdom.
E-mail address: S.C.Clarke@southampton.ac.uk (S.C. Clarke).

https://doi.org/10.1016/j.vaccine.2019.04.085
0264-410X/

1. Introduction

Streptococcus pneumoniae (the pneumococcus) is a significant human pathogen, which has the greatest impact on the youngest of the global population [1]. The 10th International Symposium on Pneumococci & Pneumococcal Diseases estimated 335,000 deaths of children worldwide were attributed to pneumococcal disease in 2015 [2]. Pneumococci are commonly carried in the upper respiratory tract (URT) as part of the commensal microflora. This is considered a risk factor for the development of invasive pneumococcal diseases (IPD) – including pneumonia, bacteraemia, meningitis and septicaemia – and non-invasive pneumococcal diseases (non-IPD) including sinusitis and acute otitis media (AOM) [3].

The polysaccharide capsule is an important virulence factor for the pneumococcus as it prevents phagocytosis and is required for colonisation and invasive disease [4]. Although there are currently at least 98 known pneumococci capsular serotypes [5], 91% of all IPD is caused by <30 serotypes [6]. New serotypes are continuously being identified [7].

There are two types of vaccines that protect against *S. pneumoniae*, the pneumococcal polysaccharide vaccine (PPV) and the pneumococcal conjugate vaccine (PCV). The current PPV (PPV23), known as Pneumovax 23®, was licensed in 1983 when the included serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F) accounted for 85–90% of IPD infections in the USA [8]. PPV23 is most efficacious in healthy young adults but universal vaccination of the elderly is advised by most developed countries [9]. However, children were left vulnerable as PPV23 is only licensed in those >2 years due to its inability to produce long-term immunological memory in younger children [10]. Currently, there are two conjugate vaccines available; Synflorix® (PCV10, GlaxoSmithKline) was licensed in 2009 and contains ten pneumococcal serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) conjugated to protein D, diphtheria or tetanus toxoid carrier proteins. Prevnar 13® (PCV13, Pfizer) was licensed in 2010 and includes a further three serotypes (3, 6A and 19A), of which all 13 serotypes are conjugated to diphtheria carrier protein. This superseded a previous heptavalent version of Prevnar that contained seven serotypes (4, 6B, 9V, 14, 18C, 19F and 23F). All PCV vaccines have been shown to be efficacious in people of all ages by invoking an immunological T cell-dependent response [10].

Vaccine availability is limited to private sales in many countries within the WHO South East Asia and Western Pacific regions, including Thailand, due to the high cost of the vaccine (~122 USD/dose [11]), the economic state of the country [12], and competing interest with other National Expanded Programme of Immunization (EPI) vaccines [13]. PCV10 and PCV13 are gradually being introduced in these regions independently and with help from The Vaccine Alliance (GAVI). GAVI aids eligible countries to introduce PCV into national immunisation programmes (NIPs) by reducing the cost of the vaccine to <10% of the original price (3.50 USD). Within the last three years, Bangladesh, Cambodia, Laos (Lao People's Democratic Republic), Myanmar, Nepal and the Republic of Korea within the WHO South East Asia and Western Pacific regions have introduced a PCV into their NIP [14] and all but the latter had the support of GAVI. In addition, Singapore implemented a PCV into their NIP in 2005 without support. As of 2018, five additional South East Asia countries (Bhutan, India, Indonesia, Sri Lanka and Timor-Leste) have been given the opportunity to apply for reduced vaccine cost through GAVI. India, Indonesia and the Philippines have already partially introduced PCV with India using support from GAVI. However, as a middle-income country, Thailand is not eligible for GAVI support and as such, PCV is currently not included in the EPI, along with four other countries within the WHO South East Asia region [14,15]. It is believed that if a PCV was introduced in Thailand, uptake would be >99% as achieved with seven current EPI vaccines in 2017 [16]. However, without financial support, PCV10 and PCV13 have been considered not cost-effective unless the price per dose is decreased by 70–90% [17].

The epidemiology of disease associated pneumococcal serotypes has been studied globally through individual studies and global projects, such as the Global Pneumococcal Sequencing Project (GPS) [18,19]. Developed countries in Europe and North America have extensive surveillance covering all ages and locations pre and post PCV introduction [20]. Asia has the fastest growing population and an estimated 185,000 deaths are attributed to IPD each year in SE Asia and so comprehensive surveillance is essential. However, the data is relatively limited and incomplete in SE Asia, particularly in individual countries [21]. In Thailand, regional data is especially lacking, along with data from adults, for both IPD and non-IPD [20]. Most significant is the lack of studies monitoring nasopharyngeal carriage, particularly in those at higher risk, as pneumococcal infection is preceded by colonisation [22].

The increasing prevalence and emergence of antibiotic resistant pneumococci in SE Asia is a serious concern [23–25]. It requires constant surveillance; however, SE Asia presents a large gap in the global study as evidenced by the global antimicrobial resistance surveillance system (GLASS) study [25]. This review summarises available information regarding pneumococcal serotype distribution in Thailand over the last 27 years. It also highlights the need for increased and continued study of disease-causing serotypes in all ages both regionally and countrywide.

2. Methods

The NCBI PubMed database and Google Scholar were used to identify relevant papers published from 1st January 1990 to 21st August 2017. The search was carried out and limited to studies published in English from Thailand. Search terms included: *Streptococcus pneumoniae, S. pneumoniae*, pneumococcus, pneumococcal infection, IPD, invasive, non-IPD, non-invasive, Thailand, Thai and serotype. They were separated by the binary operators "AND", "OR" and "()" and used to search the title, abstract and main text. Further relevant studies were identified using the reference lists of the primary papers. Studies from all provinces of Thailand were accepted alongside all those reporting on IPD and non-IPD, with non-IPD isolates defined as those causing disease that were collected from non-sterile sites. Studies that did not include serotype data were excluded from the quantitative analysis. All reported serotypes were generated or confirmed using latex agglutination or Quellung reaction. The quantitative analysis was defined as the distribution of serotypes across, where possible, the two most commonly reported age groups: ≤5 and >5 years old. Where age was not reported, or reports were combined, data were categorised as all ages.

Serotype prevalence with 95% confidence intervals was calculated using Excel 2016. Statistical analysis was performed using the Mann-Whitney *U* test to compare the predicted efficacy of two vaccines using GraphPad Prism version 7.03 for Windows [26].

3. Results

The search returned 55 articles from the NCBI PubMed database and 107 articles from Google Scholar (Fig. 1). In total, 10 studies provided information relevant to the review that reported on IPD and non-IPD and were used to analyse the serotype prevalence. Seven studies reported on IPD and three on IPD and non-IPD (Table 1). These studies represented 1922 isolates of which 1285 were IPD and 637 were non-IPD. Quellung-derived serotype data

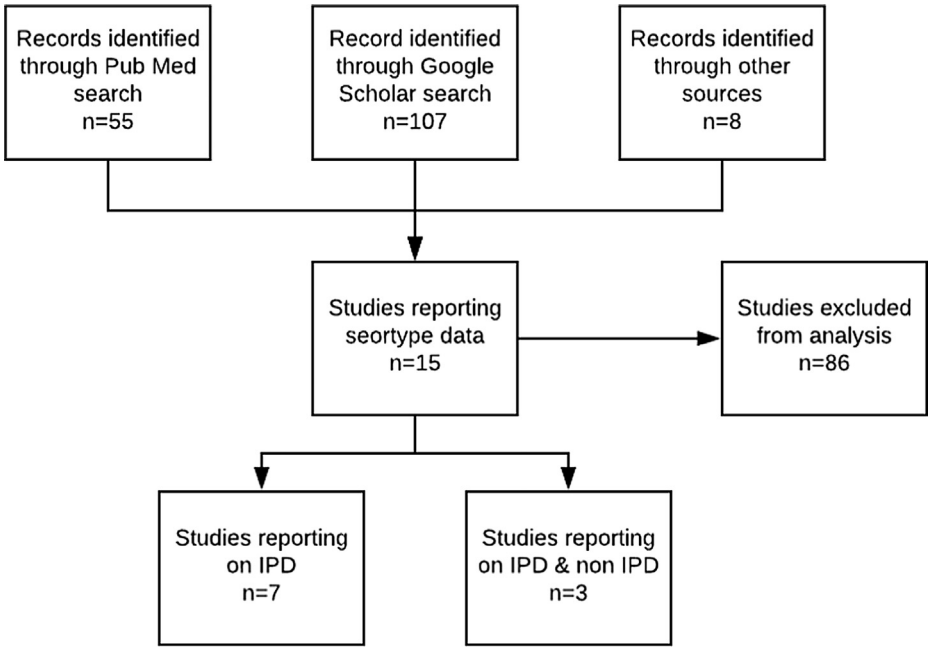

Fig. 1. Flow chart showing record identification for the systematic search.

Table 1
Summary of qualifying studies reported in Thailand.

No.	Article Title (Year)	Collection Period	No. of Isolates*	IPD/non-IPD	Age Range	Location	Serotypes Identified
1	Serotype distribution and antimicrobial susceptibility of *S. pneumoniae* causing invasive disease in Thai children younger than 5 years old, 2000–2005 (2007) [29]	2000–2005	115 (87.8%)	IPD	<5	Bangkok & Thailand National Institute of Health	6B, 23F, 14, 19F, 19A, 1, 5, 6A, 9V, 18C
2	Serotype coverage of pneumococcal conjugate vaccine and drug susceptibility of *Streptococcus pneumoniae* isolated from invasive or non-invasive diseases in central Thailand, 2006–2009 (2010) [30]	2006–2009	174 (67.2%) IPD 42 (76.2%) non-IPD	IPD & non IPD	<5 5–64 >65 <5 (non-IPD)	Bangkok, Nakorn Pratom & Nonthaburi	6B, 23F, 14, 19F, 19A, 6A, 9V, 18C, 3, 4, 7F
3	Pneumococcal Bacteremia Requiring Hospitalization in Rural Thailand: An Update on Incidence, Clinical Characteristics, Serotype Distribution, and Antimicrobial Susceptibility, 2005–2010 (2013) [27]	2005–2010	196 (82.1%)	IPD	<5 ≥5	Sa Kaeo & Nakhon Phanom	6B, 23F, 14, 19F, 19A, 1, 6A, 9V, 18C, 3, 4, 7F,
4	Serotypes and antimicrobial susceptibilities of *Streptococcus pneumoniae* isolated from hospitalized patients in Thailand. (2007) [33]	1997–2000	102 (73.5%) IPD 105 (64.8%) non-IPD	IPD & non-IPD	Not stated	Bangkok	6B, 23F, 14, 19F, 19A, 1, 6A, 9V, 18C, 3, 4, 7F
5	Changing trends in serotype distribution and antimicrobial susceptibility of *Streptococcus pneumoniae* causing invasive diseases in Central Thailand, 2009–2012 (2014) [31]	2009–2012	238 (60.1%)	IPD	≤5 6–49 50–64 ≥65	Bangkok & other provinces	6B, 23F, 19F, 19A, 3
6	Serotype distribution and antibiotic susceptibility of invasive *Streptococcus pneumoniae* isolates in patients aged 50 years or older in Thailand. (2014) [32]	2005–2012	157 (58%)	IPD	≥50	Bangkok	6B, 23F, 14, 19F, 19A, 6A, 6C, 15B/C, 34, NT
7	Serotypes and antimicrobial resistance of *Streptococcus pneumoniae* in Thailand 2002–2004 (2006) [28]	2002–2004	149 (62.4%) IPD 490 (43.3%) non-IPD	IPD & non-IPD	<5 ≥5	Sa Kaeo	6B, 23F, 14, 19F, 1, 5, 9V, 18C, 3, 4
8	Spread of Drug-Resistant *Streptococcus pneumoniae* in Asian Countries: Asian Network for Surveillance of Resistant Pathogens (ANSORP) Study (1999) [23]	1996–1997	29 (79.3%)	IPD	Not stated	Bangkok	6B, 23F, 14, 19F, 19A, 3
9	High Prevalence of Antimicrobial Resistance among Clinical *Streptococcus pneumoniae* Isolates in Asia (an ANSORP Study) (2004) [24]	Jan 2000 – Jun 2001	51 (64.7%)	IPD	<18 ≥18	Bangkok	23F, 14, 19F, 19A, 6A, 9V, 18C
10	Incidence of Pneumococcal Bacteremia Requiring Hospitalization in Rural Thailand (2009) [13]	May 2005 – June 2007	74 (81.1%)	IPD	<5 ≥5	Sa Kaeo & Nakhon Phanom	6B, 23F, 14, 19F, 19A, 1, 6A, 9V, 3, 4, 7F, 34

* Parenthesis indicates percentage of isolates with available serotype data.

were available for 69.7% (n = 896) of IPD and 49% (n = 312) of non-IPD isolates (Tables 1 and 2).

3.1. Serotype distribution among invasive pneumococci in Thailand

Across all studies, the most common serotype found causing disease in all age groups was 6B (14.7% (95CI: 12.8–16.6%)), followed by serotypes 23F (11.4% (95CI: 9.7–13.1)), 14 (7.8% (95CI: 6.3–9.3)), 19A (7.5% (95CI: 6.1–8.9)) and 19F (5.8% (95CI: 4.5–8.1)); an additional 360 (28% (95CI: 25.6–30.5)) isolates were categorised as non-vaccine types (NVTs) (Table 2 and Fig. 2). PCV10 and PCV13 vaccine types formed 55.3% (95CI: 52.6–58.0) and 69.7% (95CI: 67.2–72.2) of the dataset respectively. Across all IPD studies, 329 serotyped isolates were reported from children ≤5 years of age, showing the most prevalent serotypes to be 6B (20.3% (95CI: 16.4–24.2)), 23F (16.1% (95CI: 12.5–19.7)) and 14 (14.2% (95CI: 10.8–17.6)) (Table 2). Predicted vaccine serotype coverage of IPD isolates collected from those ≤5 years of age ranged from 68% (95CI: 63.5–72.5) for PCV10 to 80.4% (95CI: 76.5–84.3) for PCV13. There were 469 reported serotyped isolates for those >5 years of age, of which 6B was the most prevalent (10.8% (95CI: 8.6–13.1)), followed by 19A (7.8% (95CI: 5.9–9.8)), 23F (7.6% (95CI: 5.7–9.5)), 3 (6% (95CI: 4.3–7.7)) and 4 (5.6% (95CI: 3.9–7.3)) (Table 2). Vaccine serotypes found in those >5 years of

Table 2
Distribution of carried and disease-causing serotypes across ages.

	Serotype	IPD (%)			Non-IPD (%)			Totals
		≤5	>5	URD	≤5	>5	URD	
PCV7	4	0.7 (3)*	5.6 (41)	2 (3)	0.7 (2)	1.7 (3)	0 (0)	52
	6B	20.3 (83)	10.8 (79)	18.4 (27)	14.8 (44)	8.6 (15)	11 (18)	266
	9 V	2.6 (11)	2.2 (16)	1.4 (2)	1 (3)	1.7 (3)	2.4 (4)	39
	14	14.2 (58)	4.9 (36)	4.1 (6)	9.7 (29)	5.1 (9)	0 (0)	138
	18C	2.2 (9)	5.1 (37)	4.1 (6)	1.3 (4)	3.4 (6)	1.2 (2)	64
	19F	7.2 (32)	5.1 (37)	3.4 (5)	14.8 (44)	7.4 (13)	11.6 (19)	150
	23F	16.1 (66)	7.7 (56)	16.3 (24)	13.4 (40)	4.6 (8)	9.1 (15)	209
PCV10	1	2.9 (12)	3 (22)	2.7 (4)	0 (0)	2.3 (4)	0 (0)	42
	5	0.7 (3)	1 (7)	1.4 (2)	0 (0)	0 (0)	0 (0)	12
	7F	0.2 (1)	2.9 (21)	0.7 (1)	0 (0)	0 (0)	1.2 (2)	25
PCV13	3	0.2 (1)	6 (44)	5.4 (8)	2.3 (7)	2.9 (5)	3.7 (6)	71
	6A	4.2 (17)	2.2 (16)	2 (3)	1.3 (4)	0 (0)	0.6 (1)	41
	19A	8.1 (33)	13.9 (57)	4.8 (7)	0.3 (1)	0 (0)	0.6 (1)	99
	NVT	19.6 (80)	25.7 (2 6 0)	13.6 (20)	40.3 (1 2 0)	62.3 (1 0 9)	7.3 (12)	601
	NT	0 (0)	0 (0)	19.7 (29)	0 (0)	0 (0)	51.2 (84)	113
	Totals	409	729	147	298	175	164	1922

Percentage of isolates reported: IPD (n = 1285), non-IPD (n = 637). Data shows isolates from ≤5 yrs, >5 yrs and unreported (URD): ages assumed as collected across all ages. NT – Nontypeable, serotype could not be determined by Quellung reaction, NVT – Non-vaccine type, serotypes were not included in any conjugate vaccine.
* Parenthesis indicates number of isolates reported.

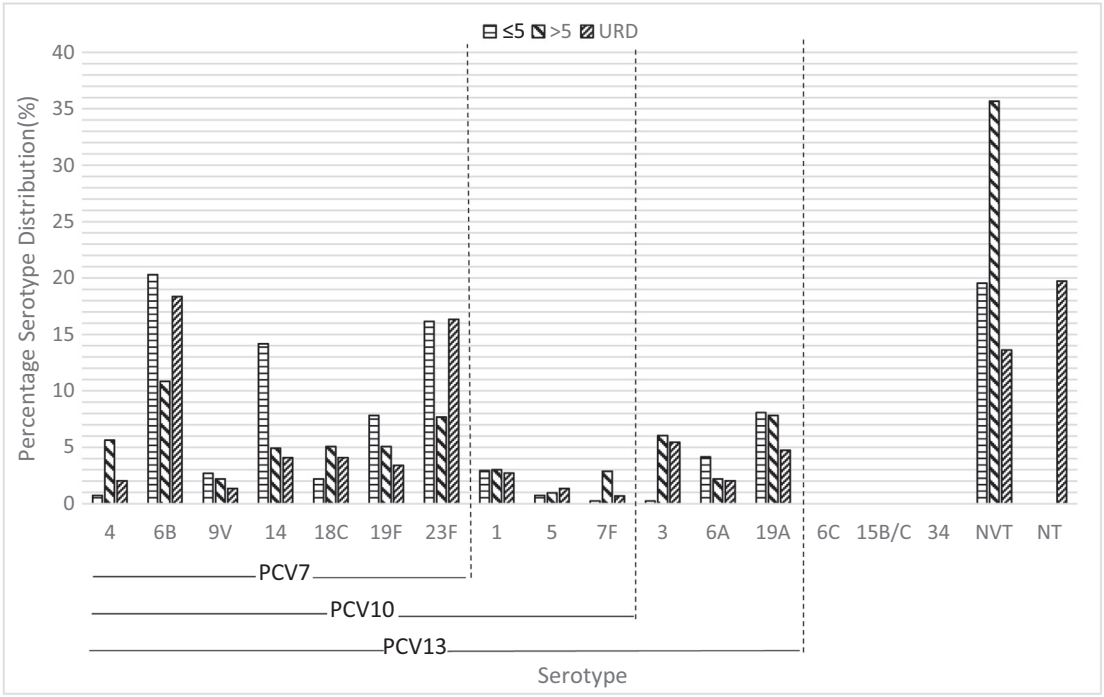

Fig. 2. Distribution of IPD Serotypes across Ages. Data shows percentage of isolates from ≤5 yrs, >5 yrs and unreported (URD) ages assumed as collected across all ages. Total number of isolates reported: ≤5 (n = 409), >5 (n = 729), unreported (n = 147). NT – Nontypeable: serotype could not be determined by Quellung reaction. NVT – Non-vaccine type, serotypes were not included in any conjugate vaccine.

age with IPD were not significantly less prevalent than those found in ≤5 years of age (48.3% and 64.3% for PCV10 (95CI: 44.7–51.9; $P > 0.05$) and PCV13 (95CI: 60.8–67.8; $P > 0.05$) respectively).

There were five studies conducted prior to the private introduction of PCV7 in Thailand in 2006 [23,24,28,29,33]. Two studies were conducted after 2006 [30,31] and two were from 2005 onwards [27,32]. Whilst the most prevalent serotypes remained the same, excluding serotype 19A, the rank order changed. Before vaccine introduction in 2006, serotype 19A was not prevalent (3.5% (95CI: 1.7–5.2%)), there was a significant increase in prevalence after 2006 (9.8% (95CI: 7.7–11.9, $P > 0.05$)). In addition, non-PCV13-types significantly increased after the introduction of PCV7 ($P > 0.05$).

Three of the studies (n = 419 IPD isolates) were observed in either the rural provinces of Nakhon Phanom or Sa Kaeo [13,27,28]. Seven studies (n = 866 isolates) reported from hospitals located in the more urbanised Central Thailand [23,24,29–33]. Serotypes 23F (13.4% (95CI: 10.1–16.7)), 14 (11% (95CI: 8–14)) and 6B (9.8% (95CI: 7–12.7)) were most prevalent in rural areas and serotypes 6B (17.1% (95CI: 14.6–19.6)), 23F (10.4% (95CI: 8.4–12.4)) and 19A (8.2% (95CI: 6.4–10) were most prevalent in urban areas. Predicted vaccine coverage of isolates collected from rural regions was insignificantly higher than those collected from urban areas with 59.9% (95CI: 55.2–64.6) and 53% (95CI: 49.7–56.3) PCV10 coverage ($P > 0.05$) and 74.9% (95CI: 70.8–79.1) and 67.2% (95CI: 64.1–70.3) for PCV13 coverage ($P > 0.05$) for rural and urban regions respectively.

3.2. Serotype distribution among non-invasive pneumococcal disease in Thailand

Three studies reported serotype data from non-IPD causing pneumococci (n = 312). The isolates were mostly collected from nasopharyngeal swabs (76.9%), the remaining sources included other respiratory specimens, ear and eye swabs and gastric washes. The most common serotypes were 6B (12.1% (95CI: 9.6–14.6)), 19F (11.9% (95CI: 9.4–14.4)) and 23F (9.9% (95CI: 7.6–12.2)) (Table 2 and Fig. 3), with a further 241 (37.8% (95CI: 34–41.6)) isolates reported as NVTs. Vaccine serotypes accounted for 45% (95CI: 41.1–48.9) for PCV10 and 49% (95CI: 45.1–52.9) for PCV13. More isolates were collected from young children (≤5 years) than those >5 years of age. In those ≤5 years of age (n = 289), the most prevalent serotypes were 6B and 19F (15.2% (95CI: 11.1–19.3)) followed by 23F (13.8% (95CI: 9.9–17.7)) with an additional 40.3% (95CI: 34.7–45.9) of the dataset reported as NVTs (Table 2). PCV10 coverage would have been 55.7% (95CI: 50.1–61.34) and PCV13 coverage would have been 59.7% (95CI: 54.1–65.3). For patients >5 years of age (n = 175), predicted PCV10 and PCV13 coverage was 34.9% (95CI: 27.8–42) and 37.7% (95CI: 30.5–44.9) and serotype 6B (8.6% (95CI: 4.5–12.8)) and 19F (7.4% (95CI: 3.5–11.3)) were also most prevalent in this age group with NVTs making up an additional 62.3% (95CI: 55.1–69.5) of the dataset (Table 2).

4. Discussion

There are limited data available regarding serotype distribution in Thailand. This review summarises the data available prior to PCV implementation to aid in the analysis of vaccine effectiveness in the future. Collection periods were taken both before and after PCV became available privately in 2006, although uptake was low and so data may be considered as pre-PCV introduction [31]. This review has highlighted serotypes 6B, 23F, 19A, 14 and 19F to be the top five most burdensome in pneumococcal disease in Thailand (Fig. 2), accounting for 47% of all disease-causing serotypes. Four of these serotypes (6B, 14, 19F and 23F) were found to be amongst the global top seven disease-causing serotypes prior to vaccine introduction [34]. The remaining three of seven serotypes, 1, 5 and 6A, were found to have low prevalence in Thailand (<6.7% combined). The three most prevalent serotypes in those ≤5 years of age (6B, 23F and 14) are part of a group known as "pae-

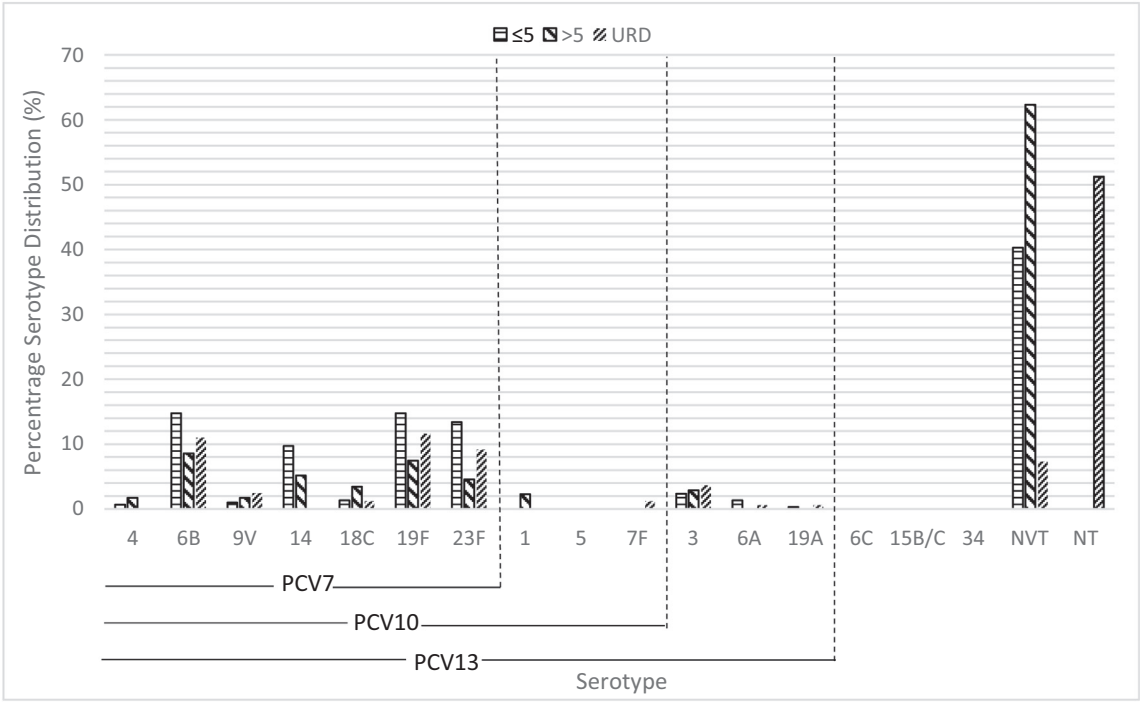

Fig. 3. Distribution of non-IPD Serotypes across Ages. Data shows percentage of isolates from ≤5 yrs, >5 yrs and unreported ages assumed as collected across all ages. Total number of isolates reported: ≤5 (n = 298), >5 (n = 175), unreported (n = 164). NT – Nontypeable: serotype could not be determined by Quellung reaction. NVT – Non-vaccine type, serotypes were not included in any conjugate vaccine.

diatric serotypes" as described in previous studies based on similar epidemiological characteristics [35]. Incidence of serotypes 3 and 4 in those >5 years of age was higher than found in young children and prevalence of these serotypes has previously been shown to be higher in adults [36]. Prevalence of non-typeable (NT) pneumococci was higher from non-IPD (13.2%) than IPD (2.3%) which could suggest the presence of non-encapsulated pneumococci and is not common for invasive infections. The prevalence of NTs from IPD is lower than recently found in Malaysia (4.9%), who have not included a PCV in the EPI, and is much lower than found in South Korea (11.9%) post PCV7 introduction [37,3].

Predicted vaccine coverage of disease-causing serotypes for PCV10 was 55.3% and for PCV13 was 69.7%. Previously in Thailand, predicted PCV13 coverage was higher at 72.6% [38], but lower in a SE Asian regional prediction at 65% [21]. This review found that vaccine serotype coverage for those ≤5 years of age ranged from 68% with PCV10 to 80.4% with PCV13. This is similar to the predicted PCV13 coverage (81.2%) that was previously found in Thailand by a systematic review conducted between 1995 and 2011, thus there has been minimal change identified by studies published in the following six years [39]. Vaccine serotypes for those >5 years of age equalled 48.3% and 64.3% of the collected pneumococci for PCV10 and PCV13 respectively, which shows a higher PCV13 coverage than previously found to be 60% [39]. Predicted vaccine coverage was found to be lower in patients >5 years of age, which is reflective of previous observations in adults across all geographic regions, although in this review, the difference was insignificant [40]. It has been suggested that elderly adults are more susceptible to PCV7 serotypes than younger adults and that their immunity to those serotypes wanes with age [40].

There are concerns that the incidence of disease-causing NVTs will increase after vaccine implementation, as observed in the USA and Europe with serotype 19A following PCV7 introduction [41,42]. The top five serotypes are all included in PCV10, except 19A, which is included in PCV13. Prevalence of serotype 19A significantly increased following the private introduction of PCV7 in Thailand and it was found to be one of the six most prevalent global NVTs found post PCV7 introduction [43]. Incidence of serotype 19A from IPD was 7.55% in Thailand and was higher in other Asian countries such as China (13.9%), who also do not include a PCV within the EPI [44]. Another study identified an increase from 0% to 26% of 19A incidence in IPD between 1991 and 2003 in South Korea and remained at 20% following PCV7 implementation [45]. As the increase was observed prior to PCV introduction, the role of PCV has been called into question and multidrug resistant (MDR) sequence type 320 isolates, among other factors, have been suggested as responsible [45]. However, in Thailand, it is difficult to establish which serotypes could fill vaccine type niches as many reports only performed serotyping for vaccine types and labelled all others as NVTs. Until recently, vaccine implementation has shown an overall decrease in pneumococcal disease that offsets the proportional increase in IPD caused by NVTs [46]. However, since 2014, an increase in NVTs and PPV23 vaccine types has been observed in the UK following the initial decrease after national PCV implementation in 2006 [47]. In addition, genetic analysis of serotypes has indicated there could be an international spread of serotypes through travel, thus changing the local serotype distribution [48].

Three studies collected IPD isolates from the rural regions of Sa Kaeo and Nakhon Phanom in North East Thailand which has a combined population of 1.2 million including >80,000 children <5 years of age [49]. Except for two studies, which accepted a small number of isolates that were submitted through the Thailand National Institute of Health from any hospital across the country, all other isolates were collected from Bangkok and its immediate surroundings. As such, this data does not represent the distribution of disease-causing serotypes countrywide. In the rural regions, vaccine coverage of disease-causing serotypes was observed to be higher than urban areas as more NVTs were identified in the urbanised Central Thailand. The observation has also been identified in other locations, including Bangladesh and Alaska [50,51]. This could be attributed to the increased availability of PCV in urban centres given both the presence of large private hospitals and a potentially more affluent populous [52,53]. Moreover, as two thirds of Thailand's population live in rural areas and given the restricted access to health care, this burden could even be an underestimation [52]. The reports of higher serotype 6A and 19A incidence in urban areas supports this hypothesis, however, serotypes 1 and 3 were reported in greater numbers in rural regions. As serotype 1 is associated with outbreaks and is rarely carried, the effect of international travel on its distribution should be low compared to commonly carried serotypes and so tourism in urban areas should not be expected to impact this [54].

There was one study, not included in this review, that reported nasopharyngeal carriage of *S. pneumoniae*. It focussed on Burmese and Karen refugees at Maela camp for displaced persons and therefore would not necessarily be representative of Thailand. The longitudinal cohort study collected monthly nasopharyngeal swabs (NPS) from 955 infants and approximately one quarter of their mothers [55–59]. The most prevalent serotypes carried were 19F, 23F, 6B and 14 which accounted for 58% of all carried isolates and the majority of isolates collected from mothers were non-encapsulated. These serotypes have also been found to be the most prevalent carried serotypes globally and in Asian children [60,61]. Vaccine types accounted for less pneumococci found in carriage and non-IPD studies than in IPD studies in Thailand, which is reflective of the decline in vaccine type colonisation [62].

This review was limited by certain factors. It is not possible to make reliable conclusions regarding non-IPD causing isolates due to the limited number of studies, and, as most data were from those ≤5 years of age, it was not possible to conduct an age analysis (Fig. 3). In addition, it was not possible to analyse the serotype distribution across anatomical sites or diseases due to the small numbers and lack of specific data. Also, the sample sizes of individual studies for both IPD and non-IPD were small and full serotyping data were not available for all isolates along with a lack of specific age data. In addition, there was only one study describing pneumococcal carriage in Thailand and this may not be representative of carriage across the entire country. This study was large, and has generated some novel findings, but specimens were collected from a refugee population on the Thailand-Myanmar border and demonstrate pneumococci found in females of mothering age and their children during a certain time period.

5. Conclusion

Overall, pneumococcal serotype data in Thailand was limited. Although there was more published data in comparison to other countries in SE Asia [21], it remains difficult to make accurate estimations of serotype disease burden. WHO and the Asia and Pacific Advisory Board stated that vaccine recommendations should be advised country by country and so without detailed pre-vaccination data, it would be difficult to estimate the impact of vaccines once implemented in the future as it is possible to underestimate the true burden [18,63].

Declaration of Competing Interest

SCC acts as principal investigator on studies conducted on behalf of University Hospital Southampton NHS Foundation Trust/University of Southampton that are sponsored by vaccine

manufacturers but receives no personal payments from them. SCC has participated in advisory boards for vaccine manufacturers but receives no personal payments for this work. SCC has received financial assistance from vaccine manufacturers to attend conferences. DWC was a post-doctoral researcher on projects funded by Pfizer and GSK between April 2014 and October 2017. All grants and honoraria are paid into accounts within the respective NHS Trusts or Universities, or to independent charities. All other authors have no conflicts of interest.

All authors attest they meet the ICMJE criteria for authorship. REH, DWC and SCC designed, planned and wrote the manuscript. SS edited the manuscript.

Acknowledgements

We thank Prof. Paul Turner for his critical inputs and feedback to this manuscript.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Simonsen L, Taylor R, Young-Xu Y, Haber M, May L, Klugman K. Impact of pneumococcal conjugate vaccination of infants on pneumonia and influenze hospitalization and mortality in all age groups in the United States. mBio 2011;2:e00309–e310.
[2] Wahl B, O'Brien KL, Greenbaum A, Liu L, Chu Y, Black R, et al. Global burden of Streptococcus pneumoniae in children younger than 5 years in the pneumococcal conjugate vaccines (PCV) era: 2000-2015. In: 10th International Symposium on Pneumococci & Pneumococcal Diseases, 26th-30th June 2016. Glasgow, Scotland; 2016.
[3] Tai SS. Streptococcus pneumoniae serotype distribution and pneumococcal conjugate vaccine serotype coverage among pediatric patients in East and Southeast Asia, 2000-2014: a pooled data analysis. Vaccines 2016;4.
[4] Shainheit MG, Mule M, Camilli A. The core promoter of the capsule operon of Streptococcus pneumoniae is necessary for colonization and invasive disease. Infect Immun 2014;82:694–705.
[5] Ndlangisa K, du Plessis M, Allam M, Wolter N, de Gouveia L, Klugman KP, et al. Invasive disease caused simultaneously by dual serotypes of streptococcus pneumoniae. J Clin Microbiol 2018;56.
[6] Martens P, Worm SW, Lundgren B, Konradsen HB, Benfield T. Serotype-specific mortality from invasive Streptococcus pneumoniae disease revisited. BMC Infect Dis 2004;4:21.
[7] Geno K, Gilbert G, Song J, Skovsted I, Klugman K, Jones C, et al. Pneumococcal capsules and their types: past, present, and future. Clin Microbiol Rev 2015;28:871–99.
[8] WHO. 23-valent pneumococcal polysaccharide vaccine – WHO position paper. Wkly Epidemiol Rec 2008;83:373–84.
[9] Falkenhorst G, Remschmidt C, Harder T, Hummers-Pradier E, Wichmann O, Bogdan C. Effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPV23) against pneumococcal disease in the elderly: systematic review and meta-analysis. PLoS ONE 2017;12:e0169368.
[10] Westerink J, Schroeder H, Nahm M. Immune responses to pneumococcal vaccines in children and adults: rationale for age-specific vaccination. Aging Disease 2012;3:51–67.
[11] WHO. Pneumococcal conjugate vaccine for childhood immunization–WHO position paper. Wkly Epidemiol Rec 2007;82:93–104.
[12] GAVI. Pneumococcal Vaccine Support. [online] Available at: https://www.gavi.org/support/nvs/pneumococcal/ [Accessed 15th March 2018].
[13] Baggett HC, Peruski LF, Olsen SJ, Thamthitiwat S, Rhodes J, Dejsirilert S, et al. Incidence of pneumococcal bacteremia requiring hospitalization in rural Thailand. Clin Infect Diseases: Official Publ Infect Diseases Soc Am 2009;48 (Suppl 2):S65–74.
[14] WHO, IVB Database. Countries with Pneumococcal Conjugate vaccine in the national immunization programme; and planned introductions in 2018. [online] Available at: http://www.who.int/immunization/monitoring_surveillance/VaccineIntroStatus.pptx [Accessed 9th January 2019].
[15] Tricarico S, McNeil HC, Cleary DW, Head MG, Lim V, Yap IKS, et al. Pneumococcal conjugate vaccine implementation in middle-income countries. Pneumonia (Nathan) 2017;9:6.
[16] WHO. WHO vaccine-preventable diseases: monitoring system. 2018 global summary WHO UNICEF estimates time series for Thailand (THA). [online] Available at: http://apps.who.int/immunization_monitoring/globalsummary/estimates?c=THA [Accessed 31st July 2018].
[17] Kulpeng W, Leelahavarong P, Rattanavipapong W, Sornsrivichai V, Baggett HC, Meeyai A, et al. Cost-utility analysis of 10- and 13-valent pneumococcal conjugate vaccines: protection at what price in the Thai context? Vaccine 2013;31:2839–47.
[18] WHO. Pneumococcal vaccines WHO position paper – 2012. Weekly Epidemiological Record. 2012; 87: 129–44.
[19] Global Pneumococcal Sequencing Project. The Global Pneumococcal Sequencing Project. [online] Available at: https://www.pneumogen.net/gps/ [Accessed 31st March 2018].
[20] O'Brien KL, Wolfson LJ, Watt JP, Henkle E, Deloria-Knoll M, McCall N, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. Lancet 2009;374:893–902.
[21] Jauneikaite E, Jefferies JM, Hibberd ML, Clarke SC. Prevalence of Streptococcus pneumoniae serotypes causing invasive and non-invasive disease in South East Asia: a review. Vaccine 2012;30:3503–14.
[22] Cardozo DM, Nascimento-Carvalho CM, Andrade AL, Silvany-Neto AM, Daltro CH, Brandao MA, et al. Prevalence and risk factors for nasopharyngeal carriage of Streptococcus pneumoniae among adolescents. J Med Microbiol 2008;57:185–9.
[23] Song J, Lee N, Ichiyama S, Yoshida R, Hirakata Y, Fu W, et al. Spread of drug-resistant Streptococcus pneumoniae in Asian Countries: Asian network for surveillance of resistant pathogens (ANSORP) study. Clin Infect Dis 1999;29:1206–11.
[24] Song J, Jung S, Ko K, Kim NY, Son J, Chang H, et al. High prevalence of antimicrobial resistance among clinical streptococcus pneumoniae isolates in Asia (an ANSORP Study). Antimicrobial Agents Chemother 2004;48:2101–7.
[25] WHO. Global antimicrobial resistance surveillance system (GLASS) report: early implementation 2016-2017. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO; 2017.
[26] Mann HB, Whitney DR. On a test of whether one of two random variables is stochastically larger than the other. Ann Math Statist 1947;18:50–60.
[27] Rhodes J, Dejsirilert S, Maloney S, Jorakate P, Kaewpan A, Salika P, et al. Pneumococcal bacteremia requiring hospitalization in rural Thailand: an update on incidence, clinical characteristics, serotype distribution, and antimicrobial susceptibility. PLoS ONE 2005–2010.;2013(8):p.e66038.
[28] Levine S, Dejsirilert S, Sangsuk L, Chantra S, Feikin DR, Dowell SF, et al. Serotypes and antimicrobial resistance of streptococcus pneumoniae in Thailand 2002–2004. Pediatr Infect Dis J 2006;25:176–8.
[29] Phongsamart W, Srifeungfung S, Dejsirilert S, Chatsuwan T, Nunthapisud P, Treerauthaweeraphong V, et al. Serotype distribution and antimicrobial susceptibility of S. pneumoniae causing invasive disease in Thai children younger than 5 years old, 2000–2005. Vaccine 2007;25:1275–80.
[30] Srifeungfung S, Tribuddharat C, Comerungsee S, Chatsuwan T, Treerauthanaweeraphong V, Rungnobhakhun P, et al. Serotype coverage of pneumococcal conjugate vaccine and drug susceptibility of Streptococcus pneumoniae isolated from invasive or non-invasive diseases in central Thailand, 2006–2009. Vaccine 2010;28:3440–4.
[31] Phongsamart W, Srifeungfung S, Chatsuwan T, Nunthapisud P, Treerauthaweeraphong V, Rungnobhakhun P, et al. Changing trends in serotype distribution and antimicrobial susceptibility of Streptococcus pneumoniae causing invasive diseases in Central Thailand, 2009–2012. Hum Vaccin Immunother 2014;10:1866–73.
[32] Srifeungfung S, Phongsamart W, Tribuddharat C, Chatsuwan T, Rungnobhakhun P, Sapcharoen S, et al. Serotype distribution and antibiotic susceptibility of invasive Streptococcus pneumoniae isolates in patients aged 50 years or older in Thailand. Hum Vaccin Immunother 2014;10:40–4.
[33] Srifeungfung S, Chokephaibulkit K, Tribuddharat C. Serotypes and antimicrobial susceptibilities of Streptococcus pneumoniae isolated from hospitalized patients in Thailand. Southeast Asian J Trop Med Public Health 2007;38:469–77.
[34] Johnson H, Deloria-Knoll M, Levine O, Stoszek S, Freimanis Hance L, Reithinger R, et al. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. PLoS Med 2010;7:p.e1000348.
[35] Feikin DR, Klugman KP, Facklam RR, Zell ER, Schuchat A, Whitney CG, et al. Increased prevalence of pediatric pneumococcal serotypes in elderly adults. Clin Infect Diseases: Official Publ Infect Diseases Soc Am 2005;41:481–7.
[36] Imohl M, Reinert RR, Ocklenburg C, van der Linden M. Association of serotypes of Streptococcus pneumoniae with age in invasive pneumococcal disease. J Clin Microbiol 2010;48:1291–6.
[37] Arushothy R, Ahmad N, Amran F, Hashim R, Samsudin N, CheAzih CR. Pneumococcal serotype distribution and antibiotic susceptibility in Malaysia: a four year study (2014–2017) on invasive paediatric isolates. Int J Infect Diseases 2018. https://doi.org/10.1016/j.ijid.2018.12.009.
[38] Le C, Yusof M, Sekaran S. Current Trend in Pneumococcal Serotype Distribution in Asia. Journal of Vaccines and Vaccination. 2011;S2:001.
[39] Hung IF, Tantawichien T, Tsai YH, Patil S, Zotomayor R. Regional epidemiology of invasive pneumococcal disease in Asian adults: epidemiology, disease burden, serotype distribution, and antimicrobial resistance patterns and prevention. Int J Infect Dis 2013;17:e364–73.
[40] Hausdorff W, Feikin D, Klugman K. Epidemiological differences among pneumococcal serotypes. Lancet Infect Dis 2005;5:83–93.
[41] Hanage WP, Finkelstein JA, Huang SS, Pelton SI, Stevenson AE, Kleinman K, et al. Evidence that pneumococcal serotype replacement in Massachusetts following conjugate vaccination is now complete. Epidemics 2010;2:80–4.
[42] Alexandre C, Dubos F, Courouble C, Pruvost I, Varon E, Hospital Network for Evaluating the Management of Common Childhood D, et al. Rebound in the incidence of pneumococcal meningitis in northern France: effect of serotype replacement. Acta Paediatr 2010;99:1686–90.

[43] McIntosh ED, Reinert RR. Global prevailing and emerging pediatric pneumococcal serotypes. Expert Rev Vaccines 2011;10:109–29.
[44] Yao KH, Wang LB, Zhao GM, Zheng YJ, Deng L, Huang JF, et al. Pneumococcal serotype distribution and antimicrobial resistance in Chinese children hospitalized for pneumonia. Vaccine 2011;29:2296–301.
[45] Choi EH, Kim SH, Eun BW, Kim SJ, Kim NH, Lee J, et al. Streptococcus pneumoniae serotype 19A in children, South Korea. Emerg Infect Dis 2008;14:275–81.
[46] Harboe ZB, Valentiner-Branth P, Benfield TL, Christensen JJ, Andersen PH, Howitz M, et al. Early effectiveness of heptavalent conjugate pneumococcal vaccination on invasive pneumococcal disease after the introduction in the Danish Childhood Immunization Programme. Vaccine 2010;28:2642–7.
[47] Houseman C, Hughes GJ, Chapman KE, Wilson D, Gorton R. Increased invasive pneumococcal disease, North East England, UK. Emerg Infect Dis 2017;23:122–6.
[48] Romney MG, Hull MW, Gustafson R, Sandhu J, Champagne S, Wong T, et al. Large community outbreak of Streptococcus pneumoniae serotype 5 invasive infection in an impoverished, urban population. Clin Infect Diseases: Official Publ Infect Diseases Soc Am 2008;47:768–74.
[49] National Economic and Social Development Board of Thailand. Population Projections Classified by sex and province, year 2010. [online] Available at: http://social.nesdb.go.th/SocialStat/StatReport_Final.aspx?reportid=1256&template=2R1C&yeartype=M&subcatid=1 [Accessed 05/12/18].
[50] Luby SP, Brooks WA, Saha SK, el-Arifeen S, Naheed A, Sack D, et al. Use of multiple surveillance modalities to assess the epidemiology of Streptococcus pneumoniae infection in Bangladesh. Clin Infect Diseases: Official Publ Infect Diseases Soc Am 2009;48(Suppl 2):S97–S102.
[51] Bruce MG, Singleton R, Bulkow L, Rudolph K, Zulz T, Gounder P, et al. Impact of the 13-valent pneumococcal conjugate vaccine (pcv13) on invasive pneumococcal disease and carriage in Alaska. Vaccine 2015;33:4813–9.
[52] Towse A, Mills A, Tangcharoensathien V. Learning from Thailand's health reforms. BMJ 2004;328:103–5.
[53] Limwattananon S, Tangcharoensathien V, Prakongsai P. Catastrophic and poverty impacts of health payments: results from national household surveys in Thailand. Bull World Health Organ 2007;85:600–6.
[54] Brueggemann AB, Griffiths DT, Meats E, Peto T, Crook DW, Spratt BG. Clonal relationships between invasive and carriage streptococcus pneumoniae and serotype- and clone-specific differences in invasive disease potential. J Infect Dis 2003;187:1424–32.
[55] Chewapreecha C, Harris SR, Croucher NJ, Turner C, Marttinen P, Cheng L, et al. Dense genomic sampling identifies highways of pneumococcal recombination. Nat Genet 2014;46:305–9.
[56] Turner P, Hinds J, Turner C, Jankhot A, Gould K, Bentley SD, et al. Improved detection of nasopharyngeal cocolonization by multiple pneumococcal serotypes by use of latex agglutination or molecular serotyping by microarray. J Clin Microbiol 2011;49:1784–9.
[57] Turner P, Melchiorre S, Moschioni M, Barocchi MA, Turner C, Watthanaworawit W, et al. Assessment of streptococcus pneumoniae pilus islet-1 prevalence in carried and transmitted isolates from mother-infant pairs on the Thailand-Burma border. Clin Microbiol Infect 2012;18:970–5.
[58] Turner P, Turner C, Jankhot A, Helen N, Lee SJ, Day NP, et al. A longitudinal study of Streptococcus pneumoniae carriage in a cohort of infants and their mothers on the Thailand-Myanmar border. PLoS ONE 2012;7:e38271.
[59] Turner P, Turner C, Jankhot A, Phakaudom K, Nosten F, Goldblatt D. Field evaluation of culture plus latex sweep serotyping for detection of multiple pneumococcal serotype colonisation in infants and young children. PLoS ONE 2013;8:e67933.
[60] Bogaert D, De Groot R, Hermans PW. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. Lancet Infect Dis 2004;4:144–54.
[61] Bravo LC, Asian strategic alliance for pneumococcal disease prevention working G. Overview of the disease burden of invasive pneumococcal disease in Asia. Vaccine 2009;27:7282–91.
[62] McNeil HC, Clarke SC. Serotype prevalence of Streptococcus pneumoniae in Malaysia – the need for carriage studies. Med J Malaysia 2016;71:134–8.
[63] Klugman K, Tam J. Pneumococcal conjugate vaccines in Asia and the Pacific, Singapore, 9–11 October 2000. Report of an Asia Pacific Advisory Board Meeting 1 For the Asia Pacific Advisory Board; 2001.