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Pneumococcal serotypes causing non-invasive pneumonia in adults from a South Indian tertiary care hospital and the impact of the newer conjugate vaccines

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Abstract

Background. *Streptococcus pneumoniae* is the leading cause of community-acquired pneumonia (CAP) in adults. Ageing, chronic conditions and comorbidities are important risk factors for pneumococcal pneumonia.

Purpose. There is lack of data on the pneumococcal serotypes causing non-invasive pneumonia in India. This study aims to determine the prevalent pneumococcal serotypes causing non-invasive pneumonia, the associated comorbidities, and the coverage of both the available pneumococcal vaccines in India and conjugate vaccines that are currently undergoing clinical trials.

Methods. A total of 280 subjects (aged >16 years) who had clinical symptoms correlating with radiological findings for non-invasive bacteremic pneumonia and microbiological evidence of *S. pneumoniae* between 2018 and 2020 were included. The clinical, demographic, radiological and microbiological findings were retrieved from the Hospital Information System (HIS).

Results. The common serotypes in order of prevalence were 19F, 9V, 23F, 6B, 11A, 13, 34, 10A, 19A and 6A. The predominant non-vaccine serotypes were 13, 34, 35B, 31 and 16F. The associated radiological findings were pneumonic consolidation and multi-lobar involvement. Other coinfected bacterial pathogens included *H. influenzae*, *S. aureus*, *K. pneumoniae* and *P. aeruginosa*.

Conclusion. The pneumococcal vaccines: PCV10/GSK, PCV10/SII, PCV13, PCV15, PCV20 and PPSV23 provide an overall serotype coverage of 36, 41, 47, 48, 61 and 69%, respectively of *S. pneumoniae* causing non-invasive pneumonia in South India. Increasing catch-up vaccination using PCV10(SII) in pre-school children could have a more significant impact on reducing pneumococcal pneumonia in adults (>50 years) in terms of increased herd immunity at an affordable cost.

INTRODUCTION

S. pneumoniae is the leading cause of community-acquired pneumonia (CAP) globally, in all age groups. It contributes to lower respiratory tract infection-related deaths than all other aetiologies combined. Countries in Sub-Saharan Africa, South Asia and Southeast Asia have the highest prevalence of lower respiratory tract infections in all age groups [1]. In the ageing population, the increasing presence of immunosenescence and chronic conditions or comorbidities make them more susceptible to respiratory infections. Thus, the burden of pneumococcal disease is high in the elderly, above 50 years of age in India [2].

The main risk factors for pneumococcal infections are asplenia, alcoholism, diabetes mellitus, heart disease, immunocompromised conditions, liver disease, lung disease, renal disease and smoking. Individuals with two or more of the following concurrent comorbid diseases: chronic kidney disease, chronic heart disease and COPD, had higher pneumococcal disease incidence rates than those who were either immunocompromised or immunosuppressed [3, 4]

Many surveillance studies focus on invasive pneumococcal disease (IPD) in children, predicting the efficacy of various pneumococcal conjugate vaccines (PCV). In adults only

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Abbreviations: CAP, community acquired pneumonia; CCI, Charlson's Comorbidity Index; COPD, chronic obstructive pulmonary disease; HAP, hospital acquired pneumonnia; HID, high invasive disease; HIV, Human Immunodeficiency Virus; IPD, invasive pneumococcal disease; LID, low invasive disease; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; VT, vaccine type.

limited data or surveillance studies are available on detecting pneumococcal serotypes in nasopharyngeal carriage and non-invasive pneumonia. The often unrecognized missing link is the protective effect that PCV in children has on adults via herd immunity [5]. The decline in IPD in adults is most closely associated with the decline in colonization and the increased vaccination coverage among toddlers and pre-school-aged children (36–59 months) [6]. Hence, the vaccination in pre-school-aged children is important in maintaining herd immunity.

Currently available vaccines for usage in adults are PCV13 and PPSV23. The recommendation is for them to be used in the elderly (≥65 years) and high-risk adults aged 19–64 years [7]. Recently it has been proven that PPSV 23 when administered after PCV13 in the elderly, produces a better immune response than with PPSV23 alone [8]. In adults ≥65 years, the CAPiTA trial found statistically significant PCV13 vaccine efficacy for first episodes of vaccine-type community-acquired pneumonia (VT-CAP; 46%), non-bacteremic/non-invasive VT-CAP (45%), and VT invasive pneumococcal disease (75%), along with an acceptable safety profile [9]. Currently PCV10 (SII) has recently been approved in India and two other conjugate vaccines, PCV15(MSD) and PCV20 (Pfizer) are currently in phase 3 trials. This study aims to determine the prevalent pneumococcal serotypes causing non-invasive pneumonia, the association with comorbidities and the coverage of various pneumococcal vaccines.

METHODS

This laboratory-based study performed on consecutive, non-duplicate, adult patients (≥16 years), who were either admitted or attended out-patient clinics between March 2018 and March 2020 in a 1500 bed tertiary care hospital. All the included patients were clinically suspected to have pneumonia (symptoms of fever, dyspnoea, productive cough, chest pain, hemoptysis, shortness of breath) and had *S. pneumoniae* in respiratory (sputum) specimens. The microbiological data correlated with clinical and radiological findings retrieved from the Hospital Information System (HIS) including the demographic details such as age, sex, smoking, alcohol use and underlying diseases. Based on the number and the seriousness of the comorbid disease Charlson's Comorbidity Index scores (CCI) were calculated for each patient [10]. The main risk factors reported for pneumococcal infections were analysed: such as chronic diseases involving the heart, lung (COPD), liver and renal systems, together with other high-risk conditions, causing the individual to be immunocompromised or immunosuppressed, such as, asplenia, CSF leaks, HIV and diabetes mellitus.

Definitions

Non-invasive bacterial pneumonia

Confirmation of non-invasive bacterial pneumonia was on clinical, radiological (chest radiograph with infiltrates interpreted as pneumonia) and microbiological evidence together with three or more clinical symptoms of pneumonia and if negative blood cultures taken up to 5 days before/after the date of collection of the respiratory specimen. Patients with a history of hospitalization in the preceding 10 days were considered to have hospital-acquired pneumonia (HAP).

Microbiological evidence

Sputum specimens that contained a significant number of leukocytes (>25 per low-power field) with or without columnar epithelial cells, and/or no or few squamous epithelial cells (<10 per low-power field) were processed. Non-invasivess confirmed after cross index for the negative blood cultures taken up to 5 days before/after the sputum specimen collection date. The sputum specimens streaked into 5% sheep blood agar, chocolate agar and MacConkey agar and incubated in a 370C incubator (the blood agar and chocolate agar plates incubated in a CO2 incubator). The next day the growth of bacterial colonies were graded as scanty, moderate or heavy [11]. The sputum specimens were regarded as positive for *S. pneumoniae,* if the specimen cultures showed more than or equal to moderate growth of *S. pneumoniae*. *S. pneumoniae* identified using standard methods including Gram stain, optochin susceptibility and bile solubility testing. All the isolates were serotyped by Quellung reaction using type-specific pneumococcal antisera from Statens Serum Institute (SSI) and sequential customised multiplex PCR as previously described [12]. Disk diffusion method of antimicrobial susceptibility testing done for three antibiotics, namely oxacillin, erythromycin and levofloxacin. Penicillin non-susceptibility was confirmed by performing minimum inhibitory concentration using E- test only for a subset of isolates (n=166).

Pneumococcal serogroup/serotypes were analysed based on their invasive disease potential. Serotypes 1, 5 and 7 F defined as high invasive disease potential (HID) and serotypes 3, 6A, 6B, 8, 19F and 23F as low invasive disease potential (LID) [13]. To analyse the impact of pneumococcal vaccines, serotypes grouped as PCV10(SII), PCV10(GSK), PCV13 serotypes, PPSV23 serotypes and non-vaccine serotypes.

Statistical analyses

Mean and standard deviation with 95% confidence interval (CI) calculated for all the numerical values. Categorical data (age) was tested using $\chi 2$ statistics with a P value of <0.05 (two-tailed) being considered significant. Data was analysed using IBM SPSS Statistics (version 20; IBM, Armonk, New York, USA).

RESULTS

Study population

During the study period, 382 consecutive adult patients screened for suspected pneumonia combined with *S. pneumoniae* positive sputum culture. Sixty-three did not fulfil the criteria for non-invasive bacterial pneumonia; four

Table 1. Demographic data, comorbidities and the radiological findings of the study population stratified by age

	16–60 years *n*=220 Mean (SD)	**≥61 years *n*=60 Mean (SD)**	***P*-value**
Age	41.14 (11.85)	67.87 (5.12)	
Male	159 (72)	50 (83)	0.081
Female	60 (28)	10 (17)	
Smoking	18 (8)	17 (28)	<0.001
Alcoholism	16 (7.2)	4 (6.6)	0.872
Comorbidities			
Cardiovascular	8 (3.6)	6 (10)	0.045
Lung disease	84 (38)	40 (66)	<0.001
Liver disease	9 (4)	1 (1.6)	0.37
Renal disease	16 (7.2)	4 (6.6)	0.872
Diabetes mellitus	31 (14)	24 (40)	<0.001
Immunocompromised	58 (26)	15 (25)	0.831
Charlson Comorbidity Index Score			
Low (0)	32 (14.5)	0	0.002
Medium (1,2)	105 (47)	0	
High (≥3)	83 (37)	60(100)	
Radiological finding			
Unilobar	55 (25)	7 (11.6)	0.027
Multilobar	165 (75)	53 (88)	
Pleural effusion	3 (1.36)	1(1.6)	0.861
Consolidation	142 (64.5)	37 (61)	0.681
Cavity	26 (11.8)	9 (15)	0.509

had simultaneous blood cultures positive for *S. pneumoniae* and 35 of them had no chest x-ray or CT. The remaining 280 subjects had clinical, radiological and microbiological evidence for non-invasive bacteremic pneumonia

Table 1 represents the study population associated demographic data, comorbidities and radiological findings stratified by age.

Bacterial pathogens

Among the 280 subjects, 132 had *S. pneumoniae* as a single pathogen and 148 had mixed infections, with at least one other organism in addition to *S. pneumoniae*. The other coinfected bacterial pathogens included *H. influenzae, S. aureus*, *K. pneumoniae* and *P. aeruginosa*.

Pneumococcal serotype distribution

A total of 53 different serotypes identified among the 280 isolates. Serotypes 19F, 9V, 23F, 6B, 11A, 13, 34, 6A, 35B and 10A constituted 54% of all the isolates. The PCV 13 and PPV23 serotype coverage was 47 and 61% respectively. The serotype coverage by the new PCV10 introduced by SII, Pune and PCV10(GSK) was 41 and 36% respectively. The serotypes with LID (3, 6A, 6B, 8, 19F and 23F) constituted around 32% of the isolates, which was significantly higher than the HID (1, 5 and 7F) serotypes (only two isolates of 7F). The non-vaccine serotypes excluding PCV13 and PPSV23 constituted 36%, among which serotypes 13, 34, 35B, 31 and 16F were predominant.

Resistance profile

The percentage non-susceptibility to erythromycin, oxacillin and levofloxacin were 62, 54 and 5.2% respectively. The penicillin non-susceptibility was 7.8% (13/166), associated with serotypes 19F, 19A, 6B, 23F and 9V.

Radiological findings and significant risk factors

Pneumonic consolidation and multilobar involvement were the major radiological finding commonly located in the inferior lobes. Pleural effusions were present in only four subjects (Table 1). Similar to previous reports, smoking,

Table 2. Percentage of serotype coverage provided by PCV10/GSK, PCV10/SII, PCV13, PCV15, PCV20 and PPSV23

	16–49 years *n*=154 *n* (%)	**50–60 years *n*=66 *n* (%)**	**≥61 years (61-82) *n*=60 *n* (%)**	**Overall percentage >16 years *n*=280 *n* (%)**
PCV10 GSK alone (excluding 3,6A,19A)	**44 (29)**	**32 (48)**	**26 (43)**	**102 (36)**
PCV10 SII alone	**54 (35)**	**30 (45)**	**31 (51)**	**115 (41)**
6A (not included inPPSV23)	8 (5.1)	2 (3)	1 (2)	11 (4)
19A	5 (3.2)	2 (3)	4 (7)	11 (4)
Additional serotypes in PCV13				
18C	2 (1.2)	4 (6)	0	6 (2.1)
4	1 (0.6)	2 (3)	0	3 (1)
3	3 (2)	2 (3)	2 (3.3)	7 (2.5)
PCV13 alone	**60 (38)**	**38 (57)**	**33 (55)**	**131 (46.7)**
Additional serotypes in PCV13				
22F	**1 (0.6)**	**0**	**1 (2)**	**2 (0.7)**
33F	**0**	**0**	**0**	**0**
PCV15 alone	**61 (39)**	**38 (57)**	**34 (56.6)**	**133 (47.5)**
PCV20 additional serotypes 8,10A,11A,12F, 15B	**25 (16.2)**	**5 (7.5))**	**7 (11.6)**	**37 (13.2)**
PCV20 alone	**86 (55.8)**	**43 (65)**	**41 (68.3)**	**170 (60.7)**
Additional serotypes in PPSV23				
2	0	0	0	0
8	4 (2.5)	1 (1.5)	0	3 (2)
9N	1 (0.6)	0	0	1 (0.3)
10A	8 (5.1)	0	3 (5)	11 (4)
11A	10 (6.4)	1 (1.5)	2 (3.3)	13 (5)
12F	1 (0.6)	0	0	1 (0.3)
15B	2 (1.2)	3 (4.5)	2 (3.3)	7 (2.5)
17F	7 (4.5)	1 (1.5)	0	8 (3)
20	0	0	0	0
22F	1 (0.6)	0	1 (2)	2 (0.7)
33F	0	0	0	0
PPSV23 alone (excluding 6A)	**86 (56)**	**42 (64)**	**40 (67)**	**167 (69)**
PCV10-GSK+PPSV23	94 (61)	44 (67)	41 (68)	178 (63)
PCV10-SII+PPSV23	94 (61)	44 (67)	41 (68)	178 (63)
PCV13+PPSV23	94 (61)	44 (67)	41 (68)	178 (63)
PCV20+PPSV23	94(61)	44 (67)	41 (68)	178 (63)
Type of pneumonia				
CAP	101 (65)	35 (53)	32 (53)	168 (60)
HAP	53 (35)	31 (47)	28 (47)	112 (40)
CCI				

Continued

Table 2. Continued

	16–49 years *n*=154 *n* (%)	**50–60 years *n*=66 *n* (%)**	**≥61 years (61-82) *n*=60 *n* (%)**	**Overall percentage >16 years *n*=280 *n* (%)**
Low	31	0	0	31
Medium	92	4	0	96
High	29	27	60	116

PCV, Pneumococcal Conjugate Vaccine; PPSV, Pneumococcal Polysaccharide vaccine; CAP, Community acquired pneumonia; HAP, Hospital Acquired Pneumonia; CCI, Charlsons Comorbidities Index; GSK, Glaxo Smith Kline; Sii, Serum Institute of India.

diabetes mellitus and lung disease were significant risk factors associated with pneumococcal pneumonia in this study.

DISCUSSION

The predominant serotypes observed in this study in order of prevalence were 19F, 9V, 23F, 6B, 11A, 13, 34, 10A, 19A and 6A and the major three non-vaccine serotypes were 13, 34 and 35B. The non-invasive pneumonia serotypes were entirely different from those usually associated with invasive pneumococcal disease (IPD) in a previous study from India [14], as serotypes 14, 8, 3, 4 were few and serotypes 1 and 5 were absent. This observation is also different from other countries such as Spain and the UK where serotype 14 is the major serotype in non-invasive pneumonia [15, 16]. There is only limited data on pneumococcal serotypes associated with non-invasive pneumonia in India. All the available studies are either on IPD or a combination of both IPD and non-IPD [14, 17, 18]. A retrospective study on IPD in Indian adults over 11 years, reported pneumonia (39%) as the most common clinical condition with the predominant serotypes being 1, 3, 5, 19F, 8, 14, 23F, 4, 19A and 6B [14].

Though vaccination details were not available for the study subjects, we describe the percentage serotype distribution based on the pneumococcal serotypes isolated from non-invasive pneumonia. This study provides a baseline serotype coverage provided by the newer and available vaccines [PCV10(GSK), PCV10/SII, PCV13 and PPSV23] in South India. The conjugate vaccines (PCV10 or PCV13) are recommended for routine immunization in pre-school children less than 5 years. Countries that have implemented PCV13 in routine immunisation have witnessed decreased IPD and carriage caused by vaccine serotypes among older adults attributed to herd immunity [19, 20]. However, both the recommended PCV13 and PPSV23 vaccines in adults offer increased serotype-specific protection against vaccine type invasive disease (75%) rather than against non-bacteremic/ non-invasive VT-CAP [21]. The duration of the protective effect of PPV23 vaccination is up to 5 years for both pneumococcal and all-cause CAP [22]. The recommended single dose of PCV13 in adults aged ≥65 years, results in a temporary reduction of vaccine serotype carriage for only 6 months after vaccination. Hence, achieving herd immunity to decrease the IPD in adults and the elderly, is associated with the decline in colonization and increased vaccination coverage among toddlers and pre-school-aged children (36–59 months) [23]. Therefore, catch-up vaccination with PCV in pre-school-aged children and adolescents is important in maintaining the herd effect.

Analysing the serotype coverage of combinations of different types of PCV and PPSV23 revealed that choosing a combination of either one of the PCVs; PCV10 (GSK/ SII) or PCV13 or PCV15 or PCV20 with PPSV23 will provide the serotype coverage of 61, 67 and 68% in the 16–49, 50–60 and >61 years age groups, respectively (Table 2). Differences will only be seen in the earlier phase, depending on the type of PCV administered, after the administration of PCV but before the administration of PPSV23. Newer vaccines such as PCV20 are expensive, and show serotype coverage similar to PPSV23, but with additional benefits of reducing nasopharyngeal carriage (Table 2). However, the choice of PCV should depend on the cost, and the need to be affordable by all to maximize vaccine coverage with the prevalent serotypes causing IPD in each specific age group, to help achieving herd immunity, which will prevent infection in the elderly.

Among the total subjects, 78% were between the ages of 16–60, 59% between the ages 16–50 and 41% were over 50 years of age. Though, there were few subjects over 60 years of age (21%), they had a high comorbidity score index. Comparing PCV10SII and PCV13, PCV13 provides an additional 4 and 8% coverage in those less than 50 years of age and those over 50 years of age, respectively (refer Table 3). PPSV23 contains all the PCV13 serotypes except 6A. Hence, considering the increased cost of higher valent PCVs (PCV15 and PCV20), priming younger adults (16–50 years) with PCV10(SII) and those over 50 years of age with PCV13 will cover all the serotypes, which are more prevalent in these respective age groups. Subsequent vaccination with PPSV23 before/after or at the age of 65 will provide increased protection against IPD. Since PCV13 is expensive, this study suggests that catch-up vaccination with PCV10(SII) in pre-school children could have a greater impact on adults (>50 years) in terms of herd immunity at an affordable cost.

This study is the first to describe radiological findings with comorbidities in non-invasive pneumonia associated with

Table 3. Comparison between PCV13, PCV10 (SII), PCV15, PCV20 and PPSV23 against different age groups

Age	PCV10 (Pneumosil -SII) n (%)	PCV13 (Prevenar- Pfizer)	PCV15	PCV20	PPSV23 (Peumovax23-Merck)	CAP	HAP	CCI		
								Low	Medium	High
16–49 *n*=154	54 (35)	60 (38)	61 (39)	86 (55.8)	86 (56)	101 (65)	53 (34)	31	92	29
50–60 *n*=66	30 (45)	38 (57)	38 (57)	43 (65)	42 (64)	35 (53)	31 (47)	0	12	52
≥61 (61-82) *n*=60	31 (51)	33 (55)	34 (56.6)	41 (68.3)	40 (67)	32 (53)	28 (47)	0	0	60

PCV, Pneumococcal Conjugate Vaccine; PPSV, Pneumococcal Polysaccharide vaccine; CAP, Community-acquired pneumonia; HAP, Hospital-Acquired Pneumonia; CCI, Charlsons Comorbidities Index; GSK, GlaxoSmithKline; SII - Serum Institute of India.

S. pneumoniae in Indian adults. This study showed that *S. pneumoniae* is a major pathogen causing more CAP (60%, 168/280) than HAP (40%, 112/280), especially in adults aged 16–49 years (Table 2). This finding is in concordance with the findings of other similar studies from India and worldwide [15, 24–30]. Indian studies predominantly include subjects from the Northern regions and have reported *K. pneumoniae* or *M. pneumoniae* as the second major etiological agents, whereas we observed that *H. influenzae* was the second major pathogen [26, 27]. However, this study could not rule out pneumonia due to atypical agents as the special methods required for their diagnosis were not carried out, this is a study limitation. The overall fatality was very low at 1.4% (four deaths), this may be because very few subjects had high risk factors such as asplenia, chronic liver disease, chronic kidney disease, immunocompromised conditions, and a smaller number of individuals over 65 years of age.

CAP is a significant risk factor for cardiovascular diseases [31] especially when patients are elderly, have significant underlying cardiovascular morbidity, and have been treated with antibiotics [32]. Recently, cardiac involvement of serotypes, such as 2, 3, 4, 5 and 9 N in post-pneumococcal pneumonia and IPD has been reported [21, 33]. In addition, neurotropism is associated with serotype 1 [34]. Compared to these, this study on non-invasive pneumonia showed a low prevalence of serotypes 3, 4 and 9 N and an absence of serotypes 1, 2 and 5. In India, serotypes 3,4 and 5 are predominant in IPD [22] and are present in both the PCV13 and PPSV23 vaccines. Alarming scenarios are serotype 9 N and 3, where serotype 9 N is a non-vaccine serotype and the protection offered by vaccine for serotype 3 is not significant. Thus, priming children >2 years and adults 16–60 years with the conjugate vaccines will reduce carriage of serotype 3, 4 and 5, indirectly protecting them from non-invasive pneumonia, while providing herd immunity to the community. The use of pneumolysin as a carrier has to be considered in the formulation of upcoming vaccines because of its role in pore formation and extensive cardiomyocyte lysis, resulting in contractile dysfunction and rhythm disturbances [32]. Though, serotype 1 (neurotropic), serotype 5 (cardiotropic) and serotype 9 N (cardiotropic) were few in this study, continuous monitoring of these serotypes and their antimicrobial resistance patterns are important for the management and prevention of non-invasive pneumococcal pneumonia.

Region-specific, continuous monitoring and customization of serotype formulations in conjugate vaccines is important to identify any emerging serotypes and to include these in subsequent vaccines [35]. Expected serotype coverage of the upcoming vaccine PCV20 is similar to PPSV23, with the additional benefits of reducing nasopharyngeal carriage. An increase in antimicrobial resistance has resulted in limited management options for CAP [36]. Since serotypes of most of the resistant isolates were all associated with vaccines, vaccination will have the additional advantage of reducing antimicrobial resistance [37]

CONCLUSION

This study is first to identify the prevalent pneumococcal serotypes in non-invasive pneumonia among South Indian adults. The common serotypes in order of prevalence were 19F, 9V, 23F, 6B, 11A, 13, 34, 10A, 19A and 6A. Smoking, diabetes and lung disease were the significant risk factors associated with non-invasive pneumococcal pneumonia. The predominant non-vaccine serotypes were 13, 34, 35B, 31 and 16F. Pneumococcal vaccines, PCV10/GSK, PCV10/SII, PCV13 and PPSV23, are expected to provide an overall serotype coverage of 36, 41, 47 and 69%, respectively. In adults more than 50 years of age, PCV20 or PPSV23 and PCV13 or PCV15 provides similar serotype coverage. Catch-up vaccination in pre-school children and an age-based and risk-based vaccination in adults >50 years will help in reducing mortality and morbidity in India. However, once herd immunity has been achieved then PCV vaccination in adults has less impact.

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Conflicts of interest
The authors declare that there are no conflicts of interest.

Ethical statement
The Christian Medical College institutional ethical committee has approved the study [institutional review board (IRB) Min.No:8200]. The age criteria for the study subjects were adults aged more than 16 years and the consent was obtained from all the study participants.

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