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Original Article

Chronic medical conditions associated with invasive pneumococcal diseases in inpatients in teaching hospitals in São Paulo city: Estimating antimicrobial susceptibility and serotype-coverage of pneumococcal vaccines

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ABSTRACT

Background: Chronic conditions increase the risk of invasive pneumococcal diseases (IPD). Pneumococcal vaccination remarkably reduced IPD morbimortality in vulnerable populations. In Brazil, pneumococcal vaccines are included in the National Immunization Program (PNI): PCV10 for < 2 years-old, and PPV23 for high risk-patients aged ≥ 2 years and institutionalized ≥ 60 years. PCV13 is available in private clinics and recommended in the PNI for individuals with certain underlying conditions.

Methods: A retrospective study was performed using clinical data from all inpatients from five hospitals with IPD from 2016 to 2018 and the corresponding data on serotype and antimicrobial-non-susceptibility of pneumococcus. Vaccine-serotype-coverage was estimated. Patients were classified according to presence of comorbidities: healthy, without comorbidities; at-risk,

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Pneumococcal vaccine
Pneumococcal conjugate vaccine

included immunocompetent persons with specific medical conditions; high-risk, with immunocompromising conditions and others
Results: 406 IPD cases were evaluated. Among 324 cases with information on medical conditions, children < 5 years were mostly healthy (55.9%), while presence of comorbidity prevailed in adults ≥ 18 years old (> 82.0%). Presence of ≥1 risk condition was reported in ≥ 34.8% of adults. High-risk conditions were more frequent than at-risk in all age groups. Among high-risk comorbidity (*n* = 211), cancer (28%), HIV/AIDS (25.7%) and hematological diseases (24.5%) were the most frequent. Among at-risk conditions (*n* = 89), asthma (16.5%) and diabetes (8.1%) were the most frequent. Among 404 isolates, 42.9% belonged to five serotypes: 19A (14.1%), 3 (8.7%), 6C (7.7%), 4 and 8 (6.2% each); 19A and 6C expressed antimicrobial-non-susceptibility. The vaccine-serotype-coverage was: PCV10, 19.1%, PCV13, 43.8%; PCV15, 47.8%; PCV20, 62.9%; PCV21, 65.8%, and PPV23, 67.3%. Information on hospital outcome was available for 283 patients, of which 28.6% died. Mortality was 54.2% for those with meningitis.
Conclusion: Vaccine with expanded valence of serotypes is necessary to offer broad prevention to IPD. The present data contribute to pneumococcal vaccination public health policies for vulnerable patients, mainly those with comorbidity and the elderly.

Introduction

Streptococcus pneumoniae is a major cause of invasive diseases (IPD) such as meningitis, bacteremic pneumonia and sepsis, associated with high morbimortality.[1] IPD affects all age groups, particularly children ≤5 years-old and the elderly, with the highest case fatality rates in individuals with chronic underlying diseases and immunocompromising conditions.[2–4]

Pneumococcal vaccines are effective in preventing IPD.[5,6] Globally, the polysaccharide 23-valente vaccine (PPV23), and the conjugate vaccines, 10-valent (PCV10) and the 13-valent (PCV13) vaccines are widely used.[7] In Brazil, two pneumococcal vaccines are available free of charge in the Public Health System of (SUS). PCV10 is the vaccine routinely used in the National Immunization Program (NIP) for < 2 years-old, and the PPV23 is recommended for children aged ≥ 2 years, adolescents and adults who have certain medical conditions and long-term care facility residents aged ≥ 60 years.[8] PCV13 is available in private vaccination clinics and, since 2019, this vaccine was included in the NIP but restricted to individuals with underlying conditions (HIV/AIDS, oncologic, and bone marrow and solid organ transplants).[8]

Due to widespread PCV-implementation, emergency of serotypes not included in the vaccines (serotype-replacement) became an important concern leading to the development of new-generation PCVs with expanded valence of serotypes.[7,9,10] Inappropriate antimicrobial use has also contributed to the emergency of non-vaccine-serotypes associated with antimicrobial resistance.[11,12] PCV15 and PCV20 were recently licensed in the United States, respectively for individuals six weeks of age and older, and adults aged ≥ 18 years.[13–15]

The PCV21 vaccine is under development.[16] The broader spectrum of the pneumococcal serotypes in PPV23 is an advantage over currently PCVs, but this vaccine has been shown to be less effective in older adults and those with comorbidities, in addition to a short duration of protection. Furthermore, the PPV23 has no effect against the acquisition of carriage, a prerequisite for herd protection.[17–19]

Brazil has a well-established national laboratory-based surveillance of invasive diseases, but there is no population surveillance except for meningitis.[9,20] Thus, limited data are available on the clinical characteristics of hospitalized patients with IPD.[21,22]

The present study aimed to assess the clinical presentation and outcomes of patients with IPD admitted to tertiary care hospitals and to describe the serotypes and antimicrobial-non-susceptibility of the pneumococcal isolates. We also estimated the extent of serotype-coverage for each available vaccine.

Material and methods

Study design and population

This was a retrospective descriptive study using clinical, demographic and laboratory data collected from medical records of inpatients with IPD defined by the isolation of *Streptococcus pneumoniae* in normally sterile fluid. Data were collected from January 2016 to December 2018 in five teaching hospitals [Hospital of Clinics of the University of São Paulo (HC), Institute of Infectious Diseases Emilio Ribas (IIER), Hospital for the State Public Servant of São Paulo (HSPE), University Hospital of the University of São Paulo (HU), and Santa Casa of São Paulo (ISCMSP)]

The hospitals in which the patients had been admitted were identified in the Adolfo Lutz Institute (IAL) database, which is the national reference laboratory for IPD in Brazil. The most representative hospitals, responsible for providing the largest numbers of pneumococcal isolates, were selected.

The electronic hospital record of each patient (personal variables, medical history and clinical outcome) was reviewed by the hospital staff who completed the study data collection form. In each hospital center, a clinical supervisor was responsible for training the hospital staff to fill in the standardized form and for checking any clinical inconsistencies. Patients of all age groups were included in the study.

Microbiology methods

Pneumococcal isolates were routinely sent to IAL by hospitals along with patient data. Species identification was confirmed by standard methods.[23] Pneumococcus was serotyped by the Quellung reaction with antisera from the Statens Serum Institute (Copenhagen, Denmark). Non-typeable (NT) isolates by Quellung reaction were confirmed by PCR-multiplex.[24]

Susceptibility to erythromycin, clindamycin, sulfamethoxazole-trimethoprim, levofloxacin, tetracycline and vancomycin was assessed using the disk-diffusion test following the Clinical and Laboratory Standards Institute (CLSI) guidelines.[25] Susceptibility to beta-lactamics was assessed by determining the minimum inhibitory concentration (MIC) by the E-test (AB BIODISK, Solna, Sweden). Non-susceptibility to penicillin and ceftriaxone (intermediate plus resistant) were defined as MIC ≥ 0.12 mg/L and ≥ 1.0 mg/L for meningitis and the corresponding MIC ≥ 4.0 mg/L and ≥ 2.0 mg/L for non-meningitis isolates.[25]

Data analysis

Clinical information and laboratory records in Excel spreadsheets were linked. Only one pneumococcal isolate per hospitalization episode was included in the analysis. For some cases, clinical data were lacking. For a few isolates, serotype or non-susceptibility data were missing. For the analysis, the following age groups were considered < 5y, 5-17y, 18-49y, 50-64y and ≥ 65y.

Patients were classified according to their medical risk profile for IPD into three categories: (1) *healthy,* patients without pre-existing comorbidities; (2) *high-risk conditions* that included immunocompromised patients and those with other disorders (cancer, HIV/AIDS, HTLV, hematologic disorder, chronic renal diseases, bone marrow/solid organ transplant, cerebrospinal leak, cochlear implant, and functional/anatomic asplenia), and (3) *at-risk conditions* that included immunocompetent persons with specific underlying medical conditions (asthma, diabetes mellitus, chronic liver diseases, chronic heart diseases, chronic lung diseases, lupus, Crohn's diseases, rheumatoid arthritis, and other unspecified chronic disease) according to previous reports.[26,27] Patients presenting simultaneous at-risk and high-risk conditions were included in the high-risk category. Those with missing data for each of the recorded comorbidities were classified as having an ignored risk profile. The sum of comorbidities included in the at-risk and high-risk categories were also recorded. Categorical variables were expressed as proportions. Antimicrobial-non-susceptibility rate was calculated by the arithmetic mean of number of non-susceptible isolates divided by the number of tested isolates. Multidrug-resistance was defined as non-susceptibility to at least three antimicrobial classes. Vaccine-serotype coverage was calculated by the proportion of pooled PCV-serotypes in each vaccine formulations divided by the total number of isolates. Coverage was calculated stratified by age group, clinical condition, and antimicrobial-non-susceptibility. PCV-formulations were: PCV10-types (serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F); additional-PCV13 (3, 6A and 19A); additional-PCV15-types (22F and 33F); additional-PCV20-types (8, 10A, 11A, 12F and 15B); PCV21-types (3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 16F, 17F, 19A, 20, 22F, 23A, 23B, 33F, 24F, 31 and 35B); PPV23-types (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F). Comparisons of proportions across strata were done using the Chi-square or the Fisher's exact test, as appropriate, in the software STATA.

Ethics

The study was submitted to the Ethics Committees of the institutions participating in the study. The research was developed observing the recommendations of Resolution No.196 dated 10/10/96 - Conselho Nacional de Saúde para Pesquisa Científica em Seres Humanos [National Health Council for Scientific Research in Human Beings].

Results

A total of 406 patients [HC (*n* = 195, 48%), IIER (*n* = 62, 15.3%), HSPE (*n* = 58, 14.3%), HU (*n* = 49, 12.1%), and ISCMSP (*n* = 42, 10.3%)] with their corresponding *S. pneumoniae* characterization were included in the study. Patients were mostly male (*n* = 232, 57.1%). Pneumonia was the predominant IPD manifestation (*n* = 236, 58.1%), followed by meningitis (*n* = 29, 7.1%). There were 88 patients (21.7%) with other conditions (bacteremia, sepsis, abscess, and ascites) and 53 patients (13.1%) with unknown manifestations. The number of cases by age group was: < 5y (*n* = 48, 11.8%), 5-17y (*n* = 20, 4.9%), 18-49y (*n* = 127, 31.3%), 50-64y (*n* = 104, 25.6%) and ≥ 65y (*n* = 107, 26.4%)

Table 1 displays the distribution of IPD cases according to the presence of specific medical conditions by age group. Among the 406 patients, information of medical condition was available for 324 patients (79.8%), of which 63 (19.5%) patients informed no previous medical condition, therefore included in the healthy category, and 261 cases (80.5%) reported the presence of at least one medical condition.

The presence of a previous medical condition was significantly lower in the age group of young children < 5y (44.1%), when comparing to the other age groups (> 80%). Overall, presence of one comorbidity by patient (*n* = 162, 62.1%) was more frequent than ≥ 2 comorbidities (*n* = 99, 37.9%), and was observed in all age groups. Young children had a much higher proportion of a single comorbidity (86.7%), as compared to the other age groups (< 65.2%). The presence of high-risk conditions was higher than that of at-risk conditions in all age groups. Simultaneous high-risk/at-risk conditions were present in 52 cases, predominating among ≥ 18y (96.1%). Patients without information on medical conditions (*n* = 82, 20.2%) were not equally distributed across the age groups, but without a clear trend (Supplementary Table S1).

Distribution of specific high-risk and at-risk comorbidities among 261 IPD cases by age group is shown in Supplementary Table S2. Cancer was the most common comorbidity (*n* = 73, 28%), followed by HIV-AIDS (*n* = 67, 25.7%) and hematological diseases (*n* = 64, including nine sickle cell anemia patients, 24.5%). Among the at-risk conditions, asthma (*n* = 43, 16.5%) was the most frequent. The distribution of specific comorbidities varied a lot by age group.

Table 1 – Risk profile of hospitalized patients with invasive pneumococcal disease (IPD) with information on medical conditions, by age group. Brazil, 2016-2018.

	Age group (years)					
	< 5 y N (%)	5 - 17 y N (%)	18 – 49 y N (%)	50 – 64 y N (%)	≥ 65 y N (%)	Total N (%)
Comorbidity status						
High risk	9 (26.5)	11 (84.6)	72 (64.2)	65 (74.7)	44 (57.1)	201 (62.2)
At risk	6 (17.6)	2 (14.3)	20 (17.9)	11 (12.6)	21 (27.3)	60 (18.3)
Healthy	19 (55.9)	1 (7.7)	20 (17.9)	11 (12.6)	12 (15.6)	63 (19.5)
Number of comorbidities*						
1	13 (86.7)	8 (61.5)	60 (65.2)	40 (52.6)	41 (63.1)	162 (62.1)
≥2	2 (13.3)	5 (38.5)	32 (34.8)	36 (47.4)	24 (36.9)	99 (37.9)
Total	34	14	112	87	77	324

Only patients with high- and at-risk profiles were included in the denominators of these proportions.

Table 2 – Demographic and clinical characteristics of hospitalized patients with invasive pneumococcal diseases (IPD) with information on outcome who were not transferred out, by outcome status. Brazil, 2016-2018.

	Outcome status		p-value
	Cure N. (%)	Death N. (%)	
Age group			
< 5 y	26 (89.7)	3 (10.3)	<0.001
5-17 y	8 (88.9)	1 (11.1)	
18-49 y	80 (82.5)	17 (17.5)	
50-64 y	45 (61.6)	28 (38.4)	
≥ 65 y	43 (57.3)	32 (42.7)	
IPD diagnosis*	11 (45.8)	13 (54.2)	0.022
Meningitis			
Pneumonia	145 (73.2)	53 (26.8)	
Other	35 (74.5)	12 (25.3)	
Comorbidity status**			
High risk	113 (72.9)	42 (27.1)	0.410
At risk	34 (66.7)	17 (33.3)	
Healthy	47 (78.3)	13 (21.7)	
Number of comorbidities***			
1	94 (72.3)	36 (27.7)	0.750
≥2	53 (69.7)	23 (30.3)	
Total	202 (71.4)	81 (28.6)	

Only for patients with information on diagnosis.

** Only for patients with information on medical conditions.
*** Only for patients with high- and at-risk profiles.

Table 2 displays the outcome status for the 283 patients for whom this information was available. Death occurred in 81 patients (28.6%), increasing with the advancing age. Among those with IPD diagnosis, meningitis (54.2%) presented higher death rate compared with pneumonia (26.8%) and other IPD (25.3%). Contrary to our expectations, the proportion of deaths did not increase with increasing comorbidity status or with having one or more comorbidities. Of the total 406 IPD patients, unfortunately there were many missing information on outcome status (n = 105, 25.9%) and some were transferred out (n = 18, 4.4%). They were not equally distributed across age groups, IPD diagnosis and comorbidity status, as shown in Supplementary Table S3.

Of the 406 isolates, blood was the predominant source of the specimen (n = 357; 87.9%), followed by cerebrospinal fluid (n = 20, 4.9%). Other body fluids (pleural fluid, abscess, ascites, bronchial alveolar lavage, vitreous humor, and synovial liquid) were the source for 21 patients (5.2%) and for eight patients (2.0%) the source was ignored.

Distribution of serotypes by age group is displayed in Table 3. Forty-three serotypes plus one NT isolate were identified. Overall, five serotypes were responsible for 42.9% of the isolates. Serotype 19A was the predominant type (14.1%) followed by serotypes 3 (8.7%), 6C (7.7%), 4 and 8 (6.2% each). Considering the age groups, serotype 19A was more frequent in < 5y (37.5%) and 18-49y (11.8%), while serotype 3 was prevalent in 50-64y (12.6%) and ≥ 65y (12.3%). Serotypes 6C (8.0%), 4 (7.4%) and 8 (7.1%) occurred mostly in those aged ≥ 18y.

Rates of antimicrobial-non-susceptibility to penicillin and ceftriaxone among meningitis isolates were respectively 20.7% and 3.4%. Antimicrobial non-susceptibility, including meningitis and non-meningitis isolates, to erythromycin, clindamycin, sulfamethoxazole-trimethoprim and tetracycline varied from 21.1% to 33.2%. Only two isolates (0.5%) showed levofloxacin non-susceptibility; all isolates were vancomycin susceptible. Multidrug-resistance was identified in 13.0% (Table 4).

Table 5 shows vaccine-serotype-coverage by age, risk-group and antimicrobial-non-susceptibility. As expected, there was a trend towards increasing serotype-coverage with increasing vaccine valence, but even PCV21 only covered 65.8% of all isolates. Serotype-coverage for PCV10 was 19.1%, with lower coverage among children < 5y (4.2%) and 5-7 (5%) as compared to the older age groups. Serotype-coverage for the other vaccines varied by age, but no clear trend was observed. Regarding risk groups, serotype-coverage for all vaccines was higher in health individuals as compared to those with comorbidities, but differences were mostly small.

Antimicrobial non-susceptibility was present in 0% for vancomycin, 0.5% (2/378) for levofloxacin, 2% (8/405) for ceftriaxone, 5.9% (24/403) for penicillin, 21.1% (83/394) for clindamycin, 26.7% (108/404) for erythromycin, 33.2% (134/404) for sulfamethoxazole-trimethoprim, 47% (178/ 379) for tetracycline and, finally, 13.1% (53/406) were multidrug-resistant.

Table 3 – Distribution of serotypes of invasive pneumococcal isolates, by age group. Brazil, 2016-2018.

Serotype	Age group (years)											
	<5 y		5-17 y		18-49 y		50-64 y		≥65 y		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
19A	18	37.4	6	30.0	15	11.8	9	8.7	9	8.5	57	14.1
3	1	2.1	2	10.0	6	4.7	13	12.6	13	12.3	35	8.7
6C	2	4.2	2	10.0	13	10.2	6	5.8	8	8.5	31	7.7
4	0	0	0	0.0	12	9.3	7	6.8	6	5.7	25	6.2
8	1	2.1	0	0.0	8	6.3	7	6.8	9	8.5	25	6.2
22F	4	8.2	0	0.0	4	3.1	3	2.9	4	3.7	15	3.7
12F	2	4.2	0	0.0	5	3.9	5	4.9	2	1.9	14	3.5
5	0	0	0	0.0	9	7.1	2	1.9	2	1.9	13	3.2
9N	0	0	1	5.0	5	3.9	3	2.8	4	3.7	13	3.2
23A	4	8.2	0	0.0	1	0.8	5	4.9	2	1.9	12	3
35B	1	2.1	0	0.0	2	1.6	4	3.9	5	4.7	12	3
7F	0	0	0	0.0	6	4.7	2	2.0	3	2.7	11	2.7
9V	1	2.1	0	0.0	7	5.5	2	1.9	1	0.9	11	2.7
11A	2	4.2	1	5.0	0	0	4	3.9	3	2.7	10	2.5
20	1	2.1	0	0.0	3	2.4	6	5.8	0	0	10	2.5
15A	2	4.2	2	10.0	2	1.6	1	1.0	2	1.9	9	2.2
16F	0	0	0	0.0	3	2.4	3	2.8	3	2.8	9	2.2
10A	2	4.2	0	0.0	2	1.6	3	2.8	1	0.9	8	2
6A	2	4.2	1	5.0	2	1.6	1	1.0	2	1.9	8	2
18A	0	0	0	0.0	2	1.6	2	1.9	3	2.7	7	1.7
23B	1	2.1	1	5.0	1	0.8	2	1.9	2	1.9	7	1.7
1	1	2.1	1	5.0	2	1.6	1	1.0	1	0.9	6	1.5
24F	1	2.1	1	5.0	1	0.8	1	1.0	2	1.9	6	1.5
23F	0	0	0	0.0	4	3.1	0	0.0	1	0.9	5	1.2
13	1	2.1	0	0.0	2	1.6	0	0.0	1	0.9	4	1
15B	1	2.1	1	5.0	1	0.8	0	0.0	1	0.9	4	1
29	0	0	0	0.0	1	0.8	1	1.0	2	1.9	4	1
34	0	0	0	0.0	2	1.6	1	1.0	1	0.9	4	1
35F	0	0	0	0.0	1	0.8	1	1.0	2	1.9	4	1
14	0	0	0	0.0	0	0	1	1.0	2	1.9	3	0.7
17F	0	0	1	5.0	0	0	1	1.0	1	0.9	3	0.7
7C	0	0	0	0.0	0	0	1	1.0	2	1.9	3	0.7
11B	0	0	0	0.0	1	0.8	0	0.0	1	0.9	2	0.6
15F	0	0	0	0.0	2	1.6	0	0.0	0	0	2	0.6
18C	0	0	0	0.0	0	0	1	1.0	1	0.9	2	0.6
25A	0	0	0	0.0	0	0	1	1.0	1	0.9	2	0.6
28A	0	0	0	0.0	0	0	1	1.0	0	0	1	0.2
31	0	0	0	0.0	1	0.8	0	0.0	0	0	1	0.2
33F	0	0	0	0.0	0	0	0	0.0	1	0.9	1	0.2
35A	0	0	0	0.0	0	0	0	0.0	1	0.9	1	0.2
36	0	0	0	0.0	1	0.8	0	0.0	0	0	1	0.2
6B	0	0	0	0.0	0	0	1	1.0	0	0	1	0.2
7A	0	0	0	0.0	0	0	1	1.0	0	0	1	0.2
NT*	0	0	0	0.0	0	0	0	0	1	0.9	1	0.2
Total	48	100.0	20	100.0	127	100.0	103	100.0	106	100.0	404	100.0

1NT, non-typeable; among 406 cases, serotype data for 2 isolates were missing.

The lower part of Table 5 shows the isolates not susceptible to each of the antibiotics and the proportion of them that were serotypes covered by each vaccine. For all antibiotics, the PCV10 vaccine only covered a minority of non-susceptible isolates. Although the serotype-coverage increased significantly for the other vaccines, it should be noted that it was only 100% for ceftriaxone with PCV21. For tetracycline, for example, out of the total of 178 non-susceptible isolates, only 79 (44.4%) had serotypes covered by the PCV15 vaccine.

Distribution of serotypes by antimicrobial-non-susceptibility by PCV-formulation is available in a Supplementary Table S4. Serotype 19A (n = 57), included in all PCVs but PCV10, was associated to non-susceptibility to penicillin (24.6%), tetracycline (70.2%), sulfamethoxazole-trimethoprim (75.4%), erythromycin (70.2%) and clindamycin (57.9%), and multidrug-resistance (50.9%). Serotype 6C (n = 31), a non-vaccine-type, expressed non-susceptibility to tetracycline (71.0), sulfamethoxazole-trimethoprim (32.3%), erythromycin

Table 4 – Antimicrobial non-susceptibility of pneumococcal invasive isolates. Brazil, 2016-2018.

Antimicrobial (N tested)	Non-susceptible N (%)
Penicillin	
meningitis (*n* = 29)	6 (20.7)
non-meningitis (*n* = 376)	18 (4.8)
Ceftriaxone	
meningitis (*n* = 29)	1 (3.4)
non-meningitis (*n* = 376)	7 (1.9)
Erythromycin (*n* = 404)	108 (26.7)
Clindamycin (*n* = 394)	83 (21.1)
Sulfamethoxazole-trimethoprim (*n* = 404)	134 (33.2)
Levofloxacin (*n* = 378)	2 (0.5)
Tetracycline (*n* = 379)	178 (46.9)
Vancomycin (*n* = 405)	0 (0.0)
Multidrug resistance[#] (*n* = 406)	53 (13.0)

[€]Non-susceptible: intermediate plus resistant criteria according to CLSI, 2020.

[#] Multidrug resistance: non-susceptibility to at least three antimicrobial classes.

(67.7%) and clindamycin (61.3%). Serotypes most associated with tetracycline-non-susceptibility were 8 (44.0%), 10A, 35B (75% each), and 20 (90.0%), included in PVC20 and PCV21, and PPV23.

Discussion

This study investigates the clinical conditions of inpatients with IPD, and the corresponding characteristics of the pneumococcal isolates at large hospitals that treat cases with clinical complexity in São Paulo.

The study involved a low proportion of inpatients aged < 5y and 5-17y versus ≥ 18y, evidencing advanced age associated with medical complication as a risk-factor for acquiring IPD.[26,28] In that regard, the substantial contribution of the widespread use of PCV10 in Brazil leading to a decline in IPD in the pediatric population was also evident, as reported by others.[29,30]

Overall, most patients presented only one risk-factor (60.6%) and high-risk comorbidities occurred more frequently (62.2%) than at-risk comorbidities (18.3%). Cancer, HIV/AIDS, hematologic disorder were the most common comorbid conditions, occurring mostly in patients aged ≥ 18 years. Asthma was also frequent in those aged ≥ 18 years, while diabetes occurred furthermost in older adults, particularly those aged ≥ 65 years. Corroborating with these findings, population-based-surveillance studies conducted in the United States and England reported that more than 50% of IPD occurred in adults aged ≥ 18 years were associated with cancer, HIV/AIDS, diabetes, chronic heart disease and chronic lung disease.[4,28] Another national-surveillance study conducted in

Table 5 – Serotype coverage of the pneumococcal vaccines by age group, risk-group for invasive pneumococcal diseases (IPD) and antimicrobial non-susceptibility. Brazil, 2016-2018.

Variables	Pneumococcal vaccine											
	PCV10		PC V13		PC V15		PC V20		PCV21		PPV23	
	N	%	N	%	N	%	N	%	N	%	N	%
Age group (years)												
<5 y (*n* = 48)	2	4.2	23	47.9	27	56.3	35	72.9	42	87.5	34	70.8
5-17 y (*n* = 20)	1	5	10	50	10	50	12	60	16	80	13	65
18-49 y (*n* = 127)	40	31.5	63	49.6	67	52.8	83	65.4	67	52.8	89	70.1
50-64 y (*n* = 103)	17	16.5	40	38.8	43	41.7	62	60.2	73	70.9	71	68.9
≥ 65 y (*n* = 106)	17	16.1	41	38.7	46	43.4	62	58.5	68	64.1	65	61.3
All ages (*n* = 404)	77	19.1	177	43.8	193	47.8	254	62.9	266	65.8	272	67.3
Risk group for IPD												
Healthy (*n* = 63)[£]	17	26.9	29	46	32	50.8	45	71.4	41	65.1	46	73
Any comorbidity (*n* = 261)	48	18.4	112	42.9	119	45.6	155	59.4	167	64	170	65.1
High-risk (*n* = 211)[§]	42	19.9	92	43.6	97	46	124	58.7	131	62.1	134	63.5
Antimicrobial non-susceptibility[€]												
PEN (*n* = 24)	3	12.5	19	79.2	19	79.2	19	79.2	20	83.3	17	70.8
CRO (*n* = 8)	0	0	7	87.5	7	87.5	7	87.5	8	100	7	87.5
TET (*n* = 178)	23	12.9	74	41.6	79	44.4	104	58.4	127	71.3	123	69.1
STX (*n* = 134)	28	20.9	75	55.9	76	56.7	86	64.2	83	61.9	90	67.2
ERY (*n* = 108)	11	10.2	58	53.7	59	54.6	61	56.5	75	69.4	67	62
CLI (*n* = 83)	5	6	42	50.6	43	51.8	45	54.2	58	69.8	53	63.8
MDR (*n* = 53)[#]	9	17	41	77.3	42	79.2	42	79.2	42	79.2	46	86.8

[£] Healthy, IPD cases without pre-existing comorbidities; high-risk conditions displayed in Table S1.

[§] At-risk and high-risk conditions were included in the high-risk category (37 cases present at-risk conditions only).

[€] Non-susceptible: intermediate plus resistant criteria according to CLSI2020; PEN, penicillin; CRO, ceftriaxone; TET, tetracycline; STX, sulfamethoxazole-trimethoprim; ERY, erythromycin; CLI, clindamycin.

[#] MDR, Multidrug-resistant, non-susceptibility to at least three antimicrobial classes; PCV, pneumococcal conjugate vaccine; PPV23, 23-valent polysaccharide vaccine; among 406 cases, serotype data for 2 isolates were missed.

Denmark reported increased risk of IPD in the presence of hematological malignancies in > 15 years of age.[31].

Regarding the outcome, we found a statistically significant increase in mortality with advancing age, reaching 42.7% at ≥ 65 years, reflecting the high IPD risk conditions among the elderly with waning immunocompetence.[2,32] Conversely, as expected, children had a higher cure rate (89.7%).[27,28] Crude associations of higher mortality with comorbidity status and number of comorbid conditions were not observed in our study, which may be related to the high proportion of missing data on comorbidities (20.2%) and on outcome status (25.9%) in this study. However, the association between higher risk conditions and bad prognosis for IPD has been widely reported by other studies.[27,28,33–35] Meningitis, a serious neurological disease, was more deadly (54.2%) than pneumonia (26.8%) and other IPD (24.6%), as expected.

Globally even with the substantial PCVs success in reducing IPD, children, the elderly and patients with comorbidities are still populations at risk for IPD, due to the occurrence of serotype replacement.[11] Thus, the global scenario is still challenging for IPD prevention. Currently, about 100 pneumococcal serotypes have been identified, based on their unique polysaccharide capsule, each one with different propensities to develop IPD.[36] Here we observe low rates of PCV10 serotypes in children and in older adults in consequence of the direct and indirect effect (herd immunity) of PCV10 vaccination, even with suboptimal vaccine-coverage of approximately 88% with two doses in the city of São Paulo during the study-period.[20,30,37]

We found high diversity of serotypes, showing the high rates of the additional PCV-types 19A and 3, and the non-PCV-type 6C, which is in accordance with data from Brazilian national-laboratory-surveillance and from other countries where PCV10 had been introduced in their vaccination program.[9,38–41] A high rate of 19A is likewise worrisome because of its relatively high potential for causing IPD, and its association with antimicrobial-non-susceptibility, similarly to what is observed for 6C.[9,36,38,40–43] Regarding serotype 3, a PCV13-serotype, although not associated with antimicrobial non-susceptibility, there is a concern about its high prevalence, because it causes high morbidity even in countries where PCV13 vaccine have been introduced, due to the abundant expression of its capsule that limits vaccine efficacy.[44–47]

Treatment of IPD with antimicrobials is decisive in the course and outcome of the disease. We observed dramatic rates of antimicrobial-non-susceptibility (> 20%) for some drugs and multidrug-resistance (13%), which can be a challenge for the IPD clinical management. Importantly, we found a low non-susceptibility to ceftriaxone (< 3.5%), and none isolate expressed non-susceptibility to vancomycin, in line with the findings of other studies.[9] These drugs are routinely prescribed to hospitalized patients with risk conditions for IPD.

PCVs with expanding serotype-valence including the additional serotypes 19A, 6A (6A may induce cross-protection with 6C[48]) besides other additional types afford growing benefits to prevent IPD in the post-PCV10 period. Regarding the PPV23, we found higher serotype-coverage (67.3%) than the 31.4% reported among patients admitted to a tertiary care hospital located in the city of Porto Alegre, in Brazil.[21] In addition, in the present study, PPV23 coverage did not vary by age groups or presence of risk conditions, which was similar to the findings of other PPV23 studies.[18] Due to its broad valence of serotypes, this polysaccharide vaccine continues to play an important role in protecting against IPD and pneumococcal pneumonia in the elderly despite its inherent immunological limitation.[18,19] In Brazil, sequential vaccination with PCV13 followed by PPV23 or PPV23 is only essentially recommended by the SUS to patients with some high-risk conditions and the elderly, respectively.[8]

This study has some limitations, which are mostly related to its retrospective design. We used laboratory data coupled with data extracted from medical records, which led to a relatively high proportion of missing and possibly inaccurate values in some key variables. Moreover, the pattern of missing data may not have been completely at random, leading to the possibility of some patients with poor outcomes, as death soon after hospital admission, having less data on comorbidity status, for example. Furthermore, statistical comparisons were difficult as some of our stratifications contained many categories, such as large number of serotypes, despite the study having a fair number of cases. It is difficult to find in the literature a study with our number of cases that matched laboratory and clinical data. Another important limitation was the lack of data on the vaccination of our patients since data was not collected in a standardized way in medical records. Our results may not be generalizable to the total number of hospitals in the metropolitan region of São Paulo and even less in Brazil, as the data were collected from public and philanthropic teaching hospitals, which usually have a more severe patient profile and can be accompanied by chronic diseases in these services.

In conclusion, this study highlights the importance of vaccines with higher valence of serotypes in the vaccination program in Brazil, which offer substantial benefit to prevent IPD in vulnerable people mainly those with underlying comorbidity and the elderly subject to high morbimortality from IPD.

Disclaimer

All authors have approved the final version of the manuscript.

Author's contributions

Conceived and designed the study: RAK, MCCB, JCM; statistical analysis: ALB, JCM; Acquisition of medical data: RR, MAPS, AEG, FR, TG; laboratory data: MCCB; revision of the manuscript: RAK, MCCB, JCM, ALB.

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Conflicts of interest

The authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjid.2023.102746.

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