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Title: Incidence, etiology and serotype coverage for pneumococcal vaccines of community-acquired pneumonia in adults: A population-based prospective active surveillance study in Brazil.

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Abstract

Objectives To determine the incidence, etiology, and pneumococcal serotype distribution of community-acquired pneumonia (CAP) in Brazilian adults during a 2-year period.

Design Prospective population-based surveillance study.

Setting Patients from two emergency hospitals in Brazil were consecutively included in this study.

Participants A total of 111 adults aged 50 years and older with radiographically-confirmed CAP requiring an emergency department visit were prospectively enrolled between January 2018 and January 2020.

Main outcome measures Incidence rates of CAP were calculated according to age and pathogen. Pathogens were identified by conventional microbiological methods. Additionally, a novel, Luminex-based serotype specific urinary antigen detection assay was used to detect serotypes included in pneumococcal vaccines.

Results Mean age of participants was 64 years and 31% were aged ≥70 years. Etiology was established in 61 (57%) patients; among identified cases, the most common pathogens were *S. pneumoniae* (42/61, 69%) and influenza (4/61, 7%). Among serotypes identified from the 42 cases of pneumococcal CAP, estimated coverage ranged by pneumococcal vaccine formulations from 47.6% (13-valent), 59.5% (20-valent, licensed in the US only), and 71.4% (23-valent). In patients with CAP, 20-valent pneumococcal vaccine serotypes were identified 2.5 times more frequently than 10-valent pneumococcal vaccine serotypes (22.5% vs. 9.0%). The incidence rate for CAP in adults aged ≥50 years was 20.1 per 10,000 person-years. In general, the incidence of CAP increased

consistently with age, reaching 54.4 (95% CI 36.8 to-76.6) per 10,000 in adults 80 years or older.

Conclusions We observed a high burden of pneumococcal CAP among adults in Brazil. Despite the routine immunization of children and high-risk adults against pneumococcal disease in the Brazilian national vaccination program, a persistent burden of pneumococcal CAP caused by vaccine serotypes remains in this population.

Word Count: 281

Keywords: Community-acquired pneumonia; Incidence; Pneumococcal vaccines; *Streptococcus pneumoniae*; Serotype distribution.

Data availability statement

Data are available on reasonable request. Ethical restrictions related to participant confidentiality prohibit the authors from making the dataset publicly available.

Strengths and limitations of this study

- Prospective, population-based active surveillance study aimed to estimate incidence rate of community-acquired pneumonia (CAP) in adults, conducted over a period of 2 consecutive years.
- All cases of CAP were radiographically confirmed and validated by clinical information.
- Molecular based tests employed to improve the detection of *S. pneumoniae* in non-bacteremic cases of CAP.
- Some patients with mild symptoms may have been missed because they did not seek an emergency department for evaluation.
- A thorough virological research was not performed.

INTRODUCTION

Community-acquired pneumonia (CAP) is associated with substantial morbidity and mortality, accounting for more than 290 million cases and 4.9% of all deaths in the world[1]. Pneumonia kills more children worldwide than any other infectious disease, claiming the lives of over 800,000 children under five every year, or around 2,200 every day[2]. In Brazil, CAP is the third cause of mortality and the leading infectious cause of hospital admission and death among adults, with 598,668 CAP-related hospitalizations and 52,776 CAP-related deaths in 2017[3,4]. Therefore, CAP is a global public health problem, responsible for a considerable burden and the utilization of health care resources in all age groups.

The incidence of CAP varies by age, being higher in children and older adults[5]. It also varies by region – estimates of annual incidences from studies conducted in community-dwelling adults aged ≥18 years living in Latin America range from 1.8 to 7.0 per 1000 person-years[6], whereas it ranges from 2.5 to 6.5 in patients hospitalized with CAP per 1000 adults in the United States, 2.5 to 11.6 cases per thousand from selected countries in Europe[7–10]. Various pathogens can cause CAP, including both bacteria and viruses, but in as many as half of cases an etiological agent cannot be identified[8]. *Streptococcus pneumoniae* has been the most commonly identified bacteria implicated in CAP in adults[8,11]; however, its contribution in the etiology of CAP differs according to reports that may reflect differences in study design, laboratory isolation of *S. pneumoniae* and the difficulty with detection of *S. pneumoniae* in nonbacteremic CAP.

Limited data are available regarding the incidence of CAP in Brazil. Most estimates were made before the routine administration of the pneumococcal conjugate vaccine in children or in adults at increased risk for pneumococcal disease. Moreover, previous

studies included only children[12] or were mostly retrospective and have not used more sensitive molecular and antigen-based laboratory diagnostic tests[5,13]. Routine childhood immunization with 10-valent pneumococcal conjugated vaccine (PCV10) in Brazil begun in 2010, with a national passive surveillance system in place, most recent publications on invasive disease, show that disease by PCV10 serotypes are declining in children, but non-PCV10 serotypes, specially 13-valent pneumococcal conjugated vaccine (PCV13) exclusive serotypes represent an important proportion of the remaining disease burden in all age groups, including the elderly[14,15]. Since most of the pneumococcal disease burden are clinically presented as CAP, additional active surveillance studies are needed to determine the incidence and etiology of CAP in Brazilian adults.

Advanced age is associated not only with a higher incidence of CAP but also with more severe disease, greater need for hospitalization, and higher mortality[16]. Thus, we conducted an active, population-based surveillance study of CAP patients requiring an emergency department visit among adults 50 years and older in Brazil. We used conventional bacteriological testing and more sensitive molecular methods to determine the incidence and microbiologic causes of CAP. In addition to information about disease burden, data on the serotype distribution of pneumococcal strains causing pneumonia in adults were presented.

METHODS

Study design and Setting

This was a prospective, multicenter, population-based, active surveillance study to identify CAP cases among adults requiring an emergency department visit.

Radiographically-confirmed CAP was further assessed by conventional and non-culture-based identification methods. The study was conducted over a period of twenty-four consecutive months, from January 3, 2018 to January 2, 2020, at two Emergency Hospitals (Unidade de Pronto Atendimento [UPA]-Barris and UPA-Brotas), in the city of Salvador, Brazil. These study sites serve the public sector of the Brazilian health system, the "Sistema Único de Saúde" (SUS), and are considered public hospitals. The hospitals were selected based on an objective review of site capability to conduct the active surveillance, capacity to enroll patients, ability to collect and test specimens, and availability of denominator data for incidence calculations. Weekly study-site visits, enrollment reports, and data audits were conducted to ensure standardized procedures in both study sites.

Study population

We sought to enroll all eligible adults 50 years of age or older. Trained nurses screened adults for enrollment at least 18 hours per day, 7 days per week. Screening was conducted in all patients attending the emergency department who presented with evidence of an acute respiratory illness or infection with at least two of the following: fever (axillar temperature ≥38.0°C), hypothermia (axillar temperature <35.5°C, measured by a healthcare provider), chills or rigors, pleuritic chest pain, new or worsening cough, purulent sputum or changes in sputum characteristics, dyspnea (shortness of breath) or tachypnea (rapid breathing, >25 breaths per minute), auscultatory findings consistent with pneumonia, leukocytosis (white blood cell count >15X10^9 white blood cells/liter or >15% bands), serum procalcitonin above ≥0.5 mg/ml, or hypoxemia (O^2 saturation <90% breathing room air or PaO^2 <60 mmHg), were considered a suspected case of pneumonia, and had a chest X-ray performed to further evaluate this diagnosis.

Only those with radiographically-confirmed CAP were considered as eligible for final inclusion in the study. The chest radiographs were interpreted by one board-certified chest radiologist (members of the research team, RB and CA) at each site, who were unaware of the clinical data. Radiographic evidence of pneumonia was defined as the presence of a radiographic infiltrate in the lung parenchyma (e.g. consolidation or other infiltrate, linear and patchy alveolar or interstitial densities), or pleural effusion[17].

Patients were excluded if they had a clinical and radiographic picture that could be explained by an illness other than CAP, resided outside the study catchment area, had been enrolled before in this study (in the previous month), or presented criteria for healthcare-associated pneumonia (HCAP). We defined HCAP according to the American Thoracic Society and Infectious Diseases Society of America guidelines, including: any patient who was hospitalized in an acute care hospital for 2 or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic[18].

Data collection

Patients and/or their caregivers were interviewed by trained staff, using a standardized questionnaire that included demographic data and information on lifestyle habits (smoking cigarettes, alcohol intake and substance abuse), and underlying medical conditions (asthma, chronic obstructive pulmonary disease, chronic heart disease, hypertension, human immunodeficiency virus infection, diabetes mellitus, chronic kidney disease, history of stroke, chronic hepatitis, and immunosuppression including cancer and immunosuppressive medication). Questions also included information on clinical signs and symptoms, antimicrobial use prior to hospitalization, and previous

immunizations (self-reported vaccination against pneumococcus or against influenza vaccine during the last influenza season).

Specimen collection and laboratory testing

Blood samples, urine samples, and nasopharyngeal swabs were obtained from the patients within 2 hours of attending the Emergency Department. In the case of patients with a productive cough, sputum was also obtained. Blood for culture was collected in BACTEC™ bottles, transported to a local certified laboratory HSR Lab (Hospital San Rafael Microbiology Laboratory, Salvador, Brazil). Urine samples for pneumococcal antigen detection were collected in a standard sterile specimen cup, refrigerated at 4°C for up to 4 hours after collection, aliquoted, stored at -70°C and shipped to Pfizer Vaccine Research and Development, (Pearl River, New York, USA,). *Streptococcus pneumoniae* was identified via BinaxNOW® (Abbott) performed following the manufacturer's recommendations[19]. We also tested the urine samples with Luminex technology-based multiplex (UAD) diagnostic assays, UAD-1, to detect the *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (covered by PCV13), and UAD-2, to detect 11 additional serotypes, including the remaining serotypes covered by the 20-valent pneumococcal conjugate vaccine (PCV20) (8, 10A, 11A, 12F, 15B, 22F and 33F), licensed in the US only, and the 23-valent pneumococcal polysaccharide vaccine (PPV23) (2, 9N, 17F,and 20). Both assays were performed at Pfizer as described elsewhere[20,21].

Nasopharyngeal specimens were collected using sterile swabs with flexible shafts, then they were promptly tested with a rapid diagnostic kit (QuickVue Influenza Test; Quidel, San Diego, Calif.) using monoclonal antibodies specific for influenza A and B virus antigens. The test was performed at each participating site as instructed by the

manufacturer[22]. When available, sputum was collected into sterile containers. Gram stain, Ziehl–Neelsen stain, and bacterial culture were performed at a local laboratory (HSRLab). Only bacterial culture from sputum of high quality (≤10 epithelial cells/low power field [lpf] and ≥25 white blood cells/lpf) were included[23]. *Mycobacterium tuberculosis* was considered a pathogen if detected in any acid-fast bacilli (AFB) sputum specimen.

Streptococcus pneumoniae serotyping

Capsular serogroups/serotypes were deduced using multiplex-PCR as described elsewhere[24]. All isolates identified as serogroup 6 in the multiplex-PCR were subjected to wciN6C–specific PCR, as previously described, for the identification of potential serotype 6C and 6D isolates[25]. Isolates with negative or equivocal multiplex PCR results were subjected to Quellung reaction testing for capsular type definition.

Statistical Analysis

Initially, a descriptive analysis of demographics and predisposing conditions for CAP was performed. Data were presented as frequencies and percentages for categorical variables and as median (IQR) for continuous variables. Incidence rates (expressed per 10,000 person-years) and 95% confidence intervals (CIs) were estimated with the Poisson exact method[26] overall, and for each of the age categories. First, we adjusted the number of CAP cases, according to age group, for the proportion of eligible adults enrolled at both study sites (72%), and for the proportion of Salvador's population depending exclusively on health care from the public sector SUS (70%)[27]. This adjusted number was then divided by the estimated population in the catchment areas of the study sites for the corresponding year and age group. This denominator was obtained by multiplying available census data on Salvador's population[28] by the proportion of all

admissions estimated by the catchment area (market share) of the study emergency hospitals. Based on data from SIH (Hospital Information System) and CNES (National Register of Heath Institutions from the public database DATASUS[29,30], the average annual market share of the emergency hospitals during the study period was 17.9% (11.1% at UPA-Barris and 6.8% at UPA-Brotas). Alternatively, we also estimated the denominator for the incidence rates by using census data for the corresponding year and age group, to sum the population living in the surrounding boroughs in the health district of each study emergency hospital, and the rates remained mostly unchanged (data not shown).

Coverage potentially afforded by different vaccines was calculated as the percentage of serotypes included in pneumococcal vaccines among the isolates obtained from CAP cases during the study period. All the statistical analyses were performed using the STATA statistical software (Version 12) (StataCorp., College Station, USA).

Ethics statements

This study was conducted in accordance with applicable laws and regulations including, but not limited to, the International Conference on Harmonization Guideline for Good Clinical Practice and the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Santo Antônio Hospital (Approval #: CAAE56884916.9.0000.0047). All participants or their caregivers provided written informed consent prior to enrollment.

RESULTS

Overall, 10,190 adults 50 years or older were screened for pneumonia at the two study sites. Among 314 patients with a clinical presentation suggestive of CAP, 154 met

eligibility criteria, including radiological findings, for CAP diagnosis and 111 (72%) of them were enrolled (Figure 1). Participants were significantly more likely to be 60 years of age or older (p=0.04) and more likely to be females (p=0.02) as compared to those who were eligible but not enrolled (data not shown).

The median age of patients with CAP was 64 years (interquartile range, 57 to 73), 51% had a multiracial background and 60% had Middle School education or less (Table 1). Self-rated overall health was fair or poor in 41%. At least one predisposing condition was present in 67% of participants with CAP, and two or more in 40%. Cough, fever, dyspnea, and pleuritic pain were the most common clinical findings. Nearly one-third of study participants had been immunized against influenza during the last influenza season, and only 3% of patients 60 years or older received PPV23 on at least one occasion. Sixty percent had a clinical score (CRB-65) prediction for hospital referral or admission. Of 111 adults with CAP, 21 (19%) were managed as outpatients, 90 (81%) were hospitalized and none were admitted to the intensive care unit (ICU).

Table 1. Characteristics of Middle-aged and Older Adults with Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020.

Characteristics	n=111	(%)
Age, median [interquartile range]	64 [57 – 73]	
Age group		
50-59 yr	35	(31)
60-69 yr	42	(38)
70-79 yr	22	(20)
≥ 80 yr	12	(11)
Race or ethnic group*		
White	10	(9)
Mixed	57	(51)
Black	41	(37)
Native American	1	(1)
Asiatic	2	(2)
Marital status		
Married or living with partner	54	(49)
Single	33	(30)
Divorced	14	(12)
Widowed	10	(9)
Educational Attainment		
Elementary/Middle School	67	(60)
High School	39	(35)
College	5	(5)
Occupation		
Employed	36	(32)
Retired	55	(50)
Unemployed	6	(5)
Housework	12	(11)
Does not work	2	(2)
Body Mass Index (BMI)		
Below normal	2	(2)
Normal	44	(40)
Above normal	38	(34)
Obesity I	16	(14)
Obesity II (severe)	9	(8)
Obesity III (morbid)	2	(2)
Self-rated overall health		
Excellent	3	(3)
Very Good	3	(3)
Good	59	(53)

Table 1. Characteristics of Middle-aged and Older Adults with Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020. (continuation)

Characteristics	n=111	(%)
Self-rated overall health		
Fair	45	(40)
Poor	1	(1)
Any underlying condition†		
Hypertension	59	(53)
Diabetes Mellitus	25	(22)
Chronic heart disease	14	(13)
Chronic obstructive pulmonary disease (COPD)	9	(8)
Asthma	8	(7)
Depression	7	(6)
Stroke	6	(6)
Sickle Cell Disease	4	(4)
Smoking history		
Never smoked	60	(54)
Smoked, but quit	33	(30)
Current smoker	18	(16)
Signs and symptoms$^{\Phi}$		
Cough	106	(95)
Fever	84	(76)
Dyspnea	66	(60)
Pleuritic pain	49	(44)
Chills	25	(22)
O^2 saturation less than 95%	17	(15)
Abnormal lung auscultation	13	(12)
Status regarding receipt of vaccine or treatment‡		
Seasonal influenza vaccination (past 12-month)	34	(31)
Pneumococcal vaccination in adults ≥60 yrs of age (n=76)	2	(3)
Outpatient antibiotic use	14	(13)
CRB-65 score§		
Likely suitable for home treatment (0)	44	(40)
Consider hospital referral (1-2)	66	(59)
Urgent hospital admission (3-4)	1	(1)

* Race and ethnic group were self-reported.

†Any underlying medical condition included asthma, chronic obstructive pulmonary disease, chronic heart disease, hypertension, human immunodeficiency virus infection, diabetes mellitus, chronic kidney disease, history of stroke, chronic hepatitis, and immunosuppression including cancer and immunosuppressive medication). The specific conditions that affected at least 4% of patients are listed here. The groups were not mutually exclusive.

ϕ A participant may report multiple signs and symptoms.

‡Data were based on self-report vaccine information. For influenza vaccine, the percentage of patients vaccinated was based on the season before admission. For pneumococcal vaccination, the percentage of patients vaccinated with pneumococcal polysaccharide vaccine was based on 76 of 111 adults (68%) who were 60 years of age or older. For both vaccines, patients were considered to be vaccinated if they had received the vaccine at least 2 weeks before admission. Outpatient antibiotics were defined as those received within 7 days before admission.

§CRB-65 is a clinical guidance score for predicting community-acquired pneumonia mortality in general practice and is determined by presence of new onset confusion, respiratory rate ≥30, systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg, and age ≥65 years old; one point is allotted for presence of each factor for total of four.

During the 2-year surveillance period, the annual incidence rate of CAP among adults 50 years or older requiring an emergency department visit was 20.1 cases (95% CI 17.6 to 22.7) per 10,000 adults (Table 2). The incidence overall increased with increasing age, rising from 15.1 cases per 10,000 adults in participants 50 to 59 years old to more than three times higher among those 80 years or older, 54.4 (95% CI 36.8 to-76.6) per 10,000 adults. *Streptococcus pneumoniae* was the pathogen detected with the highest incidence, 7.6 cases (95% CI 6.1 to 9.2) per 10,000 adults. ranging from 7.3 cases (95% CI 5.3 to 10.3) per 10,000 adults age 50 to 59 years to 13.5 cases (95% CI 6.3 to 29.8) per 10,000 adults 80 years or older.

Table 2. Estimated Annual Incidence Rates of Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020.*

Variable	Incidence of Community-acquired Pneumonia (95% CI)†
Year of study‡	
Year 1 and 2	20.1 (17.6-22.7)
Year 1	23.6 (19.8-27.9)
Year 2	16.7 (13.5-20.3)
Age group	
50-59 yr	15.1 (11.9-18.5)
60-69 yr	19.5 (15.7-23.6)
70-79 yr	26.6 (20.0-34.6)
≥80 y	54.4 (36.8-76.6)
Pathogen detected	
Streptococcus pneumoniae	7.6 (6.1-9.2)
Influenza	1.4 (0.8-2.3)
Haemophilus Influenzae	1.4 (0.8-2.3)
Mycobacterium tuberculosis	0.5 (0.3-1.2)
Staphylococcus aureus	0.4 (0.1-0.9)
Other	0.9 (0.4-1.6)

* Analyses were based on 54,758 person-years of observation.

† Number of cases per 10,000 adults per year (95% CI estimated with Poisson exact method).

‡ Annual incidence rates were calculated from Jan 3, 2018, to Jan 2, 2019, for year 1 and from Jan 3, 2019, to Jan 2, 2020, for year 2 and represent the 111 of 154 (72%) adults who had radiographic evidence of pneumonia and were enrolled during that time.

Blood for culturing was obtained from all 111 adults with radiographic evidence of pneumonia, a specimen for urinary antigen detection from 106 (96%), a sputum specimen from 87 (78%) (of whom 74 [67%] had a high-quality specimen), and nasopharyngeal swabs from 85 (77%). All specimens were obtained before the administration of antibiotic agents. A pathogen was detected in 62 patients (56% of the CAP cases): one or more bacteria were detected in 51 patients (46%), influenza virus in 5 (4%), both bacterial and

influenza virus in 3 (3%), and Mycobacteria in 3 (3%) (Figure 2). *S. pneumoniae* was detected in 38% (42/111) participants as determined by BinaxNOW®, UAD, or culture. *S. pneumoniae* was detected by culture alone in 11% (12/111), by UAD alone in 10% (11/111) patients, and by BinaxNOW® alone in 5% (6/111) cases. Another 12% (13/111) cases were detected by any combination of these three diagnostic methods (Figure 3).

A serotype of *S. pneumoniae* was identified via culture or UAD in 36 of 42 (86%) cases of pneumococcal CAP, while six cases diagnosed by BinaxNOW® alone could not be typed. The distribution of the 17 different serotypes detected is shown in Figure 4. The most commonly identified serotypes were 3, 9N, and 4. They comprised about one third of CAP caused by pneumococcus, and were found in 15 of 111 (13.5%) patients with all-cause CAP. The percentage of pneumococcal CAP caused by vaccine serotypes increased with the number of serotypes included in the formulation as follows: 23.8% (PCV10), 47.6% (PCV13), 59.5% (PCV20), and 71.4% (PPV23). Among patients with all-cause CAP, the potential coverage afforded by different pneumococcal vaccines was 9.0% (PCV10, not licensed for adults), 18.0% (PCV13), 22.5% (PCV20, licensed in the US only), and 27.0% (PPV23), as shown in Table 3.

Table 3. Coverage of Pneumococcal Vaccines Serotypes among Middle-aged and Older Adults with Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020.

	No. (%) of Subjects Positive for Serotype	
	All-cause CAP (n=111)	Pneumococcal CAP (n=42)
Serotypes covered by PCV10†	**10 (9.0)**	**10 (23.8)**
4	3 (2.7)	3 (7.1)
6B	2 (1.8)	2 (4.8)
9V	0 (0)	0 (0)
14	0 (0)	0 (0)
18C	0 (0)	0 (0)
19F	2 (1.8)	2 (4.8)
23F	2 (1.8)	2 (4.8)
1	0 (0)	0 (0)
5	1 (0.9)	1 (2.4)
7F	0 (0)	0 (0)
Any PCV10 serotypes (combined)	10 (9.0)	10 (23.8)
Serotypes covered by PCV13	**20 (18.0)**	**20 (47.6)**
Additional serotypes covered by PCV13		
3	7 (6.3)	7 (16.7)
6A	2 (1.8)	2 (4.8)
19A	1 (0.9)	1 (2.4)
Any additional PCV13 serotypes (combined)	10 (9.0)	10 (23.8)
Serotypes covered by PCV20§	**25 (22.5)**	**25 (59.5)**
Additional serotypes covered by PCV20		
8	2 (1.8)	2 (4.8)
10A	0 (0)	0 (0)
11A	2 (1.8)	2 (4.8)
12F	0 (0)	0 (0)
15B	1 (0.9)	1 (2.4)
22F	0 (0)	0 (0)
33F	0 (0)	0 (0)
Any additional PCV20 serotypes (combined)	5 (4.5)	5 (11.9)

Abbreviations: CAP, community-acquired pneumonia; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate; PPV23, 23-valent pneumococcal polysaccharide vaccine.

† -PCV10 is not licensed for adults.

§ PCV20 is licensed in the US only.

Table 3. Coverage of Pneumococcal Vaccines Serotypes among Middle-aged and Older Adults with Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020. (continuation)

	No. (%) of Subjects Positive for Serotype	
	All-cause CAP (n=111)	Pneumococcal CAP (n=42)
Serotypes covered by PPV23	**30 (27.0)**	**30 (71.4)**
Additional serotypes covered by PPV23		
2	0 (0)	0 (0)
9N	5 (4.5)	5 (11.9)
17F	2 (1.8)	2 (4.8)
20	0 (0)	0 (0)
Any additional PPV23 serotypes (combined)	7 (6.3)	7 (16.7)
Non-vaccine serotypes and untyped	**10 (9.0)**	**10 (23.8)**
6	1 (0.9)	1 (2.4)
13	1 (0.9)	1 (2.4)
15C	1 (0.9)	1 (2.4)
34	1 (0.9)	1 (2.4)
Untyped	6 (5.4)	6 (14.3)

Abbreviations: CAP, community-acquired pneumonia; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate; PPV23, 23-valent pneumococcal polysaccharide vaccine.
†-PCV10 is not licensed for adults.
§ PCV20 is licensed in the US only.

DISCUSSION

In this prospective study, we have assessed the population-based incidence and the etiology of CAP among adults 50 years or older requiring an emergency department visit in Brazil during a consecutive 24-month study period. The incidence of radiologically confirmed CAP varied from 23.6 to 16.7 per 10,000 person-years in the first and second year of study, respectively; though the rates of influenza reported in these two years were similar[31]. Age group-specific incidence rates increased with advancing age to 54.4 per

10,000 person-years in the 80 years or older age group. These estimates are similar to the annual incidences reported in the USA (20.6 and 29.2 per 10,000 person-years) by Jain et al.[8], and are lower than a previous report in three cities in South America that found CAP incidences in adults aged ≥18 years varying from 17.6 to 70.3 per 10,000 person-years; in particular, for adults older than 65 years, incidence ranged from 109.0 to 294.9 per 10,000 person-years[6]. The rates in our study are higher than those in a review of studies from several European countries where the incidence of CAP in adults ranged between 10.7 to 12.0 per 10,000 person-years and from 15.4 to 17.0 per 10,000 population. In the age group older than 65 years, CAP incidence in Spain ranged from 127 to 153 per 10,000 person-years[32]. With respect to hospitalization, in a retrospective, web-based database study in Brazil, the incidence per 10,000 of hospitalization due to all-cause pneumonia decreased from 45.1 in 2003 to 38.8 in 2007[5]. In another study, the incidence of hospitalized and outpatient pneumonia in Brazil was 61.1 and 70.6 per 10,000 inhabitants/year, respectively[33].

The wide variation in the incidence rates of CAP in previous reports may be explained by differences in study design, definition of CAP, enrollment criteria, study procedures, incidence estimations, and surveillance methods. In addition, differences in demographic characteristics and/or in the provision of and access to health care make it difficult to compare results across different studies. Variation in CAP incidence depending on age, lifestyle habits such as smoking and alcohol consumption, and chronic illnesses may also reflect true differences in these determinants between populations. Furthermore, some retrospective studies are limited to the identification of CAP cases through registries with general codes that often include unconfirmed cases, nosocomial pneumonias, readmissions, and hospitalizations due to other causes[34,35]. The CAP

incidence estimates reported here result from thorough ascertainment of cases during the active, prospective surveillance. Moreover, due to the exclusion of recently hospitalized patients and the increased specificity of radiographic confirmation in our case definition, it is unlikely that our rates are overestimated.

With respect to vaccination, there was a 31% coverage for influenza and a 3% coverage for pneumococcal vaccines (3%) in our study population, while universal pneumococcal vaccination in infants may reduce the incidence of pneumococcal diseases in adults through herd protection[36]. The impact of herd protection offered by vaccination in children varies in different populations depending on introduction of pneumococcal vaccination in national programs and its coverage.

A microbial etiology could be identified for 56% of the patients. Overall, our pathogen-detection yield is within the range (38 to 70%) of the yield in other etiologic studies of pneumonia in adults[8,37–39]. In a study combining a new diagnostic PCR platform with conventional methods in Sweden[37], respiratory viruses were identified in 29% of CAP patients, and identified in 34% of CAP in hospitalized adults in a 3-year prospective study in Norway[38]. The prompt collection of specimens for bacteria cultures might have improved the detection rates for these pathogens in our study, whereas the limited investigation of viruses likely led to missing diagnosis for these agents. Like other studies using broad diagnostic methods[8,37–39], several cases of CAP remained with no causative organism identified. Possible reasons for that include failure to obtain lower respiratory tract specimens, insensitive diagnostic tests for known pathogens, a lack of testing for virus other than influenza, and unidentified pathogens[16,40].

S. pneumoniae was the most detected pathogen (38%) in our study. Pneumococcus is a common cause of CAP in adults[10] and has been reported as a

leading cause of CAP, with 9 to 48% prevalence in other studies[41,42]. Serotype 3 was the predominant pneumococcus identified in our sample. This serotype remains a major cause of invasive pneumococcal disease in England and Wales[43], despite its inclusion in PCV13. Vaccine effectiveness has been reported as non-significant for this serotype, leading to it being recorded as a major vaccine evader[44].

The majority (52%) of pneumococcal infections in our study were detected by urinary antigen tests for pneumococcus alone (UAD and/or BinaxNOW®). These tests are more sensitive than blood culture and improve the detection of nonbacteremic pneumococcal pathogens[20,23,45]. Influenza virus was the second most common (7%) pathogen detected in our study. Noteworthy, just 31% of participants had received influenza vaccine during the past influenza season. This might have contributed to the observed frequency of this virus and emphasizes the need for improvements in influenza-vaccine uptake in our population.

About a quarter of cases of all-cause CAP were attributable to serotypes included in currently licensed pneumococcal vaccines; thus, these cases could have been potentially prevented by vaccination. Of note, the serotype-specific UAD assays utilized in this study were designed to only detect the 24 serotypes contained in licensed pneumococcal vaccines, which may have led to an underestimation of the proportion of CAP due to non-vaccine pneumococcal serotypes. Given the higher sensitivity of these assays for detecting pneumococcal serotypes compared to traditional culture methods[20,21,46], our study likely overestimates the proportion of pneumococcal disease due to vaccine serotypes.

Reports on the prevalence of pneumococcal serotypes often rely on studies using culture-based diagnostic methods that can only identify a reduced fraction of CAP with

bacteremia; thus, being limited to invasive pneumococcal disease. Along with conventional culture-based methods, this study is the first to utilize the proprietary serotype-specific urinary antigen detection assays (UAD-1 and UAD-2) to assess the distribution of vaccine pneumococcal serotypes associated with adult CAP in Brazil. These assays provided increased sensitivity over methods in previous studies, whilst ensuring a more thorough description of the prevalence of pneumococcal serotypes and better understanding of pneumococcal CAP epidemiology.

The study has some limitations. One is a potential under-identification of CAP events. It is possible that some patients with mild symptoms were missed because they were treated in outpatient clinics and did not seek an emergency department for evaluation. However, the incidence calculations were adjusted for the enrollment differences according to age. Another limitation concerns the design of the study as viral diagnosis only included detection of Influenza. Use of extensive viral testing could have afforded a better understanding of CAP epidemiology. Nevertheless, all patients had at least one specimen type available for bacterial detection, obtained before the administration of antibiotic agents. Lastly, one more limitation of this study is that, although our data from two large public hospital includes a diverse population, overall the study population includes only persons depending exclusively on health care from the public sector SUS and living in a single geographic area population. Thus, it may not be possible to extrapolate our findings to the entire Brazilian adult population, since the epidemiology of respiratory infections varies according to geographic region, timing, and other determinants.

The main strength of this study lies in its methodological design. It was an active, prospective, population-based study conducted over a period of 2 consecutive years. We

used outcome measures and definitions based on specified criteria, and the study procedures were standardized and completed in almost all subjects. In addition, all cases of CAP were radiographically confirmed and validated by clinical information. We also employed molecular based tests (UAD) to improve the detection of *S. pneumoniae* in non-bacteremic cases of CAP.

In conclusion, this study assessed the burden of CAP and provided reliable estimates for the incidence rates of CAP requiring an emergency department visit among adults in Brazil. Moreover, the serotype distribution of *S. pneumoniae* causing pneumonia allowed an estimate of the potential coverage afforded by different licensed pneumococcal vaccines, a crucial information for the overall impact of pneumococcal vaccination programs, as well as appropriate decision-making processes for informing current immunization policy. Continual surveillance is essential to monitor trends in incidence and serotype distribution, and to understand potential impact and value of high-valency pneumococcal conjugate vaccines. Pneumococcus and influenza were frequently detected, which probably reflect the lack of direct benefit of specific vaccination against these pathogens and suggest that improving the coverage and effectiveness of recommended influenza and pneumococcal vaccines could reduce the burden of pneumonia among adults.

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Contributors

FGD, MGB, SSM, JNR, JRS, RSA, RAP, RB, CAAN and EDM developed the study concept and design. SSM coordinated the study and gathered participants. FGD and EDM carried out the data analysis. FGD and MGB drafted the manuscript. All authors contributed to the interpretation of the results, provided comments and revisions. All authors read and approved the final manuscript. EDM is the guarantors of this work and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Competing Interests

Julia Regazzini Spinardi, Rodrigo Sini de Almeida, Kristen E. Allen and Ronika Alexander-Parrish are employed by Pfizer and have ownership interests in Pfizer. Edson Duarte Moreira Junior has served on advisory board member for Pfizer and has received grant support through his institution from Pfizer Inc. All other authors declare no conflict of interest.

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Data availability statement

Data are available on reasonable request. Ethical restrictions related to participant confidentiality prohibit the authors from making the dataset publicly available.

Patient and public involvement

No patient involved.

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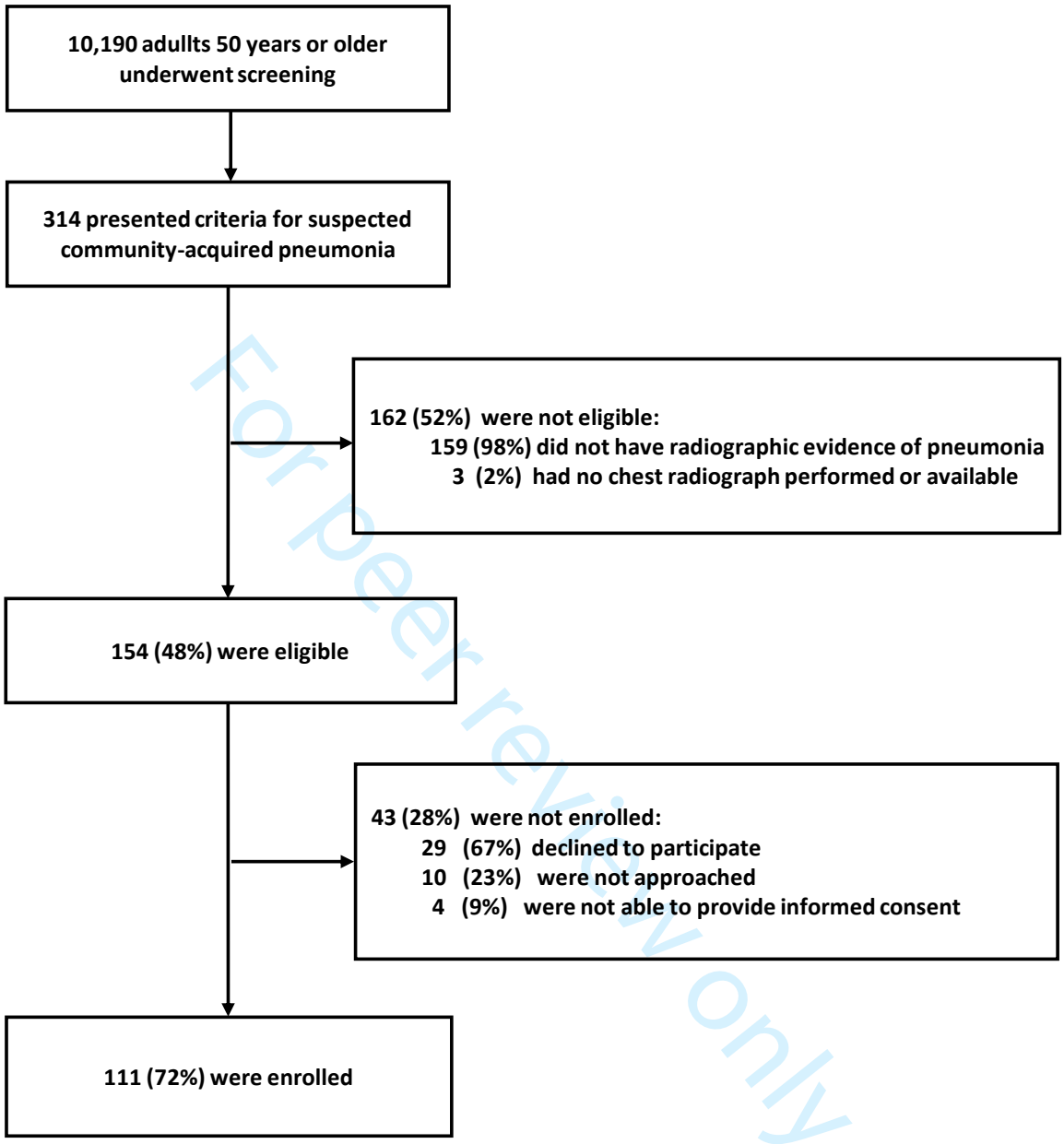
Figure 1. Screening, Eligibility, and Enrollment of Patients with Community-acquired Pneumonia, Salvador, Brazil, 2018-2020.

Figure 2. Pathogen Detection among Middle-aged and Older Adults with Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020.

Figure 3. Diagnostic method for S. pneumoniae identification among all study participants with radiographically-confirmed CAP (n=111). A total of 42 (38%) had S. pneumoniae detected by any method. UAD = proprietary serotype-specific urinary antigen detection assay. The UAD only detects 24 serotypes contained in licensed pneumococcal vaccines.

Figure 4. Serotype Distribution of Streptococcus pneumoniae isolates (n=42) among Middle-aged and Older Adults with Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020.



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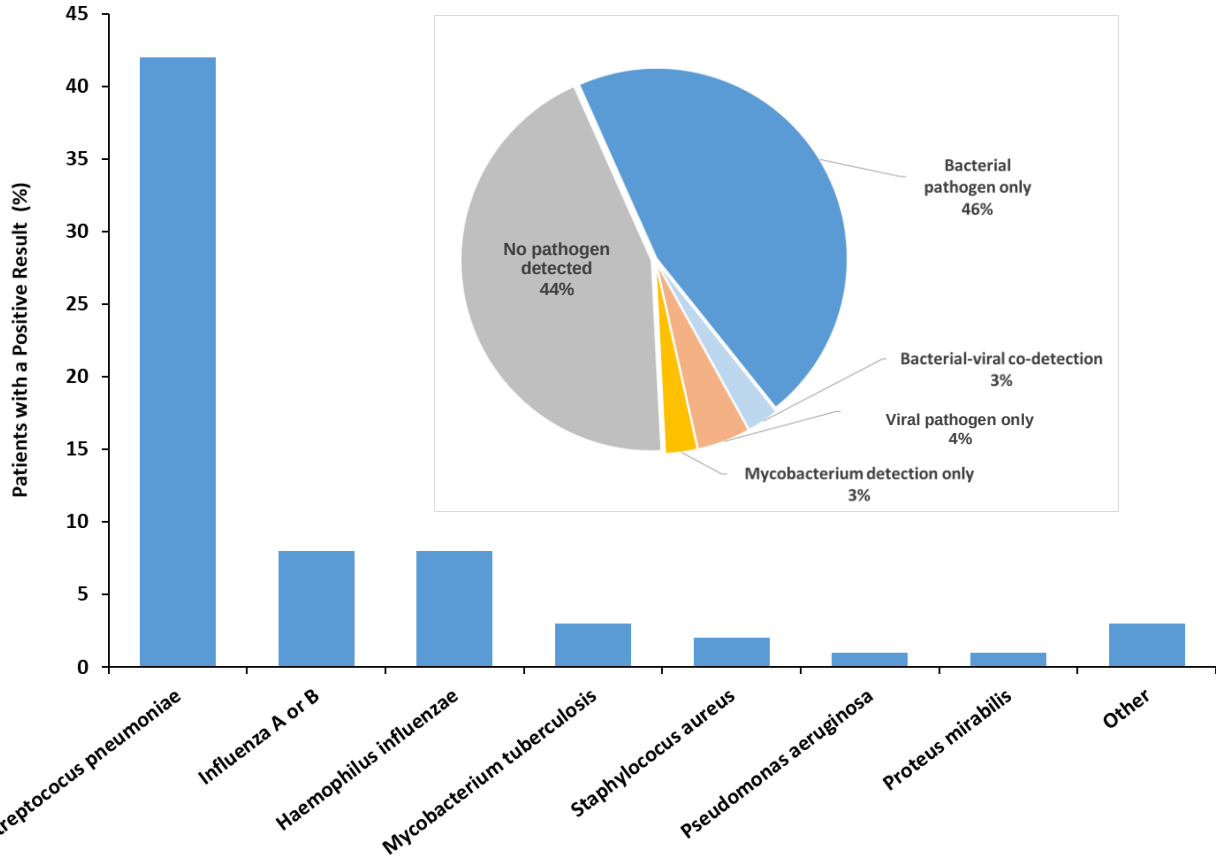

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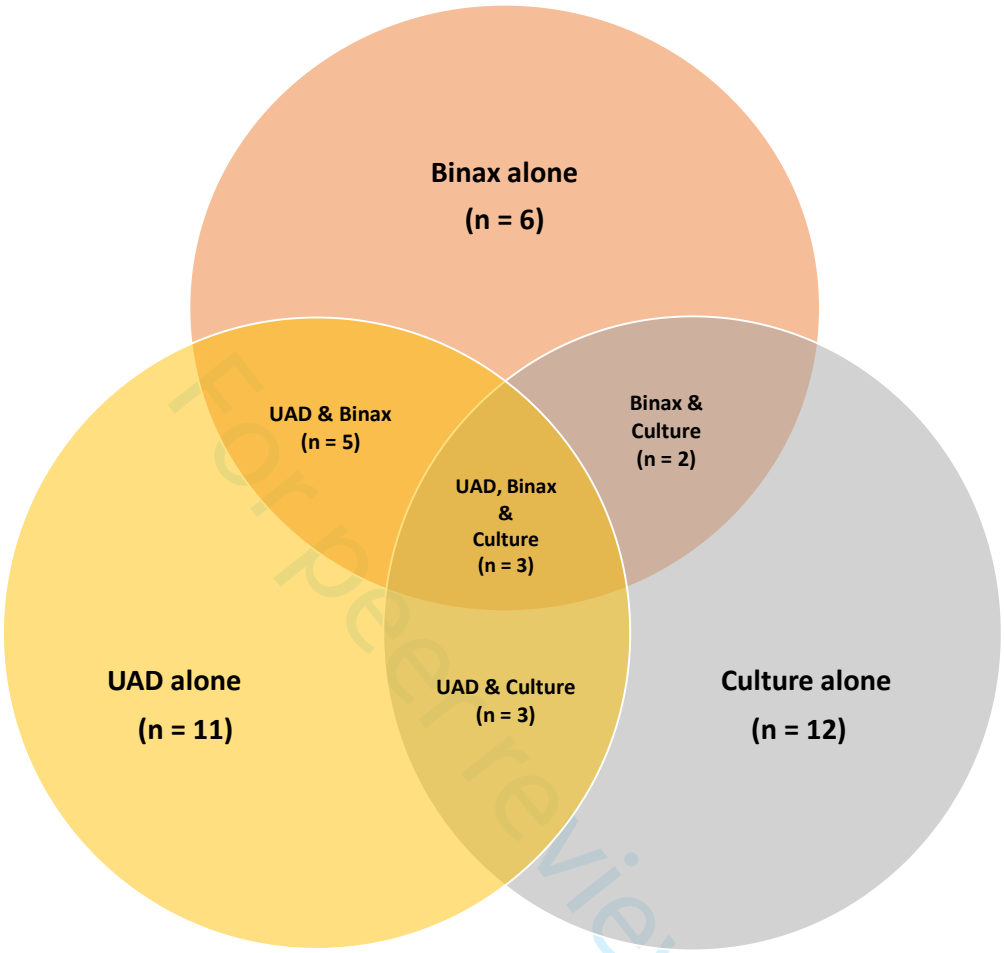

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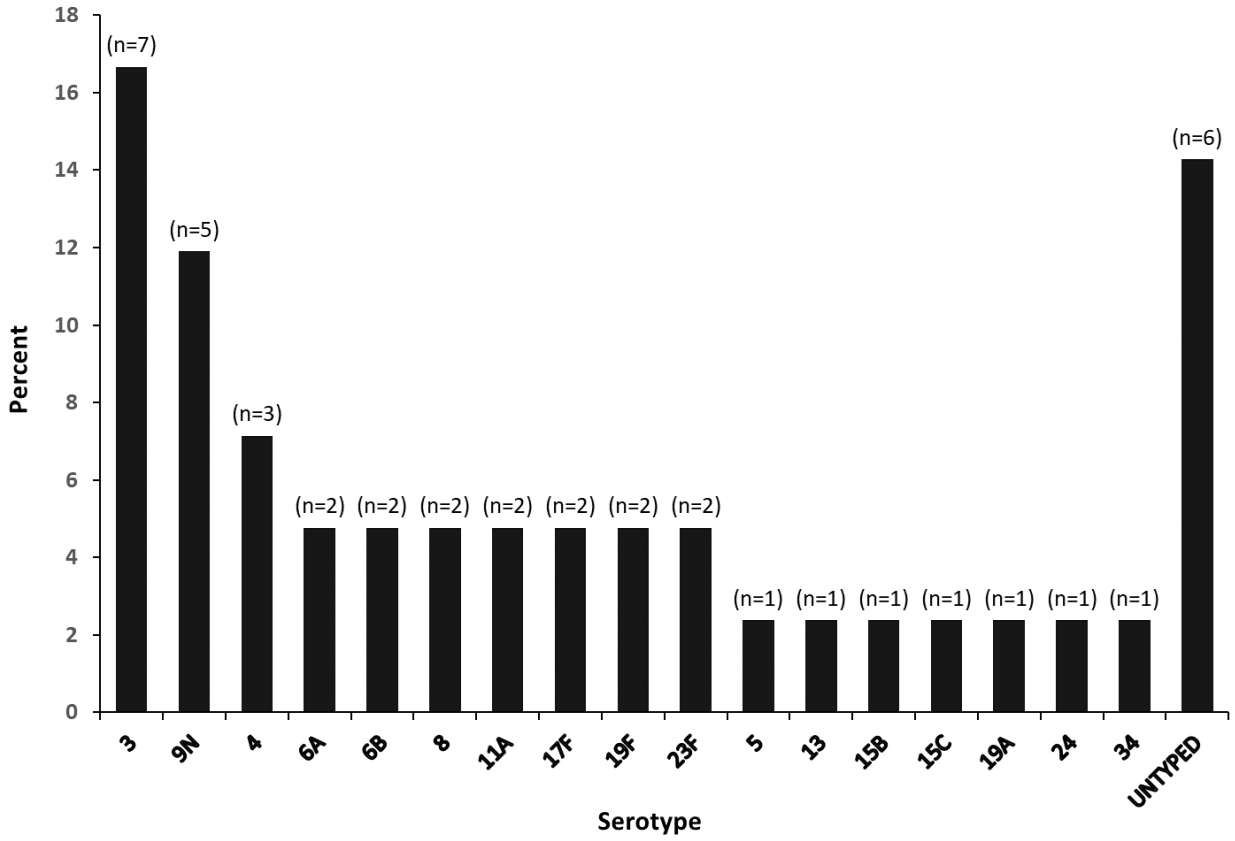

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Title: Incidence, etiology and serotype coverage for pneumococcal vaccines of community-acquired pneumonia in adults: A population-based prospective active surveillance study in Brazil.

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Abstract

Objectives To determine the incidence, etiology, and pneumococcal serotype distribution of community-acquired pneumonia (CAP) in Brazilian adults during a 2-year period.

Design Prospective population-based surveillance study.

Setting Patients from two emergency hospitals in Brazil were consecutively included in this study.

Participants A total of 111 adults aged 50 years and older with radiographically-confirmed CAP requiring an emergency department visit were prospectively enrolled between January 2018 and January 2020.

Main outcome measures Incidence rates of CAP were calculated according to age and pathogen. Pathogens were identified by conventional microbiological methods. Additionally, a novel, Luminex-based serotype specific urinary antigen detection assay was used to detect serotypes included in pneumococcal vaccines.

Results Mean age of participants was 64 years and 31% were aged ≥70 years. Etiology was established in 61 (57%) patients; among identified cases, the most common pathogens were *S. pneumoniae* (42/61, 69%) and influenza (4/61, 7%). Among serotypes identified from the 42 cases of pneumococcal CAP, estimated coverage ranged by pneumococcal vaccine formulations from 47.6% (13-valent), 59.5% (20-valent, licensed in the US only), and 71.4% (23-valent). In patients with CAP, 20-valent pneumococcal vaccine serotypes were identified 2.5 times more frequently than 10-valent pneumococcal vaccine serotypes (22.5% vs. 9.0%). The incidence rate for CAP in adults aged ≥50 years was 20.1 per 10,000 person-years. In general, the incidence of CAP increased

consistently with age, reaching 54.4 (95% CI 36.8 to-76.6) per 10,000 in adults 80 years or older.

Conclusions We observed a high burden of pneumococcal CAP among adults in Brazil. Despite the routine immunization of children and high-risk adults against pneumococcal disease in the Brazilian national vaccination program, a persistent burden of pneumococcal CAP caused by vaccine serotypes remains in this population.

Word Count: 281

Keywords: Community-acquired pneumonia; Incidence; Pneumococcal vaccines; *Streptococcus pneumoniae*; Serotype distribution.

Data availability statement

Data are available on reasonable request. Ethical restrictions related to participant confidentiality prohibit the authors from making the dataset publicly available.

Strengths and limitations of this study

- Prospective, population-based active surveillance study aimed to estimate incidence rate of community-acquired pneumonia (CAP) in adults, conducted over a period of 2 consecutive years.
- All cases of CAP were radiographically confirmed and validated by clinical information.
- Non-culured-based tests employed to improve the detection of *S. pneumoniae* in non-bacteremic cases of CAP.
- Some patients with mild symptoms may have been missed because they did not seek an emergency department for evaluation.
- A thorough virological research was not performed.

INTRODUCTION

Community-acquired pneumonia (CAP) is associated with substantial morbidity and mortality, accounting for more than 290 million cases and 4.9% of all deaths in the world[1]. Pneumonia kills more children worldwide than any other infectious disease, claiming the lives of over 800,000 children under five every year, or around 2,200 every day[2]. In Brazil, CAP is the third cause of mortality and the leading infectious cause of hospital admission and death among adults, with 598,668 CAP-related hospitalizations and 52,776 CAP-related deaths in 2017[3,4]. Therefore, CAP is a global public health problem, responsible for a considerable burden and the utilization of health care resources in all age groups.

The incidence of CAP varies by age, being higher in children and older adults[5]. It also varies by region – estimates of annual incidences from studies conducted in community-dwelling adults aged ≥18 years living in Latin America range from 1.8 to 7.0 per 1000 person-years[6], whereas it ranges from 2.5 to 6.5 in patients hospitalized with CAP per 1000 adults in the United States, 2.5 to 11.6 cases per thousand from selected countries in Europe[7–10]. Various pathogens can cause CAP, including both bacteria and viruses, but in as many as half of cases an etiological agent cannot be identified[8]. *Streptococcus pneumoniae* has been the most commonly identified bacteria implicated in CAP in adults[8,11]; however, its contribution in the etiology of CAP differs according to reports that may reflect differences in study design, laboratory isolation of *S. pneumoniae* and the difficulty with detection of *S. pneumoniae* in nonbacteremic CAP.

Limited data are available regarding the incidence of CAP in Brazil. Most estimates were made before the routine administration of the pneumococcal conjugate vaccine in children or in adults at increased risk for pneumococcal disease. Moreover, previous

studies included only children[12] or were mostly retrospective and have not used more sensitive antigen-based laboratory diagnostic tests[5,13]. Routine childhood immunization with 10-valent pneumococcal conjugated vaccine (PCV10) in Brazil begun in 2010, averaging a vaccination coverage of 85.5%[14]. The 13-valent pneumococcal conjugated vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPV23) have been available on the National Immunization Program since 2019, but only for children and adults at higher risk of developing a pneumococcal infection[15]. A national passive surveillance system in place, shows that disease by PCV10 serotypes are declining in children, but non-PCV10 serotypes, specially PCV13 exclusive serotypes represent an important proportion of the remaining disease burden in all age groups, including the elderly[16,17]. Since most of the pneumococcal disease burden are clinically presented as CAP, additional active surveillance studies are needed to determine the incidence and etiology of CAP in Brazilian adults.

Advanced age is associated not only with a higher incidence of CAP but also with more severe disease, greater need for hospitalization, and higher mortality[18]. Thus, we conducted an active, population-based surveillance study of CAP patients requiring an emergency department visit among adults 50 years and older in Brazil. We used conventional bacteriological testing and more sensitive non-culture-based methods to determine the incidence and microbiologic causes of CAP. In addition to information about disease burden, data on the serotype distribution of pneumococcal strains causing pneumonia in adults were presented.

METHODS

Study design and Setting

This was a prospective, multicenter, population-based, active surveillance study to identify CAP cases among adults requiring an emergency department visit. Radiographically-confirmed CAP was further assessed by conventional and non-culture-based identification methods. The study was conducted over a period of twenty-four consecutive months, from January 3, 2018 to January 2, 2020, at two Emergency Hospitals (Unidade de Pronto Atendimento [UPA]-Barris and UPA-Brotas), in the city of Salvador, Brazil. These study sites serve the public sector of the Brazilian health system, the "Sistema Único de Saúde" (SUS), and are considered public hospitals. The hospitals were selected based on an objective review of site capability to conduct the active surveillance, capacity to enroll patients, ability to collect and test specimens, and availability of denominator data for incidence calculations. Weekly study-site visits, enrollment reports, and data audits were conducted to ensure standardized procedures in both study sites.

Study population

We sought to enroll all eligible adults 50 years of age or older. Trained nurses screened adults for enrollment at least 18 hours per day, 7 days per week. Screening was conducted in all patients attending the emergency department who presented with evidence of an acute respiratory illness or infection with at least two of the following: fever (axillar temperature ≥38.0°C), hypothermia (axillar temperature <35.5°C, measured by a healthcare provider), chills or rigors, pleuritic chest pain, new or worsening cough, purulent sputum or changes in sputum characteristics, dyspnea (shortness of breath) or tachypnea (rapid breathing, >25 breaths per minute), auscultatory findings consistent with pneumonia, leukocytosis (white blood cell count >15X10^9 white blood cells/liter or >15% bands), serum procalcitonin above ≥0.5 mg/ml, or hypoxemia (O^2 saturation <90%

breathing room air or PaO^2 <60 mmHg), were considered a suspected case of pneumonia, and had a chest X-ray performed to further evaluate this diagnosis.

Only those with radiographically-confirmed CAP were considered as eligible for final inclusion in the study. The chest radiographs were interpreted by one board-certified chest radiologist (members of the research team, RB and CA) at each site, who were unaware of the clinical data. Radiographic evidence of pneumonia was defined as the presence of a radiographic infiltrate in the lung parenchyma (e.g. consolidation or other infiltrate, linear and patchy alveolar or interstitial densities), or pleural effusion[19].

Patients were excluded if they had a clinical and radiographic picture that could be explained by an illness other than CAP, resided outside the study catchment area, had been enrolled before in this study (in the previous month), or presented criteria for healthcare-associated pneumonia (HCAP). We defined HCAP according to the American Thoracic Society and Infectious Diseases Society of America guidelines, including: any patient who was hospitalized in an acute care hospital for 2 or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic[20].

Data collection

Patients and/or their caregivers were interviewed by trained staff, using a standardized questionnaire that included demographic data and information on lifestyle habits (smoking cigarettes, alcohol intake and substance abuse), and underlying medical conditions (asthma, chronic obstructive pulmonary disease, chronic heart disease, hypertension, human immunodeficiency virus infection, diabetes mellitus, chronic kidney disease, history of stroke, chronic hepatitis, and immunosuppression including cancer

and immunosuppressive medication). Questions also included information on clinical signs and symptoms, antimicrobial use prior to hospitalization, and previous immunizations (self-reported vaccination against pneumococcus or against influenza vaccine during the last influenza season).

Specimen collection and laboratory testing

Blood samples, urine samples, and nasopharyngeal swabs were obtained from the patients within 2 hours of attending the Emergency Department. In the case of patients with a productive cough, sputum was also obtained. Blood for culture was collected in BACTEC™ bottles, transported to a local certified laboratory HSR Lab (Hospital San Rafael Microbiology Laboratory, Salvador, Brazil). Urine samples for pneumococcal antigen detection were collected in a standard sterile specimen cup, refrigerated at 4°C for up to 4 hours after collection, aliquoted, stored at -70°C and shipped to Pfizer Vaccine Research and Development, (Pearl River, New York, USA,). *Streptococcus pneumoniae* was identified via BinaxNOW® (Abbott) performed following the manufacturer's recommendations[21]. We also tested the urine samples with Luminex technology-based multiplex (UAD) diagnostic assays, UAD-1, to detect the *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (covered by PCV13), and UAD-2, to detect 11 additional serotypes, including the remaining serotypes covered by the 20-valent pneumococcal conjugate vaccine (PCV20) (8, 10A, 11A, 12F, 15B, 22F and 33F), licensed in the US only, and the 23-valent pneumococcal polysaccharide vaccine (PPV23) (2, 9N, 17F,and 20). Both assays were performed at Pfizer as described elsewhere[22,23].

Nasopharyngeal specimens were collected using sterile swabs with flexible shafts, then they were promptly tested with a rapid diagnostic kit (QuickVue Influenza Test;

Quidel, San Diego, Calif.) using monoclonal antibodies specific for influenza A and B virus antigens. The test was performed at each participating site as instructed by the manufacturer[24]. When available, sputum was collected into sterile containers. Gram stain, Ziehl–Neelsen stain, and bacterial culture were performed at a local laboratory (HSRLab). Only bacterial culture from sputum of high quality (≤10 epithelial cells/low power field [lpf] and ≥25 white blood cells/lpf) were included[25]. *Mycobacterium tuberculosis* was considered a pathogen if detected in any acid-fast bacilli (AFB) sputum specimen.

Streptococcus pneumoniae serotyping

Capsular serogroups/serotypes were deduced using multiplex-PCR as described elsewhere[26]. All isolates identified as serogroup 6 in the multiplex-PCR were subjected to wciN6C–specific PCR, as previously described, for the identification of potential serotype 6C and 6D isolates[27]. Isolates with negative or equivocal multiplex PCR results were subjected to Quellung reaction testing for capsular type definition.

Statistical Analysis

Initially, a descriptive analysis of demographics and predisposing conditions for CAP was performed. Data were presented as frequencies and percentages for categorical variables and as median (IQR) for continuous variables. Incidence rates (expressed per 10,000 person-years) and 95% confidence intervals (CIs) were estimated with the Poisson exact method[28] overall, and for each of the age categories. First, we adjusted the number of CAP cases, according to age group, for the proportion of eligible adults enrolled at both study sites (72%), and for the proportion of Salvador's population depending exclusively on health care from the public sector SUS (70%)[29]. This adjusted number was then divided by the estimated population in the catchment areas of the study

sites for the corresponding year and age group. This denominator was obtained by multiplying available census data on Salvador's population[30] by the proportion of all admissions estimated by the catchment area (market share) of the study emergency hospitals. Based on data from SIH (Hospital Information System) and CNES (National Register of Heath Institutions from the public database DATASUS[31,32], the average annual market share of the emergency hospitals during the study period was 17.9% (11.1% at UPA-Barris and 6.8% at UPA-Brotas). Alternatively, we also estimated the denominator for the incidence rates by using census data for the corresponding year and age group, to sum the population living in the surrounding boroughs in the health district of each study emergency hospital, and the rates remained mostly unchanged (data not shown).

Coverage potentially afforded by different vaccines was calculated as the percentage of serotypes included in pneumococcal vaccines among the isolates obtained from CAP cases during the study period. All the statistical analyses were performed using the STATA statistical software (Version 12) (StataCorp., College Station, USA).

Ethics statements

This study was conducted in accordance with applicable laws and regulations including, but not limited to, the International Conference on Harmonization Guideline for Good Clinical Practice and the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Santo Antônio Hospital (Approval #: CAAE56884916.9.0000.0047). All participants or their caregivers provided written informed consent prior to enrollment.

RESULTS

Overall, 10,190 adults 50 years or older were screened for pneumonia at the two study sites. Among 314 patients with a clinical presentation suggestive of CAP, 154 met eligibility criteria, including radiological findings, for CAP diagnosis and 111 (72%) of them were enrolled (Figure 1). Participants were significantly more likely to be 60 years of age or older (p=0.04) and more likely to be females (p=0.02) as compared to those who were eligible but not enrolled (data not shown).

The median age of patients with CAP was 64 years (interquartile range, 57 to 73), 51% had a multiracial background and 60% had Middle School education or less (Table 1). Self-rated overall health was fair or poor in 41%. At least one predisposing condition was present in 67% of participants with CAP, and two or more in 40%. Cough, fever, dyspnea, and pleuritic pain were the most common clinical findings. Nearly one-third of study participants had been immunized against influenza during the last influenza season, and only 3% of patients 60 years or older received PPV23 on at least one occasion. Sixty percent had a clinical score (CRB-65) prediction for hospital referral or admission. Of 111 adults with CAP, 21 (19%) were managed as outpatients, 90 (81%) were hospitalized and none were admitted to the intensive care unit (ICU).

Table 1. Characteristics of Middle-aged and Older Adults with Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020.

Characteristics	n=111	(%)
Age, median [interquartile range]	64 [57 – 73]	
Age group		
50-59 yr	35	(31)
60-69 yr	42	(38)
70-79 yr	22	(20)
≥ 80 yr	12	(11)
Race or ethnic group*		
White	10	(9)
Mixed	57	(51)
Black	41	(37)
Native American	1	(1)
Asiatic	2	(2)
Marital status		
Married or living with partner	54	(49)
Single	33	(30)
Divorced	14	(12)
Widowed	10	(9)
Educational Attainment		
Elementary/Middle School	67	(60)
High School	39	(35)
College	5	(5)
Occupation		
Employed	36	(32)
Retired	55	(50)
Unemployed	6	(5)
Housework	12	(11)
Does not work	2	(2)
Body Mass Index (BMI)		
Below normal	2	(2)
Normal	44	(40)
Above normal	38	(34)
Obesity I	16	(14)
Obesity II (severe)	9	(8)
Obesity III (morbid)	2	(2)
Self-rated overall health		
Excellent	3	(3)
Very Good	3	(3)
Good	59	(53)

Table 1. Characteristics of Middle-aged and Older Adults with Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020. (continuation)

Characteristics	n=111	(%)
Self-rated overall health		
Fair	45	(40)
Poor	1	(1)
Any underlying condition†		
Hypertension	59	(53)
Diabetes Mellitus	25	(22)
Chronic heart disease	14	(13)
Chronic obstructive pulmonary disease (COPD)	9	(8)
Asthma	8	(7)
Depression	7	(6)
Stroke	6	(6)
Sickle Cell Disease	4	(4)
Smoking history		
Never smoked	60	(54)
Smoked, but quit	33	(30)
Current smoker	18	(16)
Signs and symptoms$^{\Phi}$		
Cough	106	(95)
Fever	84	(76)
Dyspnea	66	(60)
Pleuritic pain	49	(44)
Chills	25	(22)
O^2 saturation less than 95%	17	(15)
Abnormal lung auscultation	13	(12)
Status regarding receipt of vaccine or treatment‡		
Seasonal influenza vaccination (past 12-month)	34	(31)
Pneumococcal vaccination in adults ≥60 yrs of age (n=76)	2	(3)
Outpatient antibiotic use	14	(13)
CRB-65 score§		
Likely suitable for home treatment (0)	44	(40)
Consider hospital referral (1-2)	66	(59)
Urgent hospital admission (3-4)	1	(1)

* Race and ethnic group were self-reported.

†Any underlying medical condition included asthma, chronic obstructive pulmonary disease, chronic heart disease, hypertension, human immunodeficiency virus infection, diabetes mellitus, chronic kidney disease, history of stroke, chronic hepatitis, and immunosuppression including cancer and immunosuppressive medication). The specific conditions that affected at least 4% of patients are listed here. The groups were not mutually exclusive.

ϕ A participant may report multiple signs and symptoms.

‡Data were based on self-report vaccine information. For influenza vaccine, the percentage of patients vaccinated was based on the season before admission. For pneumococcal vaccination, the percentage of patients vaccinated with pneumococcal polysaccharide vaccine was based on 76 of 111 adults (68%) who were 60 years of age or older. For both vaccines, patients were considered to be vaccinated if they had received the vaccine at least 2 weeks before admission. Outpatient antibiotics were defined as those received within 7 days before admission.

§CRB-65 is a clinical guidance score for predicting community-acquired pneumonia mortality in general practice and is determined by presence of new onset confusion, respiratory rate ≥30, systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg, and age ≥65 years old; one point is allotted for presence of each factor for total of four.

During the 2-year surveillance period, the annual incidence rate of CAP among adults 50 years or older requiring an emergency department visit was 20.1 cases (95% CI 17.6 to 22.7) per 10,000 adults (Table 2). The incidence overall increased with increasing age, rising from 15.1 cases per 10,000 adults in participants 50 to 59 years old to more than three times higher among those 80 years or older, 54.4 (95% CI 36.8 to-76.6) per 10,000 adults. *Streptococcus pneumoniae* was the pathogen detected with the highest incidence, 7.6 cases (95% CI 6.1 to 9.2) per 10,000 adults. ranging from 7.3 cases (95% CI 5.3 to 10.3) per 10,000 adults age 50 to 59 years to 13.5 cases (95% CI 6.3 to 29.8) per 10,000 adults 80 years or older.

Table 2. Estimated Annual Incidence Rates of Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020.*

Variable	Incidence of Community-acquired Pneumonia (95% CI)†
Year of study‡	
Year 1 and 2	20.1 (17.6-22.7)
Year 1	23.6 (19.8-27.9)
Year 2	16.7 (13.5-20.3)
Age group	
50-59 yr	15.1 (11.9-18.5)
60-69 yr	19.5 (15.7-23.6)
70-79 yr	26.6 (20.0-34.6)
≥80 y	54.4 (36.8-76.6)
Pathogen detected	
Streptococcus pneumoniae	7.6 (6.1-9.2)
Influenza	1.4 (0.8-2.3)
Haemophilus Influenzae	1.4 (0.8-2.3)
Mycobacterium tuberculosis	0.5 (0.3-1.2)
Staphylococcus aureus	0.4 (0.1-0.9)
Other	0.9 (0.4-1.6)

* Analyses were based on 54,758 person-years of observation.

† Number of cases per 10,000 adults per year (95% CI estimated with Poisson exact method).

‡ Annual incidence rates were calculated from Jan 3, 2018, to Jan 2, 2019, for year 1 and from Jan 3, 2019, to Jan 2, 2020, for year 2 and represent the 111 of 154 (72%) adults who had radiographic evidence of pneumonia and were enrolled during that time.

Blood for culturing was obtained from all 111 adults with radiographic evidence of pneumonia, a specimen for urinary antigen detection from 106 (96%), a sputum specimen from 87 (78%) (of whom 74 [67%] had a high-quality specimen), and nasopharyngeal swabs from 85 (77%). All specimens were obtained before the administration of antibiotic agents. A pathogen was detected in 62 patients (56% of the CAP cases): one or more bacteria were detected in 51 patients (46%), influenza virus in 5 (4%), both bacterial and

influenza virus in 3 (3%), and Mycobacteria in 3 (3%) (Figure 2). *S. pneumoniae* was detected in 38% (42/111) participants as determined by BinaxNOW®, UAD, or culture. *S. pneumoniae* was detected by culture alone in 11% (12/111), by UAD alone in 10% (11/111) patients, and by BinaxNOW® alone in 5% (6/111) cases. Another 12% (13/111) cases were detected by any combination of these three diagnostic methods (Figure 3).

A serotype of *S. pneumoniae* was identified via culture or UAD in 36 of 42 (86%) cases of pneumococcal CAP, while six cases diagnosed by BinaxNOW® alone could not be typed. The distribution of the 17 different serotypes detected is shown in Figure 4. The most commonly identified serotypes were 3, 9N, and 4. They comprised about one third of CAP caused by pneumococcus, and were found in 15 of 111 (13.5%) patients with all-cause CAP. The percentage of pneumococcal CAP caused by vaccine serotypes increased with the number of serotypes included in the formulation as follows: 23.8% (PCV10), 47.6% (PCV13), 59.5% (PCV20), and 71.4% (PPV23). Among patients with all-cause CAP, the potential coverage afforded by different pneumococcal vaccines was 9.0% (PCV10, not licensed for adults), 18.0% (PCV13), 22.5% (PCV20, licensed in the US only), and 27.0% (PPV23), as shown in Table 3.

Table 3. Coverage of Pneumococcal Vaccines Serotypes among Middle-aged and Older Adults with Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020.

	No. (%) of Subjects Positive for Serotype	
	All-cause CAP (n=111)	Pneumococcal CAP (n=42)
Serotypes covered by PCV10†	**10 (9.0)**	**10 (23.8)**
4	3 (2.7)	3 (7.1)
6B	2 (1.8)	2 (4.8)
9V	0 (0)	0 (0)
14	0 (0)	0 (0)
18C	0 (0)	0 (0)
19F	2 (1.8)	2 (4.8)
23F	2 (1.8)	2 (4.8)
1	0 (0)	0 (0)
5	1 (0.9)	1 (2.4)
7F	0 (0)	0 (0)
Any PCV10 serotypes (combined)	10 (9.0)	10 (23.8)
Serotypes covered by PCV13	**20 (18.0)**	**20 (47.6)**
Additional serotypes covered by PCV13		
3	7 (6.3)	7 (16.7)
6A	2 (1.8)	2 (4.8)
19A	1 (0.9)	1 (2.4)
Any additional PCV13 serotypes (combined)	10 (9.0)	10 (23.8)
Serotypes covered by PCV20§	**25 (22.5)**	**25 (59.5)**
Additional serotypes covered by PCV20		
8	2 (1.8)	2 (4.8)
10A	0 (0)	0 (0)
11A	2 (1.8)	2 (4.8)
12F	0 (0)	0 (0)
15B	1 (0.9)	1 (2.4)
22F	0 (0)	0 (0)
33F	0 (0)	0 (0)
Any additional PCV20 serotypes (combined)	5 (4.5)	5 (11.9)

Abbreviations: CAP, community-acquired pneumonia; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate; PPV23, 23-valent pneumococcal polysaccharide vaccine.

† -PCV10 is not licensed for adults.

§ PCV20 is licensed in the US only.

Table 3. Coverage of Pneumococcal Vaccines Serotypes among Middle-aged and Older Adults with Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020. (continuation)

	No. (%) of Subjects Positive for Serotype	
	All-cause CAP (n=111)	**Pneumococcal CAP (n=42)**
Serotypes covered by PPV23	**30 (27.0)**	**30 (71.4)**
Additional serotypes covered by PPV23		
2	0 (0)	0 (0)
9N	5 (4.5)	5 (11.9)
17F	2 (1.8)	2 (4.8)
20	0 (0)	0 (0)
Any additional PPV23 serotypes (combined)	7 (6.3)	7 (16.7)
Non-vaccine serotypes and untyped	**10 (9.0)**	**10 (23.8)**
6	1 (0.9)	1 (2.4)
13	1 (0.9)	1 (2.4)
15C	1 (0.9)	1 (2.4)
34	1 (0.9)	1 (2.4)
Untyped	6 (5.4)	6 (14.3)

Abbreviations: CAP, community-acquired pneumonia; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate; PPV23, 23-valent pneumococcal polysaccharide vaccine.
†-PCV10 is not licensed for adults.
§ PCV20 is licensed in the US only.

DISCUSSION

In this prospective study, we have assessed the population-based incidence and the etiology of CAP among adults 50 years or older requiring an emergency department visit in Brazil during a consecutive 24-month study period. The incidence of radiologically confirmed CAP varied from 23.6 to 16.7 per 10,000 person-years in the first and second year of study, respectively; though the rates of influenza reported in these two years were similar[33]. Age group-specific incidence rates increased with advancing age to 54.4 per

10,000 person-years in the 80 years or older age group. These estimates are similar to the annual incidences reported in the USA (20.6 and 29.2 per 10,000 person-years) by Jain et al.[8], and are lower than a previous report in three cities in South America that found CAP incidences in adults aged ≥18 years varying from 17.6 to 70.3 per 10,000 person-years; in particular, for adults older than 65 years, incidence ranged from 109.0 to 294.9 per 10,000 person-years[6]. The rates in our study are higher than those in a review of studies from several European countries where the incidence of CAP in adults ranged between 10.7 to 12.0 per 10,000 person-years and from 15.4 to 17.0 per 10,000 population. In the age group older than 65 years, CAP incidence in Spain ranged from 127 to 153 per 10,000 person-years[34]. With respect to hospitalization, in a retrospective, web-based database study in Brazil, the incidence per 10,000 of hospitalization due to all-cause pneumonia decreased from 45.1 in 2003 to 38.8 in 2007[5]. In another study, the incidence of hospitalized and outpatient pneumonia in Brazil was 61.1 and 70.6 per 10,000 inhabitants/year, respectively[35].

The wide variation in the incidence rates of CAP in previous reports may be explained by differences in study design, definition of CAP, enrollment criteria, study procedures, incidence estimations, and surveillance methods. In addition, differences in demographic characteristics and/or in the provision of and access to health care make it difficult to compare results across different studies. Variation in CAP incidence depending on age, lifestyle habits such as smoking and alcohol consumption, and chronic illnesses may also reflect true differences in these determinants between populations. Furthermore, some retrospective studies are limited to the identification of CAP cases through registries with general codes that often include unconfirmed cases, nosocomial pneumonias, readmissions, and hospitalizations due to other causes[36,37]. The CAP

incidence estimates reported here result from thorough ascertainment of cases during the active, prospective surveillance. Moreover, due to the exclusion of recently hospitalized patients and the increased specificity of radiographic confirmation in our case definition, it is unlikely that our rates are overestimated.

With respect to vaccination, there was a 31% coverage for influenza and a 3% coverage for pneumococcal vaccines (3%) in our study population, while universal pneumococcal vaccination in infants may reduce the incidence of pneumococcal diseases in adults through herd protection[38]. The impact of herd protection offered by vaccination in children varies in different populations depending on introduction of pneumococcal vaccination in national programs and its coverage.

A microbial etiology could be identified for 56% of the patients. Overall, our pathogen-detection yield is within the range (38 to 70%) of the yield in other etiologic studies of pneumonia in adults[8,39–41]. In a study combining a new diagnostic PCR platform with conventional methods in Sweden[39], respiratory viruses were identified in 29% of CAP patients, and identified in 34% of CAP in hospitalized adults in a 3-year prospective study in Norway[40]. The prompt collection of specimens for bacteria cultures might have improved the detection rates for these pathogens in our study, whereas the limited investigation of viruses likely led to missing diagnosis for these agents. Like other studies using broad diagnostic methods[8,39–41], several cases of CAP remained with no causative organism identified. Possible reasons for that include previous antibiotic use, failure to obtain lower respiratory tract specimens, insensitive diagnostic tests for known pathogens, a lack of testing for virus other than influenza, and unidentified pathogens[18,42].

S. pneumoniae was the most detected pathogen (38%) in our study. Pneumococcus is a common cause of CAP in adults[10] and has been reported as a leading cause of CAP, with 9 to 48% prevalence in other studies[43,44]. Serotype 3 was the predominant pneumococcus identified in our sample. This serotype remains a major cause of invasive pneumococcal disease in England and Wales[45], despite its inclusion in PCV13. Vaccine effectiveness has been reported as non-significant for this serotype, leading to it being recorded as a major vaccine evader[46].

The majority (52%) of pneumococcal infections in our study were detected by urinary antigen tests for pneumococcus alone (UAD and/or BinaxNOW®). These tests are more sensitive than blood culture and improve the detection of nonbacteremic pneumococcal pathogens[22,25,47]. Influenza virus was the second most common (7%) pathogen detected in our study. Noteworthy, just 31% of participants had received influenza vaccine during the past influenza season. This might have contributed to the observed frequency of this virus and emphasizes the need for improvements in influenza-vaccine uptake in our population.

About a quarter of cases of all-cause CAP were attributable to serotypes included in currently licensed pneumococcal vaccines; thus, these cases could have been potentially prevented by vaccination. Of note, the serotype-specific UAD assays utilized in this study were designed to only detect the 24 serotypes contained in licensed pneumococcal vaccines, which may have led to an underestimation of the proportion of CAP due to non-vaccine pneumococcal serotypes. Given the higher sensitivity of these assays for detecting pneumococcal serotypes compared to traditional culture methods[22,23,48], our study likely overestimates the proportion of pneumococcal disease due to vaccine serotypes.

Reports on the prevalence of pneumococcal serotypes often rely on studies using culture-based diagnostic methods that can only identify a reduced fraction of CAP with bacteremia; thus, being limited to invasive pneumococcal disease. Along with conventional culture-based methods, this study is the first to utilize the proprietary serotype-specific urinary antigen detection assays (UAD-1 and UAD-2) to assess the distribution of vaccine pneumococcal serotypes associated with adult CAP in Brazil. These assays provided increased sensitivity over methods in previous studies, whilst ensuring a more thorough description of the prevalence of pneumococcal serotypes and better understanding of pneumococcal CAP epidemiology.

The study has some limitations. One is a potential under-identification of CAP events. It is possible that some patients with mild symptoms were missed because they were treated in outpatient clinics and did not seek an emergency department for evaluation. In addition, some eligible patients declined to participate or were not able to consent. However, the incidence calculations were adjusted for the enrollment differences according to age. Another limitation concerns the design of the study as viral diagnosis only included detection of Influenza. Use of extensive viral testing could have afforded a better understanding of CAP epidemiology. Nevertheless, all patients had at least one specimen type available for bacterial detection, obtained before the administration of antibiotic agents. Lastly, one more limitation of this study is that, although our data from two large public hospital includes a diverse population, overall the study population includes only persons depending exclusively on health care from the public sector SUS and living in a single geographic area population. Thus, it may not be possible to extrapolate our findings to the entire Brazilian adult population, since the epidemiology of

respiratory infections varies according to geographic region, timing, and other determinants.

The main strength of this study lies in its methodological design. It was an active, prospective, population-based study conducted over a period of 2 consecutive years. We used outcome measures and definitions based on specified criteria, and the study procedures were standardized and completed in almost all subjects. In addition, all cases of CAP were radiographically confirmed and validated by clinical information. We also employed non-culture-based tests (UAD) to improve the detection of *S. pneumoniae* in non-bacteremic cases of CAP.

In conclusion, this study assessed the burden of CAP and provided reliable estimates for the incidence rates of CAP requiring an emergency department visit among adults in Brazil. Moreover, the serotype distribution of *S. pneumoniae* causing pneumonia allowed an estimate of the potential coverage afforded by different licensed pneumococcal vaccines, a crucial information for the overall impact of pneumococcal vaccination programs, as well as appropriate decision-making processes for informing current immunization policy. Continual surveillance is essential to monitor trends in incidence and serotype distribution, and to understand potential impact and value of high-valency pneumococcal conjugate vaccines. Pneumococcus and influenza were frequently detected, which probably reflect the lack of direct benefit of specific vaccination against these pathogens and suggest that improving the coverage and effectiveness of recommended influenza and pneumococcal vaccines could reduce the burden of pneumonia among adults.

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Contributors

FGD, MGB, SSM, JNR, JRS, RSA, RAP, RB, CAAN and EDM developed the study concept and design. SSM coordinated the study and gathered participants. FGD and EDM carried out the data analysis. FGD and MGB drafted the manuscript. All authors contributed to the interpretation of the results, provided comments and revisions. All authors read and approved the final manuscript. EDM is the guarantors of this work and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Competing Interests

Julia Regazzini Spinardi, Rodrigo Sini de Almeida, Kristen E. Allen and Ronika Alexander-Parrish are employed by Pfizer and have ownership interests in Pfizer. Edson Duarte Moreira Junior has served on advisory board member for Pfizer and has received grant support through his institution from Pfizer Inc. All other authors declare no conflict of interest.

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Data availability statement

Data are available on reasonable request. Ethical restrictions related to participant confidentiality prohibit the authors from making the dataset publicly available.

Patient and public involvement

No patient involved.

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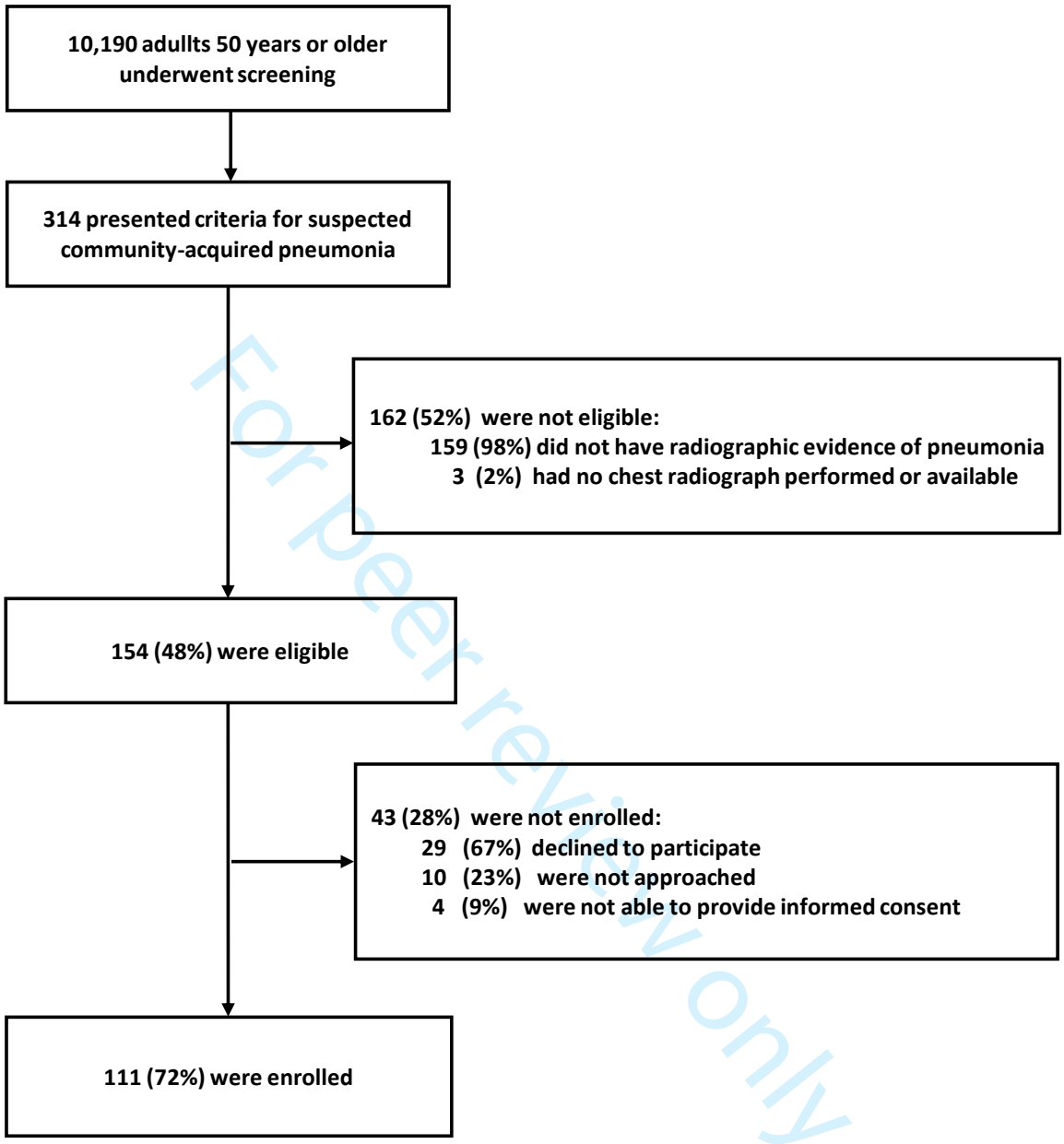
Figure 1. Screening, Eligibility, and Enrollment of Patients with Community-acquired Pneumonia, Salvador, Brazil, 2018-2020.

Figure 2. Pathogen Detection among Middle-aged and Older Adults with Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020.

Figure 3. Diagnostic method for S. pneumoniae identification among all study participants with radiographically-confirmed CAP (n=111). A total of 42 (38%) had S. pneumoniae detected by any method. UAD = proprietary serotype-specific urinary antigen detection assay. The UAD only detects 24 serotypes contained in licensed pneumococcal vaccines.

Figure 4. Serotype Distribution of Streptococcus pneumoniae isolates (n=42) among Middle-aged and Older Adults with Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020.



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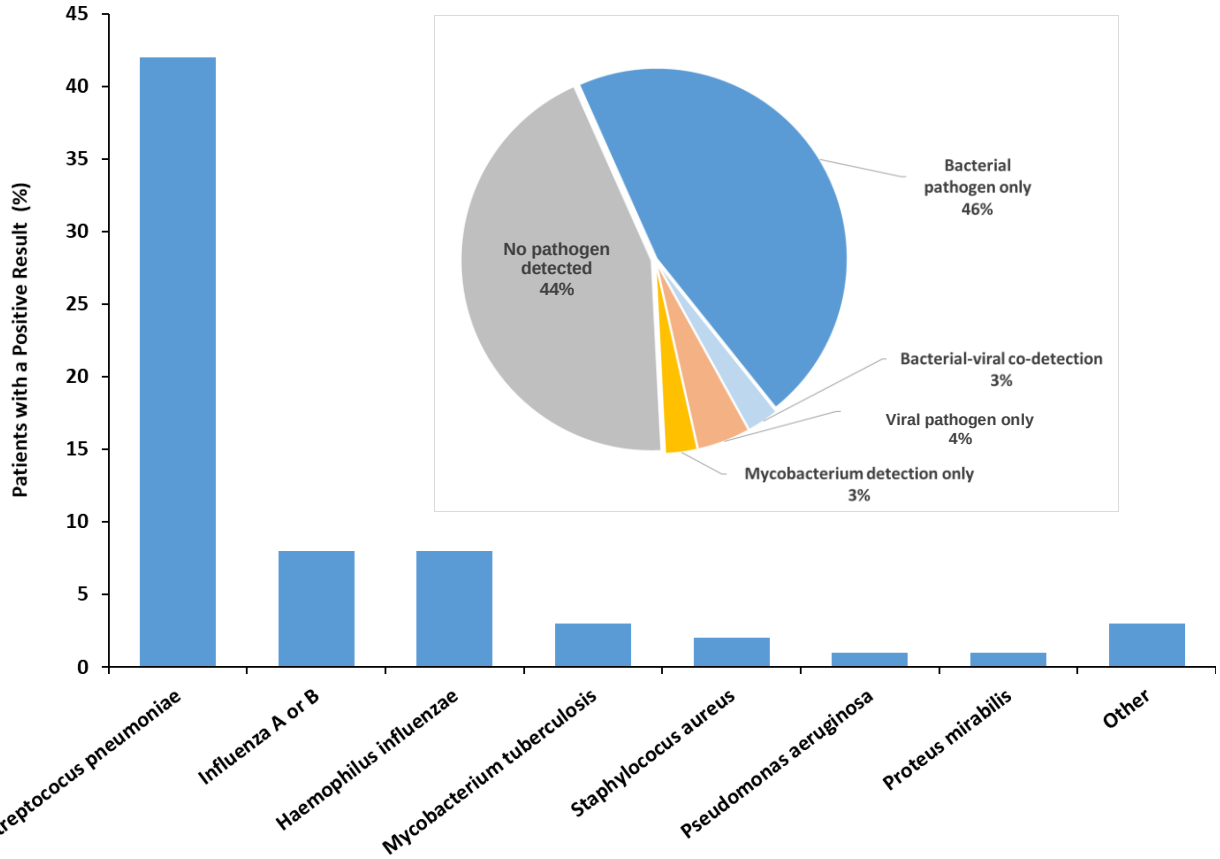

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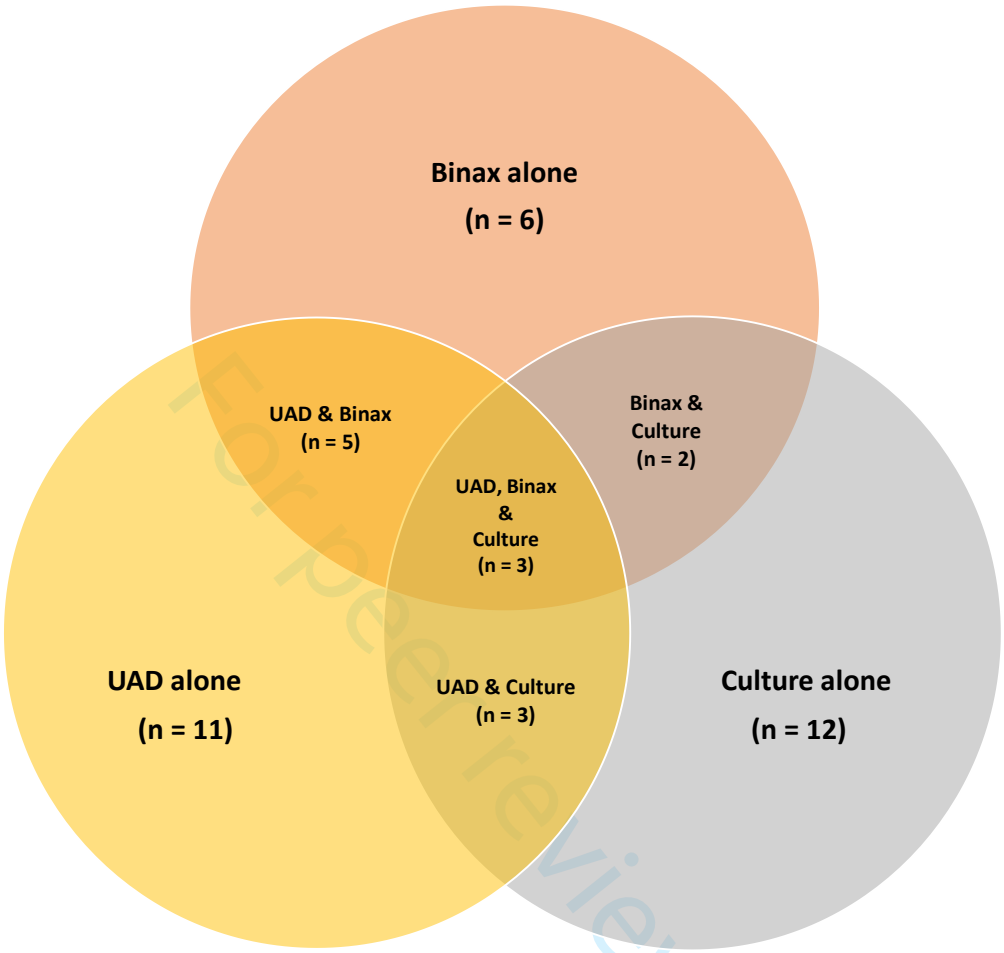

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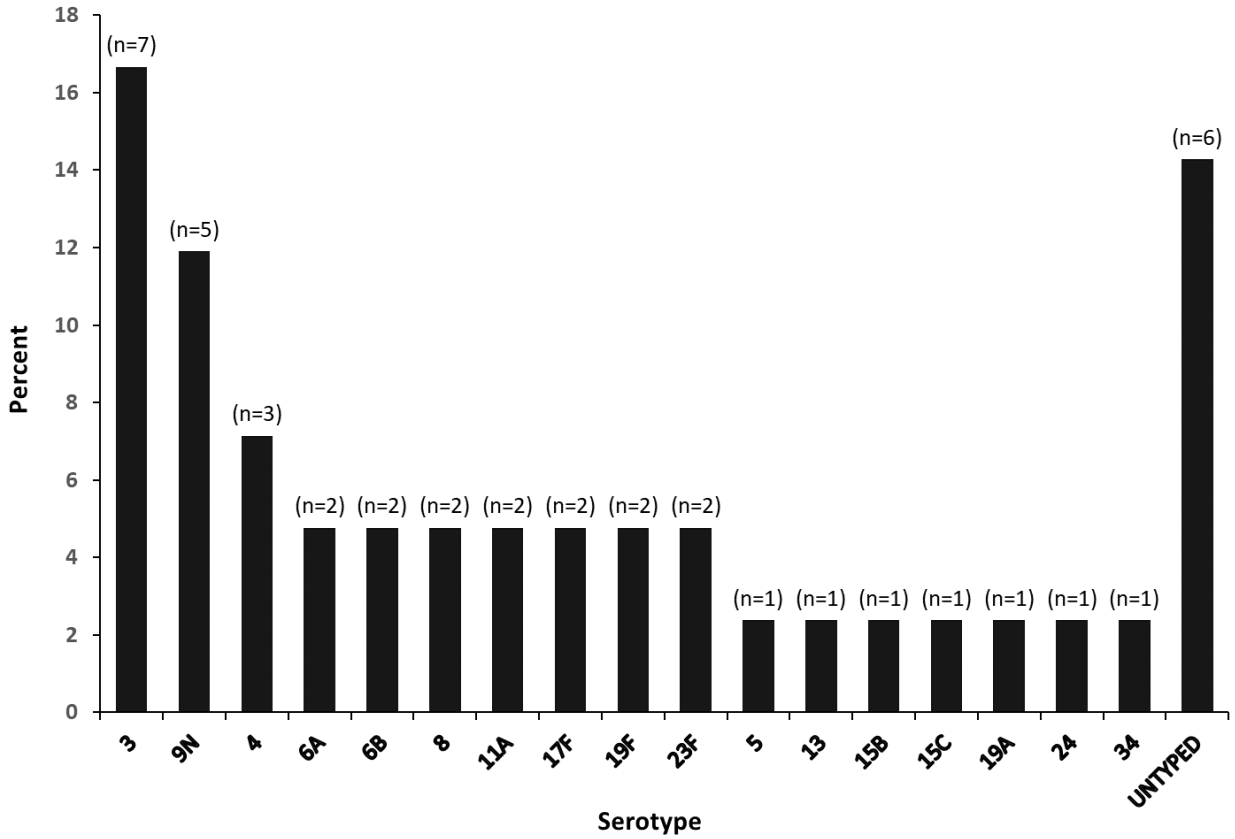

Figure 4. Serotype Distribution of *Streptococcus pneumoniae* isolates (n=42) among Middle-aged and Older Adults with Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract: **Title**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **(Page 3)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **(Page 6, Para 3)**
Objectives	3	State specific objectives, including any prespecified hypotheses **(Page 7, Para 2)**
Methods		
Study design	4	Present key elements of study design early in the paper **(Page 8, Para 1)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **(Page 8, 9 and 10)**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **(Page 8, Para 2)** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **(Page 9, Para 3) (Page 10 and 11)**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **(Page 10, Para 2)**
Bias	9	Describe any efforts to address potential sources of bias **(Page 9, Para 3)**
Study size	10	Explain how the study size was arrived at **(Page 11, Para 3)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **(Page 12, Para 1)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **(Page 11, Para 3)**
		(*b*) Describe any methods used to examine subgroups and interactions **(NA)**
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **(NA)** *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **(NA)**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **(Page 13, Para 1)**
		(b) Give reasons for non-participation at each stage **(Fig 1)**
		(c) Consider use of a flow diagram **(Fig 1)**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **(Page 13)**
		(b) Indicate number of participants with missing data for each variable of interest **(NA)**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **(NA)**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **(Page 16, Para 1)**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **(Page 16, Para 1)**
		(*b*) Report category boundaries when continuous variables were categorized **(Page 16, Para 1)**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **(NA)**
Discussion		
Key results	18	Summarise key results with reference to study objectives **(Page 20, Para 1)**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **(Page 24, Para 2)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **(Page 25, Para 2)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **(Page 25, Para 2)**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **(Page 26, Para 4)**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Incidence, etiology and serotype coverage for pneumococcal vaccines of community-acquired pneumonia in adults: A population-based prospective active surveillance study in Brazil.

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Keywords:	BACTERIOLOGY, EPIDEMIOLOGY, Epidemiology < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, PUBLIC HEALTH

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Title: Incidence, etiology and serotype coverage for pneumococcal vaccines of community-acquired pneumonia in adults: A population-based prospective active surveillance study in Brazil.

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Word Count: 3,946

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Dr. Duarte and Dr. Barberino contributed equally to this work.

Abstract

Objectives To determine the incidence, etiology, and pneumococcal serotype distribution of community-acquired pneumonia (CAP) in Brazilian adults during a 2-year period.

Design Prospective population-based surveillance study.

Setting Patients from two emergency hospitals in Brazil were consecutively included in this study.

Participants A total of 111 adults aged 50 years and older with radiographically-confirmed CAP requiring an emergency department visit were prospectively enrolled between January 2018 and January 2020.

Main outcome measures Incidence rates of CAP were calculated according to age and pathogen. Pathogens were identified by conventional microbiological methods. Additionally, a novel, Luminex-based serotype specific urinary antigen detection assay was used to detect serotypes included in pneumococcal vaccines.

Results Mean age of participants was 64 years and 31% were aged ≥70 years. Etiology was established in 61 (57%) patients; among identified cases, the most common pathogens were *S. pneumoniae* (42/61, 69%) and influenza (4/61, 7%). Among serotypes identified from the 42 cases of pneumococcal CAP, estimated coverage ranged by pneumococcal vaccine formulations from 47.6% (13-valent), 59.5% (20-valent, licensed in the US only), and 71.4% (23-valent). In patients with CAP, 20-valent pneumococcal vaccine serotypes were identified 2.5 times more frequently than 10-valent pneumococcal vaccine serotypes (22.5% vs. 9.0%). The incidence rate for CAP in adults aged ≥50 years was 20.1 per 10,000 person-years. In general, the incidence of CAP increased

consistently with age, reaching 54.4 (95% CI 36.8 to-76.6) per 10,000 in adults 80 years or older.

Conclusions We observed a high burden of pneumococcal CAP among adults in Brazil. Despite the routine immunization of children and high-risk adults against pneumococcal disease in the Brazilian national vaccination program, a persistent burden of pneumococcal CAP caused by vaccine serotypes remains in this population.

Word Count: 281

Keywords: Community-acquired pneumonia; Incidence; Pneumococcal vaccines; *Streptococcus pneumoniae*; Serotype distribution.

Data availability statement

Data are available on reasonable request. Ethical restrictions related to participant confidentiality prohibit the authors from making the dataset publicly available.

Strengths and limitations of this study

- Prospective, population-based active surveillance study aimed to estimate incidence rate of community-acquired pneumonia (CAP) in adults, conducted over a period of 2 consecutive years.
- All cases of CAP were radiographically confirmed and validated by clinical information.
- Non-culured-based tests employed to improve the detection of *S. pneumoniae* in non-bacteremic cases of CAP.
- Some patients with mild symptoms may have been missed because they did not seek an emergency department for evaluation.
- A thorough virological research was not performed.

INTRODUCTION

Community-acquired pneumonia (CAP) is associated with substantial morbidity and mortality, accounting for more than 290 million cases and 4.9% of all deaths in the world[1]. Pneumonia kills more children worldwide than any other infectious disease, claiming the lives of over 800,000 children under five every year, or around 2,200 every day[2]. In Brazil, CAP is the third cause of mortality and the leading infectious cause of hospital admission and death among adults, with 598,668 CAP-related hospitalizations and 52,776 CAP-related deaths in 2017[3,4]. Therefore, CAP is a global public health problem, responsible for a considerable burden and the utilization of health care resources in all age groups.

The incidence of CAP varies by age, being higher in children and older adults[5]. It also varies by region – estimates of annual incidences from studies conducted in community-dwelling adults aged ≥18 years living in Latin America range from 1.8 to 7.0 per 1000 person-years[6], whereas it ranges from 2.5 to 6.5 in patients hospitalized with CAP per 1000 adults in the United States, 2.5 to 11.6 cases per thousand from selected countries in Europe[7–10]. Various pathogens can cause CAP, including both bacteria and viruses, but in as many as half of cases an etiological agent cannot be identified[8]. *Streptococcus pneumoniae* has been the most commonly identified bacteria implicated in CAP in adults[8,11]; however, its contribution in the etiology of CAP differs according to reports that may reflect differences in study design, laboratory isolation of *S. pneumoniae* and the difficulty with detection of *S. pneumoniae* in nonbacteremic CAP.

Limited data are available regarding the incidence of CAP in Brazil. Most estimates were made before the routine administration of the pneumococcal conjugate vaccine in children or in adults at increased risk for pneumococcal disease. Moreover, previous

studies included only children[12] or were mostly retrospective and have not used more sensitive antigen-based laboratory diagnostic tests[5,13]. Routine childhood immunization with 10-valent pneumococcal conjugated vaccine (PCV10) in Brazil begun in 2010, averaging a vaccination coverage of 85.5%[14]. The 13-valent pneumococcal conjugated vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPV23) have been available on the National Immunization Program since 2019, but only for children and adults at higher risk of developing a pneumococcal infection[15]. A national passive surveillance system in place, shows that disease by PCV10 serotypes are declining in children, but non-PCV10 serotypes, specially PCV13 exclusive serotypes represent an important proportion of the remaining disease burden in all age groups, including the elderly[16,17]. Since most of the pneumococcal disease burden are clinically presented as CAP, additional active surveillance studies are needed to determine the incidence and etiology of CAP in Brazilian adults.

Advanced age is associated not only with a higher incidence of CAP but also with more severe disease, greater need for hospitalization, and higher mortality[18]. Thus, we conducted an active, population-based surveillance study of CAP patients requiring an emergency department visit among adults 50 years and older in Brazil. We used conventional bacteriological testing and more sensitive non-culture-based methods to determine the incidence and microbiologic causes of CAP. In addition to information about disease burden, data on the serotype distribution of pneumococcal strains causing pneumonia in adults were presented.

METHODS

Study design and Setting

This was a prospective, multicenter, population-based, active surveillance study to identify CAP cases among adults requiring an emergency department visit. Radiographically-confirmed CAP was further assessed by conventional and non-culture-based identification methods. The study was conducted over a period of twenty-four consecutive months, from January 3, 2018 to January 2, 2020, at two Emergency Hospitals (Unidade de Pronto Atendimento [UPA]-Barris and UPA-Brotas), in the city of Salvador, Brazil. These study sites serve the public sector of the Brazilian health system, the "Sistema Único de Saúde" (SUS), and are considered public hospitals. The hospitals were selected based on an objective review of site capability to conduct the active surveillance, capacity to enroll patients, ability to collect and test specimens, and availability of denominator data for incidence calculations. Weekly study-site visits, enrollment reports, and data audits were conducted to ensure standardized procedures in both study sites.

Study population

We sought to enroll all eligible adults 50 years of age or older. Trained nurses screened adults for enrollment at least 18 hours per day, 7 days per week. Screening was conducted in all patients attending the emergency department who presented with evidence of an acute respiratory illness or infection with at least two of the following: fever (axillar temperature ≥38.0°C), hypothermia (axillar temperature <35.5°C, measured by a healthcare provider), chills or rigors, pleuritic chest pain, new or worsening cough, purulent sputum or changes in sputum characteristics, dyspnea (shortness of breath) or tachypnea (rapid breathing, >25 breaths per minute), auscultatory findings consistent with pneumonia, leukocytosis (white blood cell count >15X10^9 white blood cells/liter or >15% bands), serum procalcitonin above ≥0.5 mg/ml, or hypoxemia (O^2 saturation <90%

breathing room air or PaO^2 <60 mmHg), were considered a suspected case of pneumonia, and had a chest X-ray performed to further evaluate this diagnosis.

Only those with radiographically-confirmed CAP were considered as eligible for final inclusion in the study. The chest radiographs were interpreted by one board-certified chest radiologist (members of the research team, RB and CA) at each site, who were unaware of the clinical data. Radiographic evidence of pneumonia was defined as the presence of a radiographic infiltrate in the lung parenchyma (e.g. consolidation or other infiltrate, linear and patchy alveolar or interstitial densities), or pleural effusion[19].

Patients were excluded if they had a clinical and radiographic picture that could be explained by an illness other than CAP, resided outside the study catchment area, had been enrolled before in this study (in the previous month), or presented criteria for healthcare-associated pneumonia (HCAP). We defined HCAP according to the American Thoracic Society and Infectious Diseases Society of America guidelines, including: any patient who was hospitalized in an acute care hospital for 2 or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic[20].

Data collection

Patients and/or their caregivers were interviewed by trained staff, using a standardized questionnaire that included demographic data and information on lifestyle habits (smoking cigarettes, alcohol intake and substance abuse), and underlying medical conditions (asthma, chronic obstructive pulmonary disease, chronic heart disease, hypertension, human immunodeficiency virus infection, diabetes mellitus, chronic kidney disease, history of stroke, chronic hepatitis, and immunosuppression including cancer

and immunosuppressive medication). Questions also included information on clinical signs and symptoms, antimicrobial use prior to hospitalization, and previous immunizations (self-reported vaccination against pneumococcus or against influenza vaccine during the last influenza season).

Specimen collection and laboratory testing

Blood samples, urine samples, and nasopharyngeal swabs were obtained from the patients within 2 hours of attending the Emergency Department. In the case of patients with a productive cough, sputum was also obtained. Blood for culture was collected in BACTEC™ bottles, transported to a local certified laboratory HSR Lab (Hospital San Rafael Microbiology Laboratory, Salvador, Brazil). Urine samples for pneumococcal antigen detection were collected in a standard sterile specimen cup, refrigerated at 4°C for up to 4 hours after collection, aliquoted, stored at -70°C and shipped to Pfizer Vaccine Research and Development, (Pearl River, New York, USA,). *Streptococcus pneumoniae* was identified via BinaxNOW® (Abbott) performed following the manufacturer's recommendations[21]. We also tested the urine samples with Luminex technology-based multiplex (UAD) diagnostic assays, UAD-1, to detect the *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (covered by PCV13), and UAD-2, to detect 11 additional serotypes, including the remaining serotypes covered by the 20-valent pneumococcal conjugate vaccine (PCV20) (8, 10A, 11A, 12F, 15B, 22F and 33F), licensed in the US only, and the 23-valent pneumococcal polysaccharide vaccine (PPV23) (2, 9N, 17F,and 20). Both assays were performed at Pfizer as described elsewhere[22,23].

Nasopharyngeal specimens were collected using sterile swabs with flexible shafts, then they were promptly tested with a rapid diagnostic kit (QuickVue Influenza Test;

Quidel, San Diego, Calif.) using monoclonal antibodies specific for influenza A and B virus antigens. The test was performed at each participating site as instructed by the manufacturer[24]. When available, sputum was collected into sterile containers. Gram stain, Ziehl–Neelsen stain, and bacterial culture were performed at a local laboratory (HSRLab). Only bacterial culture from sputum of high quality (≤10 epithelial cells/low power field [lpf] and ≥25 white blood cells/lpf) were included[25]. *Mycobacterium tuberculosis* was considered a pathogen if detected in any acid-fast bacilli (AFB) sputum specimen.

Streptococcus pneumoniae serotyping

Capsular serogroups/serotypes were deduced using multiplex-PCR as described elsewhere[26]. All isolates identified as serogroup 6 in the multiplex-PCR were subjected to wciN6C–specific PCR, as previously described, for the identification of potential serotype 6C and 6D isolates[27]. Isolates with negative or equivocal multiplex PCR results were subjected to Quellung reaction testing for capsular type definition.

Statistical Analysis

Initially, a descriptive analysis of demographics and predisposing conditions for CAP was performed. Data were presented as frequencies and percentages for categorical variables and as median (IQR) for continuous variables. Incidence rates (expressed per 10,000 person-years) and 95% confidence intervals (CIs) were estimated with the Poisson exact method[28] overall, and for each of the age categories. First, we adjusted the number of CAP cases, according to age group, for the proportion of eligible adults enrolled at both study sites (72%), and for the proportion of Salvador's population depending exclusively on health care from the public sector SUS (70%)[29]. This adjusted number was then divided by the estimated population in the catchment areas of the study

sites for the corresponding year and age group. This denominator was obtained by multiplying available census data on Salvador's population[30] by the proportion of all admissions estimated by the catchment area (market share) of the study emergency hospitals. Based on data from SIH (Hospital Information System) and CNES (National Register of Heath Institutions from the public database DATASUS[31,32], the average annual market share of the emergency hospitals during the study period was 17.9% (11.1% at UPA-Barris and 6.8% at UPA-Brotas). Alternatively, we also estimated the denominator for the incidence rates by using census data for the corresponding year and age group, to sum the population living in the surrounding boroughs in the health district of each study emergency hospital, and the rates remained mostly unchanged (data not shown).

Coverage potentially afforded by different vaccines was calculated as the percentage of serotypes included in pneumococcal vaccines among the isolates obtained from CAP cases during the study period. All the statistical analyses were performed using the STATA statistical software (Version 12) (StataCorp., College Station, USA).

Ethics statements

This study was conducted in accordance with applicable laws and regulations including, but not limited to, the International Conference on Harmonization Guideline for Good Clinical Practice and the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Santo Antônio Hospital (Approval #: CAAE56884916.9.0000.0047). All participants or their caregivers provided written informed consent prior to enrollment.

RESULTS

Overall, 10,190 adults 50 years or older were screened for pneumonia at the two study sites. Among 314 patients with a clinical presentation suggestive of CAP, 154 met eligibility criteria, including radiological findings, for CAP diagnosis and 111 (72%) of them were enrolled (Figure 1). Participants were significantly more likely to be 60 years of age or older (p=0.04) and more likely to be females (p=0.02) as compared to those who were eligible but not enrolled (data not shown).

The median age of patients with CAP was 64 years (interquartile range, 57 to 73), 51% had a multiracial background and 60% had Middle School education or less (Table 1). Self-rated overall health was fair or poor in 41%. At least one predisposing condition was present in 67% of participants with CAP, and two or more in 40%. Cough, fever, dyspnea, and pleuritic pain were the most common clinical findings. Nearly one-third of study participants had been immunized against influenza during the last influenza season, and only 3% of patients 60 years or older received PPV23 on at least one occasion. Sixty percent had a clinical score (CRB-65) prediction for hospital referral or admission. Of 111 adults with CAP, 21 (19%) were managed as outpatients, 90 (81%) were hospitalized and none were admitted to the intensive care unit (ICU).

Table 1. Characteristics of Middle-aged and Older Adults with Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020.

Characteristics	n=111	(%)
Age, median [interquartile range]	64 [57 – 73]	
Age group		
50-59 yr	35	(31)
60-69 yr	42	(38)
70-79 yr	22	(20)
≥ 80 yr	12	(11)
Race or ethnic group*		
White	10	(9)
Mixed	57	(51)
Black	41	(37)
Native American	1	(1)
Asiatic	2	(2)
Marital status		
Married or living with partner	54	(49)
Single	33	(30)
Divorced	14	(12)
Widowed	10	(9)
Educational Attainment		
Elementary/Middle School	67	(60)
High School	39	(35)
College	5	(5)
Occupation		
Employed	36	(32)
Retired	55	(50)
Unemployed	6	(5)
Housework	12	(11)
Does not work	2	(2)
Body Mass Index (BMI)		
Below normal	2	(2)
Normal	44	(40)
Above normal	38	(34)
Obesity I	16	(14)
Obesity II (severe)	9	(8)
Obesity III (morbid)	2	(2)
Self-rated overall health		
Excellent	3	(3)
Very Good	3	(3)
Good	59	(53)

Table 1. Characteristics of Middle-aged and Older Adults with Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020. (continuation)

Characteristics	n=111	(%)
Self-rated overall health		
Fair	45	(40)
Poor	1	(1)
Any underlying condition†		
Hypertension	59	(53)
Diabetes Mellitus	25	(22)
Chronic heart disease	14	(13)
Chronic obstructive pulmonary disease (COPD)	9	(8)
Asthma	8	(7)
Depression	7	(6)
Stroke	6	(6)
Sickle Cell Disease	4	(4)
Smoking history		
Never smoked	60	(54)
Smoked, but quit	33	(30)
Current smoker	18	(16)
Currrent alcohol use	33	(30)
Signs and symptoms$^{\phi}$		
Cough	106	(95)
Fever	84	(76)
Dyspnea	66	(60)
Pleuritic pain	49	(44)
Chills	25	(22)
O^2 saturation less than 95%	17	(15)
Abnormal lung auscultation	13	(12)
Status regarding receipt of vaccine or treatment‡		
Seasonal influenza vaccination (past 12-month)	34	(31)
Pneumococcal vaccination in adults ≥60 yrs of age (n=76)	2	(3)
Outpatient antibiotic use	14	(13)
CRB-65 score§		
Likely suitable for home treatment (0)	44	(40)
Consider hospital referral (1-2)	66	(59)
Urgent hospital admission (3-4)	1	(1)

* Race and ethnic group were self-reported.

†Any underlying medical condition included asthma, chronic obstructive pulmonary disease, chronic heart disease, hypertension, human immunodeficiency virus infection, diabetes mellitus, chronic kidney disease, history of stroke, chronic hepatitis, and immunosuppression including cancer and immunosuppressive medication). The specific conditions that affected at least 4% of patients are listed here. The groups were not mutually exclusive.

ϕ A participant may report multiple signs and symptoms.

‡Data were based on self-report vaccine information. For influenza vaccine, the percentage of patients vaccinated was based on the season before admission. For pneumococcal vaccination, the percentage of patients vaccinated with pneumococcal polysaccharide vaccine was based on 76 of 111 adults (68%) who were 60 years of age or older. For both vaccines, patients were considered to be vaccinated if they had received the vaccine at least 2 weeks before admission. Outpatient antibiotics were defined as those received within 7 days before admission.

§CRB-65 is a clinical guidance score for predicting community-acquired pneumonia mortality in general practice and is determined by presence of new onset confusion, respiratory rate ≥30, systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg, and age ≥65 years old; one point is allotted for presence of each factor for total of four.

During the 2-year surveillance period, the annual incidence rate of CAP among adults 50 years or older requiring an emergency department visit was 20.1 cases (95% CI 17.6 to 22.7) per 10,000 adults (Table 2). The incidence overall increased with increasing age, rising from 15.1 cases per 10,000 adults in participants 50 to 59 years old to more than three times higher among those 80 years or older, 54.4 (95% CI 36.8 to-76.6) per 10,000 adults. *Streptococcus pneumoniae* was the pathogen detected with the highest incidence, 7.6 cases (95% CI 6.1 to 9.2) per 10,000 adults. ranging from 7.3 cases (95% CI 5.3 to 10.3) per 10,000 adults age 50 to 59 years to 13.5 cases (95% CI 6.3 to 29.8) per 10,000 adults 80 years or older.

Table 2. Estimated Annual Incidence Rates of Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020.*

Variable	Incidence of Community-acquired Pneumonia (95% CI)†
Year of study‡	
Year 1 and 2	20.1 (17.6-22.7)
Year 1	23.6 (19.8-27.9)
Year 2	16.7 (13.5-20.3)
Age group	
50-59 yr	15.1 (11.9-18.5)
60-69 yr	19.5 (15.7-23.6)
70-79 yr	26.6 (20.0-34.6)
≥80 y	54.4 (36.8-76.6)
Pathogen detected	
Streptococcus pneumoniae	7.6 (6.1-9.2)
Influenza	1.4 (0.8-2.3)
Haemophilus Influenzae	1.4 (0.8-2.3)
Mycobacterium tuberculosis	0.5 (0.3-1.2)
Staphylococcus aureus	0.4 (0.1-0.9)
Other	0.9 (0.4-1.6)

* Analyses were based on 54,758 person-years of observation.

† Number of cases per 10,000 adults per year (95% CI estimated with Poisson exact method).

‡ Annual incidence rates were calculated from Jan 3, 2018, to Jan 2, 2019, for year 1 and from Jan 3, 2019, to Jan 2, 2020, for year 2 and represent the 111 of 154 (72%) adults who had radiographic evidence of pneumonia and were enrolled during that time.

Blood for culturing was obtained from all 111 adults with radiographic evidence of pneumonia, a specimen for urinary antigen detection from 106 (96%), a sputum specimen from 87 (78%) (of whom 74 [67%] had a high-quality specimen), and nasopharyngeal swabs from 85 (77%). All specimens were obtained before the administration of antibiotic agents. A pathogen was detected in 62 patients (56% of the CAP cases): one or more bacteria were detected in 51 patients (46%), influenza virus in 5 (4%), both bacterial and

influenza virus in 3 (3%), and Mycobacteria in 3 (3%) (Figure 2). *S. pneumoniae* was detected in 38% (42/111) participants as determined by BinaxNOW®, UAD, or culture. *S. pneumoniae* was detected by culture alone in 11% (12/111), by UAD alone in 10% (11/111) patients, and by BinaxNOW® alone in 5% (6/111) cases. Another 12% (13/111) cases were detected by any combination of these three diagnostic methods (Figure 3).

A serotype of *S. pneumoniae* was identified via culture or UAD in 36 of 42 (86%) cases of pneumococcal CAP, while six cases diagnosed by BinaxNOW® alone could not be typed. The distribution of the 17 different serotypes detected is shown in Figure 4. The most commonly identified serotypes were 3, 9N, and 4. They comprised about one third of CAP caused by pneumococcus, and were found in 15 of 111 (13.5%) patients with all-cause CAP. The percentage of pneumococcal CAP caused by vaccine serotypes increased with the number of serotypes included in the formulation as follows: 23.8% (PCV10), 47.6% (PCV13), 59.5% (PCV20), and 71.4% (PPV23). Among patients with all-cause CAP, the potential coverage afforded by different pneumococcal vaccines was 9.0% (PCV10, not licensed for adults), 18.0% (PCV13), 22.5% (PCV20, licensed in the US only), and 27.0% (PPV23), as shown in Table 3.

Table 3. Coverage of Pneumococcal Vaccines Serotypes among Middle-aged and Older Adults with Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020.

	No. (%) of Subjects Positive for Serotype	
	All-cause CAP (n=111)	Pneumococcal CAP (n=42)
Serotypes covered by PCV10†	**10 (9.0)**	**10 (23.8)**
4	3 (2.7)	3 (7.1)
6B	2 (1.8)	2 (4.8)
9V	0 (0)	0 (0)
14	0 (0)	0 (0)
18C	0 (0)	0 (0)
19F	2 (1.8)	2 (4.8)
23F	2 (1.8)	2 (4.8)
1	0 (0)	0 (0)
5	1 (0.9)	1 (2.4)
7F	0 (0)	0 (0)
Any PCV10 serotypes (combined)	10 (9.0)	10 (23.8)
Serotypes covered by PCV13	**20 (18.0)**	**20 (47.6)**
Additional serotypes covered by PCV13		
3	7 (6.3)	7 (16.7)
6A	2 (1.8)	2 (4.8)
19A	1 (0.9)	1 (2.4)
Any additional PCV13 serotypes (combined)	10 (9.0)	10 (23.8)
Serotypes covered by PCV20§	**25 (22.5)**	**25 (59.5)**
Additional serotypes covered by PCV20		
8	2 (1.8)	2 (4.8)
10A	0 (0)	0 (0)
11A	2 (1.8)	2 (4.8)
12F	0 (0)	0 (0)
15B	1 (0.9)	1 (2.4)
22F	0 (0)	0 (0)
33F	0 (0)	0 (0)
Any additional PCV20 serotypes (combined)	5 (4.5)	5 (11.9)

Abbreviations: CAP, community-acquired pneumonia; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate; PPV23, 23-valent pneumococcal polysaccharide vaccine.

† -PCV10 is not licensed for adults.

§ PCV20 is licensed in the US only.

Table 3. Coverage of Pneumococcal Vaccines Serotypes among Middle-aged and Older Adults with Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020. (continuation)

	No. (%) of Subjects Positive for Serotype	
	All-cause CAP (n=111)	**Pneumococcal CAP (n=42)**
Serotypes covered by PPV23	**30 (27.0)**	**30 (71.4)**
Additional serotypes covered by PPV23		
2	0 (0)	0 (0)
9N	5 (4.5)	5 (11.9)
17F	2 (1.8)	2 (4.8)
20	0 (0)	0 (0)
Any additional PPV23 serotypes (combined)	7 (6.3)	7 (16.7)
Non-vaccine serotypes and untyped	**10 (9.0)**	**10 (23.8)**
6	1 (0.9)	1 (2.4)
13	1 (0.9)	1 (2.4)
15C	1 (0.9)	1 (2.4)
34	1 (0.9)	1 (2.4)
Untyped	6 (5.4)	6 (14.3)

Abbreviations: CAP, community-acquired pneumonia; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate; PPV23, 23-valent pneumococcal polysaccharide vaccine.
†-PCV10 is not licensed for adults.
§ PCV20 is licensed in the US only.

DISCUSSION

In this prospective study, we have assessed the population-based incidence and the etiology of CAP among adults 50 years or older requiring an emergency department visit in Brazil during a consecutive 24-month study period. The incidence of radiologically confirmed CAP varied from 23.6 to 16.7 per 10,000 person-years in the first and second year of study, respectively; though the rates of influenza reported in these two years were similar[33]. Age group-specific incidence rates increased with advancing age to 54.4 per

10,000 person-years in the 80 years or older age group. These estimates are similar to the annual incidences reported in the USA (20.6 and 29.2 per 10,000 person-years) by Jain et al.[8], and are lower than a previous report in three cities in South America that found CAP incidences in adults aged ≥18 years varying from 17.6 to 70.3 per 10,000 person-years; in particular, for adults older than 65 years, incidence ranged from 109.0 to 294.9 per 10,000 person-years[6]. The rates in our study are higher than those in a review of studies from several European countries where the incidence of CAP in adults ranged between 10.7 to 12.0 per 10,000 person-years and from 15.4 to 17.0 per 10,000 population. In the age group older than 65 years, CAP incidence in Spain ranged from 127 to 153 per 10,000 person-years[34]. With respect to hospitalization, in a retrospective, web-based database study in Brazil, the incidence per 10,000 of hospitalization due to all-cause pneumonia decreased from 45.1 in 2003 to 38.8 in 2007[5]. In another study, the incidence of hospitalized and outpatient pneumonia in Brazil was 61.1 and 70.6 per 10,000 inhabitants/year, respectively[35].

The wide variation in the incidence rates of CAP in previous reports may be explained by differences in study design, definition of CAP, enrollment criteria, study procedures, incidence estimations, and surveillance methods. In addition, differences in demographic characteristics and/or in the provision of and access to health care make it difficult to compare results across different studies. Variation in CAP incidence depending on age, lifestyle habits such as smoking and alcohol consumption, and chronic illnesses may also reflect true differences in these determinants between populations. Of note, hypertension was the most frequent underlying condition reported in our survey, that hypertension has not been identified previously as a risk factor for CAP. Furthermore, some retrospective studies are limited to the identification of CAP cases through registries

with general codes that often include unconfirmed cases, nosocomial pneumonias, readmissions, and hospitalizations due to other causes[36,37]. The CAP incidence estimates reported here result from thorough ascertainment of cases during the active, prospective surveillance. Moreover, due to the exclusion of recently hospitalized patients and the increased specificity of radiographic confirmation in our case definition, it is unlikely that our rates are overestimated.

With respect to vaccination, there was a 31% coverage for influenza and a 3% coverage for pneumococcal vaccines (3%) in our study population, while universal pneumococcal vaccination in infants may reduce the incidence of pneumococcal diseases in adults through herd protection[38]. The impact of herd protection offered by vaccination in children varies in different populations depending on introduction of pneumococcal vaccination in national programs and its coverage.

A microbial etiology could be identified for 56% of the patients. Overall, our pathogen-detection yield is within the range (38 to 70%) of the yield in other etiologic studies of pneumonia in adults[8,39–41]. In a study combining a new diagnostic PCR platform with conventional methods in Sweden[39], respiratory viruses were identified in 29% of CAP patients, and identified in 34% of CAP in hospitalized adults in a 3-year prospective study in Norway[40]. The prompt collection of specimens for bacteria cultures might have improved the detection rates for these pathogens in our study, whereas the limited investigation of viruses likely led to missing diagnosis for these agents. Like other studies using broad diagnostic methods[8,39–41], several cases of CAP remained with no causative organism identified. Possible reasons for that include previous antibiotic use, failure to obtain lower respiratory tract specimens, insensitive diagnostic tests for known

pathogens, a lack of testing for virus other than influenza, and unidentified pathogens[18,42].

S. pneumoniae was the most detected pathogen (38%) in our study. Pneumococcus is a common cause of CAP in adults[10] and has been reported as a leading cause of CAP, with 9 to 48% prevalence in other studies[43,44]. Serotype 3 was the predominant pneumococcus identified in our sample. This serotype remains a major cause of invasive pneumococcal disease in England and Wales[45], despite its inclusion in PCV13. Vaccine effectiveness has been reported as non-significant for this serotype, leading to it being recorded as a major vaccine evader[46].

The majority (52%) of pneumococcal infections in our study were detected by urinary antigen tests for pneumococcus alone (UAD and/or BinaxNOW®). These tests are more sensitive than blood culture and improve the detection of nonbacteremic pneumococcal pathogens[22,25,47]. Influenza virus was the second most common (7%) pathogen detected in our study. Noteworthy, just 31% of participants had received influenza vaccine during the past influenza season. This might have contributed to the observed frequency of this virus and emphasizes the need for improvements in influenza-vaccine uptake in our population.

About a quarter of cases of all-cause CAP were attributable to serotypes included in currently licensed pneumococcal vaccines; thus, these cases could have been potentially prevented by vaccination. Of note, the serotype-specific UAD assays utilized in this study were designed to only detect the 24 serotypes contained in licensed pneumococcal vaccines, which may have led to an underestimation of the proportion of CAP due to non-vaccine pneumococcal serotypes. Given the higher sensitivity of these assays for detecting pneumococcal serotypes compared to traditional culture

methods[22,23,48], our study likely overestimates the proportion of pneumococcal disease due to vaccine serotypes.

Reports on the prevalence of pneumococcal serotypes often rely on studies using culture-based diagnostic methods that can only identify a reduced fraction of CAP with bacteremia; thus, being limited to invasive pneumococcal disease. Along with conventional culture-based methods, this study is the first to utilize the proprietary serotype-specific urinary antigen detection assays (UAD-1 and UAD-2) to assess the distribution of vaccine pneumococcal serotypes associated with adult CAP in Brazil. These assays provided increased sensitivity over methods in previous studies, whilst ensuring a more thorough description of the prevalence of pneumococcal serotypes and better understanding of pneumococcal CAP epidemiology.

The study has some limitations. One is a potential under-identification of CAP events. It is possible that some patients with mild symptoms were missed because they were treated in outpatient clinics and did not seek an emergency department for evaluation. In addition, some eligible patients declined to participate or were not able to consent. However, the incidence calculations were adjusted for the enrollment differences according to age. Another limitation concerns the design of the study as viral diagnosis only included detection of Influenza. Use of extensive viral testing could have afforded a better understanding of CAP epidemiology. Nevertheless, all patients had at least one specimen type available for bacterial detection, obtained before the administration of antibiotic agents. Lastly, one more limitation of this study is that, although our data from two large public hospital includes a diverse population, overall the study population includes only persons depending exclusively on health care from the public sector SUS and living in a single geographic area population. Thus, it may not be possible to

extrapolate our findings to the entire Brazilian adult population, since the epidemiology of respiratory infections varies according to geographic region, timing, and other determinants.

The main strength of this study lies in its methodological design. It was an active, prospective, population-based study conducted over a period of 2 consecutive years. We used outcome measures and definitions based on specified criteria, and the study procedures were standardized and completed in almost all subjects. In addition, all cases of CAP were radiographically confirmed and validated by clinical information. We also employed non-culture-based tests (UAD) to improve the detection of *S. pneumoniae* in non-bacteremic cases of CAP.

In conclusion, this study assessed the burden of CAP and provided reliable estimates for the incidence rates of CAP requiring an emergency department visit among adults in Brazil. Moreover, the serotype distribution of *S. pneumoniae* causing pneumonia allowed an estimate of the potential coverage afforded by different licensed pneumococcal vaccines, a crucial information for the overall impact of pneumococcal vaccination programs, as well as appropriate decision-making processes for informing current immunization policy. Continual surveillance is essential to monitor trends in incidence and serotype distribution, and to understand potential impact and value of high-valency pneumococcal conjugate vaccines. Pneumococcus and influenza were frequently detected, which probably reflect the lack of direct benefit of specific vaccination against these pathogens and suggest that improving the coverage and effectiveness of recommended influenza and pneumococcal vaccines could reduce the burden of pneumonia among adults.

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Contributors

FGD, MGB, SSM, JNR, JRS, RSA, RAP, RB, CAAN and EDM developed the study concept and design. SSM coordinated the study and gathered participants. FGD and EDM carried out the data analysis. FGD and MGB drafted the manuscript. All authors contributed to the interpretation of the results, provided comments and revisions. All authors read and approved the final manuscript. EDM is the guarantors of this work and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Competing Interests

Julia Regazzini Spinardi, Rodrigo Sini de Almeida, Kristen E. Allen and Ronika Alexander-Parrish are employed by Pfizer and have ownership interests in Pfizer. Edson Duarte Moreira Junior has served on advisory board member for Pfizer and has received grant support through his institution from Pfizer Inc. All other authors declare no conflict of interest.

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Obras Sociais Irmã Dulce and Pfizer. The funder had no role in study design, data collection and analysis.

Data availability statement

Data are available on reasonable request. Ethical restrictions related to participant confidentiality prohibit the authors from making the dataset publicly available.

Patient and public involvement

No patient involved.

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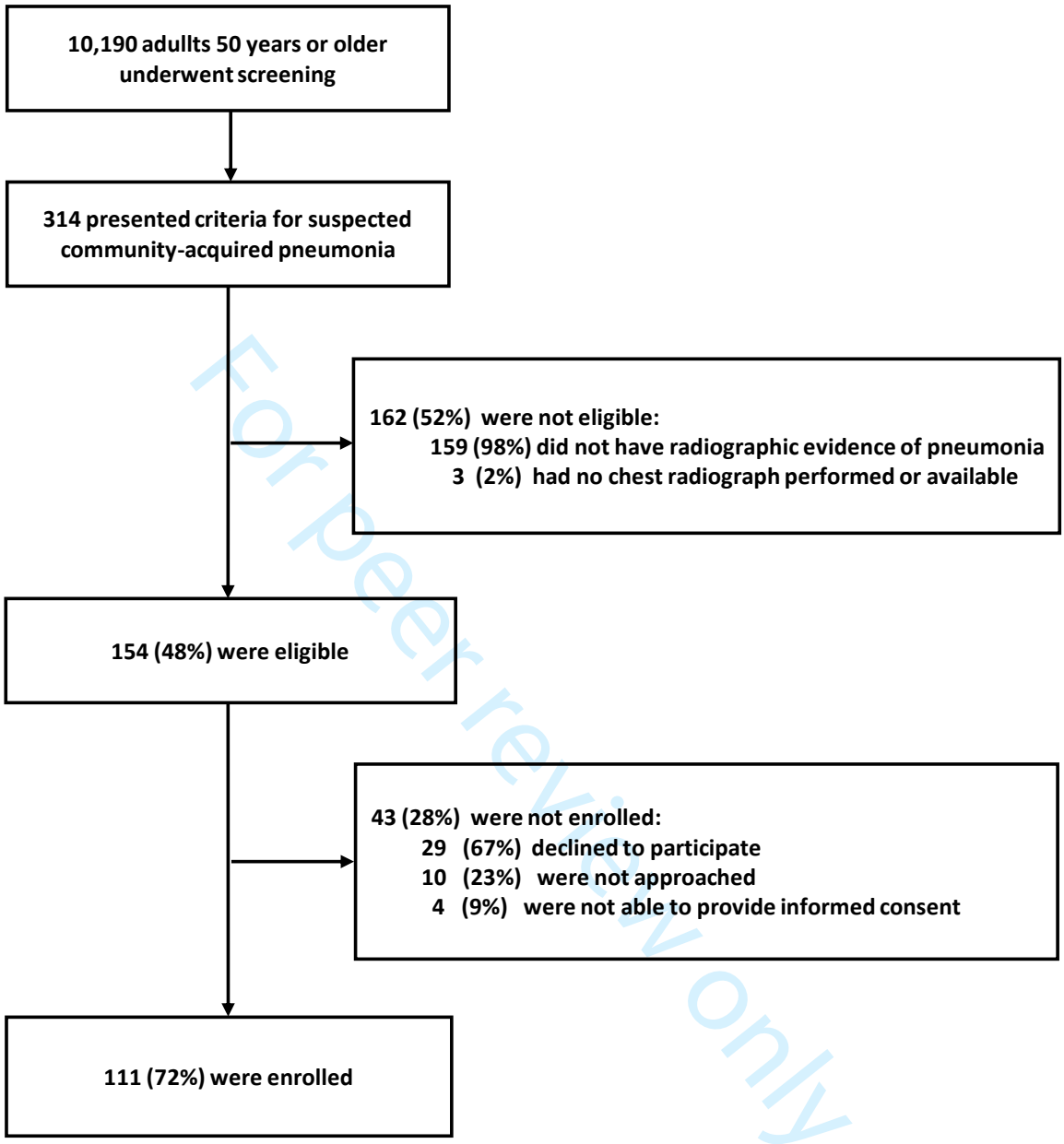
Figure 1. Screening, Eligibility, and Enrollment of Patients with Community-acquired Pneumonia, Salvador, Brazil, 2018-2020.

Figure 2. Pathogen Detection among Middle-aged and Older Adults with Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020.

Figure 3. Diagnostic method for S. pneumoniae identification among all study participants with radiographically-confirmed CAP (n=111). A total of 42 (38%) had S. pneumoniae detected by any method. UAD = proprietary serotype-specific urinary antigen detection assay. The UAD only detects 24 serotypes contained in licensed pneumococcal vaccines.

Figure 4. Serotype Distribution of Streptococcus pneumoniae isolates (n=42) among Middle-aged and Older Adults with Community-Acquired Pneumonia, Salvador, Brazil, 2018-2020.



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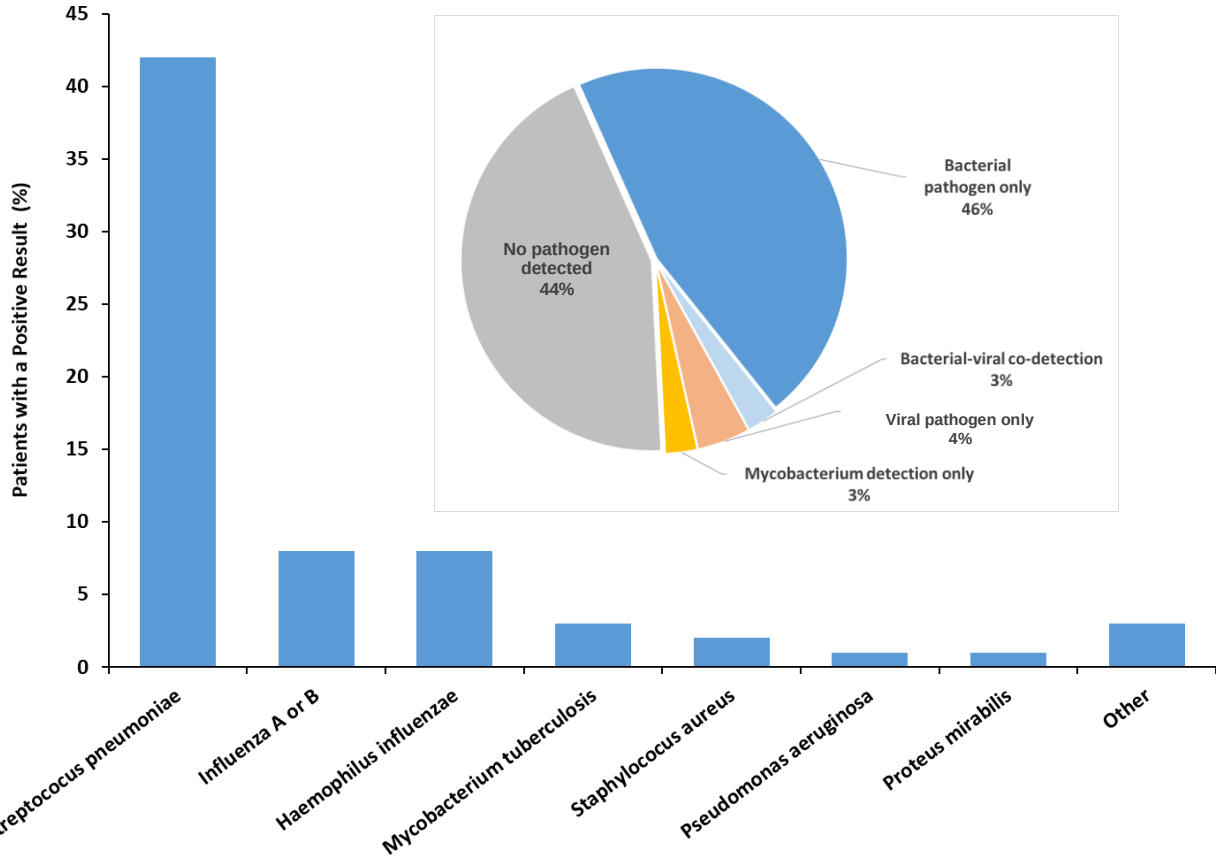

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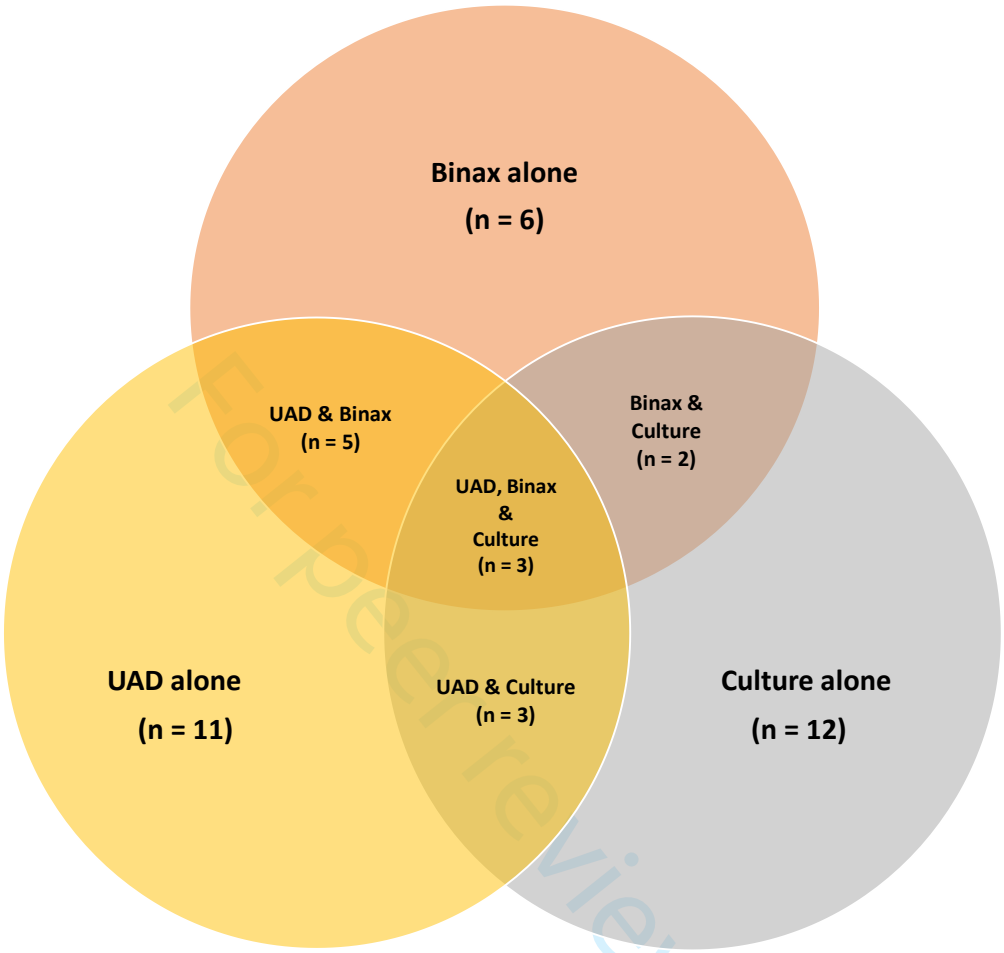

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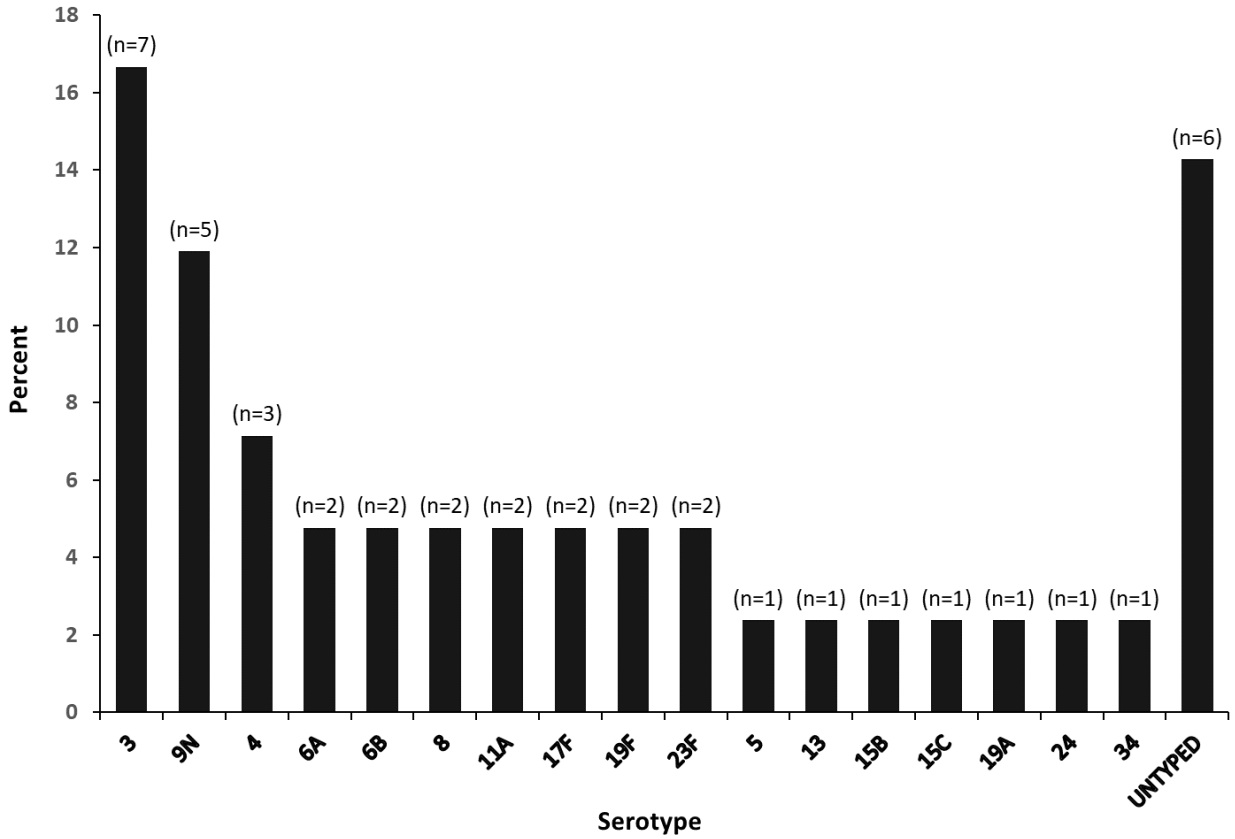

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract: **Title**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **(Page 3)**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **(Page 6, Para 3)**
Objectives	3	State specific objectives, including any prespecified hypotheses **(Page 7, Para 2)**
Methods		
Study design	4	Present key elements of study design early in the paper **(Page 8, Para 1)**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **(Page 8, 9 and 10)**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **(Page 8, Para 2)** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **(Page 9, Para 3) (Page 10 and 11)**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **(Page 10, Para 2)**
Bias	9	Describe any efforts to address potential sources of bias **(Page 9, Para 3)**
Study size	10	Explain how the study size was arrived at **(Page 11, Para 3)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **(Page 12, Para 1)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **(Page 11, Para 3)**
		(*b*) Describe any methods used to examine subgroups and interactions **(NA)**
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **(NA)** *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **(NA)**

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **(Page 13, Para 1)**
		(b) Give reasons for non-participation at each stage **(Fig 1)**
		(c) Consider use of a flow diagram **(Fig 1)**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **(Page 13)**
		(b) Indicate number of participants with missing data for each variable of interest **(NA)**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **(NA)**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **(Page 16, Para 1)**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **(Page 16, Para 1)**
		(*b*) Report category boundaries when continuous variables were categorized **(Page 16, Para 1)**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **(NA)**
Discussion		
Key results	18	Summarise key results with reference to study objectives **(Page 20, Para 1)**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **(Page 24, Para 2)**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **(Page 25, Para 2)**
Generalisability	21	Discuss the generalisability (external validity) of the study results **(Page 25, Para 2)**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **(Page 26, Para 4)**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.