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Invasive pneumococcal disease associated with high case fatality in India

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Abstract

Objective: To study the seroepidemiology and antimicrobial resistance pattern of invasive pneumococcal disease (IPD) in older subjects who are admitted to hospitals in India.

Study Design and Setting: Prospective surveillance of IPD in patients older than 18 years in seven large academic teaching hospitals in India from 1993 to 2008. All subjects who had *Streptococcus pneumoniae* isolated from normally sterile body fluids or were antigen positive in cerebrospinal fluid, ascitic fluid, and pleural fluid were identified as IPD cases in the study. Serotype/group (STG) and minimum inhibitory concentration for penicillin, chloramphenicol, co-trimoxazole (trimethoprim−sulfamethoxazole), erythromycin, and cefotaxime were determined.

Results: A total of 1,037 adult subjects with suspected invasive bacterial infection were recruited in the study. *S pneumoniae* was identified from normally sterile body fluids in 449 (43.3%) subjects. Meningitis (34.3%) and pneumonia (33.9%) were the most common clinical conditions associated with IPD. The case fatality was 25−30% across all age groups. Penicillin resistance was low at 2.7% overall. Resistance to co-trimoxazole was noted to be high and increasing in the study period from 42.9% in 1993 to 85.2% in 2008 ($P = 0.001$). The most common STG was serotype 1, which accounted for 22.9% of all isolates. The 23-valent pneumococcal polysaccharide vaccine covered 83.3% of the STGs (49/54; 95% confidence interval: 79.7, 96.9) for patients older than 60 years.

Conclusion: IPD continues to be a problem in India and is associated with high case fatality in spite of treatment in the hospital setting. Penicillin resistance is currently low in India. More than 80% of invasive STGs causing disease in the elderly in India are included in the formulation of polysaccharide pneumococcal vaccine.

Keywords: Surveillance; Invasive pneumococcal disease; Antimicrobial resistance; Serotype group; 23-valent pneumococcal polysaccharide vaccine; PPV23; *S pneumoniae*; STG

1. Introduction

The population of older people in the community is increasing [1] in India as the country goes through demographic transition. Globally, invasive pneumococcal disease (IPD) continues to have high case fatality rate and contributes significantly to morbidity and mortality, particularly in the older population above 60 years of age [2]. Although there is some controversy on the usefulness of polysaccharide pneumococcal vaccine (PPV23) in adult population [3,4], administration of PPV23 is recommended in populations at high risk for pneumococcal infection, including those older than 65 years in the United States and Europe. Reports suggest that PPV23 has 60−80% efficacy in reducing the burden of IPD and also decreases hospitalization and health care expenditure [5,6]. We have limited data on antimicrobial resistance (AMR) of IPD in India and the distribution of invasive pneumococcal serotype/groups (STGs) in the country to develop treatment guidelines and preventive policies. Although the Geriatric Society of India has recommended routine use of PPV23 in the elderly [7], The Expert Group of the Association of Physicians of India on Adult Immunization has recently stated that the available evidence is insufficient to

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recommend its routine use in the older population [8]. Currently, immunization rates with pneumococcal vaccine are very low in India. Lack of information on STG causing invasive disease may be one reason, so it was decided to review adult data from the Invasive Bacterial Infection Surveillance (IBIS) study. The present study describes the characteristics of IPD in hospitalized adult patients over a 15-year period in seven tertiary care centers across India with special reference to AMR pattern and the distribution of STGs.

1.1. Study objectives

The objectives were to study the STG and AMR pattern of IPD in India and assess the potential coverage offered by PPV23 in older subjects who are admitted to hospitals in India.

2. Methods

The study design was a prospective 15-year hospital surveillance.

2.1. Participating centers

Prospective hospital surveillance for suspected IPD was undertaken in seven large academic referral hospitals of the Indian Clinical Epidemiology Network (IndiaCLEN) by the IBIS study group from 1993 to 2008. The participating institutions include All India Institute of Medical Sciences (AIIMS), New Delhi; King George Medical College, Lucknow (KGMC), Lucknow; Government Medical College (GMC), Nagpur; Madras Medical College, Chennai; Christian Medical College, Vellore; Medical College, Trivandrum; Lokmana Thilak Medical College, Mumbai (LTM). Adult subjects were recruited in the study during 1993–1997 (phase 1) and 1999–2008 (phase 2). Geographic distribution of the study centers in India is given in Fig. 1. A report on phase 1 of the study primarily dealing with childhood disease (IBIS-1) was published earlier [9]. The study protocol was reviewed and approved by the institutional review boards of the seven participating hospitals as well as Johns Hopkins Bloomberg School of Public Health and the Institutional Review Board of International Clinical Epidemiology Network (INCLEN).

2.2. Study subjects

Adult patients older than 15 years attending the outpatient and inpatient setting from the network hospitals with the following syndromes were recruited: clinical evidence of pneumonia with or without radiographic evidence; clinically suspected pyogenic meningitis with suggestive cerebrospinal fluid (CSF) (>10 white blood cells/mL); and fever at a temperature of at least 39°C for 5 days or less, with hypotension, without definite urinary or gastrointestinal focus (hospital-based recruitment). Informed written consent was obtained from all recruited subjects before study-related procedures. Exclusion criterion was admission to the hospital during the 10 days before presentation to avoid hospital-acquired infections. In addition, hospital and laboratory records of the network hospitals were scrutinized every day and patients with isolates of *Streptococcus pneumoniae* from normally sterile sites were included, if they met the study criteria and the patient was available for follow-up in the ward prospectively (laboratory-based recruitment).

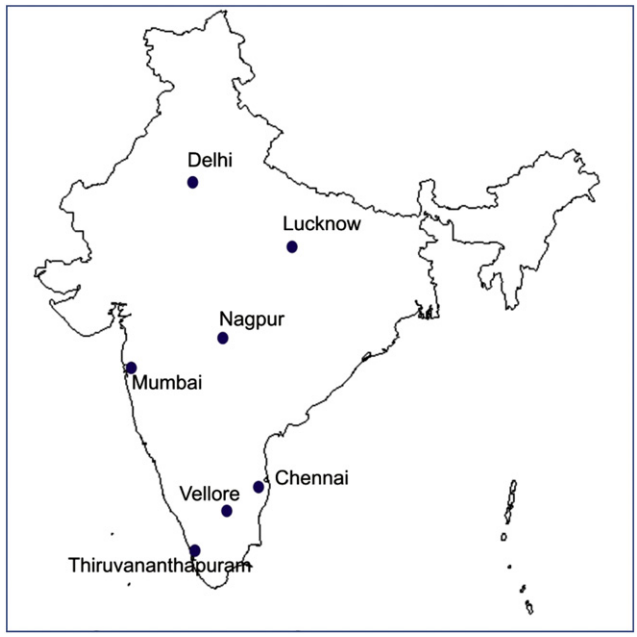

Fig. 1. Geographic distribution of study centers in India.

Adult subjects were recruited in the study during 1993–1997 (phase 1) and in 1999–2008 (phase 2). Information on the history, course, and outcome of illness was recorded on standardized study data forms. Subject recruitment was similar in the two phases of the study. The difference was primarily in the source of funding and minor variation in microbiology technique (described in laboratory methods).

2.3. Laboratory

During both phases of the study, 5–10 mL of normally sterile body fluids were collected for bacteriologic identification. In phase 1 of the study, blood samples were collected in trypticase soy broth and subcultured according to the World Health Organization (WHO) manual for AMR [9]. For detailed laboratory methods during phase 1, refer to the IBIS-1 report [10]. During phase 2, blood samples were inoculated on standard commercial HiMedia primary culture blood agar plates (HiMedia Laboratories, Mumbai). At the reference laboratory, blood was collected in BacT/ALERT automated blood culture media (bioMerieux Inc, Durham, NC) for primary culture. In presence of any growth after 12–24 hours, subculture was done and held for 7 days on

trypticase soy agar (Difco; Becton, Dickinson and Company, Detroit, MI, USA) with 5% locally obtained sheep blood. CSF and other body fluids were inoculated directly onto chocolate and sheep blood agar during both phases of the study.

All positive pneumococcal isolates were either lyophilized or sent on chocolate or sheep blood agar slants to the reference laboratory at the Christian Medical College, Vellore, for identification, serotyping, and serogrouping. The reference laboratory used the Quellung technique or coagglutination technique [11] with antisera obtained from the Statens Serum Institut (Copenhagen, Denmark). Antimicrobial susceptibility testing was performed by the Kirby–Bauer disc diffusion method [12], and minimum inhibitory concentration (MIC) was determined by agar dilution [13]. On selected isolates, the Etest [14] (AB BIODISK, Solna, Sweden) was done. Standard National Committee for Clinical Laboratory Standards criteria of zone size and MIC values were used to classify isolates as susceptible, intermediate, or resistant [15,16]. From 2008 onward, CSF samples suggestive of pyogenic meningitis wherever available were also tested for pneumococcal antigen using a latex agglutination (LA) test [17] or by rapid immunochromatographic assay (BinaxNow; Alere Inc., Waltham, MA, USA).

Any subject who had an isolate of *S pneumoniae* from normally sterile body fluid or had LA test (Directigen; Becton, Dickinson and Company) or a positive BinaxNOW test in CSF, ascitic fluid, or pleural fluid was classified as a case of IPD.

2.4. Quality control

Quality control procedures for this multicenter study included a written manual modified from a WHO manual for AMR (WHO/Centers for Disease Control and Prevention [CDC] manual) [9] and standardization workshops for the clinical and microbiology laboratory investigators. Double entry of all data was done into a single database for analysis. In addition, staff of all study laboratories participated in a quality control program of the reference center at CMC, Vellore, every year during phase 1 of the study and four times during phase 2 period. Standard reference strains of *S pneumoniae* and *Staphylococcus aureus* were used to test all batches of locally prepared media for adequate growth. The study reference laboratory participated in an external validation for serotyping with the WHO reference center at the Statens Serum Institut during phase 1 and CDC, Atlanta, during phase 2.

2.5. Statistical issues

Statistical analysis was performed using a PC-based statistical software (SPSS version 12; IBM SPSS Inc.). Analysis of categorical data was done by a two-tailed χ^2 test. Test for trend was assessed by Mantel–Haenszel test for linear association.

3. Results

A total of 1,037 adult subjects were recruited in the study, 329 (31.7%) during the first and 708 (68.3%) during the second phase of the study. The proportion of laboratory-based recruitment was 33% in phase 1 and 30% in phase 2. Demographic characteristics of the subjects recruited in the two phases of the study are given in Table 1. IPD was diagnosed in 449 (43.3%) patients overall, 140 (42.5%) from the first phase and 309 (46.5%) from the second phase. Of the 449 IPD patients, 416 (92.65%) were culture positive. *Haemophilus influenzae* was the causative pathogen in 25 (2.4%) patients, 17 (7.8%) in the age group of 50–60 years and 8 (3.6%) in the age group of >60 years, respectively. Other pathogens were seen in 25 subjects, and in the remaining 571 subjects of 1,037 (55%), no etiological agents could be identified.

During the 2007–2008 period, rapid immunochromatographic assay (BinaxNOW) was done on CSF and other normally sterile body fluids in 157 patients with suspected IPD. There were 33 additional cases of suspected IPD identified as pneumococcal infections by the BinaxNOW test during this period, which formed 7.3% (33/449).

3.1. Clinical syndromes

The clinical syndromes associated with IPD with the clinical outcome are given in Table 2. Meningitis (34.3%) and pneumonia (33.9%) were the most common clinical conditions associated with IPD, accounting for 68.2% of all cases. Other conditions were septicemia, peritonitis, pleural effusion, deep-seated abscess, and pericardial effusion.

3.2. Clinical outcomes

Clinical outcome was available for 1,015 of 1,037 (97.9%; 95% confidence interval [CI]: 96.8, 98.59) recruited subjects. IPD in the adults was associated with an overall case fatality of 26.4% (115/435; 95% CI: 22.5, 30.8). Meningitis and sepsis were associated with higher case fatality rates of 36.9% (55/149; 95% CI: 29.6, 44.9)

Table 1. Recruitment of surveillance data and demography

	Phase of study, *n* (%)		
Demographics	**Phase 1**	**Phase 2**	**Total, *n* (%)**
Age groups (yr)			
<50	208 (34)	406 (66)	614 (100)
50–60	78 (34)	153 (66)	231 (100)
>60	43 (22)	149 (78)	192 (100)
Total	329	708	1,037
Sex			
Male	243 (34)	471 (66)	714 (100)
Female	86 (27)	237 (73)	323 (100)
Total	329	708	1,037

Table 2. Clinical presentation and outcome

Demographics	*n* (%)	Case fatality (95% CI)
Age groups (yr)		
<50	279 (62.1)	68/270 = 25.2% (20.4, 30.7)
50–60	101 (22.5)	29/96 = 30.2% (21.9, 40.0)
>60	69 (15.4)	18/69 = 26.1% (17.2, 37.5)
		$\chi^2 = 0.924$; df = 2; $P = 0.63$
Gender		
Male	330 (73.5)	93/322 = 28.8% (24.2, 34.1)
Female	119 (26.5)	22/113 = 19.5% (13.2, 27.7)
		$\chi^2 = 3.81$; df = 1; $P = 0.051$
Clinical syndromes		
Meningitis	154 (34.3)	55/149 = 36.9% (29.6, 44.9)
Pneumonia	152 (33.9)	31/149 = 20.8% (15.1, 28.0)
Septicemia	42 (9.4)	15/41 = 36.6% (23.6, 51.9)
Peritonitis	21 (4.7)	1/20 = 5% (0.89, 23.6)
Deep pus	6 (1.3)	2/5 = 40% (11.8, 76.9)
Others	74 (16.5)	11/71 = 15.5% (8.9, 25.6)
Total	449 (100)	115/2,435 = 26.4% (22.5, 30.8)
		$\chi^2 = 22.58$; df = 5; $P < 0.001$

Abbreviation: CI, confidence interval.

Table 3. Comorbidities in IPD subjects and clinical outcome

	Clinical outcome		
Comorbid conditions	Improved	Worsened/dead, *n* (%)	Total
No comorbidities	89	64 (42)	153
HIV or immunocompromised	12	4 (25)	16
Nephrotic syndrome	2	1 (33)	3
Renal disease	5	6 (55)	11
Malignancy[a]	6	11 (65)	17
Sickle/HB-pathies/ splenectomy	2	0 (0)	2
Steroid treatment	9	2 (18)	11
Diabetes	18	7 (28)	25
Others[b]	35	20 (36)	55
Total	178	115 (39)	293
		Pearson $\chi^2 = 0.14$; df = 8	

Abbreviations: IPD, invasive pneumococcal disease; HIV, human immunodeficiency virus; HB-pathiesh, Hemoglobinopathies; CSF, cerebrospinal fluid.

Information was not available for 147 subjects on comorbidities and 14 subjects on clinical outcome.

[a] Includes leukemia, lymphomas, generalized malignancies, and myeloma.

[b] Include chronic liver disease, chronic heart failure, chronic lung disease, smoking, CSF leak, and transplants.

and 36.6% (15/41; 95% CI: 23.6, 51.9), respectively, when compared with pneumonia with a case fatality rate of 20.8% (31/149; 95% CI: 15.1, 28.0; $P = 0.004$). The overall case fatality was 25.2% (95% CI: 20.4, 30.7), 30.2% (95% CI: 21.9, 40), and 26.1% (95% CI: 17.2, 37.5) for the age groups of <50 years, 50–60 years, and >60 years, respectively ($P = 0.63$; df = 2). Clinical outcome was not recorded in 14 (3.1%) subjects, and 8 (1.7%) patients left the hospital against medical advice in poor clinical condition. Six percent (9/149; 95% CI: 3.2, 11.1) of the subjects with meningitis were noted to have sequelae to pneumococcal disease at discharge. Clinical improvement was observed in 273 (62.8%; 95% CI: 58.1, 67.2) patients, and 162 (37.2%; 95% CI: 32.8, 41.9) patients worsened (including patients discharged at request) or died, with no significant difference between the different age groups ($P = 0.434$).

A worse clinical outcome was found in 46.3% (95% CI: 38.5, 54.3) of the patients with meningitis, 36.9% (95% CI: 29.6, 44.9) of the patients with pneumonia, and 41.5% (95% CI: 27.7, 56.6) of the patients with sepsis; this was significantly more than that for patients with other conditions (20.8%; 95% CI: 14.7, 31.1; $P = 0.002$).

There were 302 of 449 IPD patients in whom information on comorbidities was available. Table 3 describes the frequency of comorbidities and their association with clinical outcome. Eleven of 17 (65%; 95% CI: 41.3, 82.7) of those with malignancy were noted to have worsened or died as compared with 64 of 153 (42%; 95% CI: 34.3, 49.7) with no comorbidities, chi-square $P = 0.07$.

3.3. Culture

S pneumoniae was cultured most frequently from CSF in patients with suspected meningitis in the study. Of the 449 patients with IPD, positive *S pneumoniae* in the culture was obtained from 416 (92.7%) patients, whereas in remaining 33 (7.3%) patients, pneumococcal antigen was detected in CSF and other normally sterile body fluids by LA or Binax-NOW test. Of the 416 culture positive isolates, 194 (46.6%) were obtained from CSF, 132 (31.7%) from blood, and 90 (21.6%) from other fluids. When there was more than one isolate from a patient (e.g., blood and CSF), the more invasive isolate (CSF > blood > others) was used for further analysis.

3.4. Antimicrobial susceptibility

Antimicrobial susceptibility was assessed for 408 (98.07%) isolates of *S pneumoniae* (Fig. 2). Invasive isolates of *S pneumoniae* with penicillin nonsusceptibility were not seen during the first 10 years of surveillance from 1993 to 2003. The first isolate that showed intermediate levels of susceptibility was seen in 1996. Overall penicillin

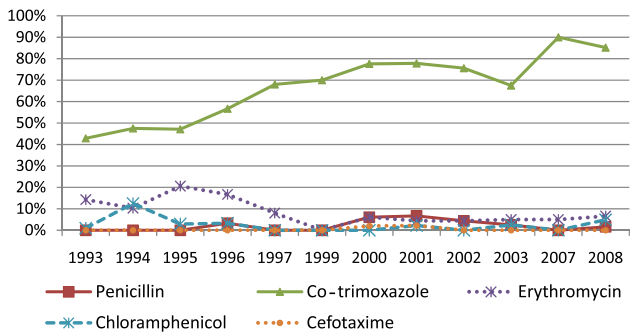

Fig. 2. Antimicrobial resistance of *Streptococcus pneumoniae* by disc diffusion.

nonsusceptible strains were 2.7% (11/408). One isolate was noted to have intermediate susceptibility to cefotaxime in the year 2000, and one was noted to be resistant during 2001. Co-trimoxazole resistance was noted to be high and increasing during the study period and moving up from 42.9% in 1993 to 85.2% ($P = 0.001$) in 2008. The overall nonsusceptible isolates were 68.9% (281/408) for co-trimoxazole. Chloramphenicol nonsusceptible isolates were noted to be decreasing over time from 12.5% in 1994 to 4.9% ($P = 0.008$) in 2008. Overall nonsusceptibility for chloramphenicol was 2.9% (11/409).

3.5. Distribution of STGs

A total of 378 (90.9%) *S pneumoniae* were serotyped and grouped from 416 isolates. The most common STG in these adults was STG 1, which accounted for 22.9% of all isolates. STG 3 formed the second most common isolate, with 6.9% in all older age groups. Distribution of invasive STGs is given in Fig. 3. STGs 1, 3, 4, 5, 6, 7, 8, 12, 15, and 19 were the 10 most common STGs in all adults, accounting for 69.2% of all STGs. During phase 1 of the study, we obtained 93% concordance for STG results with the Statens Serum Institut, Copenhagen 2010 and during phase 2 of the project 84% concordance with the pneumococcal laboratory in CDC, Atlanta, in external quality control of the reference laboratory.

3.6. PPV23-specific STGs

The PPV23 includes STGs 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F [18]. In the present study, adults with IPD had STGs 1, 3, 4, 5, 6, 7, 8, 12, 15, and 19 (10 most common STGs), which accounted for 69.2% of all serotypes. The STGs included in the PPV23 contains 82.3% (311/378; 95% CI: 78.1, 85.8) serotypes of *S pneumoniae*, which were isolated from adult patients with IPD during this study. In patients aged older than 60 years, PPV23 contains STGs that were involved in 83.3% (45/54; 95% CI: 70.7, 92.1) cases of IPD. The potential protection as measured by cumulative coverage of invasive serotypes by PPV23 in the patients aged younger than 50 years was 80.8% (214/234; 95% CI: 87.1, 94.7), whereas for the patients aged between 50 and 60 years, the STGs included in PPV23 were 87.8% (85/90; 95% CI: 87.5, 98.2) and for the patients aged older than 60 years, the STGs included in PPV23 were 83.3% (49/54; 95% CI: 79.7, 96.9). The differences between age groups were not significant ($P = 0.98$; df = 2) (Fig. 4).

4. Discussion

To our knowledge, this is the first report of adult pneumococcal disease from India, with more than 1,000 patients that covers multiple hospitals and more than a decade of surveillance. Although India has approximately 25% of the world's population, there are only few documented reports on IPD from this country confirmed with isolation of the bacteria [19,20]. Although a randomized controlled trial to prove the efficacy of PPV23 among the adult population in India would be ideal, this study shows the distribution of the STGs causing IPD in India, which can be used for vaccine development and testing and for identifying high-risk groups that could be targeted.

IPD still contributes considerably to morbidity and mortality in the Indian setting [21,22]. In the present study, the case fatality for IPD in patients older than 60 years was nearly 26% overall. As expected, a variety of clinical syndromes are associated with different case fatality rates, with meningitis having highest case fatality of more than 35%. Among all older subjects, pneumonia is associated with a case fatality of around 28%, which is much higher than that observed in children [9].

The AMR pattern of IPD fortunately remains relatively favorable in the Indian setting. In the initial 10-year period, there was only one isolate resistant to penicillin. However,

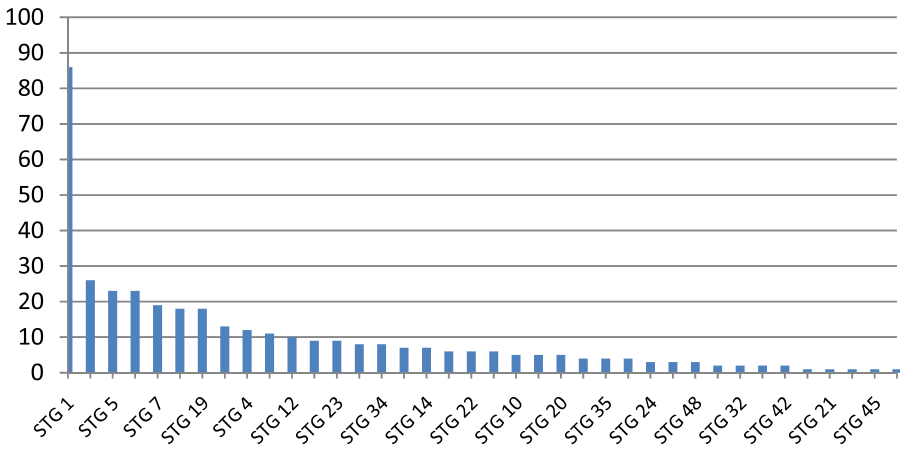

Fig. 3. Distribution of *Streptococcus pneumoniae* serotype/group among adults.

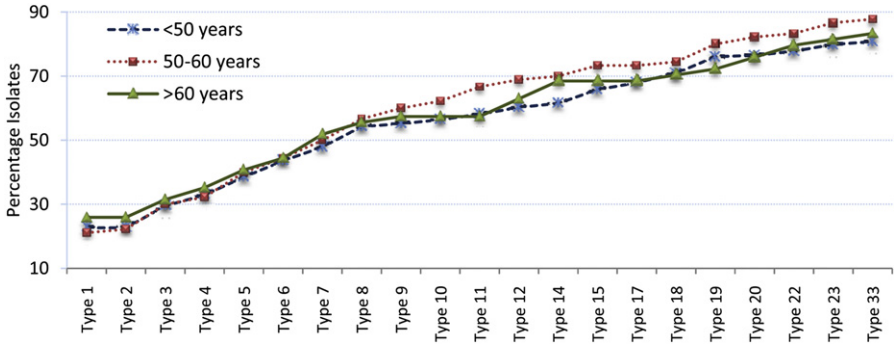

Fig. 4. Cumulative serotype/group coverage by age group with PPV23.

intermediate resistance was noted in 2.5−6.7% of the adult isolates from 1996 to 2003. This picture is remarkably different from the AMR pattern observed in many other countries [23]. Sri Lanka that is geographically close to India has reported very high levels of penicillin resistance [24]. Highest levels of resistance are seen in South Korea, Spain, United States, Britain, and South Africa [25−29]. The resistance to co-trimoxazole was noted to be high, probably because of its widespread use for presumptive treatment of pneumonia. These data suggest that penicillin remains the drug of choice in suspected pneumococcal sepsis, meningitis, and community-acquired pneumonia with lobar consolidation in India.

High levels of co-trimoxazole resistance were noted in the early part of the study in 1993. However, till recently the recommendation for treatment for acute respiratory infections (ARI) in the community care setting continued to be co-trimoxazole. Oral amoxicillin is now the treatment of choice for outpatient management of ARI, particularly in children who also show similar pattern of AMR with high resistance to co-trimoxazole. The delay in translation of evidence to policy is highlighted.

In this study, pneumococcal antigen detection was also done by a rapid diagnostic test (RDT) (BinaxNOW) in the body fluids in a subset of patients. The detection rate of *S pneumoniae* antigen by RDT in normally sterile body fluids, except blood, was found to be very high as compared with culture (31% vs. 19%).

In our earlier report of phase 1, because of limited sample size, the results of all adult subjects were classified together into a single age group older than 5 years. Kanungo et al. [30] described the distribution in adults aged between 16 and 65 years, limiting assessment when considering potential protection for the Indian elderly population who are at maximum risk. We report here the most common serotypes in three separate age groups to clarify the disease burden in the different age groups.

A previous report from the study group demonstrated that the most common serogroup responsible for IPD in children was STG 6 and that in adults was STG 1 [9] in India. The present study shows that STG 1 continues to be responsible for approximately 20% of invasive isolates, whereas it has largely disappeared from many of the developed countries. However, it is interesting to note that the prevalence of STG 1 trended down from 24% (30/125) to 17.3% (31/179) during the 10-year study period ($P = 0.15$; df = 1). Studies in the United States and France have demonstrated that there have been changes in the proportion of infections caused by different STGs [31,32]. The trends observed in this study need to be followed to assess regional and national trends.

In the United States, PPV23 is recommended for immune-competent adults aged 65 years and older and immunocompromised adults of all age groups. Efficacy of the vaccine in immune-competent elderly individuals and in individuals with underlying illnesses that predispose to IPD has been demonstrated [33]. Although there is some doubt about the efficacy of polysaccharide vaccine in reducing all-cause pneumonia in the subgroup of severely immunocompromised elderly at the highest risk of infections, nonrandomized studies clearly suggest that vaccination in a susceptible population results in decrease in mortality and hospitalization due to pneumonia [34]. A case−control study evaluating the efficacy of PPV23 in the Indian setting substantiated this observation [35]. The present study provides some rationale to believe that similar results may be obtained in India because more than 80% of the invasive serotypes from this hospital study from the region are included in the 23 Valent vaccine. However, the cost-effectiveness of this potential intervention remains to be evaluated in this setting.

In the setting of increasing penicillin resistance in many countries around the world including the South Asian countries [24], the use of an appropriate conjugate vaccine for children and polysaccharide vaccine for adults may reduce the spread of resistant *S pneumoniae* clones further into the population. Surveillance of pneumococcal disease is very important to understand the changing trends of AMR pattern and serotype distribution in this setting. The information will help in formulating an evidence-based AMR policy for case management and developing more appropriate preventive strategies for the region.

5. Conclusion

IPD continues to be a problem in India and is associated with high case fatality in spite of treatment in the hospital setting. Penicillin resistance is low and remains the drug of choice in the management of suspected pneumococcal sepsis. There is a very high level of co-trimoxazole resistance. More than 80% of the invasive STGs causing disease in the elderly in India are included in the formulation of PPV23. Currently, the use of PPV23 is very low in India. With the evidence presented, it may be prudent to use this in populations at high risk of invasive pneumococcal infection.

Acknowledgments

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