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Review

Invasive Pneumococcal Disease burden and PCV coverage in children under five in Southeast Asia: implications for India

Shafi Kolhapure[1], Vijay Yewale[2], Ashish Agrawal[3], Pradyumna Krishnappa[1], Lamine Soumahoro[4]

[1] *Medical Affairs Department, GSK, Mumbai, India*
[2] *Dr. Yewale Children's Hospital, Mumbai, India*
[3] *Medical Affairs Department, GSK, Hyderabad, India*
[4] *Global Medical Affairs, GSK, Wavre, Belgium*

Abstract

Introduction: Pneumococcal diseases, though preventable, are a major public health problem in Southeast Asia and particularly in India. Pneumococcal conjugate vaccines (PCVs) are used in the region for over a decade, but to understand their impact, invasive pneumococcal diseases (IPD) burden and PCV coverage data in the region are needed.

Methodology: A literature search was conducted to identify i) key evidence published between February 2008 and February 2018 on IPD burden, serotype prevalence and antibiotic resistance in Southeast Asia, and ii) PCV serotype and vaccination coverage in Southeast Asia.

Results: 49 relevant articles were included in the final analysis. Mortality in children under 5 years remains high in Southeast Asian countries, with around 25% of deaths due to IPD in India and Pakistan. There was a lack of recent data on IPD incidence. Antibiotic resistance to IPD isolates is increasing, with high resistance rates especially for meningeal isolates. Based on serotype distribution data, primarily for India, available PCVs would cover around 70-80% of IPD-causing serotypes. Vaccine coverage was around 15-20% in India to 98% in South Korea.

Conclusions: Widespread PCV use could successfully reduce IPD burden in the region due to high serotype coverage by available PCVs; emphasis should be placed on increasing vaccination uptake, for every child, particularly in India. Reducing health system barriers and improving surveillance and awareness is essential to improve coverage and effectively prevent IPD morbidity and mortality particularly in at risk regions.

Key words: Children; Southeast Asia; India; pneumococcal conjugate vaccines; invasive pneumococcal disease; pneumonia.

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Introduction

Despite a 53% reduction worldwide since 1990, the South Asian region continues to report very high under-five mortality rates (U5MR). Of the estimated 5.83 million global deaths in children under five years in 2015, around a fifth happened in India [1,2], and an estimated 294,000 (uncertainty range, 192,000–366,000) were caused by pneumococcal infections [1]. India and Pakistan were the major contributors of pneumococcal deaths in the region in 2015 [3]. *Streptococcus pneumoniae* (*S. pneumoniae*) are Gram-positive bacteria normally present without causing symptoms in the nasopharynx of healthy individuals. Children under two years are at higher risk of having the bacteria invading the bloodstream, thereby causing severe invasive pneumococcal diseases (IPD) such as pneumococcal meningitis, or pneumococcal septicemia, bacteremia or even pneumonia that can tend to be invasive. IPD result in high morbidity, mortality and long-term health and financial consequences. *S. pneumoniae* is also the leading cause of less severe but more frequent diseases like acute otitis media (AOM) in children [4-8]. The burden of pneumococcal disease in children can be prevented through vaccination with pneumococcal conjugate vaccines (PCVs) that are indicated for infants starting from 6 weeks. In addition, PCVs reduce carriage, thereby reducing transmission and also provide protection to unvaccinated individuals across age groups via herd immunity [9]. The 23-valent pneumococcal polysaccharide vaccine, though effective against pneumococcal diseases, is poorly immunogenic in young children (recommended over 2 years of age), does not elicit long-term protection and does not reduce carriage [10]. With the emergence of drug resistance, including increasing pneumococcal resistance to antibiotics, vaccination can help reduce the disease burden, as many serotypes causing resistance are included in PCVs [11], and reduce the subsequent

demand for antibiotics [12]. Considering the high IPD burden and mortality in Southeast Asia and India, PCVs can have an immense impact in reducing IPD and other pneumococcal diseases [4]. Although PCVs have been available in the region for over a decade, lack of awareness and realisation of their importance has limited their widespread use. While there are ample data from Western countries, the impact of PCVs on the Indian population and neighboring Southeast Asian countries has not yet been evaluated. Hence, understanding the current IPD burden and disease-causing serotypes becomes crucial to inform public health decisions and to understand the impact of PCVs in the near future. Thus, the objective of this review is a) to summarize existing data on the burden (in children under five years), antibiotic resistance and serotype distribution of IPD in Southeast Asia, and, b) to present serotype and vaccination coverage of PCVs in the region.

Current status of PCVs

Pneumococcal Non-Typeable *Haemophilus influenzae* (NT*Hi*) protein D conjugate vaccine (PHiD-CV, *Synflorix,* GSK), *Pneumosil* (PCV-10, Serum Institute of India) and 13-valent pneumococcal conjugate vaccine (PCV-13, *Prevnar*, Pfizer) are WHO pre-qualified, and currently licensed for active prevention of invasive disease and pneumonia caused by their respective vaccine serotypes [1, 5]. Further, PHiD-CV is also approved for use against cross-reactive serotype 19A. Also, only PHiD-CV and PCV-13 are approved for use against AOM caused by *S. pneumoniae*. PHiD-CV is also approved for use against AOM caused by NT*Hi.* PHiD-CV and PCV-13 have demonstrated an indirect effect on IPD and pneumonia in unvaccinated populations (herd effect) [5,13,14]. Both vaccines have a favourable safety profile in infants and young children [1] (Table 1). A few Indian states with a high IPD burden implemented PCV-13 (financially supported by Gavi, the Vaccine Alliance) in their national immunization program (NIP) from 2017 [7,15]. Both PCVs are also available in the private sector. Bangladesh, Nepal, Myanmar and Indonesia have also introduced PCV for Universal Mass Vaccination (UMV) [16].

Methodology

Two (non-systematic) literature searches were conducted: the first was to identify studies on the epidemiology and burden of IPD in Southeast Asia including India, and the second was to identify studies and national statistics on the PCV serotype and vaccination coverage in the region. Three online medical literature databases (i.e., PubMed, Embase and Google Scholar) were searched using keywords and Mesh terms for English-language human study reports published between February 2008 and February 2018 (see Appendix 1 for search strategies and iInclusion/exclusion criteria). We included studies published during this interval since the majority of countries in Southeast Asia started to adopt PCVs either in the private sector or in their NIP during this period. Eleven countries of the World Health Organization (WHO) Southeast Asia region were included as well as Pakistan and South Korea due to their proximity and similar epidemiology. Outcomes of interest included mortality (reported as U5M from all causes, pneumococcal case-fatality rate or number of pneumococcal deaths), pneumococcal incidence, most common serotypes, vaccine serotype coverage, antibiotic resistance (or decreased sensibility) rates. In total, 296 records were identified. High-impact studies

Table 1. Features of Pneumococcal conjugate vaccines.

Parameters for India	**PHiD-CV (*Synflorix*, GSK) [43]**	**PCV-13 (*Prevnar*, Pfizer) [13]**	**PCV-10 (*Pneumosil*, Serum Institute of India)[44]**
Recommendation in children up to 5 years	Yes	Yes	≤ 2 years
Schedule	3+1, 2+1, 1+1	3+1, 2+1, 1+1, 1	3+0
Schedule flexibility	Yes	Yes	No
Immunogenicity data	Yes	Yes	Yes
6A,19A immunogenicity	Yes	Yes	Yes
Efficacy data	Yes	No[$]	No
Real world IPD protection	Yes	Yes	No
AOM protection*	Yes *S.p.* + Nt*Hi*	*S.p.*	No
Pre term data	Yes	Yes	No

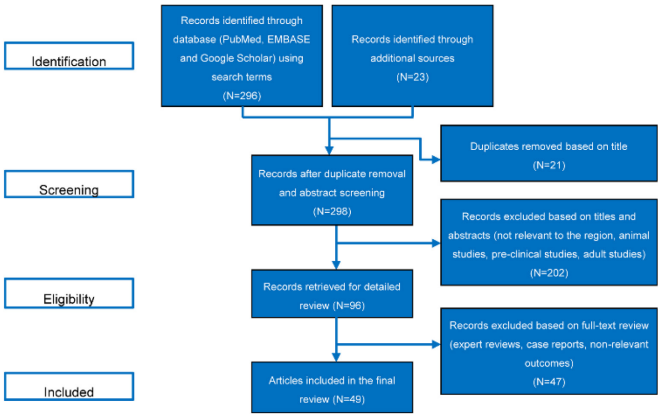
AOM: acute otitis media; IPD: invasive pneumococcal disease; PCV: pneumococcal conjugate vaccine; *Both *Streptococcus pneumoniae* (*S.p.*) and Non-typeable *Haemophilus influenzae* (NT*Hi*) cause AOM, and NT*Hi* protein-D conjugate vaccine (PHiD-CV) protects against both causes; [$]Efficacy established with PCV7.

(N=49) presenting relevant outcomes of IPD epidemiology or PCV data in India and Southeast Asia were retained for qualitative analysis, after applying inclusion and exclusion critera, and supplementing with relevant additional studies identified from searching reference lists (Figure 1). Due to this cross-referencing approach, older studies were also included. In order to identify data on the use of PCVs, government statistics and national/regional websites were also searched for PCV use (e.g., NIP or private market coverage) within the last 10 years (Appendix 1).

Results

Forty-nine articles were included in the final analysis. Considerable overlap existed in the articles included for analysis of the burden and coverage data described below. IPD epidemiology and PCV vaccination and serotype coverage varied widely in Southeast Asia, as studies used different surveillance methods (e.g., population or hospital-based) and time periods (Tables 2 and 3).

Figure 1. Literature review findings.



N: number of articles in each category. Screening was performed by 2 independent reviewers. Search strategies are detailed in Supplemental methods.

Table 2. Studies mentioning all-cause U5M and IPD/pneumococcal incidence, deaths and CFRs.

Country	Reference Study type	Study period	All-cause deaths, children < 5y	Pneumonia/ meningitis deaths, children < 5y	CFR (%)	IPD / Pneumococcal incidence
India	Liu 2016 [2] Population-based model	2000-2015	1,200,998	143,228 pneumonia 21,106 meningitis	-	-
	Jayaraman 2018 [21] Hospital-based sentinel surveillance network	2012-2013	-	-	-	Meningitis: 82.9% (213/257) in children < 5y
	Nisarga 2015 [22] Hospital-based surveillance	2009-2011	-	-	-	IPD: 17.8/100,000 in children < 5y, (49.9/ 100,000 for in children 6-12 months old), Pneumonia: 2,109/ 100,000
	Farooqi 2015 [23] Population-based model	2010	-	356,300 all-cause pneumonia 105,100 *S.p* pneumonia	9.96%	Severe pneumonia incidence: 30.7/1000 children < 5y *S.p.* pneumonia episodes: 564,200
	Jaiswal 2014a [32] Systematic review of 10 hospital-based prospective studies	1982-2008	-	-	-	IPD: 29.06%, pneumonia 24.3%, pyogenic meningitis 32.78%. *S. p.* causes 29.06% of IPD, 24.33% of pneumonia cases, and 32.78% of meningitis cases in children < 12y with confirmed bacterial diseases
	Lin 2010 [19], Population-based surveillance (Bangalore city)	2006	-	-	8.0%	IPD: 1,500/100,000 in children < 5y
	Bravo 2009 [18] Prospective hospital-based surveillance (IBIS-INCLEN group)	2004	2,210,000	410,000 pneumonia	19%	
Bangladesh	Liu 2016 [2] Population-based model	2000-2015	119,326	12,953 pneumonia 1,825 meningitis	-	-
	Brooks 2007 [45] Population-based surveillance	2004-2006	-	-	-	IPD: 447/100,000 in children < 5y, Pneumonia: 113/100,000, Meningitis: 105/100,000
Sri Lanka	Liu 2016 [2] Population-based model	2000-2015	3,091	139 pneumonia 26 meningitis	-	-
	Kularatna 2015 [46] Population and hospital-based surveillance	2005-2009	-	-	-	IPD: 206.3/100,000 in children < 5y, pneumonia: 147.9/100,000, meningitis: 13.2/100,000, sepsis: 45.2/100,000
	Bravo 2009 [18] (from WHO UNICEF data)	2004	5,000	0 pneumonia	9%	-
	Batuwanthudawe 2009 [47] Hospital sentinel surveillance	2004	-	-	-	Meningitis: 7.8/100,000 in children < 5y
Nepal	Liu 2016 [2] Population-based model	2000-2015	19,900	2,257 pneumonia 323 meningitis	-	-
	Kelly 2011 [48] Hospital study	2005-2006	-	-	-	Bacteremia, meningitis or pneumonia in children < 12y: *S.p.* in 16% (23/142) of blood cultures of bacteremia
Maldives	Liu 2016 [2] Population-based model	2000-2015	67	4 pneumonia 1 meningitis	-	-
Pakistan	Liu 2016 [2] Population-based model	2000-2015	431,568	49,578 pneumonia 5,239 meningitis	-	-
	Owais 2010 [17] Population surveillance	2007-2008	55/1000 live births	22% of all U5M	8%	IPD: 25/100,000 child-years in children < 5y, pneumonia: 0.26 episodes/child year, pneumococcal meningitis: 19.7/100,000 in children < 5y
	Zaidi 2009 [49] Hospital network surveillance	2005-2006	-		25%	

	Bravo 2009 [18] (from community and hospital-based studies)	2004	478,000	92,000 pneumonia	19%	-
Thailand	Liu 2016 [2] Population-based model	2000-2015	9,173	639 pneumonia 79 meningitis	-	-
	Baggett 2009 [20] Hospital study	2005-2007	-	-	14.1%	IPD: 10.6–28.9/100,000 persons in children < 5y
	Bravo 2009 [18] (from population-based studies)	2004	21,000	2,000 pneumonia	11%	-
	Sirinavin 2003 [50] Hospital study	1971-2000	-	-	5.7% (< 15y)	-
	Leelarasamee 1999 [51] Hospital study	1992-1998	-	-	10.0%	-
Bhutan	Liu 2016 [2] Population-based model	2000-2015	414	49 pneumonia 5 meningitis	-	-
Timor-Leste	Liu 2016 [2] Population-based model	2000-2015	2,642	471 pneumonia 51 meningitis	-	-
Indonesia	Liu 2016 [2] Population-based model	2000-2015	147,162	21,197 pneumonia 2,457 meningitis	-	-
	Lin 2010 [19], Hospital studies	2006	-		17%	IPD: 283–347/100,000 in children < 5y
	Bravo 2009 [18] (from hospital-based studies)	2004	171,000	25,000 pneumonia	14%	-
Democratic People's Republic of Korea	Liu 2016 [2] Population-based model	2000-2015	9,271	1,135 pneumonia 184 meningitis	-	-
South Korea	Liu 2016 [2] Population-based model	2000-2015	1,559	37 pneumonia 23 meningitis	-	-
	Choe 2013 [52] Hospital studies	1999-2005	-	-	-	45.3% (140/309) of infections were caused by pneumococci
	Bravo 2009 [18] (from hospital-based studies)	2004	3,000	0 pneumonia	2%	
Myanmar	Liu 2016 [2] Population-based model	2000-2015	46,284	6,157 pneumonia 898 meningitis	-	-

CFR: case fatality rate; IPD: invasive pneumococcal diseases; *S.p.*: *Streptococcus pneumoniae*, U5M: under-five mortality; y: year.

Table 3. Studies mentioning the most common serotypes, serotype coverage and antibiotic resistance.

Country	Reference	Study period	Number of isolates / IPD cases	Most common ST(s)	Other STs and findings	Serotype Coverage	Antibiotic resistance
India	Verghese 2017 [33]	2008-2016	311 isolates (72 meningitis and 239 non-meningeal) in < 5y olds	14 (22 isolates), 19F (17), 6B (13), 6A (11), 23F (7), 9V (7), 5 (7) in meningeal isolates	2 isolates each: 4, 6A, 7F, 23F, 38 1 isolate each: 1, 6C, 7A, 10A, 10C, 11A, 11C, 15B, 18C, 19A, 22F, 23A, 24B, 27	-	Penicillin resistance and cefotaxime non-susceptibility: 43/72 (59.7%) resistant in meningeal isolates 3/239 (1.2%) in non-meningeal isolates
	Singh 2017 [12]	2007-2016	7 studies included in final analysis	14, 1, 19F, 6B, 5, 6A, 9V, 23F	-	PHiD-CV: 67.3%, PCV-13: 78.4%	Co-trimoxazole: 81%, erythromycin: 37%, penicillin: 10%, chloramphenicol: 8%, levofloxacin: 6%, cefotaxime: 4%
	Manoharan 2017 [24]	2011-2015	361 cases	14 (14%), 1 (14%), 5 (10%), 19F (9%)	-	PCV-7: 63%, PHiD-CV: 68%, PCV-13: 74%, PPV-23: 80%	Penicillin: 8%, co-trimoxazole: 66%, erythromycin: 37%, chloramphenicol: 9%. MDR: 9%
	Jaiswal 2014b [25]	1993-2015	17 studies (4 from India)	14	Followed by 5, 1, 19F,6B	PCV-7: 28%, PHiD-CV: 62%, PCV-13: 70%	95% to levofloxacin
	Jayaraman 2018 [21]	2012-2013	29 isolates from pneumococcal meningitis patients <5y old	6B (5 isolates), 14 (4), 6A (4), 19F (3),	4, 5, 7F (2 isolates each) 9V, 18C, 23F, 19A, 8, 18A, 9N (1 isolate each)	From 29 isolates: PCV-7: 59% PCV-10: 72% PCV-13: 90%	Non-susceptible to cotrimoxazole: 29 (100%) Non-susceptible to erythromycin: 11 (37.9%) Non-susceptible to penicillin: 4 (13.8%) of which 3 non-susceptible to erythromycin and 2 to cefotaxime
	Molander 2013 [53]	2007-2011	Isolates from 244 IPD patients	1 (34%) 5 (22%) 19F (18%) 6B (18%) 14 (17%) 3 (12%) 19A (10%)		Serotype coverage in <2y / 2-17y: PCV-10: 60% / 58% PCV-13: 68% / 70%	Penicillin: 1.6% Erythromycin: 11.1% Chloramphenicol: 1.6% Cotrimoxazole: 74.2% Cefotaxime: 0.4% Oxacillin: 3.3% MDR: 5.3%
	Nisarga 2015 [22]	2009-2011	40 cases	6A (16.7%); 14 (13.9%); 5 (11.1%); 6B (11.1%)	1, 18C, 19A (each 8.3%)	-	Antibiotic resistance observed in STs 6A, 14, 6B, 1, 18C, 19A, 9V, 4, 10C, and 18A
	Shariff 2013 [54]	2007-2010	126 isolates tested for AMR and 108 isolates	19 (26%), 6 (11%), 7 (10%), 1 (9%), 14 (7%), 9 (5%), 33 (4%), 17 (4%), 11 (2%), 3 (2%)	-	PCV-7: 34%, PHiD-CV: 54%, PCV-13: 73%	Penicillin: 33%, erythromycin: 16%, ciprofloxacin: 15%, tetracycline: 30%, co-trimoxazole: 82%, chloramphenicol: 13%, cefotaxime: 8%
	Kim 2012 [34]	2008-2009	-	-	-	PCV-7: 56.5% PHiD-CV: 82.6% PCV-13: 95.7%	-
	Lin 2010 [19] (based on Kanungo 2001 [55]	1996-2000	-	-	-	PCV-7: 50% PHiD-CV: 73% PCV-13: 77%	-

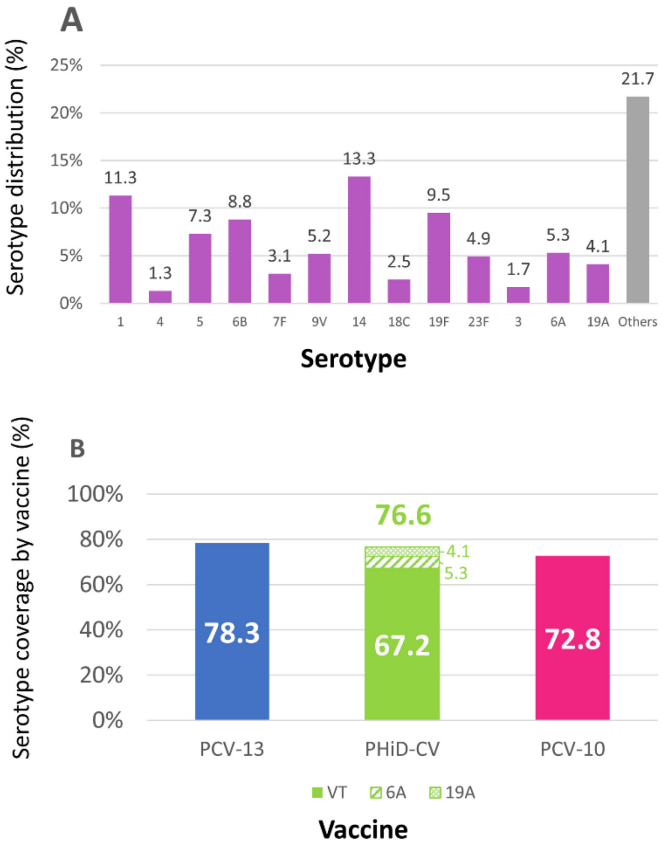
	Bravo 2009 [18], IBIS INCLEN study 1999 [56]	1993-1997	307 cases + 7 isolates	6, 1, 19, 14, 4, 5, 45, 12, 7	1 and 5 accounted for 29% of disease	PCV-7: 52.5%, PCV-9: 71.4%, PCV-13: 75.4%	Co-trimoxazole: 56%, chloramphenicol: 17%, penicillin (intermediate resistance): 1.3%
Bangladesh	Saha 2009 [27]	2004-2007	139 isolates	2 (17%), 1 (12%), 14 (7%), 5 (6%), 7F (6%), 45 (7%), 12A (4%)	Total of 37 STs isolated	PCV-7: 20% (95% CI, 13-27%), PHiD-CV: 43% (95% CI, 35-51%), PCV-13: 50% (95% CI, 42-58%)	Penicillin: 0%, chloramphenicol, 6%, co-trimoxazole: 32%
	Arifeen 2009 [57]	2004-2007	-	-	-	PCV-7: 31%, PHiD-CV: 58%, PCV-13: 69%	-
	Jaiswal 2014b [25]	1992-2007	17 studies (6 from Bangladesh)	14 (population-based, 2 studies)	Then 12F, 7F, 15B, 15, 2, 1, and 14 (hospital-based, 4 studies)	PCV-7: 20%, PHiD-CV: 40%, PCV-13: 42%	-
	Brooks 2007 [45]	2004-2006	-	-	-	PCV-7: 41%, PHiD-CV: 59%, PCV-13: 62%	-
Sri Lanka	Bravo 2009 [18], ANSORP study [34, 58]	2000-2001 2008-2009	-	23, 19F, 14	-	-	Ciprofloxacin: 11.8%, penicillin: 22%, co-trimoxazole: 67%
	Kim 2012 [34]	2008-2009	-	-	-	PCV-7: 73.7 PHiD-CV: 73.7 PCV-13: 78.9	-
	Lin 2010 [19], Batuwanthudawe 2009 [47]	2005-2007	-	19F, 14, 23F, and 6B	-	PCV-7: 61%, PHiD-CV: 61%, PCV-13: 65%	Penicillin: 91.3%, co-trimoxazole: 73.9%, erythromycin: 60.9%, cefotaxime: 47.8%, chloramphenicol: 26.1%
Nepal	Jaiswal 2014b [25]	2004-2008	17 studies (4 from Nepal)	1	Followed by 5 and 12A	PCV-7: 13-14%, PHiD-CV: 48%, PCV-13: 50%	Co-trimoxazole: high resistance of over 50%
	Shah 2009 [59]	2004-2007	-	-	-	PCV-7: 15%, PHiD-CV: 56%, PCV-13: 63%	Co-trimoxazole: 68%, penicillin: 4%, chloramphenicol: 0%, erythromycin: 7%, cefotaxime: 4%
Pakistan	Shakoor 2014 [28]	2005-2013	87 IPD cases	19F (32.2%)	31 (14.9%), 16 (13.8%), 19A (12.6%)	PHiD-CV: 66.7%, PCV-13: 69%	-
	Jaiswal 2014b [25]	1986-1989 2005-2013	17 studies – (2 from Pakistan)	-	-	PCV-7: 30-32%, PHiD-CV: 37%, PCV-13: 54%	-
	Ghafoor et al, 1990 [60]	1986-1989		6, 9, 15, 16, 19, 31	-	-	-
	Mastro et al, 1991 [61]	1986-1989	-	19F	31, 16, 19A, 9V, 15C, 6A	-	Co-trimoxazole: 31%, chloramphenicol, 39%, penicillin (moderately resistant): 9%. Overall 97% decreased susceptibility to at least one antimicrobial agent.
Thailand	Tai 2016 [26]	2000-2014	>200 isolates	23F (20%), 6B (18.6%), 14 (15.8%), 19F (11.7%), 19A (6.9%)	-	PCV-7: 68.3% PHiD-CV: 69.0%, PCV-13: 82.8%	-
	Kim 2012 [34]	2008-2009	-	-	-	PCV-7: 57.1% PHiD-CV: 58.5% PCV-13: 70.8%	-
	Bravo 2009 [18], Phongsamart 2007 [62], Lin 2010 [19]	2000-2005	-	6B (27.8%), 23F (20.0%), 14 (10.4%), 19F (9.6%)	-	PCV-7: 74%, PHiD-CV: 77% PCV-13: 88%	Penicillin:70%
	Levine 2006 [63]	2003-2004	-	6B, 19F, 23F	-	PCV-7: 62%	Penicillin: 48%
	Srifeungfung 2007 [64]	2003-2004	-	6 (22.5%), 23 (18.9%), 19 (16.6%), 3 (7.7%), 11 (5.3%)	-	-	Erythromycin: 42%, penicillin: 52%
Indonesia	Said 2017 [65]	2014	13 isolates	19F, 3, and 15A	13, 23A, 6, 34, 17F, 16F	PCV-13: 55%	-
	Lin 2010 [19], based on Soewignjo 2001 [66]	1997	221 children	6, 23, 15, 33 and 12	-	PCV-7: 62%, PHiD-CV: 63%, PCV-13: 67%	Chloramphenicol: 6%, penicillin: 0%, cefotaxime: 0%
South Korea	Tai 2016 [26]	2000-2014	>200 isolates	19A (18.5%), 19F (12.1%), 6B (10.1%), 6A, (7.1%), 23F (5.5%)	-	Post PCV-7 introduction: PCV-7: 34.6%, PHiD-CV: 35.5%, PCV-13: 61.7%	-
	Kim 2012 [34]	2008-2009	-	-	-	PCV-7: 38.2 PHiD-CV: 39.8 PCV-13: 67.3	-
	Choi et al, 2008 [67]	1991-2006	-	-	19F (21.0%), 23F (17.8%), 19A (10.8%), 6B (9.3%), 6A (8.0%), 14 (7.4%) and 9V (4.5%)	PCV-7: 64.1%	-
	Lin et al, 2010 [19]	1995-2005	-	-	-	PCV-7: 63%	-
	Song 2004a [68], Song 2004b [58]	1998-2001	-	-	-	-	Penicillin: 31-55%, erythromycin: 75-85%
	Lee et al, 1995 [69]	1991-1993	-	-	-	PCV-7: 82% PHiD-CV: 82% PCV-13: 84%	-

The serotype coverage does not take into account potential cross-protection. AMR: antimicrobial resistance; CI: confidence interval; IPD: invasive pneumococcal diseases; MDR: multi-drug resistance; PCV-7: 7-valent pneumococcal conjugate vaccine; PCV-9: 9-valent pneumococcal conjugate vaccine; PCV-10: 10-valent pneumococcal conjugate vaccine; PCV-13: 13-valent pneumococcal conjugate vaccine; PHiD-CV: pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine; PPV-23: 23-valent pneumococcal polysaccharide vaccine; ST: serotype; y: year.

IPD mortality and incidence

Despite important decreases in U5MR between 1990 and 2015, the Sustainable Development Goal target has not been reached in several Southeast Asian countries. A global population-based model estimated all-cause U5M in 2015 to be highest in India (1,200,998 all-cause deaths), with high numbers also estimated for Pakistan (431,568), Indonesia (147,162) and Bangladesh (119,326) in Southeast Asia [2]. Pneumococcal deaths in India were the highest contributor to U5M in the region [2]. In India alone, pneumonia, sepsis and meningitis were collectively the largest contributors to U5M, accounting for 30% of U5M in 2000 and declining to 25% (on a par with preterm birth complications) by 2015 [2]. Similarly in Pakistan, it was estimated that 22% of all U5M was due to IPD [17]. The highest case fatality rates (CFRs) for pneumococcal diseases in children under five years in Asian countries, according to WHO data, were reported in India and Pakistan (both 19% [18]), followed by Indonesia (14-17% [18,19]), Sri Lanka and Thailand (ranging from 9 to 14% [18,20]). Table 2 presents burden data by study. Recent data on IPD incidence in children under five years in Southeast Asia were generally lacking. A large hospital-based sentinel surveillance network in India reported that in 2012-2013, the vast majority (82.9%) of bacterial meningitis cases in children <5 years were caused by *S. pneumoniae* [21]. In India, a hospital-based surveillance study from 2009-2011 estimated IPD incidence to be 17.8/100,000 in children < 5 years, and as high as 49.9/100,000 in children 6-12 months old [22]. A population-based modelling study using risk factors for severe pneumonia by state in India, estimated the incidence of severe pneumonia in children <5 years in India to be 30.7/1,000 in 2010. There was great regional variability, with some states reporting a much higher severe pneumococcal pneumonia burden in children under five years than others e.g., Uttar Pradesh (24% of cases and 26% of deaths), Bihar (16% cases, 22% deaths), Madhya Pradesh (9% cases, 12% deaths), and Rajasthan (8% cases, 11% deaths) [23]. Similarly, in Pakistan, IPD incidence in children <5 years was estimated to be 25/100,000 in 2007-2008, from population-based surveillance data [17].

Figure 2. A: Serotype distribution in India (based on Singh et al); B: Vaccine serotype coverage.



Vaccine serotypes: PCV-13: 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F, 3, 6A, 19A; PHiD-CV: 1, 4, 5, 6B, 7F, 9V, 14, 23F, 18C, 19F, 6A*, 19A* (*cross-reactive serotype); PCV-10: 1, 5, 6B, 7F, 9V, 14, 19F, 23F, 6A, 19A.

Antibiotic resistance

A systematic review (including data from six hospital-based observational studies) on the antibiotic resistance pattern to IPD isolates in India reported penicillin non-susceptibility (10%, range 3-20%), resistance to cefotaxime (3%, range 1-10%), erythromycin (37%, range 28-45%), cotrimoxazole (81%, range 44-100%), chloramphenicol (8%, range 5-9%) and levofloxacin (6%, range 4-7%) (Table 3) [12]. Another prospective hospital laboratory study in India found that resistance to IPD isolates varied considerably between isolates causing meningitis and non-meningeal isolates. In this study, among pneumococcal meningeal isolates, in children <5 years, 59.7% were resistant to penicillin (vs. 1.2% for non-meningeal isolates) and 18% were also non-susceptible to cefotaxime. In addition, penicillin resistance and cefotaxime non-susceptibility increased in meningeal isolates from 9.5% to 42.8% and from 4.7% to 28.5%, respectively, between 2008 and 2016 [11]. Table 3 presents serotype and antibiotic resistance data by study.

Serotype distribution

A systematic review (including seven hospital-based studies in India) reported pneumococcal serotype data (from 2007-2016) from IPD in children < 5 years. The most common serotypes were 14, 1, 19F, 6B and 5 (Figure 2) [12]. The Alliance for Surveillance of Invasive Pneumococci study in India collected data from 11 states from 2011 to 2015. Serotype distribution was found to be fairly similar across regions in India [24]. No recent data were identified from other countries, however serotype distribution differs in each country in the region (Table 3). A systematic review conducted in 2014 in South Asian Association for Regional Cooperation (SAARC) countries concluded, for children < 12 years, that the most common serotype was serotype 1 in Nepal, serotype 14 in Bangladesh and India, and serotype 19F in Sri Lanka and Pakistan [25].

Serotype coverage of PCVs

The most recent studies were from India. From a systematic review of IPD serotype prevalence data in children < 5 years India (2007-2016), vaccine serotypes would cover 67.3% (PHiD-CV), 72.8% (PCV-10) and 78.4% (PCV-13) of IPD-causing serotypes [12]. When considering that PHiD-CV provides cross-reactive protection against serotypes 6A and 19A as well, PHiD-CV serotype coverage for India would increase to 76.6% (Figure 2).

A review from 2014 of countries in the SAARC region showed that, on average, PHiD-CV serotypes covered 50% of IPD strains (from 37% in Pakistan to 62% in India) while PCV-13 serotypes covered 55% of IPD strains (from 42% in Bangladesh to 70% in India). The strain coverage for PHiD-CV and PCV-13 was 60% and 65% in Sri Lanka, 48% and 50% in Nepal and 37% and 54% in Pakistan, respectively [25]. A pooled data analysis (of studies published in 2000-2014) among pediatric patients concluded that serotype coverage for PHiD-CV and PCV-13 was 35.5% and 61.7% in South Korea and 69.0% and 82.8% in Thailand, respectively [26].

Other studies showed serotype coverage can differ by invasive disease e.g., pneumonia or meningitis. In Bangladesh, a multicenter surveillance network analyzed serotype distribution of IPD in hospitalized children < 5 years, prior to the introduction of PCVs. PHiD-CV and PCV-13 would cover 43% (95% confidence interval [CI], 35%–51%) and 50% (95% CI, 42%–58%) of IPD cases overall, respectively, or 58% and 75% of pneumonia cases, 53% and 63% of sepsis cases, and, 38% and 42% of meningitis cases [27]. In Pakistan, serotypes were analyzed from 59 children <5 years (in 2009-2013) with meningitis: 66.1% and 67.8% of serotypes would be covered by PHiD-CV and PCV-13, respectively [28].

The selection of a PCV vaccine should not be based on serotype coverage alone, as efficacy against serotypes can differ between vaccines, in addition to other factors, such as herd protection or cross-reactive protection against non-vaccine serotypes [29]. PHiD-CV, for example, also induces a cross-reactive antibody response to serotypes 6A and 19A, although these serotypes are not included in the vaccine [1, 5]. In addition, PHiD-CV may provide greater protection than PCV-13 against AOM, a common condition in young children which leads to significant antibiotic use. This is due to the fact that both *S. pneumoniae* and NT*Hi* cause around 50-80% of AOM, and that PHiD-CV protects against both causes, as it is a NT*Hi* protein-D conjugate vaccine.

Vaccination coverage

As per the recent WHO United Nations International Children's Emergency Fund estimates, full course (i.e., all doses) PCV vaccination coverage in 2019 was 98% in South Korea, 97% in Bangladesh, 90% in Myanmar, 83% in Nepal and 75% in Pakistan while it was only 3% in Indonesia and 15% in India [16]. The national coverage of 15% in India was based on a reported 57% coverage in 26% of the target population, as few states have implemented universal PCV programs [30]. PCV vaccination coverage in the private sector in India was very low at around 0.33% overall but in large metropolitan areas, rates were 13.31% (Mumbai, Maharashtra state), 0.76% (Lucknow, Uttar Pradesh), 1.93% (Kolkata, West Bengal), and 4.92% (Chennai, Tamil Nadu), highlighting the role urban centers play in PCV use [31].

Discussion

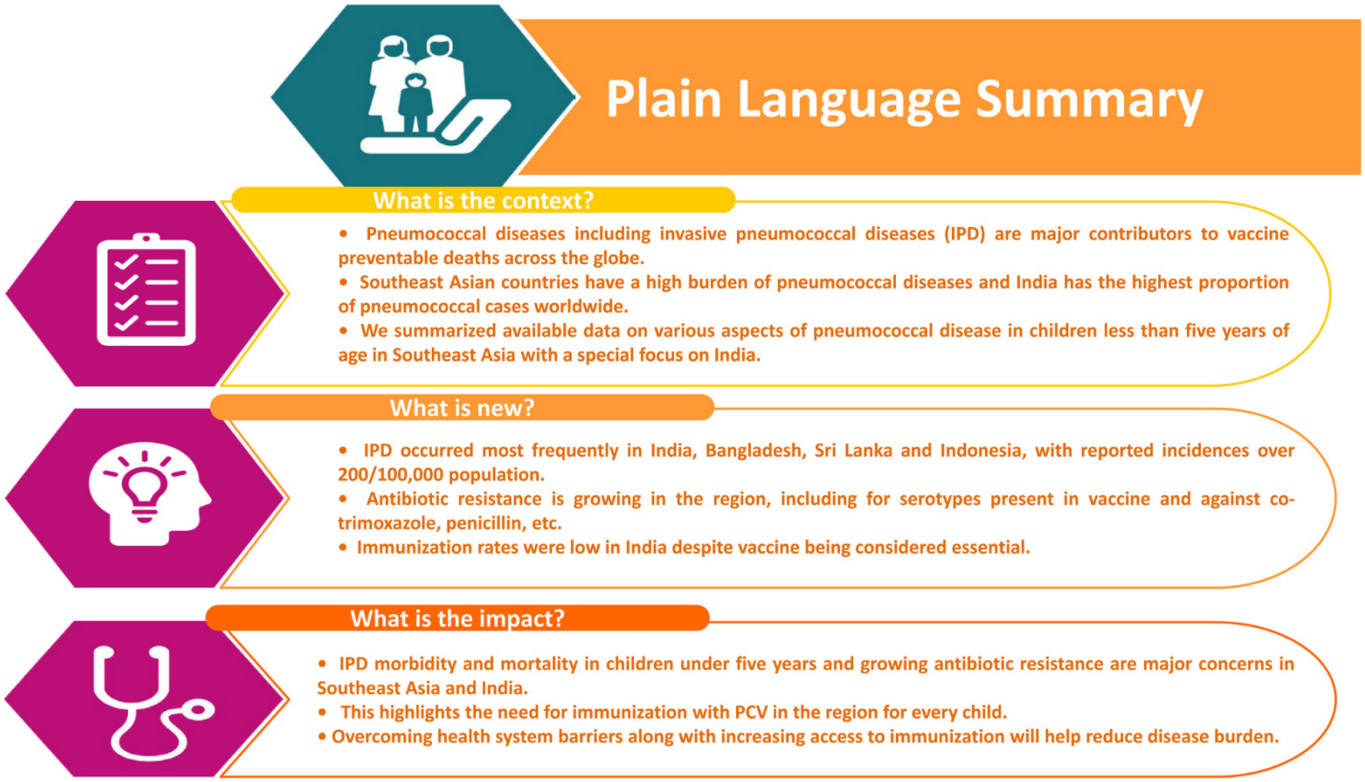
Our results reiterate that *S. pneumoniae* is considered the leading cause of high morbidity and mortality associated with pneumococcal disease in developing countries. Despite recent important decreases in pneumococcal under-five mortality, not enough is being done to meet global child mortality targets set for developing countries by 2030. Bhutan, Maldives, Sri Lanka and Thailand had the lowest U5M and pneumococcal deaths among studied countries, and the highest burden was in India (e.g., high case-fatality due to IPD in young children) [32]. Antibiotic resistance to penicillin was estimated at 10% (range up to 20%) for IPD overall in India [12], however

considerably higher rates of nearly 60% were reported when considering meningitis isolates [33]. Sri Lanka, on the other hand, had lower mortality numbers, yet high resistance to almost all antibiotics. Antibiotic resistance was also high in Thailand and South Korea. Our review also highlighted variations in epidemiology (e.g., significantly higher U5MR in India versus other countries) and in vaccine serotype coverage (e.g., from 37% in Pakistan to around 70% in India) in the region, consistent with previous findings [26,34]. However, discrepancies in robustness might exist in the surveillance systems in these countries. Vaccination is a crucial preventive means to reduce IPD. Available PCVs offer an opportunity to significantly reduce the disease burden, and help to reduce the growing problem of antibiotic resistance, as many serotypes that cause resistance are included in the vaccines [12,24]. It is estimated that expanding vaccination programs with PCVs could significantly decrease current antibiotic use associated with diseases such as IPD [35].

As far as the available PCVs are concerned, they are immunogenic in infants for the serotypes included in vaccines. In addition, PHiD-CV is also immunogenic against serotypes 6A and 19A [5]. Following routine use of PHiD-CV and PCV-13 in the NIP of several Latin American countries, a recent systematic review of these data found no evidence of the superiority of one vaccine over the other on pneumonia, IPD or meningitis hospitalization reductions in children < 5 years [36]. Similarly, the latest global review of PCV impact evidence [5] used to formulate WHO recommendations found both PCVs had a comparable impact on disease outcomes [1] and carriage [37]. This comparable real-world impact has also been seen in countries where additional vaccine serotype coverage was 10-20% higher for PCV-13 compared to PHiD-CV e.g., Sweden [38], Quebec (Canada) [39] and Morocco [40].

PCV immunization coverage was very low both in rural and urban areas in India, and in Indonesia. PCV coverage in India in the private market is low and effforts to increase it are needed. These can be achieved by increasing awareness among healthcare providers as well as the public about the significant burden of pneumococcal disease and the prevention options available. India will need to make significant progress in the coming years to reduce acute respiratory infections in children under five years, and, preventing pneumococcal infection will significantly improve survival in this age group. The need of the hour is to increase coverage through public and private sector efforts. Recent estimates for Gavi-eligible countries support the importance of high coverage and predict

Figure 3. Plain Language Summary.



that universal PCV with high coverage could prevent 21 million cases of pneumococcal disease, and save 1.5 million lives [4].

There are many barriers and challenges to overcome in order to improve access to PCVs in countries where prevalence is still high. Obtaining national burden surveillance data estimates is critical to gauge the real burden of IPD, however financial and technical support are needed to improve surveillance. Other barriers include difficulties in diagnosing *S. pneumoniae* cases due to a lack of good surveillance sites, high cost of serotyping, surveillance issues that include poor quality culture techniques and limited access to higher sensitivity diagnostics, extensive antibiotic use before diagnostic work-up and, a lack of standardization in diagnostic and surveillance methods [41,42]. The establishment of sentinel surveillance networks is critical to generate local epidemiology data to inform national decision-making, and to assess the impact of PCVs.

This review article was limited by including a selection of PCV data from the past ten years for countries in Southeast Asia with a focus on India. Though all attempts were made to include data from various sources, some studies might have been missed due to the key words used in the search strategy. While this was not a systematic review of all evidence, an effort was made to include well-conducted large studies covering IPD burden and PCV use in the region of interest.

Conclusions

S. pneumoniae infection, and specifically IPD, is a leading cause of morbidity and mortality in Southeast Asia. In India, over 1.2 million deaths occurred in children < 5 years in 2015, of which 25% were due to IPD. The burden of pneumococcal disease in the region is significant, yet no clear data are available in some countries. PCV coverage varied (i.e., 15% in India to 98% in South Korea) although roughly 50 to 80% of prevalent IPD serotypes in the region, including those causing resistant disease, would be covered by PCVs. To conclude, it is important to improve access and widespread implementation of preventive measures including increase coverage of PCVs. This will ensure reduction in childhood mortality and morbidity, thereby permit achieving a meaningful disease reduction (Figure 3).

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Authors contribution

Shafi Kolhapure, Ashish Agrawal and Pradyumna Krishnappa have contributed to the concept and design of the report and to drafting the manuscript. All authors have substantially contributed for analysis and interpretation of data; revised the article critically for important intellectual content, and approved the final version to be published.

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Corresponding author

Ashish Agrawal, PhD
Medical Affairs Department, GSK, 62 SD Road, Hyderabad, India
Phone: +912224959405
Email: ashish.8.agrawal@gsk.com

Conflict of interests: Shafi Kolhapure, Ashish Agrawal and Lamine Soumahoro are employees of the GSK group of companies. Shafi Kolhapure and Lamine Soumahoro hold shares in the GSK group of companies. Pradyumna Krishnappa was an employee of the GSK group of companies at the time of study conduct. Shafi Kolhapure, Ashish Agrawal, Pradyumna Krishnappa and Lamine Soumahoro declare no other financial or non-financial relationships and activities. Dr Vijay Yewale declares no financial and non-financial relationships and activities and no conflicts of interest.

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Additional files

Additional file 1 – Supplemental methods. Search strategies

SEARCH 1 – **Burden/epidemiology of IPD in S/SE Asia**

- The search string used was (("meningitis, pneumococcal"(1)) or ("pneumococcal infections"(1)) or ("pneumococcal infections"(1) and "otitis media"(1))) AND (Burden OR incidence OR prevalence OR serotype) AND (India OR Nepal OR Myanmar OR Pakistan OR "Sri Lanka" OR Timor-Leste OR Maldives OR Indonesia OR Democratic People's Republic of Korea OR South Korea OR Bangladesh OR Thailand OR Bhutan OR "South east Asia")

SEARCH 2 – PCV studies in SE Asia

- ("Streptococcal Vaccines"(1) OR "Pneumococcal Vaccines" OR "13-valent" OR "PHiD-CV" OR "10-valent" OR "pneumococcal conjugate vaccine") AND (India OR Nepal OR Myanmar OR Pakistan OR "Sri Lanka" OR Timor-Leste OR Maldives OR Indonesia OR Democratic People's Republic of Korea OR South Korea OR Bangladesh OR Thailand OR Bhutan OR "South east Asia")
- Filters applied: Meta-Analysis, Comparative Study, Clinical Trial, Multicenter Study, Systematic Reviews, Observational Study

SEARCH 3 – PCV coverage in Southeast Asia and India (internet search)

The following websites were searched:

- https://mohfw.gov.in/right-information-rti/rti-act-for-ministry/departments-health-and-family-welfare/immunization
- http://www.who.int/immunization/monitoring_surveillance/data/ind.pdf
- https://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragedtp3.html

The following key terms were used: PCV immunization coverage in WHO Southeast Asia region, National immunization program coverage in India 2017-18, PCV10/PHiD-CV coverage in India or usage in India, PCV13 coverage in India

Table Inclusion and Exclusion criteria.

	Inclusion	Exclusion
Countries	Bangladesh, Bhutan, India, Indonesia, Maldives, Myanmar, Nepal, Democratic People's Republic of Korea, Sri Lanka, Thailand, Timor-Leste, Pakistan, South Korea	All other countries
Study design	Observational studies, hospital studies (prospective and retrospective), comparative studies, clinical trials, systematic reviews and meta-analyses	expert reviews, case reports, abstracts without full-texts
Human/Animal	Human studies	Animal studies
Languages	English	Other languages
Age groups	Children (<5 years if available)	Adults

1. Jain K, Sankar MJ, Nangia S, Ballambattu VB, Sundaram V, Ramji S, Plakkal N, Kumar P, Jain A, Sivanandan S, Vishnubhatla S, Chellani H, Deorari A, Paul VK, Agarwal R (2019) Causes of death in preterm neonates (<33 weeks) born in tertiary care hospitals in India: analysis of three large prospective multicentric cohorts. J Perinatol 39: 13-19.