IJID Regions 8 (2023) 49–57

Contents lists available at ScienceDirect

IJID Regions

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

Outcomes among Thai children with risk conditions hospitalized for pneumococcal disease (invasive or non-bacteraemic pneumonia): A multi-centre, observational study

Wanatpreeya Phongsamart[a,†], Kristen E. Allen[b,†,*], Warunee Punpanich Vandepitte[c], Chonnamet Techasaensiri[d], Pope Kosalaraksa[e], Kamolwish Laoprasopwattana[f], Puttichart Khantee[f], Songkiat Udompornwattana[g], Detchvijitr Suwanpakdee[h], Tavitiya Sudjaritruk[i], Thanyawee Puthanakit[j], Suvaporn Anugulruengkitt[j], Jo Southern[b], Mark A. Fletcher[k], Eileen M. Dunne[b], Ruangwit Thamaree[l], Graciela Morales[b], Kulkanya Chokephaibulkit[a], Tawee Chotpitayasunondh[c]

[a] *Department of Paediatrics, Division of Infectious Diseases, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand*
[b] *Pfizer Biopharma Group, Collegeville, PA, USA*
[c] *Queen Sirikit National Institute of Child Health, Bangkok, Thailand*
[d] *Division of Infectious Diseases, Department of Paediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*
[e] *Division of Infectious Disease, Department of Paediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand*
[f] *Department of Paediatrics, Faculty of Medicine, Prince of Songkla University, Songkla, Thailand*
[g] *Buddhachinaraj Hospital, Phitsanulok, Thailand*
[h] *Paediatric Infectious Disease Unit, Phramongkutklao Hospital, Bangkok, Thailand*
[i] *Department of Paediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*
[j] *Division of Paediatric Infectious Diseases, Department of Paediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*
[k] *Pfizer Biopharma Emerging Markets Medical Affairs, Vaccines, Paris, France*
[l] *Pfizer Biopharma Group, Emerging Markets Asia, Bangkok, Thailand*

ARTICLE INFO

Keywords:
Invasive pneumococcal disease (IPD)
Pneumococcal pneumonia
Non-bacteraemic pneumococcal pneumonia
Pneumococcal conjugate vaccine
PCV13

ABSTRACT

Objective: To describe the risk condition status and clinical outcomes among Thai children hospitalized with pneumococcal disease.

Methods: In this retrospective analysis, children with invasive pneumococcal disease (IPD) or x-ray-confirmed non-bacteraemic pneumococcal pneumonia (NBPP) were identified from nine hospitals in Thailand between 2010 and 2019. Data on risk factors and outcomes were extracted from medical records.

Results: In total, 413 cases were identified: 319 IPD and 94 NBPP. Overall, 133 (32.2%) patients were admitted to intensive care units and 11/406 (2.7%) died. Twenty-seven percent of IPD cases had at-risk conditions and 15% had high-risk conditions. Most IPD cases (32.9%) occurred in children aged 2–4 years, and most NBPP cases (28.7%) occurred in infants aged 0–11 months. Of 51 *Streptococcus pneumoniae* isolates collected, 41 (80%) were pneumococcal 13-valent conjugate vaccine serotypes. Only 5.1% of children had received a pneumococcal vaccine.

Conclusions: Most children with IPD and NBPP did not have high-risk or at-risk conditions, while 42% had at-risk or high-risk conditions for pneumococcal disease. Very few children in the cohort had received any type of pneumococcal vaccine. Increasing the availability of pneumococcal conjugate vaccines should be considered to reduce the burden of pneumococcal disease among children in Thailand.

* Corresponding author. Pfizer Biopharma Group, 500 Arcola Road, Collegeville, PA 19426, USA.
E-mail address: Kristen.Allen@pfizer.com (K.E. Allen).
† These authors contributed equally to this manuscript.

https://doi.org/10.1016/j.ijregi.2023.06.001
Received 15 March 2023; Received in revised form 26 May 2023; Accepted 1 June 2023

Introduction

Each year, *Streptococcus pneumoniae* causes approximately 14% of all deaths in children aged <5 years worldwide [1], with most deaths occurring in low- or middle-income countries [2]. *S. pneumoniae* causes a spectrum of diseases, from mucosal infections [e.g. acute otitis media and non-bacteraemic pneumococcal pneumonia (NBPP)] to severe invasive pneumococcal disease (IPD), including septicemia, meningitis and bacteraemic pneumonia [3,4].

The most effective method for prevention of pneumococcal disease is vaccination [5]. Pneumococcal conjugate vaccines (PCVs) have been approved in more than 100 countries, and are recommended by national vaccine technical committees for administration in children, adolescents and adults. As of 2022, PCVs were included in the national immunization programmes (NIPs) of 152 countries [6]. Pneumococcal 7-valent conjugate vaccine (PCV7), pneumococcal 10-valent conjugate vaccine (PCV10)/*Haemophilus influenzae* protein D-conjugate vaccine (PHiD-CV) and pneumococcal 13-valent conjugate vaccine (PCV13) are licensed for use in Thailand; however, PCVs are not included in the Thai NIP [6]. Based on two published studies, the estimated incidence of IPD in at-risk/high-risk Thai children aged <5 years is approximately 20–120 per 100,000 [7,8]. However, there is limited evidence regarding the demographics, clinical characteristics and outcomes of children presenting with IPD in Thailand.

The primary objective of this study was to describe the risk condition status and clinical outcomes among Thai children hospitalized with pneumococcal disease. This study was conducted using available medical databases and clinical records from nine university and tertiary hospitals, and included children discharged with a diagnosis of IPD or NBPP over a 10-year period (2010–2019).

Methods

Ethics statement

Prior to initiation of data abstraction, the protocol was approved by the institutional review boards of each of the nine participating hospitals: Ramathibodi Hospital, Queen Sirikit National Institute of Child Health, Siriraj Hospital, King Chulalongkorn Memorial Hospital, Phramongkutklao Hospital, Srinagarind Hospital, Buddhachinaraj Hospital, Prince of Songkla University Hospital and Chiang Mai University Hospital. The nine hospitals were located throughout five provinces in Thailand (Figure S1, see online supplementary material). The study was conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996, 2008). Additionally, the study was conducted in accordance with the principles of the International Conference on Harmonization Guideline on Good Clinical Practice, and applicable local regulatory requirements and laws.

Study design and population

This was a retrospective database study of paediatric patients aged ≤15 years discharged from nine tertiary or university hospitals in Thailand between January 2010 and December 2019 with pneumococcal disease, confirmed by microbiological evidence of IPD (from normally sterile sites) or NBPP (based on tracheal suction or bronchoalveolar lavage).

Case definitions and clinical specimens

Two data abstractors at each of the nine hospitals searched the electronic medical record or medical chart for International Classification of Diseases Version 10 codes (Table 1) to identify episodes of IPD and NBPP. To be counted as a case, individuals had to have one of the discharge diagnosis codes in Table 1, and laboratory confirmation of *Streptococcus pneumoniae* from a specimen obtained as standard of care.

Pneumococcal identification was conducted at each hospital's laboratory using standard methods, including isolation of *S. pneumoniae* by antigen detection assay (latex agglutination), polymerase chain reaction (PCR), or culture from blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, joint, bone or any other normally sterile site. Serotyping was performed at Siriraj Hospital, Queen Sirikit National Institute of Child Health, King Chulalongkorn Memorial Hospital, Phramongkutklao Hospital, Prince of Songkla University Hospital and Ramathibodi Hospital using standard methods including the Quellung reaction or sequential multiplex PCR [9]. All study hospitals have International Organization for Standardization accreditation.

The case definition for IPD was detection of *S. pneumoniae* by latex agglutination, PCR, or culture from blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, joint, bone or any other normally sterile site [9]. Individuals with x-ray-confirmed pneumonia who had a positive culture for *S. pneumoniae* from a normally sterile fluid (e.g. blood and pleural fluid) were counted as bacteraemic pneumonia and included in the IPD group.

The case definition for NBPP was x-ray-confirmed pneumonia and a positive culture of *S. pneumoniae* from a sample obtained from the lower respiratory tract by tracheal suction or bronchoalveolar lavage. If a child had *S. pneumoniae* identified from both a normally sterile site (IPD) and the lower respiratory tract (NBPP), they were counted as an IPD case alone.

Antibiotic susceptibility testing was carried out as part of standard of care using customary methods including disk diffusion, ETEST gradient strips and VITEK 2 (bioMérieux, Marcy l'Etoile, France). For a subset of isolates, pneumococcal serotyping was performed using the Quellung reaction and/or sequential multiplex PCR.

Medical conditions were classified a priori as being either at risk or high risk based on the recommendations of the United States Advisory Committee on Immunization Practices [10]. At-risk conditions included diabetes mellitus, chronic pulmonary disease (interstitial pulmonary disease, asthma, etc.), chronic heart disease and chronic liver disease. High-risk conditions included congenital immunodeficiency/other acquired immunodeficiency, chronic renal disease (nephrotic syndrome), human immunodeficiency virus (HIV) infection and sickle cell disease/asplenia, as well as cochlear implant and cerebrospinal fistula. Other conditions classified as at-risk conditions by the investigators included: haemoglobinopathy/thalassaemia, G6PD deficiency, preterm birth, subglottic stenosis, meningoencephalocele, Chiari malformation, Downs syndrome, cerebral palsy, global delay development, spastic cerebral palsy, suspected congenital dystrophy and congenital myopathy.

If a child had both high-risk and at-risk conditions, they were categorized as 'high-risk conditions'. Children with none of the aforementioned conditions were categorized as 'without at-risk/high-risk conditions'.

Discharge status was recorded as noted by the treating physician in the medical record. Recovered was defined as the disease/condition had fully resolved without any sequelae. Improved was defined as clinical improvement of the disease/condition, but not yet fully resolved. Worsening was defined as a clinical course of the disease/condition that worsened with complications and/or sequelae. Death was classified as death from any cause.

Data management

Abstracted data were collected in a case report form that included information on demographics, diagnosis, hospitalization, clinical specimens and laboratory results, radiographic assessment, treatment, pneumococcal vaccination history and risk category information. The data abstraction was completed by one abstractor at each site, and the data for each subject were reviewed and checked by an abstractor at the central site. The data were entered into an Access database (Microsoft Corp., Redmond, WA, USA).

Table 1
Invasive pneumococcal disease (IPD) and non-bacteraemic pneumococcal pneumonia (NBPP) International Classification Version 10 (ICD-10) codes and specimen source [34].

Condition	Source	ICD-10 code(s)
IPD		
Bacteraemic pneumococcal pneumonia	Blood	J11, J13, J15, J17, J18, A40, A40.3, A40.9, A41, R65.1, R65.20, R65.21, R78.81
Complicated pneumococcal pneumonia	Pleural fluid	J85.1, J86
Pneumococcal meningitis	Cerebrospinal fluid	G00.1
Pneumococcal bacteraemia	Blood	A40, A40.3, A40.9, R65.1, R56.21, R78.81, R65.20
Pneumococcal peritonitis	Peritoneal	K65, B95
Pneumococcal septic arthritis	Joint/synovial fluid	M00, M00.1, M00.10, M00.11-M00.19
Pneumococcal osteomyelitis	Bone	M86, B95
Other pneumococcal infections	Other normally sterile internal body sites (e.g. lymph node, brain, etc.)	B95.3
NBPP		
Non-bacteraemic pneumococcal pneumonia	Tracheal suction or bronchoalveolar lavage	J11, J13, J15, J17, J18

Statistical analysis

Descriptive statistics were performed for all study variables, including frequency for categorical variables, and mean (standard deviation) or median (range) for continuous variables.

Percentages were calculated for the total number of children per age group or IPD/NBPP group. Odds ratios (OR) and 95% confidence intervals (CI) based on the Wald method comparing outcomes of children with at-risk and high-risk conditions with children without at-risk/high-risk conditions were calculated and adjusted for age. All analyses were conducted using SAS Studio (SAS Inc., Cary, NC, USA).

Results

In total, 413 cases were included in the final dataset: 319 IPD and 94 NBPP (Table 2a). Ten subjects were excluded due to missing source (i.e. not defined as sterile or non-sterile site) of specimen data, six subjects were excluded due to missing age information or age >15 years, and one subject was excluded due to hospitalization for >2 years due to other conditions. The majority of IPD cases were identified through blood culture (264/319, 82.8%). Of the IPD cases, 15.4% (49/319) had a discharge diagnosis code of pneumococcal meningitis (G00.1). Twenty-seven percent (85/319) of IPD cases had at-risk conditions, 15% (49/319) had high-risk conditions and 58% (185/319, 58.0%) did not have at-risk or high-risk conditions. Of the NBPP cases, 1% (1/94) had a high-risk condition, 41.5% (39/94) had at-risk conditions and 57% (54/94) did not have at-risk or high-risk conditions. Overall, 57.9% (239/413) of children with IPD or NBPP were not identified as having at-risk or high-risk conditions. Immunodeficiency (31/413, 7.5%) and chronic renal disease/nephrotic syndromic (20/413, 4.8%) were the most common high-risk conditions. The most common at-risk conditions were chronic heart disease (42/413, 10.2%), chronic liver disease (25/413, 6.1%) and premature birth (19/413, 4.6%).

Overall, slightly more males (235/413, 56.9%) than females (166/413, 40.2%) were included in this study (Table 2a). Most of the IPD cases were in the 2–4-years age group (105/319, 32.9%); however, among the IPD cases with high-risk conditions, over half were in the 5–15-years age group (27/49, 55.1%). Over half of the IPD cases with a discharge diagnosis of pneumococcal pneumonia (G00.1) were aged 0–11 months (31/49, 63.3%), 8.2% (4/49) were aged 12–23 months, 12.2% (6/49) were aged 2–4 years and 16.3% (8/49) were aged 5–15 years. Of children with IPD aged 5–15 years, 43.9% (29/66) did not have at-risk or high-risk conditions. The most common age group for NBPP cases was 0–11 months (27/95, 28.7%), and the age group distribution was similar regardless of risk group (Table 2a).

The median length of hospitalization was 13 (range 0–555) days, and this was similar regardless of pneumococcal disease type or medical condition risk group (Table 2b). Of 133 cases requiring admission to an intensive care unit (ICU), 33.1% (44/133) were aged 0–11 months, 20.3% (27/133) were aged 12–23 months, 24.1% (32/133) were aged 2–4 years and 22.6% (30/133) were aged 5–15 years. Although there were 11 deaths (11/406, 2.7%) – eight in IPD cases (8/319, 2.5%) and three in NBPP cases (3/94, 3.2%) – most IPD and NBPP cases recovered or had an improved condition upon discharge (392/413, 94.9%) (Table 2b). Nonetheless, the proportion of NBPP cases admitted to the ICU was higher (64/94, 68.1%) compared with IPD cases (69/319, 21.6%). Ventilator use was also higher in NBPP cases (59/94, 62.8%) compared with IPD cases (54/319, 16.9%) (Table 2b).

Only 21 children (21/413, 5.1%) had documentation of receipt of a pneumococcal vaccine (PCV). PCV13 was the most commonly received vaccine, received by 16/413 (3.9%) children (Table 2a). One of the 21 children (4.8%) who had received a PVC was fully vaccinated (PCV13).

There were 51/413 (12.3%) cases with *S. pneumoniae* isolates that were serotyped; of these, 41 (80.3%) were PCV13 serotypes. The most frequently identified vaccine serotypes were 19F (8/51, 15.7%), 6B (7/51, 13.7%) and 19A (5/51, 9.8%). Ten cases had non-vaccine serotypes (10/51, 19.6%) (Figure 1a). The *S. pneumoniae* isolates that were serotyped were identified, by year, in 2010 (n=10), 2011 (n=4), 2012 (n=6), 2013 (n=16), 2014 (n=4), 2015 (n=8), 2016 (n=2) and 2018 (n=1) (Figure 1b).

Antibiotic susceptibility testing was performed for at least one antibiotic for all isolates (Table 3). Susceptibility was good for levofloxacin (IPD: 72/73, 98.6%; NBPP: 40/43, 93.0%), vancomycin (IPD: 229/234, 98.7%; NBPP: 87/87, 100%) and linezolid (IPD: 49/49, 100%; NBPP: 28/28, 100%). The antibiotics most commonly associated with resistance were erythromycin (IPD: 60.3%; NBPP: 76.3%), tetracycline (IPD: 74.5%; NBPP: 72.7%) and trimethoprim-sulfamethoxazole (IPD: 62.2%; NBPP: 63.6%) (Table 3). Penicillin (oral) showed reduced susceptibility (intermediate or resistant) in 21.9% of IPD isolates (12.1% intermediate, 18.2% resistant) and 21.0% of NBPP isolates (28.6% intermediate, 14.3% resistant). Meropenem showed reduced susceptibility, with 16.7% of IPD isolates displaying intermediate resistance.

This study investigated whether children with high-risk or at-risk conditions had higher odds of poor outcomes (i.e. more likely to have worsening disease or death upon discharge) compared with children without high-risk or at-risk conditions. None of the NBPP cases with high-risk conditions had poor outcomes, so OR analysis was not conducted for this group. Among IPD cases with high-risk conditions, the adjusted OR was 1.22 (95% CI 0.13–11.85), and for NBPP cases with at-risk conditions, the adjusted OR was 1.57 (95% CI 0.20–12.32). No significant differences were observed for either IPD or NBPP cases as the 95 CIs were wide (Table 4a).

This study also investigated the odds of death among IPD cases with high-risk or at-risk conditions. The case fatality ratio among cases with high-risk or at-risk conditions was 5/132 (3.8%) for IPD and 2/39 (5.1%) for NBPP, although cause of death data were not available. Those IPD cases with either high-risk or at-risk conditions were 2.48 (95% CI

Table 2a
Characteristics and vaccination status of hospitalized children aged 0–15 years with invasive pneumococcal disease and non-bacteraemic pneumococcal pneumonia, by risk group from nine tertiary hospitals in Thailand, 2010–2019.

	Pneumococcal disease type															
	Invasive pneumococcal disease								Non-bacteraemic pneumococcal pneumonia							
	Risk group						All (*n*=319)		Risk group						All (*n*=94)	
	High-risk (*n*=49)		At-risk (*n*=85)		No high-risk/at-risk conditions (*n*=185)				High-risk (*n*=1)		At-risk (*n*=39)		No high-risk/at-risk conditions (*n*=54)			
	n	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*
Sex																
Female	12	(24.5)	37	(43.5)	83	(44.9)	132	(41.4)	0	(0)	18	(46.2)	16	(29.6)	34	(36.2)
Male	36	(73.5)	44	(51.8)	99	(53.5)	179	(56.1)	1	(100.0)	18	(46.2)	37	(68.5)	56	(59.6)
Missing data	1	(2.0)	4	(4.7)	3	(1.6)	8	(2.5)	0	(0)	3	(7.7)	1	(1.9)	4	(4.3)
Total	49	(100.0)	85	(100.0)	185	(100.0)	319	(100.0)	1	(100.0)	39	(100.0)	54	(100.0)	94	(100.0)
Age group																
0–11 months	3	(6.1)	33	(38.8)	50	(27.0)	86	(27.0)	0	(0)	12	(30.8)	15	(27.8)	27	(28.7)
12–23 months	4	(8.2)	19	(22.4)	39	(21.1)	62	(19.4)	0	(0)	10	(25.6)	13	(24.1)	23	(24.5)
2–4 years	15	(30.6)	23	(27.1)	67	(36.2)	105	(32.9)	0	(0)	8	(20.5)	12	(22.2)	20	(21.3)
5–15 years	27	(55.1)	10	(11.8)	29	(15.7)	66	(20.7)	1	(100.0)	9	(23.1)	14	(25.9)	24	(25.5)
Total	49	(100.0)	85	(100.0)	185	(100.0)	319	(100.0)	1	(100.0)	39	(100.0)	54	(100.0)	94	(100.0)
Received vaccine																
PCV7	1	(2.0)	0	(0)	0	(0)	1	(0.3)	0	(0)	0	(0)	0	(0)	0	(0)
PCV10/PHiD-CV	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	1	(2.6)	1	(1.9)	2	(2.1)
PCV13	2	(4.1)	5	(5.9)	4	(2.2)	11	(3.4)	0	(0)	3	(7.7)	2	(3.7)	5	(5.3)
PPSV23	0	(0)	1	(1.2)	1	(0.5)	2	(0.6)	0	(0)	0	(0)	0	(0)	0	(0)

PCV7, pneumococcal 7-valent conjugate vaccine; PCV10/PHiD-CV, pneumococcal 10-valent conjugate vaccine *Haemophilus influenzae* protein D-conjugate vaccine; PCV13, pneumococcal 13-valent conjugate vaccine; PPSV23, pneumococcal polysaccharide vaccine.

Table 2b
Hospital course and status at discharge of hospitalized children aged 0–15 years with invasive pneumococcal disease and non-bacteraemic pneumococcal pneumonia, by risk group, from nine tertiary hospitals in Thailand, 2010–2019.

	Pneumococcal disease type															
	Invasive pneumococcal disease								Non-bacteraemic pneumococcal pneumonia							
	Risk group						All (*n*=319)		Risk group						All (*n*=94)	
	High-risk (*n*=49)		At-risk (*n*=85)		No high-risk/at-risk conditions (*n*=185)				High-risk (*n*=1)		At-risk (*n*=39)		No high-risk/at-risk conditions (*n*=54)			
	n	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*
Length of stay (days)																
Median (range)	15	(4–55)	14	(1–217)	10	(0–72)	13	(0–217)	3	(3–3)	13	(4–261)	14	(2–555)	14	(2–555)
Missing data	0	(0)	2	(2.35)	2	(1.08)	4	(1.25)	0	(0)	1	(2.56)	0	(0)	1	(1.06)
ICU admission																
Yes	9	(18.4)	25	(29.4)	35	(18.9)	69	(21.6)	0	(0)	28	(71.8)	36	(66.7)	64	(68.1)
Missing data	2	(4.1)	7	(8.2)	8	(4.3)	17	(5.3)	0	(0)	0	(0)	2	(3.7)	2	(2.1)
Total	49	(100.0)	85	(100.0)	185	(100.0)	319	(100.0)	1	(100.0)	39	(100.0)	54	(100.0)	94	(100.0)
Days in ICU																
Median (range)	1	(0–10)	5	(0–150)	5	(0–72)	4	(0–150)	-	-	6	(0–47)	8	(1–56)	7	(0–56)
Missing data	0	(0)	0	(0)	1	(1.9)	1	(1.5)	-	-	0	(0)	0	(0)	0	(0)
Ventilator use																
Yes	6	(12.2)	19	(22.4)	29	(15.7)	54	(16.9)	0	(0)	28	(71.8)	31	(57.4)	59	(62.8)
Missing data	2	(4.1)	8	(9.4)	11	(5.9)	21	(6.6)	0	(0)	1	(2.6)	2	(3.7)	3	(3.2)
Total	49	(100.0)	85	(100.0)	185	(100.0)	319	(100.0)	1	(100.0)	39	(100.0)	54	(100.0)	94	(100.0)
Days on ventilator																
Median (range)	0	(0–5)	3	(0–145)	3	(0–40)	3	(0–145)	-	-	5.5	(1–38)	5	(0–42)	5	(0–42)
Missing data	0	(0)	0	(0)	0	(0)	0	(0)	-	-	0	(0)	0	(0)	0	(0)
Discharge status																
Recovered	19	(38.8)	26	(30.6)	81	(43.8)	126	(39.5)	0	(0)	8	(20.5)	4	(7.4)	12	(12.8)
Improved	28	(57.1)	54	(63.5)	96	(51.9)	178	(55.8)	1	(100.0)	28	(71.8)	47	(87.0)	76	(80.9)
Worsening (complication or sequalae)	0	(0)	0	(0)	2	(1.1)	2	(0.6)	0	(0)	0	(0)	1	(1.9)	1	(1.1)
Deceased	1	(2.0)	4	(4.7)	3	(1.6)	8	(2.5)	0	(0)	2	(5.1)	1	(1.9)	3	(3.2)
Missing data	1	(2.0)	1	(1.2)	3	(1.6)	5	(1.6)	0	(0)	1	(2.6)	1	(1.9)	2	(2.1)
Total	49	(100.0)	85	(100.0)	185	(100.0)	319	(100.0)	1	(100.0)	39	(100.0)	54	(100.0)	94	(100.0)
Case fatality ratio	1/48	(2.1)	4/84	(4.8)	3/182	(1.6)	8/314	(2.5)	0/1	(0)	2/38	(5.3)	2/53	(3.8)	3/92	(3.3)

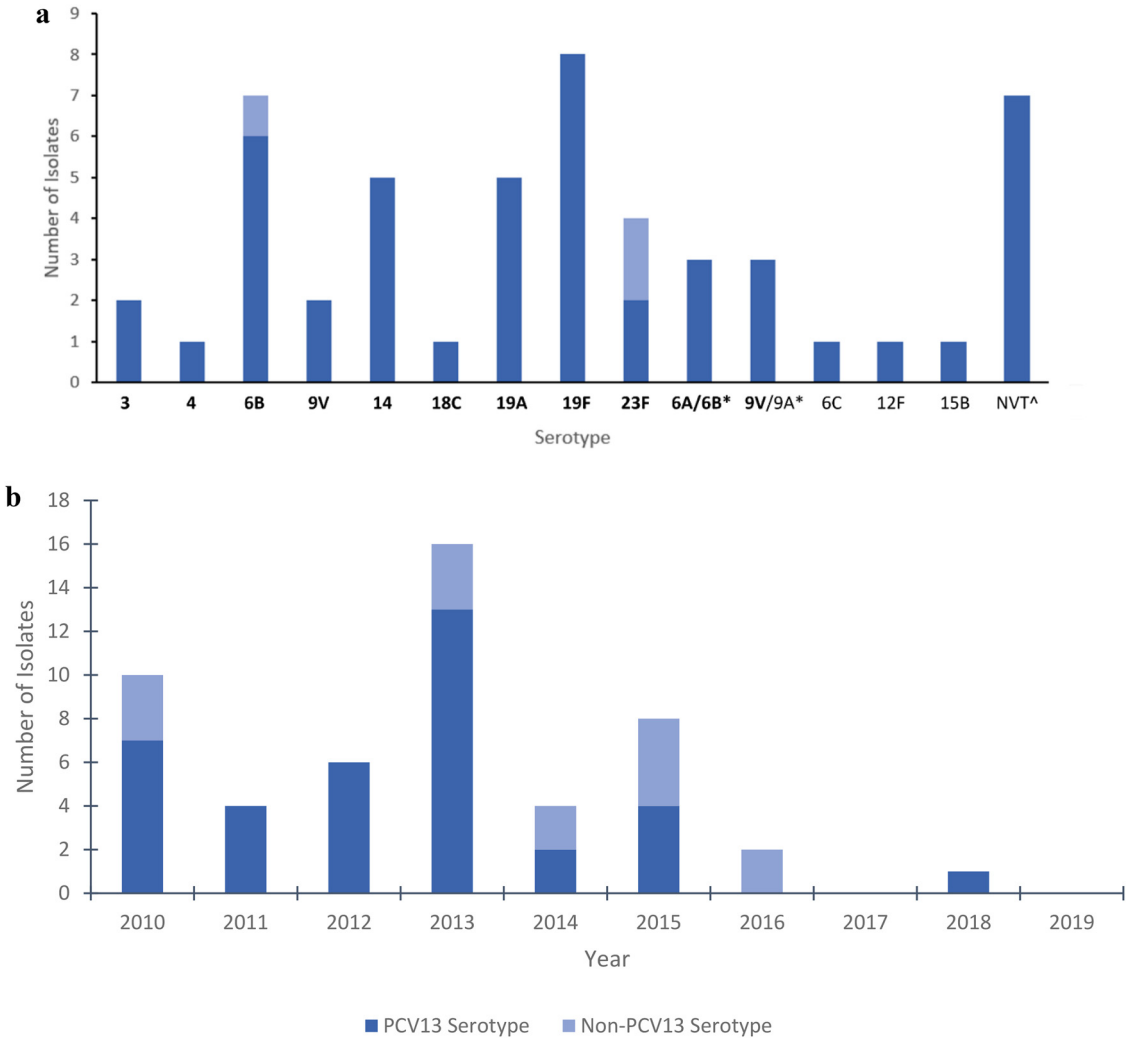

Figure 1. (a) Serotypes of *Streptococcus pneumoniae* isolates from children aged 0–15 years with invasive pneumococcal disease (IPD) or non-bacteraemic pneumococcal pneumonia (NBPP) from nine tertiary hospitals in Thailand, 2010–2019 (*n*=51). PCV13 serotypes are in bold. NVT, non-vaccine serotype. *Determined to serogroup level using polymerase chain reaction. ^Other, serotype unspecified. (b) Serotyped *S. pneumoniae* isolates from children aged 0–15 years with IPD or NBPP from nine tertiary hospitals in Thailand by year of identification, 2010–2019 (*n*=51). PCV13, pneumococcal 13-valent conjugated vaccine.

0.58–10.62) times more likely to die during hospitalization compared with children without at-risk or high-risk conditions, adjusted for age (Table 4b).

Discussion

This study used available medical databases and clinical records from nine hospitals to describe the risk condition status and clinical outcomes among Thai children hospitalized with pneumococcal disease (IPD or NBPP) over a 10-year period (2010–2019).

This study demonstrated that 42.0% of IPD and NBPP cases had at-risk or high-risk conditions. One-third of all cases (IPD and NBPP) required ICU admission. Compared with IPD cases, a higher proportion of NBPP cases required ICU admission and ventilator use. The overall case fatality ratio in the study cohort was 2.7%; however, slightly higher case fatality ratios were seen in children with high-risk or at-risk conditions: 3.8% for IPD and 5.1% for NBPP.

Although serotyping data in this study were limited, serotypes 19F, 6B, 19A and 14 were the most common serotypes, all of which are included in both PCV13 and the new, higher-valency vaccines (PCV15 and PCV20).

Reduced susceptibility to penicillin in the study cohort was 21.9% for IPD and 21.0% for NBPP, obtained from the lower respiratory tract. Although relatively low in this study, antimicrobial resistance is a documented problem in Asia [11,12]. In a retrospective chart review of hospitalized IPD cases aged <15 years in Bangkok from 1971 to 2000, 42% of isolates showed intermediate resistance and 58% of isolates were resistant to penicillin [13,14]. A surveillance study in Thailand from 2000 to 2005 reported intermediate resistance to penicillin in 26% of isolates and resistance in 44% of isolates from hospitalized children aged <5 years [13]. In the present cohort, 16.7% of isolates tested for meropenem susceptibility showed intermediate resistance (83.3% susceptible). Although no isolates in the present study were resistant to meropenem, a global study between 2015 and 2017 reported that meropenem susceptibility was <60.9% in Africa, Asia and the Middle East, and >81.6% in Europe, North America and Latin America [15]. One of the strategies in Thailand's strategic plan on antimicrobial resistance 2017–2021 was containment of antimicrobial resistance in humans [16]. Utilization of antibiotics and resistance is likely to continue to rise; however, pneumococcal vaccination may be an important tool to combat this problem.

Chronic heart disease (10.2%) was the most common at-risk condition in the study cohort, and immunodeficiency (7.5%) was the most

Table 3
Antimicrobial susceptibility of *Streptococcus pneumoniae* isolates collected from children aged 0–15 years with invasive pneumococcal disease or non-bacteraemic pneumococcal pneumonia from nine tertiary hospitals in Thailand, 2010–2019.

Antimicrobial agents	Invasive pneumococcal disease							Non-bacteraemic pneumococcal pneumonia					
	Susceptibility (%)												
	Total isolates tested	Susceptible		Intermediate		Resistance		Total isolates tested	Susceptible		Intermediate		Resistance	
		n	(%)	*n*	(%)	*n*	(%)		*n*	(%)	*n*	(%)	*n*	(%)
Penicillin (oral)	66	46	(69.7)	8	(12.1)	12	(18.2)	7	4	(57.1)	2	(28.6)	1	(14.3)
Penicillin (parenteral)	247	193	(78.1)	11	(4.5)	43	(17.4)	81	64	(79.0)	2	(2.5)	15	(18.5)
Amoxicillin/clavulanate	7	7	(100)	0	(0)	0	(0)	2	2	(100)	0	(0)	0	(0)
Ceftriaxone	87	80	(92.0)	1	(5.8)	2	(2.3)	4	4	(100)	0	(0)	0	(0)
Cefuroxime	6	0	(0)	1	(16.7)	5	(83.3)	2	0	(0)	0	(0)	2	(100)
Chloramphenicol	67	50	(74.6)	0	(0)	17	(25.4)	65	54	(83.1)	0	(0)	11	(16.9)
Levofloxacin	73	72	(98.6)	0	(0)	1	(1.4)	43	40	(93.0)	0	(0)	3	(7.0)
Moxifloxacin	3	3	(100)	0	(0)	0	(0)	0	0	(0)	0	(0)	0	(0)
Erythromycin	184	68	(37.0)	5	(2.7)	111	(60.3)	80	18	(22.5)	1	(1.3)	61	(76.3)
Azithromycin	5	1	(20)	0	(0)	4	(80)	2	0	(0)	0	(0)	2	(100)
Vancomycin	232	229	(98.7)	2	(0.9)	1	(0.4)	87	87	(100)	0	(0)	0	(0)
TMP/SMX	164	43	(26.2)	19	(11.6)	102	(62.2)	44	11	(25)	5	(11.4)	28	(63.6)
Clindamycin	93	51	(54.8)	1	(1.1)	41	(44.1)	53	21	(39.6)	0	(0)	32	(60.4)
Tetracycline	98	21	(21.4)	4	(4.1)	73	(74.5)	33	8	(24.2)	1	(3.0)	24	(72.7)
Cefepime	1	1	(100)	0	(0)	0	(0)	5	5	(100)	0	(0)	0	(0)
Cefotaxime	183	172	(81.7)	6	(3.3)	5	(2.7)	41	38	(92.7)	2	(4.9)	1	(2.4)
Daptomycin	1	0	(0)	0	(0)	1	(100)	0	0	(0)	0	(0)	0	(0)
Ertapenem	1	0	(0)	0	(0)	1	(100)	0	0	(0)	0	(0)	0	(0)
Linezolid	49	49	(100)	0	(0)	0	(0)	28	28	(100)	0	(0)	0	(0)
Meropenem	24	20	(83.3)	4	(16.7)	0	(0)	0	0	(0)	0	(0)	0	(0)
Tigecycline	2	2	(100)	0	(0)	0	(0)	1	0	(0)	0	(0)	1	(100)

TMP/SMX, trimethoprim-sulfamethoxazole.

Table 4a
Odds of poor clinical outcomes (worsening/death) by risk level among hospitalized children aged 0–15 years with invasive pneumococcal disease and non-bacteraemic pneumococcal pneumonia in tertiary hospitals in Thailand, 2010–2019.

Risk group	Invasive pneumococcal disease			Non-bacteraemic pneumococcal pneumonia		
	Worsening or death *n/N* (%)	OR[a] (95% CI)	aOR[b] (95% CI)	Worsening or death *n/N* (%)	OR[a] (95% CI)	aOR[b] (95% CI)
High risk	1/48 (2.1)	0.75 (0.09–6.60)	1.22 (0.13–11.85)	0/1 (0)	-	-
At risk	4/84 (4.8)	1.77 (0.46–6.77)	1.54 (0.40–5.97)	2/38 (5.3)	1.42 (0.19–10.53)	1.57 (0.20–12.32)
Not at risk or high risk	5/184 (2.8)	Ref	Ref	2/53 (3.8)	Ref	Ref

OR, odds ratio; aOR, adjusted OR; CI, confidence interval.
[a] OR vs counterparts without at-risk/high-risk conditions, recovered/improved.
[b] OR vs counterparts without at-risk/high-risk conditions, recovered/improved, adjusted for age group (0–11 months, 12–23 months, 2–4 years, 5–15 years).

Table 4b
Odds of death by risk level among hospitalized children aged 0–15 years with invasive pneumococcal disease in tertiary hospitals in Thailand, 2010–2019.

Risk group	Invasive pneumococcal disease		
	Death *n/N* (%)	OR[a] (95% CI)	aOR[b] (95% CI)
High risk or at risk	5/132 (3.8)	2.35 (0.55–10.00)	2.48 (0.58–10.62)
Not at risk or high risk	3/182 (1.7)	Ref	Ref

OR, odds ratio; aOR, adjusted OR; CI, confidence interval.
[a] OR vs counterparts without at-risk/high-risk conditions.
[b] OR vs counterparts without at-risk/high-risk conditions, adjusted for age group (0–11 months, 12–23 months, 2–4 years, 5–15 years).

common high-risk condition. A case–control study among children aged <5 years in a high-HIV-prevalence setting, South Africa, revealed that underlying medical conditions were associated with IPD in children who were not infected with HIV (adjusted OR 1.99, 95% CI 1.22–3.22) [17]. In the USA, a retrospective cohort analysis found that the risk of IPD in children aged <17 years with high-risk condition(s) varied from four- to 40-fold across medical conditions compared with children without high-risk or at-risk conditions [7]. In the UK, during the period after PCV13 introduction, 20.6% of IPD patients aged <5 years had an underlying condition, with immunosuppression being the most common [18].

In the present study, the case fatality ratio was 2.7% overall and 2.5% for IPD. This case fatality ratio is lower than that reported from other countries such as the UK, where the case fatality rate of IPD in children during a similar time period was 5.1%; however, the UK study only included children aged <5 years [18]. A review published in 2009 reported an 11% case fatality rate for pneumonia among Thai paediatric cases aged <5 years; however, this was not specific to pneumococcal pneumonia. A retrospective study in Korea of invasive infections in immunocompetent children from 2006 to 2010 found that the case fatality rate for *S. pneumoniae* was 8.4% (13/155) [19]. Case fatality rates for IPD vary depending on geography and study population; a review

of paediatric IPD in Europe found that case fatality rates for children aged <5 years ranged from 0.7% to 36.4% [20]. Reasons for the lower fatality rate in the present study could include improved access to care and improved quality of care during the study period. Additionally, the present study included older children and adolescents, who typically have a lower case fatality rate.

In this study, risk conditions were not significantly associated with increased likelihood of poor outcomes or death; however, the 95% CIs were wide due to relatively small numbers, and the point estimates for ORs were >1. In the UK, the OR of a fatal outcome from IPD among children aged 2–15 years was 2.5 times higher for children with one or more risk factors compared with children without risk factors [21].

Strengths of this study include the long study period and data collection from nine tertiary hospitals, representing both Bangkok and regional areas. This study provides new data on the characteristics of paediatric IPD and NBPP in Thailand. However, this study also has several limitations. Data were missing or incomplete for a number of cases. Missing data or low numbers for several data categories meant that certain comparisons or statistical analyses could not be performed. Additionally, incidence could not be calculated as the population denominators were not available. Pneumococcal serotyping data in the study cohort were only available for 12% of cases. Despite this limitation, the results were similar to a study by Phongsamart et al. [22], which found that the most common S. pneumoniae serotypes in Thai children aged <5 years with invasive disease were 6B (27.8%), 23F (20.0%), 14 (10.4%) and 19F (9.6%). A study examining IPD in Central Thailand between 2012 and 2016 found that, for children aged <5 years, serotypes 6B, 14, 19A and 19F were the most common, and 71.3% of IPD cases in this age group were caused by PCV13 serotypes [23]. A nasopharyngeal colonization study in Thai children aged <5 years also showed that 6B, 19F and 23F were the most common serotypes isolated [11]. The high proportion of PCV13 serotypes identified in the present study (80%) is likely due to limited use of PCV in Thailand. Only 5% of patients in this study had documented receipt of PCV.

Between 2007 and 2011, several PCVs (PCV7, PCV10/ PHiD-CV and PCV13) were licensed for use in Thailand. As of 2022, pneumococcal vaccination has not been included in the Thai NIP [24,25]. The current estimated uptake rates of PCV13 and PCV10/ PHiD-CV in Thai children are approximately 13% and 3%, respectively (personal communication with Dr. Wanatpreeya Phongsamart, unpublished data).

PCVs are included in the paediatric NIPs of 152 countries, and are recommended by national vaccine technical committees for administration in children, adolescents and adults. Studies conducted in other countries in the region have demonstrated that routine pneumococcal vaccination in children reduces vaccine-type IPD and is cost-effective compared with no pneumococcal vaccination [25–29]. In 2013, a cost-utility analysis was conducted based on PCV vaccine implementation for the entire birth cohort. As a result of that study, the decision to introduce PCVs was postponed [30]. A more recent study has demonstrated that, after accounting for herd immunity effects, PCV13 and PCV10/PhiD-CV would be cost-effective in Thailand [25,31]. Moreover, significant lifetime productivity losses due to pneumococcal disease could be prevented with PCV13 immunization during infancy [25,32]. Enhancing nationwide pneumococcal disease surveillance, including sample management and serotyping, will be critical to further assess the value of PCVs in Thailand.

The World Health Organization (WHO) recommends the inclusion of PCVs in paediatric immunization programmes worldwide [33]. Additionally, the US Advisory Committee on Immunization Practices recommends PCV13 vaccination for children aged 2–59 months and 60–71 months with chronic and immunocompromising conditions. In Thailand, risk conditions were common among the IPD and NPBB patients in this study, suggesting that children with underlying conditions known to increase the risk of pneumococcal disease may particularly benefit from PCV immunization. Nonetheless, more than half of the patients in this cohort did not have any known risk condition other than their young age. An ideal vaccination programme in line with WHO recommendations would include PCV in the routine infant NIP. The majority of cases in this study did not have high-risk or at-risk conditions, indicating that pneumococcal vaccination is needed for all young children, regardless of risk condition. However, children with risk conditions could be prioritized for PCV immunization in the face of resource constraints. As expected, most cases of IPD and NPBB occurred in children aged <5 years. For IPD, a high proportion (56%) of older children aged 5–15 years had a high-risk or at-risk condition, suggesting a targeted, risk-based PCV vaccination programme might be appropriate for older children. Older children with risk conditions could also be considered in the design of potential catch-up campaigns to provide protection to those most vulnerable to severe pneumococcal infections.

Conclusions

This study adds important descriptive data on IPD and NBPP cases in children aged ≤15 years over a 10-year period in Thailand. Forty-two percent of the paediatric patients in this study had at-risk or high-risk conditions for pneumococcal disease; however, receipt of any type of PCV in the study cohort was minimal. The most commonly identified serotypes in the cohort are included in the PCV13 vaccine. Increasing the availability of PCVs should be considered as a public health tool to reduce the burden of pneumococcal disease in Thailand.

Conflict of interest statement

Kristen Allen, Jo Southern, Mark Fletcher and Eileen Dunne are employees of, and may hold stock and/or stock options in, Pfizer Inc.

Acknowledgements

The authors wish to thank: Amgad Gamil for his early support of the project; Qin Jiang and Kaijie Pan, the study statisticians; and Bajaree Chotpitayasunondh, the study data manager. Editorial assistance was provided by Qi Yan (Pfizer Inc).

Funding

This study was funded by Pfizer Inc as a collaborative research agreement (WI234821).

Author contributions

Tawee Cjotpitaysunondh, Mark Fletcher and Ruangwit Thamaree conceived this study. Wanatpreeya Phongsamart, Warunee Punpanich Vandepitte, Chonnamet Techasaensiri, Pope Kosalaraksa, Kamolwish Laoprasopwattana, Puttichart Khantee, Songkiat Udompornwattana, Detchvijitr Suwanpakdee, Tavitiya Sudjaritruk, Thanyawee Puthanakit, Suvaporn Anugulruengkitt, and Kulkanya Chokephaibulkit collected the data. Kristen Allen conducted the analysis. Kristen Allen, Eileen Dunne and Mark Fletcher wrote the first draft of the manuscript. Kristen Allen, Eileen Dunne, Mark Fletcher, Ruangwit Thamaree, Jo Southern, Wanatpreeya Phongsamart and Kulkanya Chokephaibulkit critically revised the manuscript. All authors read and approved the final version to be published.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2023.06.001.

References

[1] *World Health Organization. Pneumonia*, Geneva: WHO; 2022. Available at:. https://www.who.int/news-room/fact-sheets/detail/pneumonia.

[2] Luna CM. Impact of vaccination on the epidemiology and prognosis of pneumonia. *Revista de la SEQ* 2022;**35**(Suppl. 1):104–10.

[3] Shoar S, Musher DM. Etiology of community-acquired pneumonia in adults: a systematic review. *Pneumonia* 2020;**12**:11.

[4] Noordzij M, van Diepen M, Caskey FC, Jager KJ. Relative risk versus absolute risk: one cannot be interpreted without the other. *Nephrol Dial Transplant* 2017;**32** ii13–8.

[5] Diao W-Q, Shen N, Yu P-X, Liu B-B, He B. Efficacy of 23-valent pneumococcal polysaccharide vaccine in preventing community-acquired pneumonia among immunocompetent adults: a systematic review and meta-analysis of randomized trials. *Vaccine* 2016;**34**:1496–503.

[6] World Health Organization. Introduction of PCV (pneumococcal conjugate vaccine). Geneva: WHO. Available at: https://immunizationdata.who.int/pages/vaccine-intro-by-antigen/pneumo_conj.html?ISO_3_CODE=&YEAR= (accessed 1 May 2023).

[7] Pelton SI, Weycker D, Farkouh RA, Strutton DR, Shea KM, Edelsberg J. Risk of pneumococcal disease in children with chronic medical conditions in the era of pneumococcal conjugate vaccine. *Clin Infect Dis* 2014;**59**:615–23.

[8] Rhodes J, Dejsirilert S, Maloney SA, 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, 2005–2010. *PLoS One* 2013;**8**:e66038.

[9] Werno AM, Murdoch DR. Laboratory diagnosis of invasive pneumococcal disease. *Clin Infect Dis* 2008:926–32.

[10] Centers for Disease Control and PreventionUse of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among children aged 6–18 years with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2013;**62**:521–4.

[11] 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.

[12] Song JH, Lee NY, 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;**28**:1206–11.

[13] Lin TY, Shah NK, Brooks D, Garcia CS. Summary of invasive pneumococcal disease burden among children in the Asia-Pacific region. *Vaccine* 2010;**28**:7589–605.

[14] Sirinavin S, Vorachit M, Thakkinstian A, Hongsanguensri S, Wittayawongsruji P. Pediatric invasive pneumococcal disease in a teaching hospital in Bangkok. *Int J Infect Dis* 2003;**7**:183–9.

[15] Zhang Z, Chen M, Yu Y, Pan S, Liu Y. Antimicrobial susceptibility among Streptococcus pneumoniae and Haemophilus influenzae collected globally between 2015 and 2017 as part of the Tigecycline Evaluation and Surveillance Trial (TEST). *Infect Drug Resist* 2019;**12**:1209–20.

[16] Sumpradit N, Wongkongkathep S, Malathum K, Janejai N, Paveenkittiporn W, Yingyong T, et al. Thailand's national strategic plan on antimicrobial resistance: progress and challenges. *Bull World Health Organ* 2021;**99**:661–73.

[17] von Mollendorf C, Cohen C, de Gouveia L, Naidoo N, Meiring S, Quan V, et al. Risk factors for invasive pneumococcal disease among children less than 5 years of age in a high HIV prevalence setting, South Africa, 2010 to 2012. *Pediatr Infect Dis J* 2015;**34**:27–34.

[18] Makwana A, Sheppard C, Borrow R, Fry N, Andrews NJ, Ladhani SN. Characteristics of children with invasive pneumococcal disease after the introduction of the 13-valent pneumococcal conjugate vaccine in England and Wales, 2010–2016. *Pediatr Infect Dis J* 2018;**37**:697–703.

[19] Rhie K, Choi EH, Cho EY, Lee J, Kang JH, Kim DS, et al. Etiology of invasive bacterial infections in immunocompetent children in Korea (2006–2010): a retrospective multicenter study. *J Korean Med Sci* 2018;**33**:e45.

[20] Isaacman DJ, McIntosh ED, Reinert RR. Burden of invasive pneumococcal disease and serotype distribution among Streptococcus pneumoniae isolates in young children in Europe: impact of the 7-valent pneumococcal conjugate vaccine and considerations for future conjugate vaccines. *Int J Infect Dis* 2010;**14**:e197–209.

[21] van Hoek AJ, Andrews N, Waight PA, Stowe J, Gates P, George R, et al. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. *J Infect* 2012;**65**:17–24.

[22] 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.

[23] Phongsamart W, Srifeungfung S, Chatsuwan T, Rungnobhakhun P, Maleesatharn A, Chokephaibulkit K. Streptococcus pneumoniae causing invasive diseases in children and adults in Central Thailand, 2012–2016. *Vaccines (Basel)* 2022;**10**:1368.

[24] 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.

[25] Gamil A, Chokephaibulkit K, Phongsamart W, Techasaensiri C, Piralam B, Thamaree R. Pneumococcal disease in Thailand. *Int J Infect Dis* 2021;**102**:429–36.

[26] Haasis MA, Ceria JA, Kulpeng W, Teerawattananon Y, Alejandria M. Do pneumococcal conjugate vaccines represent good value for money in a lower-middle income country? A cost-utility analysis in the Philippines. *PLoS One* 2015;**10**:e0131156.

[27] Tyo KR, Rosen MM, Zeng W, Yap M, Pwee KH, Ang LW, et al. Cost-effectiveness of conjugate pneumococcal vaccination in Singapore: comparing estimates for 7-valent, 10-valent, and 13-valent vaccines. *Vaccine* 2011;**29**:6686–94.

[28] Wu DB, Roberts C, Lee VW, Hong LW, Tan KK, Mak V, et al. Cost-effectiveness analysis of infant universal routine pneumococcal vaccination in Malaysia and Hong Kong. *Hum Vaccin Immunother* 2016;**12**:403–16.

[29] Turner P, Leab P, Ly S, Sao S, Miliya T, Heffelfinger JD, et al. Impact of 13-valent pneumococcal conjugate vaccine on colonization and invasive disease in Cambodian children. *Clin Infect Dis* 2020;**70**:1580–8.

[30] 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.

[31] Dilokthornsakul P, Kengkla K, Saokaew S, Permsuwan U, Techasaensiri C, Chotpitayasunondh T, et al. An updated cost-effectiveness analysis of pneumococcal conjugate vaccine among children in Thailand. *Vaccine* 2019;**37**:4551–60.

[32] Ounsirithupsakul T, Dilokthornsakul P, Kongpakwattana K, Ademi Z, Liew D, Chaiyakunapruk N. Estimating the productivity burden of pediatric pneumococcal disease in Thailand. *Appl Health Econ Health Policy* 2020;**18**:579–87.

[33] World Health Organization. Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. *Wkly Epidemiol Rec* 2019;**94**:85–104.

[34] 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.