Review

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

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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 meningal 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.

J Infect Dev Ctries 2021; 15(6):749-760. doi:10.3855/jidc.12166

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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 summarise 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* (NTHi) 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 NTHi. 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 inclusion/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 | 3+0 |
| Schedule flexibility | Yes | Yes | No |
| Immunogenicity data | Yes | Yes | Yes |
| 6A,19A immunogenicity | Yes | Yes | Yes |
| Efficacy data | Yes | No$^a$ | No |
| Real world IPD protection | Yes | Yes | No |
| AOM protection* | Yes *S.p.* + *Nthi* | *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* (NTHi) cause AOM, and NTHi protein-D conjugate vaccine (PHiD-CV) protects against both causes; $^a$Efficacy established with PCV7.
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]         | 2000-2015    | 1,206,998                       | 21,106 meningitis                           | -       | Meningitis: 82.9% (213/257) in children < 5y |
|           | Jayaraman 2018 [21]  | 2012-2013    | -                               | -                                           | -       | 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 [22]    | 2009-2011    | -                               | -                                           | -       | Severe pneumonia incidence: 30.7/1000 children < 5y |
|           | Faqasi 2015 [23]     | 2010         | -                               | 356,300 all-cause pneumonia                 | 9.96%   | S. pneumonia episodes: 564,200 IPD: 29.06%, pneumonia 24.5%, pyogenic meningitis 32.78%, S. pneumonia causes 29.6% of IPD, 24.3% of pneumonia cases, and 32.78% of meningitis cases in children < 12y with confirmed bacterial diseases |
|           | Jaiswal 2014a [32]   | 2014         | -                               | -                                           | -       | IPD: 1,500/100,000 in children < 5y |
| Bangladesh| Liu 2010 [19],       | 2006         | -                               | -                                           | 8.0%    | IPD: 503/100,000 in children < 5y, pneumonia 147/ 100,000, meningitis: 32/100,000, septis: 45.2/100,000 |
|           | Prospective hospital-based surveillance (IBIS-INCaLEN group) | 2004 | 2,210,000 | 410,000 pneumonia | 19% |
|           | Liu 2016 [2]         | 2000-2015    | 119,326                         | 12,953 pneumonia                            | -       | IPD: 119/100,000 in children < 5y, Pneumonia: 113/100,000, Meningitis: 105/100,000 |
|           | Brooks 2007 [45]     | 2004-2006    | -                               | -                                           | -       | IPD: 447/100,000 in children < 5y, Pneumonia: 113/100,000, Meningitis: 105/100,000 |
| Sri Lanka | Liu 2016 [2]         | 2000-2015    | 3,091                           | 139 pneumonia                               | -       | IPD: 206,3100,000 in children < 5y, pneumonia: 147/100,000, meningitis: 13.2/100,000, septis: 45.2/100,000 |
|           | Kularatna 2015 [46]  | 2005-2009    | -                               | -                                           | -       | Meningitis: 7/100,000 in children < 5y |
|           | Hospital sentinel surveillance | 2004 | 5,000 | 0 pneumonia | 9% |
| Nepal     | Liu 2016 [2]         | 2000-2015    | 19,900                          | 2,257 pneumonia                             | -       | Bacteremia, meningitis or pneumonia in children < 12y: S. pneumonia in 16% (25/142) of blood cultures of bacteremia |
|           | Kelly 2014 [48]      | 2005-2006    | -                               | -                                           | -       | - |
| Maldives  | Liu 2016 [2]         | 2000-2015    | 67                              | 4 pneumonia                                  | -       | - |
| Pakistan  | Liu 2016 [2]         | 2000-2015    | 431,568                         | 49,578 pneumonia                            | -       | IPD: 25/100,000 child-years in children < 5y, pneumonia: 0.26 episodes/child year, pneumococcal meningitis: 19.7/100,000 in children < 5y |
|           | Owais 2010 [17]      | 2007-2008    | 55/1000 live births             | 22% of all U5M                              | 8%      | - |
|           | Zaidi 2009 [49]      | 2005-2006    | -                               | -                                           | 25%     | - |

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

| Country          | Reference               | Study period | Number of isolates / IPD cases | Most common STs (and number) | Other STs and findings | Serotype Coverage | Antibiotic resistance                                      |
|------------------|-------------------------|--------------|--------------------------------|------------------------------|------------------------|-------------------|----------------------------------------------------------|
| India            | Verghese 2017 [33]      | 2008-2016    | 311 isolates (92 meningitis and 239 non-meningeal) in < 5y olds | 14 (22 isolates), 19F (15), 6B (13), 6A (11), 23F (7), 9V (7), 5 (7) in meningeval 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 (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, 9B, 23F | -                      | PHID-CV: 67.3%, PCV-13: 78.4% | -                | Co-trimoxazole: 81%, erythromycin: 37%, penicillin: 10%, chloramphenicol: 8%, levofloxacin: 4% |
|                  | Manoharan 2017 [24]     | 2011-2015    | 361 cases                        | 14 (14%), 1 (14%), 5 (50%), 9B (9%) | -                      | PCV-7: 63%, PHID-CV: 68%, PCV-13: 74%, PPM-23: 80% | -                | Penicillin: 8%, co-trimoxazole: 66%, erythromycin: 37%, chloramphenicol: 8%, MDR: 9% |
|                  | Jaiswal 2014b [25]      | 2013-2015    | 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 (6A, 4A, 19F, 3), 4, 5, 7F (2 isolates each) | 9V, 18C, 23F, 19A, 8, 18A, 9N (1 isolate each) | -                | Non-susceptible to ceftriaxone: 29 (100%)                 |
|                  | Molander 2013 [53]      | 2007-2011    | Isolates from 244 IPD patients    | 1 (34%), 5 (22%), 19F (18%), 6B (10%), 14 (17%), 3 (12%), 19A (10%), 6A (16.7%), 14 (13.9%), 5 (11.1%), 6B (11.1%) | 1, 18C, 19A (each 8.3%) | -                | 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 |
|                  | Nisarga 2015 [22]       | 2009-2011    | 40 cases                         | 6A (16.7%), 14 (13.9%), 5 (11.1%), 6B (11.1%) | 19 (20%), 6 (11%), 7 (10%), 1 (9%), 14 (17%), 9 (95%), 33 (4%), 17 (4%), 11 (2%), 3 (2%) | -                | Penicillin: 1.6%, Erythromycin: 11.5% Chloramphenicol: 1.6% Ceftriaxone: 74.2% Oxacillin: 3.3% MDR: 5.3% |
|                  | Shariff 2013 [54]       | 2007-2010    | 126 isolates tested for AMR       | 6A (16.7%), 14 (13.9%), 5 (11.1%), 6B (11.1%) | 19 (20%), 6 (11%), 7 (10%), 1 (9%), 14 (17%), 9 (95%), 33 (4%), 17 (4%), 11 (2%), 3 (2%) | -                | Antibiotic resistance observed in STs 6A, 14, 6B, 1, 18C, 19A, 9V, 4, 10C, and 18A |
|                  | Kim 2012 [34]           | 2008-2009    | -                                | -                              | -                      | PCV-7: 34%, PHID-CV: 54%, PCV-13: 73% | -                | Penicillin: 33%, erythromycin: 16%, ceftriaxone: 15%, tetracycline: 50%, co-trimoxazole: 82%, chloramphenicol: 13%, cefotaxime: 8% |
|                  | Liu 2010 [19]           | 1996-2000    | -                                | -                              | -                      | PCV-7: 50%, PHID-CV: 73%, PCV-13: 77% | -                | -                                                        |

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

| Year   | Study Details                  | Serotypes       | PCV-7 | PCV-9 | PCV-10 | PCV-13 | PCV-15 | PCV-23 | PHiD-CV | Co-trimoxazole   |
|--------|--------------------------------|-----------------|-------|-------|--------|--------|--------|--------|---------|-----------------|
| 1993-1997 | Bravo 2009 [18], IBIS INCLEN study [56] | 301 cases + 7 isolates | 6, 1, 19, 14, 4, 5, 45, 12, 7 | i and 5 accounted for 29% of disease | 52.5% | 71.4% | 75.8% | 20% (95% CI, 13-27%) | 56% (95% CI, 42-58%) |
| 2004-2007 | Saha 2009 [27] | 139 isolates | 2 (17%), 1 (12%), 14 (7%), 5 (6%), 7F (6%), 45 (7%), 12A (4%) | Total of 37 STs isolated | 56% (95% CI, 42-58%) |

### Sri Lanka

| Year   | Study Details                  | Serotypes       | PCV-7 | PCV-9 | PCV-10 | PCV-13 | PCV-15 | PCV-23 | PHiD-CV | Co-trimoxazole   |
|--------|--------------------------------|-----------------|-------|-------|--------|--------|--------|--------|---------|-----------------|
| 2000-2001 | Bravo 2009 [18], ANSORP study [34, 58] | - | 19F, 14 | - | - | - | 73.7% | - | 31% |
| 2007-2009 | Kim 2012 [34] | - | 19F, 14, 23F, and 6B | - | - | - | 31% | - | 66% |

### Nepal

| Year   | Study Details                  | Serotypes       | PCV-7 | PCV-9 | PCV-10 | PCV-13 | PCV-15 | PCV-23 | PHiD-CV | Co-trimoxazole   |
|--------|--------------------------------|-----------------|-------|-------|--------|--------|--------|--------|---------|-----------------|
| 2004-2008 | Jaiswal 2014b [25] | - | 17 studies (4 from Nepal) | 1 | Followed by 5 and 12A | 13-14% | 48% | 50% | 66% | 34% |
| 2009 [59] | Shah 2009                   | - | - | - | - | - | - | - | 56% |

### Pakistan

| Year   | Study Details                  | Serotypes       | PCV-7 | PCV-9 | PCV-10 | PCV-13 | PCV-15 | PCV-23 | PHiD-CV | Co-trimoxazole   |
|--------|--------------------------------|-----------------|-------|-------|--------|--------|--------|--------|---------|-----------------|
| 2005-2013 | Shakoor 2014 [28] | 19F (32.2%) | 31 (14.9%), 16 (13.3%), 19A (12.6%) | - | - | - | - | - | 31% |
| 2014 [34] | Jaiswal 2014b [25] | 19F (32.2%) | 31 (14.9%), 16 (13.3%), 19A (12.6%) | - | - | - | - | - | 34% |

### Thailand

| Year   | Study Details                  | Serotypes       | PCV-7 | PCV-9 | PCV-10 | PCV-13 | PCV-15 | PCV-23 | PHiD-CV | Co-trimoxazole   |
|--------|--------------------------------|-----------------|-------|-------|--------|--------|--------|--------|---------|-----------------|
| 2000-2014 | Tai 2016 [26] | >200 isolates | 23F (20%), 6B (18.6%), 14 (15.8%), 19F (11.7%), 19A (6.9%) | - | - | - | - | - | 56% |
| 2008-2009 | Kim 2012 [34] | - | - | - | - | - | - | - | 57.1% |

### Indonesia

| Year   | Study Details                  | Serotypes       | PCV-7 | PCV-9 | PCV-10 | PCV-13 | PCV-15 | PCV-23 | PHiD-CV | Co-trimoxazole   |
|--------|--------------------------------|-----------------|-------|-------|--------|--------|--------|--------|---------|-----------------|
| 2014 | Said 2017 [65] | 13 isolates | 19F, 3, and 15A | 13, 23A, 6, 34, 17F, 16F | - | - | - | - | 56% |
| 1997 | Lin 2010 [19], based on Suweingjo 2001 [66] | 211 children | 6, 23, 15, 33 and 12 | - | - | - | - | 56% |

### South Korea

| Year   | Study Details                  | Serotypes       | PCV-7 | PCV-9 | PCV-10 | PCV-13 | PCV-15 | PCV-23 | PHiD-CV | Co-trimoxazole   |
|--------|--------------------------------|-----------------|-------|-------|--------|--------|--------|--------|---------|-----------------|
| 2000-2014 | Tai 2016 [26] | >200 isolates | 19A (18.5%), 19F (12.1%), 6B (10.1%), 6A, (7.1%), 23F (5.5%) | - | - | - | - | - | 56% |
| 2008-2009 | Kim 2012 [34] | - | - | - | - | - | - | - | 56% |

### Serotype Coverage

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].

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 meningeval isolates, in children <5 years, 59.7% were resistant to penicillin (vs. 1.2% for non-meningeval isolates) and 18% were also non-susceptible to cefotaxime. In addition, penicillin resistance and cefotaxime non-susceptibility increased in meningeval 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.

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.
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 NTHi cause around 50-80% of AOM, and that PHiD-CV protects against both causes, as it is a NTHi 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 efforts 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

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**Figure 3. Plain Language Summary.**

**What is the context?**
- Pneumococcal diseases including invasive pneumococcal diseases (IPD) are major contributors to vaccine preventable deaths across the globe.
- Southeast Asian countries have a high burden of pneumococcal diseases and India has the highest proportion of pneumococcal cases worldwide.
- We summarized available data on various aspects of pneumococcal disease in children less than five years of age in Southeast Asia with a special focus on India.

**What is new?**
- IPD occurred most frequently in India, Bangladesh, Sri Lanka and Indonesia, with reported incidences over 200/100,000 population.
- Antibiotic resistance is growing in the region, including for serotypes present in vaccine and against co-trimoxazole, penicillin, etc.
- Immunization rates were low in India despite vaccine being considered essential.

**What is the impact?**
- IPD morbidity and mortality in children under five years and growing antibiotic resistance are major concerns in Southeast Asia and India.
- This highlights the need for immunization with PCV in the region for every child.
- Overcoming health system barriers along with increasing access to immunization will help reduce disease burden.
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).

Acknowledgements

The authors would like to thank Business & Decision Life Sciences platform for editorial assistance and manuscript coordination, on behalf of GSK. Amandine Radziejwoski coordinated manuscript development and editorial support. The authors would also like to thank Kavi Littlewood (Littlewood Writing Solutions, on behalf of GSK) for medical writing support.

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.

Funding

GlaxoSmithKline Biologicals S.A. funded this study and all costs related to the development of the publication.

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**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.

**Trademarks:** Synflorix is a trademark owned by or licensed to the GSK group of companies. Pneumosil is a trademark owned by or licensed to the Serum Institute of India. Prevnar is a trademark owned by or licensed to Pfizer.
Additional files

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 |
| Study design                                   | expert reviews, case reports, abstracts without full-texts |
| Human/Animal                                   | Human studies       |
| Languages                                      | English             |
| Age groups                                     | Children (<5 years if available) |

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