


BMJ Open 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.

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 two consecutive years.
- All cases of CAP were radiographically confirmed and validated by clinical information.
- Non-cultured-based tests employed to improve the detection of *Streptococcus pneumoniae* in non-bacteraemic 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 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.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 hospitalised with CAP per 1000 adults in the USA, 2.5–11.6 cases per 1000 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 aetiological 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 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 children¹² or were mostly retrospective and have not used more sensitive antigen-based laboratory diagnostic tests.^{5 13} Routine childhood immunisation 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 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.¹⁸ 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 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 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 $\geq 38.0^\circ\text{C}$), hypothermia (axillary temperature $< 35.5^\circ\text{C}$, 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 $> 15 \times 10^9$ white blood cells/litre or $> 15\%$ bands), serum procalcitonin above ≥ 0.5 mg/mL or hypoxaemia (O_2 saturation $< 90\%$ breathing room air or $\text{PaO}_2 < 60$ 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 CA dAN) 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.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 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

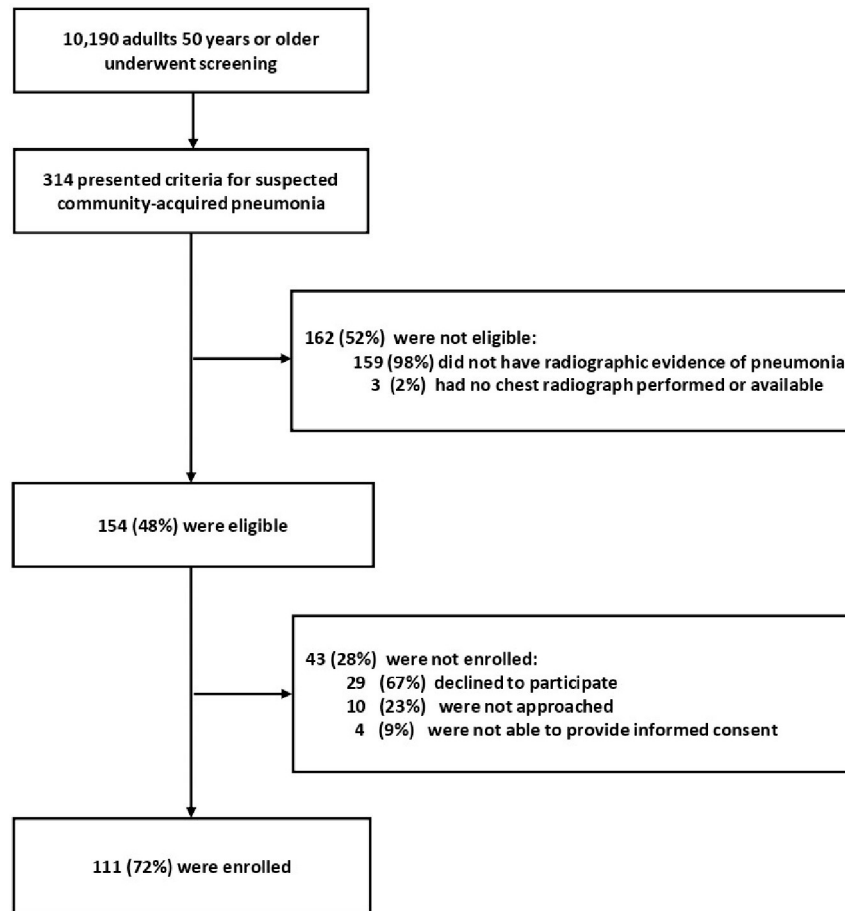


Figure 1 Screening, eligibility and enrolment of patients with community-acquired pneumonia, Salvador, Brazil, 2018–2020.

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

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)
Any underlying condition†		
Hypertension	59	(53)
Diabetes mellitus	25	(22)
Chronic heart disease	14	(13)

Continued

Table 1 Continued

Characteristics	n=111	(%)
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)
Current alcohol use	33	(30)
Signs and symptoms‡		
Cough	106	(95)
Fever	84	(76)
Dyspnoea	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 years 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, 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.²⁵ *Mycobacterium tuberculosis* was considered a pathogen if detected in any acid-fast bacilli sputum specimen.

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 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	
<i>Streptococcus pneumoniae</i>	7.6 (6.1 to 9.2)
Influenza	1.4 (0.8 to 2.3)
<i>Haemophilus Influenzae</i>	1.4 (0.8 to 2.3)
<i>Mycobacterium tuberculosis</i>	0.5 (0.3 to 1.2)
<i>Staphylococcus aureus</i>	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.

S. 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% 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 Salvador'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 population³⁰ 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 Health 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 (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 participants with CAP, and two or more in 40%. Cough, fever, dyspnoea and pleuritic pain were the most common clinical findings. Nearly one-third of study participants had been immunised against influenza during the last influenza season, and only 3% of patients 60 years or older received PPV23 on at least one occasion. Sixty per cent 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 hospitalised and none were admitted to the intensive care unit.

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

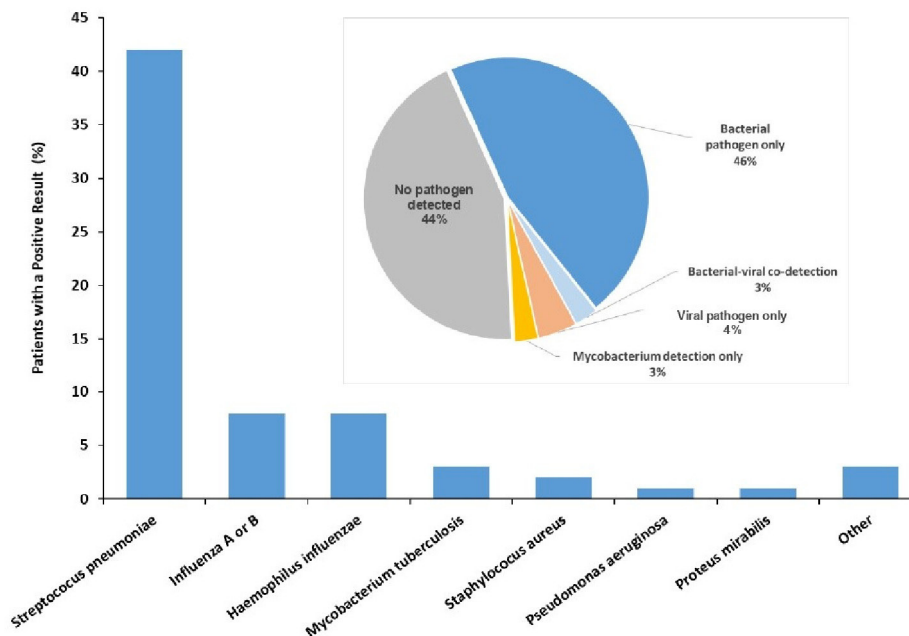


Figure 2 Pathogen detection among middle aged and older adults with community-acquired pneumonia, Salvador, Brazil, 2018–2020.

incidence overall increased with increasing age, rising from 15.1 cases per 10000 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 10000 adults. *S. pneumoniae* was the pathogen detected with the highest incidence, 7.6 cases (95% CI 6.1 to 9.2) per 10000 adults. Ranging from 7.3 cases (95% CI 5.3 to 10.3) per 10000 adults age 50 to 59 years to 13.5 cases (95% CI 6.3 to 29.8) per 10000 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

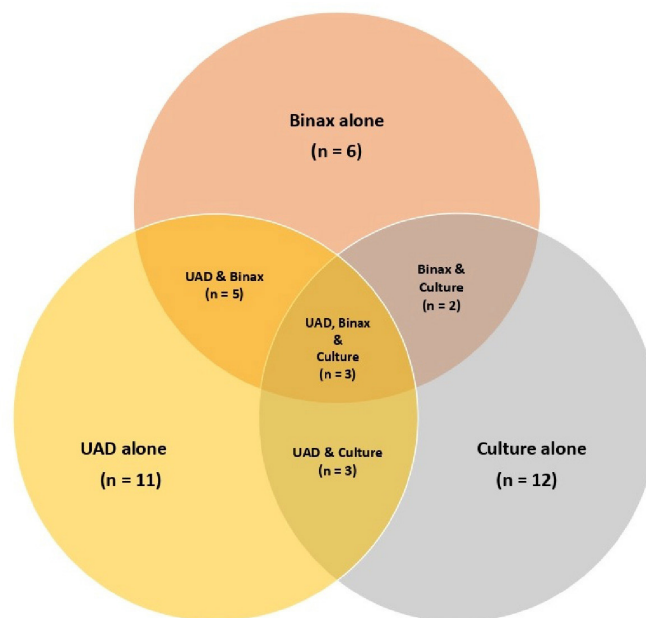


Figure 3 Diagnostic method for *Streptococcus pneumoniae* identification among all study participants with radiographically-confirmed community-acquired pneumonia (n=111). A total of 42 (38%) had *S. pneumoniae* detected by any method. UAD, proprietary serotype-specific urinary antigen detection assay.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

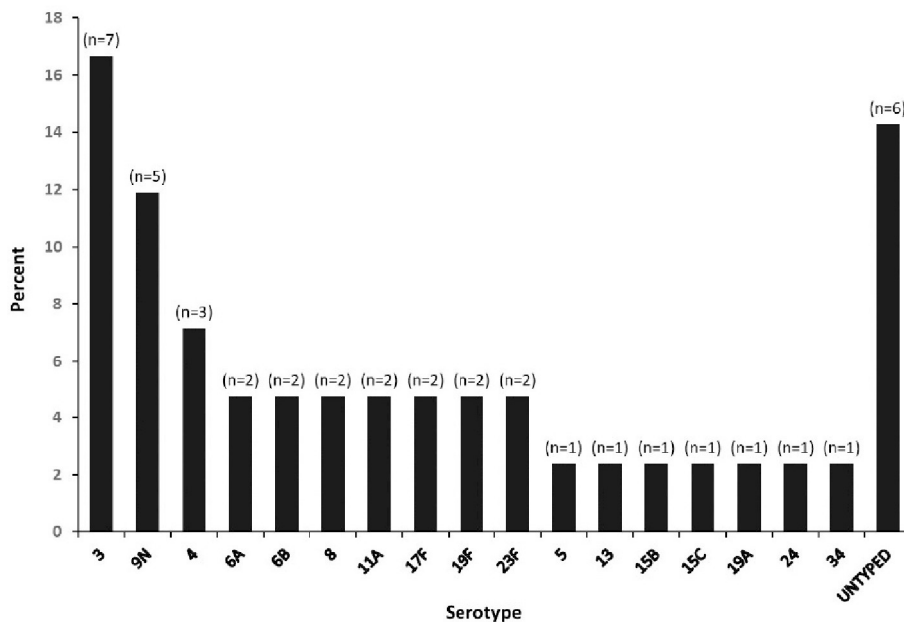


Figure 4 Serotype distribution of *Streptococcus pneumoniae* isolates (n=42) among middle aged and older adults with community-acquired pneumonia, Salvador, Brazil, 2018–2020.

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.³³ 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*,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 10000 person-years; in particular, for adults older than 65 years, incidence ranged from 109.0 to 294.9 per 10000 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 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 153 per 10000 person-years.³⁴ 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 2007.⁵ In another study, the

incidence of hospitalised and outpatient pneumonia in Brazil was 61.1 and 70.6 per 10000 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, 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.^{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 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.³⁸ The impact of herd protection offered by vaccination in children varies in different populations

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		Pneumococcal CAP	
	(n=111)		(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)
	No. (%) of subjects positive for serotype			
	All-cause CAP		Pneumococcal CAP	
	(n=111)		(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)

Continued

Table 3 Continued

	No. (%) of subjects positive for serotype			
	All-cause CAP		Pneumococcal CAP	
	(n=111)		(n=42)	
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.

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 adults¹⁰ and has been reported as a leading cause of CAP, with 9%–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 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 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 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 geographical 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 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 licensed 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 recommended influenza and pneumococcal vaccines could reduce the burden of pneumonia among adults.

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Contributors FGD, MGB, SdSM, JNR, JRS, RSdA, RA-P, RB, CAdAN and EDM developed the study concept and design. SdSM 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.

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REFERENCES

- Vos T, Allen C, Arora M, *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the global burden of disease study 2015. *The Lancet* 2016;388:1545–602.
- Pneumonia in Children Statistics - UNICEF DATA. Available: <https://data.unicef.org/topic/child-health/pneumonia/> [Accessed 21 Apr 2021].
- Corrêa RdeA, José BPdeS, Malta DC, *et al*. Carga de doença POR infecções do trato respiratório inferior no Brasil, 1990 a 2015: estimativas do estudo global burden of disease 2015. *Rev Bras Epidemiol* 2017;20:171–81.
- TabNet Win32 3.0: Mortalidade - Brasil. Available: <http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sim/cnv/obt10uf.def> [Accessed 21 Apr 2021].
- Berezin EN, de Moraes JC, Hong T, *et al*. Pneumonia hospitalization in Brazil from 2003 to 2007. *Int J Infect Dis* 2012;16:e583–90.
- Lopardo GD, Fridman D, Raimondo E, *et al*. Incidence rate of community-acquired pneumonia in adults: a population-based prospective active surveillance study in three cities in South America. *BMJ Open* 2018;8:e019439.
- Ramirez JA, Wiemken TL, Peyrani P, *et al*. Adults hospitalized with pneumonia in the United States: incidence, epidemiology, and mortality. *Clin Infect Dis* 2017;65:1806–12.
- Jain S, Self WH, Wunderink RG, *et al*. Community-Acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med* 2015;373:415–27.
- Jokinen C, Heiskanen L, Juvonen H, *et al*. Incidence of community-acquired pneumonia in the population of four municipalities in eastern Finland. *Am J Epidemiol* 1993;137:977–88.
- Woodhead MA, Macfarlane JT, Mccracken JS, *et al*. Prospective study of the aetiology and outcome of pneumonia in the community. *The Lancet* 1987;329:671–4.
- Pakhale S, Mulpuru S, Verheij TJM, *et al*. Antibiotics for community-acquired pneumonia in adult outpatients. *Cochrane Database Syst Rev* 2014;27:CD002109.
- Andrade ALSSde, Silva SAE, Martelli CMT, *et al*. Population-Based surveillance of pediatric pneumonia: use of spatial analysis in an urban area of central Brazil. *Cad Saude Publica* 2004;20:411–21.
- Rodrigues FE, Tatto RB, Vauchinski L. Mortalidade POR pneumonia em crianças brasileiras até 4 anos de idade. *J Pediatr* 2011;87:111–4.
- Domingues CMAS, Maranhão AGK, Teixeira AM. The Brazilian national immunization program: 46 years of achievements and challenges. *Cad Saude Publica* 2020;36:e00222919.
- Ministério da Saúde - Brasil. *Ministério da Saúde - Brasil. Secretaria de Vigilância em Saúde. Manual dos Centros de Referência para Imunobiológicos Especiais, Coordenação-Geral do Programa Nacional de Imunizações*. 5th ed. Brasília:Ministério da Saúde, 2019. http://bvsms.saude.gov.br/bvs/publicacoes/manual_centros_imunobiologicos_
- Brandileone M-CC, Almeida SCG, Minamisava R, *et al*. Distribution of invasive *Streptococcus pneumoniae* serotypes before and 5 years after the introduction of 10-valent pneumococcal conjugate vaccine in Brazil. *Vaccine* 2018;36:2559–66.
- Andrade AL, Minamisava R, Policena G, *et al*. Evaluating the impact of PCV-10 on invasive pneumococcal disease in Brazil: a time-series analysis. *Hum Vaccin Immunother* 2016;12:285–92.

- 18 Mandell LA, Wunderink RG, Anzueto A, *et al.* Infectious diseases Society of America/American thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;44 Suppl 2:S27–72.
- 19 Müller NL, Franquet T, Lee KS. *Imaging of pulmonary infections*. Philadelphia, PA, 2007.
- 20 American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171.
- 21 Binaxnow Streptococcus pneumoniae antigen card | Abbott point of care testing. Available: <https://www.globalpointofcare.abbott/en/product-details/binaxnow-streptococcus-pneumoniae-us.html#helpfuldocuments> [Accessed 7 Aug 2021].
- 22 Pride MW, Huijts SM, Wu K, *et al.* Validation of an immunodiagnostic assay for detection of 13 Streptococcus pneumoniae serotype-specific polysaccharides in human urine. *Clin Vaccine Immunol* 2012;19:1131–41.
- 23 Kalina WV, Souza V, Wu K, *et al.* Qualification and clinical validation of an immunodiagnostic assay for detecting 11 additional Streptococcus pneumoniae serotype-specific polysaccharides in human urine. *Clin Infect Dis* 2020;71:E430–8.
- 24 Quickvue package insert. Available: https://www.quidel.com/sites/default/files/product/documents/EF1350313EN00_1.pdf [Accessed 3 May 2021].
- 25 Bartlett RC. *Medical microbiology: quality, cost and clinical relevance*, 1974.
- 26 Streptococcus lab resources and protocols | CDC. Available: <https://www.cdc.gov/streplab/pneumococcus/resources.html> [Accessed 6 May 2021].
- 27 Carvalho MG, Pimenta FC, Gertz RE. Pcr-Based quantitation and clonal diversity of the current prevalent invasive serogroup 6 pneumococcal serotype, 6C, in the United States in 1999 and 2006 to 2007. *J Clin Microbiol* 2009;47:554–9.
- 28 Ulm K. Simple method to calculate the confidence interval of a standardized mortality ratio (SMR). *Am J Epidemiol* 1990;131:373–5.
- 29 Instituto Brasileiro de Geografia e Estatística - IBGE. Pesquisa Nacional de Saúde (PNS) - 2019. Available: <https://www.ibge.gov.br/estatisticas/sociais/saude/9160-pesquisa-nacional-de-saude.html?edicao=28655&t=sobre> [Accessed 10 Aug 2021].
- 30 IBGE | portal do IBGE | IBGE. Available: <https://www.ibge.gov.br/> [Accessed 26 May 2021].
- 31 Cadastro Nacional de Estabelecimentos de Saúde. Available: <http://cnes.datasus.gov.br/pages/downloads/arquivosBaseDados.jsp> [Accessed 6 May 2021].
- 32 DATASUS–DATASUS. Available: <https://datasus.saude.gov.br/sobre-o-datasus/> [Accessed 6 May 2021].
- 33 Doença E Agravado influenza, Secretaria da Saúde do Estado da Bahia (Sesab). Available: <http://www.saude.ba.gov.br/agravo/influenza/> [Accessed 9 Aug 2021].
- 34 Torres A, Peetermans WE, Viegi G, *et al.* Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax* 2013;68:1057–65.
- 35 Buzzo AR, Roberts C, Mollinedo LG, *et al.* Morbidity and mortality of pneumonia in adults in six Latin American countries. *Int J Infect Dis* 2013;17:e673–7.
- 36 Guevara RE, Butler JC, Marston BJ. Accuracy of ICD-9-CM codes in detecting community-acquired pneumococcal pneumonia for incidence and vaccine efficacy studies. *Am J Epidemiol* 1999;149:282–9.
- 37 Yu O, Nelson JC, Bounds L, *et al.* Classification algorithms to improve the accuracy of identifying patients hospitalized with community-acquired pneumonia using administrative data. *Epidemiol Infect* 2011;139:1296–306.
- 38 Nelson JC, Jackson M, Yu O, *et al.* Impact of the introduction of pneumococcal conjugate vaccine on rates of community acquired pneumonia in children and adults. *Vaccine* 2008;26:4947–54.
- 39 Johansson N, Kalin M, Tiveljung-Lindell A, *et al.* Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. *Clin Infect Dis* 2010;50:202–9.
- 40 Holter JC, Müller F, Bjørg O, *et al.* Etiology of community-acquired pneumonia and diagnostic yields of microbiological methods: a 3-year prospective study in Norway. *BMC Infect Dis* 2015;15.
- 41 Sangil A, Calbo E, Robles A, *et al.* Aetiology of community-acquired pneumonia among adults in an H1N1 pandemic year: the role of respiratory viruses. *Eur J Clin Microbiol Infect Dis* 2012;31:2765–72.
- 42 Bartlett JG. Diagnostic tests for agents of community-acquired pneumonia. *Clin Infect Dis* 2011;52:S296–304.
- 43 Isturiz RE, Luna CM, Ramirez J. Clinical and economic burden of pneumonia among adults in Latin America. *Int J Infect Dis* 2010;14:e852–6.
- 44 Song J-H, Thamlikitkul V, Hsueh P-R. Clinical and economic burden of community-acquired pneumonia amongst adults in the Asia-Pacific region. *Int J Antimicrob Agents* 2011;38:108–17.
- 45 Ladhani SN, Collins S, Djennad A, *et al.* Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000–17: a prospective national observational cohort study. *Lancet Infect Dis* 2018;18:441–51.
- 46 Andrews N, Kent A, Amin-Chowdhury Z, *et al.* Effectiveness of the seven-valent and thirteen-valent pneumococcal conjugate vaccines in England: the indirect cohort design, 2006–2018. *Vaccine* 2019;37:4491–8.
- 47 Murdoch DR, Laing RT, Mills GD, *et al.* Evaluation of a rapid immunochromatographic test for detection of Streptococcus pneumoniae antigen in urine samples from adults with community-acquired pneumonia. *J Clin Microbiol* 2001;39:3495–8.
- 48 Sherwin RL, Gray S, Alexander R, *et al.* Distribution of 13-valent pneumococcal conjugate vaccine Streptococcus pneumoniae serotypes in US adults aged ≥50 years with community-acquired pneumonia. *J Infect Dis* 2013;208:1813–20.