Incidence, aetiology 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, aetiology 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. Aetiology was established in 61 (57%) patients; among identified cases, the most common pathogens were Streptococcus 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, licenced in the USA 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 immunisation of children and high-risk adults against pneumococcal disease in the Brazilian national vaccination programme, a persistent burden of pneumococcal CAP caused by vaccine serotypes remains in this population.

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 5 years of age every year, or around 2200 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 hospitalisations 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 utilisation of healthcare resources in all age groups.

The incidence of CAP varies by age, being higher in children and older adults.3 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, whereas it ranges from 2.5 to 6.5 in patients hospitalised with CAP per 1000 adults in the USA. 2.5–11.6 cases per 1000 from selected countries in Europe. Various pathogens can cause CAP, including both bacteria and viruses, but in as many as half of cases an aetiological agent cannot be identified. Streptococcus pneumoniae has been the most commonly identified bacteria implicated in CAP in adults; however, its contribution in the aetiology 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 non-bacteraemic 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 or were mostly retrospective and have not used more sensitive antigen-based laboratory diagnostic tests. Routine childhood immunisation with 10-valent pneumococcal conjugated vaccine (PCV10) in Brazil begun in 2010, averaging a vaccination coverage of 85.5%. 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. 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. Since most of the pneumococcal disease burden are clinically presented as CAP, additional active surveillance studies are needed to determine the incidence and aetiology 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 hospitalisation and higher mortality. Thus, we conducted an active, population-based surveillance study of patients with CAP 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 microbiological 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, multicentre, 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 24 consecutive months, from 3 January 2018 to 2 January 2020, at twoemergency 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 enrol patients, ability to collect and test specimens and availability of denominator data for incidence calculations. Weekly study-site visits, enrolment reports and data audits were conducted to ensure standardised procedures in both study sites.

Study population
We sought to enrol all eligible adults 50 years of age or older. Trained nurses screened adults for enrolment 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 (axillary temperature ≥38.0°C), hypothermia (axillary temperature <35.5°C, measured by a healthcare provider), chills or rigours, pleuritic chest pain, new or worsening cough, purulent sputum or changes in sputum characteristics, dyspnoea (shortness of breath) or tachypnoea (rapid breathing, >25 breaths per min), auscultatory findings consistent with pneumonia, leucocytosis (white blood cell count >15×10⁹ white blood cells/litre or >15% bands), serum procalcitonin above ≥0.5 mg/mL or hypoxaemia (O₂ saturation <90% breathing room air or PaO₂ <60 mm Hg), 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 CAdAN) 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 (eg, consolidation or other infiltrate, linear and patchy alveolar or interstitial densities), or pleural effusion. 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 hospitalised 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 haemodialysis clinic.20

Data collection
Patients and/or their caregivers were interviewed by trained staff, using a standardised 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, HIV 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 hospitalisation and previous immunisations (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.). S. 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 USA only, and the 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, California) 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

Figure 1  Screening, eligibility and enrolment of patients with community-acquired pneumonia, Salvador, Brazil, 2018–2020.
Table 1  Characteristics of middle aged and older adults with community-acquired pneumonia, Salvador, Brazil, 2018–2020

| Characteristics                                      | n=111 (%) |
|------------------------------------------------------|-----------|
| Age, median (IQR)                                    | 64 (57 – 73) |
| Age group                                            |           |
| 50–59 years                                          | 35 (31)   |
| 60–69 years                                          | 42 (38)   |
| 70–79 years                                          | 22 (20)   |
| ≥80 years                                            | 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                                      |           |
| 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)   |
| Characteristics                                      | n=111 (%) |
| Self-rated overall health                            |           |
| Fair                                                 | 45 (40)   |
| Poor                                                 | 1 (1)     |
| Smoking history                                      |           |
| Never smoked                                         | 60 (54)   |
| Smoked, but quit                                     | 33 (30)   |
| Current smoker                                       | 18 (16)   |
| Current alcohol use                                  | 33 (30)   |
| Smoking history                                      |           |
| Cough                                                | 106 (95)  |
| Fever                                                | 84 (76)   |
| Dyspnoea                                             | 66 (60)   |
| Pleuritic pain                                       | 49 (44)   |
| Chills                                               | 25 (22)   |
| O₂ saturation less than 95%                          | 17 (15)   |
| Abnormal lung auscultulation                          | 13 (12)   |
| Status regarding receipt of vaccine or treatment§    |           |
| Seasonal influenza vaccination (past 12 month)        | 34 (31)   |
| Pneumococcal vaccination in adults ≥60 years of age   | 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, COPD, chronic heart disease, hypertension, HIV 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.
‡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 mm Hg or diastolic blood pressure <60 mm Hg and age ≥65 years old; one point is allotted for presence of each factor for total of four.

local laboratory (HSR Lab). Only bacterial culture from sputum of high quality (≤10 epithelial cells/low power field (lpf) and ≥25 white blood cells/lpf) were included. Mycobacterium tuberculosis was considered a pathogen if detected in any acid-fast bacilli sputum specimen.
method28 overall, and for each of the age categories. First,
years) and 95% CIs were estimated with the Poisson exact
variables. Incidence rates (expressed per 10 000 person-
were presented as frequencies and percentages for cate-
Initially, a descriptive analysis of demographics and
Statistical analysis
were subjected to Quellung reaction testing for capsular
Capsular serogroups/serotypes were deduced using
multiplex-PCR as described elsewhere.26 All isolates iden-
tified 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 cate-
gorical variables and as median (IQR) for continuous
variables. Incidence rates (expressed per 10 000 person-
years) and 95% CIs were estimated with the Poisson exact
method28 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 Salvado-
or's population depending exclusively on healthcare
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 popula-
tion30 by the proportion of all admissions estimated by
the catchment area (market share) of the study emer-
gency hospitals. Based on data from SIH (Hospital Infor-
mation System) and CNES (National Register of Heath
Institutions from the public database DATASUS31 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 anal-
yses were performed using the Stata statistical software
(V.12) (StataCorp).

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.

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 women (p=0.02) as compared with those who were
eligible but not enrolled (data not shown).
The median age of patients with CAP was 64 years
(IQR, 57–73), 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 partici-
pants with CAP, and two or more in 40%. Cough, fever,
dyspnoea and pleuritic pain were the most common clin-
ical findings. Nearly one-third of study participants had

\[ S. pneumoniae \] serotyping
Capsular serogroups/serotypes were deduced using
multiplex-PCR as described elsewhere.26 All isolates iden-
tified 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.

\[ \text{incidence of community-acquired pneumonia (95% CI) } \]

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

*Number of cases per 10 000 adults per year (95% CI estimated with Poisson exact method).
†Annual incidence rates were calculated from 3 January 2018 to 2 January 2019 for year 1 and from 3 January 2019 to 2 January 2020 for year 2 and represent the 111 of 154 (72%) adults who had radiographic evidence of pneumonia and were enrolled during that time.
‡Analyses were based on 54 758 person-years of observation.

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incidence overall increased with increasing age, rising from 15.1 cases per 10 000 adults in participants 50–59 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. *S. 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.

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

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**Figure 2** Pathogen detection among middle aged and older adults with community-acquired pneumonia, Salvador, Brazil, 2018–2020.

**Figure 3** Diagnostic method for *Streptococcus pneumoniae* identification among all study participants with radiographically-confirmed community-acquired pneumonia (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 licenced pneumococcal vaccines.
afforded by different pneumococcal vaccines was 9.0% (PCV10, not licenced for adults), 18.0% (PCV13), 22.5% (PCV20, licenced in the USA only) and 27.0% (PPV23), as shown in table 3.

DISCUSSION
In this prospective study, we have assessed the population-based incidence and the aetiology 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 10000 person-years in the first and second year of study, respectively; though the rates of influenza reported in these 2 years were similar. Age group-specific incidence rates increased with advancing age to 54.4 per 10000 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 10000 person-years) by Jain et al, 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 10000 person-years; in particular, for adults older than 65 years, incidence ranged from 109.0 to 294.9 per 10000 person-years. 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 10000 person-years and from 15.4 to 17.0 per 10000 population. In the age group older than 65 years, CAP incidence in Spain ranged from 127 to 155 per 10000 person-years. With respect to hospitalisation, in a retrospective, web-based database study in Brazil, the incidence per 10000 of hospitalisation due to all-cause pneumonia decreased from 45.1 in 2003 to 38.8 in 2007. In another study, the incidence of hospitalised and outpatient pneumonia in Brazil was 61.1 and 70.6 per 10000 inhabitants/year, respectively.

The wide variation in the incidence rates of CAP in previous reports may be explained by differences in study design, definition of CAP, enrolment criteria, study procedures, incidence estimations and surveillance methods. In addition, differences in demographic characteristics and/or in the provision of and access to healthcare 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 hospitalisations due to other causes. The CAP incidence estimates reported here result from thorough ascertainment of cases during the active, prospective surveillance. Moreover, due to the exclusion of recently hospitalised 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.

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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Table 3  Coverage of pneumococcal vaccines serotypes among middle aged and older adults with community-acquired pneumonia, Salvador, Brazil, 2018–2020

| Serotypes covered by PCV10* | No. (%) of subjects positive for serotype | All-cause CAP (n=111) | Pneumococcal CAP (n=42) |
|----------------------------|------------------------------------------|-----------------------|------------------------|
| 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)              |
| 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)              |
| 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)               |

| Serotypes covered by PPV23 | No. (%) of subjects positive for serotype | All-cause CAP (n=111) | Pneumococcal CAP (n=42) |
|----------------------------|------------------------------------------|-----------------------|------------------------|
| 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)                |

Continued
depending on introduction of pneumococcal vaccination in national programmes and its coverage. A microbial aetiology could be identified for 56% of the patients. Overall, our pathogen-detection yield is within the range (38%–70%) of the yield in other aetiological 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 patients with CAP, and identified in 34% of CAP in hospitalised 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%–48% prevalence in other studies. 3 43 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 non-bacteraemic 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 emphasises 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 licenced pneumococcal vaccines; thus, these cases could have been potentially prevented by vaccination. Of note, the serotype-specific UAD assays used in this study were designed to only detect the 24 serotypes contained in licenced 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 with traditional culture methods, 22 23 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 bacteraemia; thus, being limited to invasive pneumococcal disease. Along with conventional culture-based methods, this study is the first to use 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, while 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 underidentification 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 enrolment 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 healthcare from the public sector SUS and living in a single geograhical area population. Thus, it may not be possible to extrapolate our findings to the entire Brazilian adult population, since the epidemiology of respiratory

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**Table 3 Continued**

| No. (%) of subjects positive for serotype | All-cause CAP | Pneumococcal CAP |
|------------------------------------------|---------------|------------------|
| Untyped                                  | 6 (5.4)       | 6 (14.3)         |

*PCV10 is not licenced for adults.
†PCV20 is licenced in the USA only.
CAP, community-acquired pneumonia; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine.

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infections varies according to geographical 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 two consecutive years. We used outcome measures and definitions based on specified criteria, and the study procedures were standardised 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-bacteraemic 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 licenced pneumococcal vaccines, a crucial information for the overall impact of pneumococcal vaccination programmes, as well as appropriate decision-making processes for informing current immunisation 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 recommend influenza and pneumococcal vaccines could reduce the burden of pneumonia among adults.

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**Contributors**

FGD, MGB, SuSM, JNR, JRS, RSDA, RA-P, RB, CaFAn and EDM developed the study concept and design. SuSM 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 guarantor of this work and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Competing interests**

JRS, RSDA, KEA and RA-P are employed by Pfizer and have ownership interests in Pfizer. EDM 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.

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication**

Not applicable.

**Ethics approval**

The study protocol was approved by the Ethics Committee of the Santo Antônio Hospital (Approval: 2016.1.14.0000.0047). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Data availability statement**

Data are available upon reasonable request.

**Open access**

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