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Incidence rate of community-acquired pneumonia in adults: a population-based prospective active surveillance study in three cities in South America

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ABSTRACT

Objective To determine the incidence rate and mortality of community-acquired pneumonia (CAP) in adults in three cities in Latin America during a 3-year period.

Design Prospective population-based surveillance study.

Setting Healthcare facilities (outpatient centres and hospitals) in the cities of General Roca (Argentina), Rivera (Uruguay) and Concepción (Paraguay).

Participants 2302 adults aged 18 years and older with CAP were prospectively enrolled between January 2012 and March 2015.

Main outcome measures Incidence rates of CAP in adults, predisposing conditions for disease, mortality at 14 days and at 1 year were estimated. Incidence rate of CAP, within each age group, was calculated by dividing the number of cases by the person-years of disease-free exposure time based on the last census; incidence rates were expressed per 1000 person-years.

Results Median age of participants was 66 years, 46.44% were men, 68% were hospitalised. Annual incidence rate was 7.03 (95% CI 6.64 to 7.44) per 1000 person-years in General Roca, 6.33 (95% CI 5.92 to 6.78) per 1000 person-years in Rivera and 1.76 (95% CI 1.55 to 2.00) per 1000 person-years in Concepción. Incidence rates were highest in participants aged over 65 years. 82.4% had at least one predisposing condition and 48% had two or more (multimorbidity). Chronic heart disease (43.6%) and smoking (37.3%) were the most common risk factors. 14-day mortality rate was 12.1% and 1-year mortality was 24.9%. Multimorbidity was associated with an increased risk of death at 14 days (OR 2.91; 95% CI 2.23 to 3.80) and at 1 year (OR 3.00; 95% CI 2.44 to 3.70).

Conclusions We found a high incidence rate of CAP in adults, ranging from 1.76 to 7.03 per 1000 person-years, in three cities in South America, disclosing the high burden of disease in the region. Efforts to improve prevention strategies are needed.

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 in three cities during a 3-year period.
- ► Included hospitalised and outpatients with CAP.
- ► All episodes of CAP were radiographically confirmed.
- ► A thorough microbiological research was not performed.
- ► Some CAP episodes managed on an outpatient basis may not have been captured by the active surveillance.

INTRODUCTION

Community-acquired pneumonia (CAP) is a common acute infection in adults resulting in considerable clinical and economic impact.[1 2] The 2010 Global Burden of Disease Study reported that lower respiratory tract infections, including pneumonia, are the fourth most common cause of death worldwide,[3] placing significant burden on healthcare resources.[4]

Certain population groups are more susceptible to develop CAP, particularly the elderly and individuals suffering from chronic conditions. Incidence varies depending on age, lifestyle habits such as smoking and alcohol consumption, and chronic illnesses namely chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), cerebrovascular disease (CBVD), chronic liver or renal disease, diabetes mellitus and conditions causing immunosuppression.[2 5 6]

The incidence of CAP shows U-shaped age distribution, with highest rates in infants and the elderly.[7] Ageing of the population is a major risk factor for CAP.[8–10] In adults, annual incidence rates range from 1.07 to 14 per 1000 persons-years and have not changed substantially in recent decades.[11–13] A limited number of reports indicate CAP incidence variations between countries and are mainly focused on CAP hospitalisations with rates ranging from 1.48 per 1000 population in

England, 2.75 in Germany, 3.61 in Portugal to 6.27 in Spain.[14–17] Only a few large database studies have been published on the clinical burden of CAP in older adults showing incidence rates from 7.65 to 13.4 per 1000 population.[15 16]

Case fatality rates for CAP are particularly high in the elderly,[8 18] mortality is associated not only to age, but also to chronic illnesses, severity of episode and treatment setting. Studies have reported high mortality rates ranging from 5% to 15% in hospitalised patients increasing to over 20% in patients admitted to intensive care unit (ICU), compared with rates below 1% for outpatients.[19–21]

In most countries, robust national epidemiology monitoring for CAP is lacking. In Latin America, updated information on the burden of pneumonia in adults is not available and more comprehensive epidemiological data are needed such as information on non-hospitalised CAP cases and age-stratified incidence.

We conducted a prospective population-based study to estimate overall and age-specific incidence rates, epidemiology and mortality rates for CAP in adult residents from three cities in the Southern Cone region of South America during a 3-year period.

METHODS

Design, study setting and participants

The Neumonía Adquirida en la Comunidad Regional 1 (NACREG1) study was a prospective, active, population-based, surveillance study conducted in three cities in South America designed to estimate the incidence rate of CAP in adults. The surveillance population included all residents of the cities of General Roca in Argentina, Rivera in Uruguay and Concepcion in Paraguay, 18 years of age or older who presented symptoms and signs of acute lower respiratory tract infection. The cities were selected based on similarities in healthcare systems, relative geographical isolation and because of the relatively small number of residents: 90 711 inhabitants in the city of General Roca (census 2010), 64 485 in Rivera (census 2011) and 78 072 in Concepcion (census 2012), which facilitated surveillance tasks.[22–24] An additional advantage was the reduced number of health centres at each city. General Roca has universal health coverage; the city has 391 hospital beds, 60% from the private sector. Rivera has universal health coverage; the city has 110 hospital beds from the public sector and a home care system that assists 50 patients a day on average. In Concepción, public system covers about 65% of the population; the city has 205 beds, 63% from the public sector. CAP surveillance was conducted between 2 January 2012 and 31 March 2015. Clinicians and general practitioners (GPs) assessed individuals with acute lower respiratory tract infections, requested laboratory tests, microbiological analyses, chest X-rays, CT scans and prescribed antimicrobial treatment. Treating physicians were asked to report suspected pneumonia cases to the research team using a toll-free telephone number. A member of the study team made daily telephone calls and visits to all the health facilities in the city including outpatient centres and hospitals and assessed all ambulatory and hospitalised participants considered to have CAP. Study personnel were not involved in patients' care.

Participants were eligible for inclusion in the study if they (1) were 18 years of age or older, (2) resided in the study area, (3) presented evidence of an acute lower respiratory infection (less than 7 days' duration) with at least two of the following: new or worsening cough, purulent sputum or changes in sputum characteristics, dyspnoea, tachypnoea, auscultatory findings consistent with pneumonia, fever (>38°C), hypothermia (<35°C), hypoxaemia (O_2 saturation <90% breathing room air or PaO_2 <60 mm Hg), white cell count (WCC) >10 x 10^9/L or >15% immature neutrophils (bands) irrespective of WCC and (4) presented radiologically confirmed pneumonia defined as new or progressive pulmonary infiltrate(s) on chest radiography or CT scan consistent with pneumonia. To validate each CAP episode, chest radiographs and CT scans were digitalised and read by two members of the research team. When investigators disagreed, the group of experts was consulted. Digital photographs of all chest radiographs were stored in the study database.

Written informed consent was obtained from all participants or caregivers before enrolment. The study protocol design was conceived by a clinical research team from FUNCEI (Fundación Centro de Estudios Infectológicos), Buenos Aires, Argentina.

The study comprised three visits. The baseline visit was carried out at the patient's treatment site, at the hospital in the case of hospitalised patients or in the outpatient setting in ambulatory cases, during which a structured questionnaire was used to collect demographic data and information on lifestyle habits (smoking cigarettes, alcohol intake and substance abuse), comorbidities (COPD, CVD, CBVD, neurological or psychiatric disorders, chronic kidney or liver conditions, diabetes mellitus, immunosuppression including cancer and immunosuppressive medication), and living conditions (overcrowding defined as more than three persons per room).[25] Questions also included information on clinical signs and symptoms, prior immunisations (any vaccination against pneumococcus and influenza vaccine during the last influenza season). Criteria to define healthcare-associated pneumonia (HCAP) were assessed according to the guidelines established by the American Thoracic Society and Infectious Diseases Society of America 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.[26]

The microbiological studies requested by GPs were in accordance with the standard of care of each of the participating countries and institutions. During the baseline visit, a urine sample was collected for urine

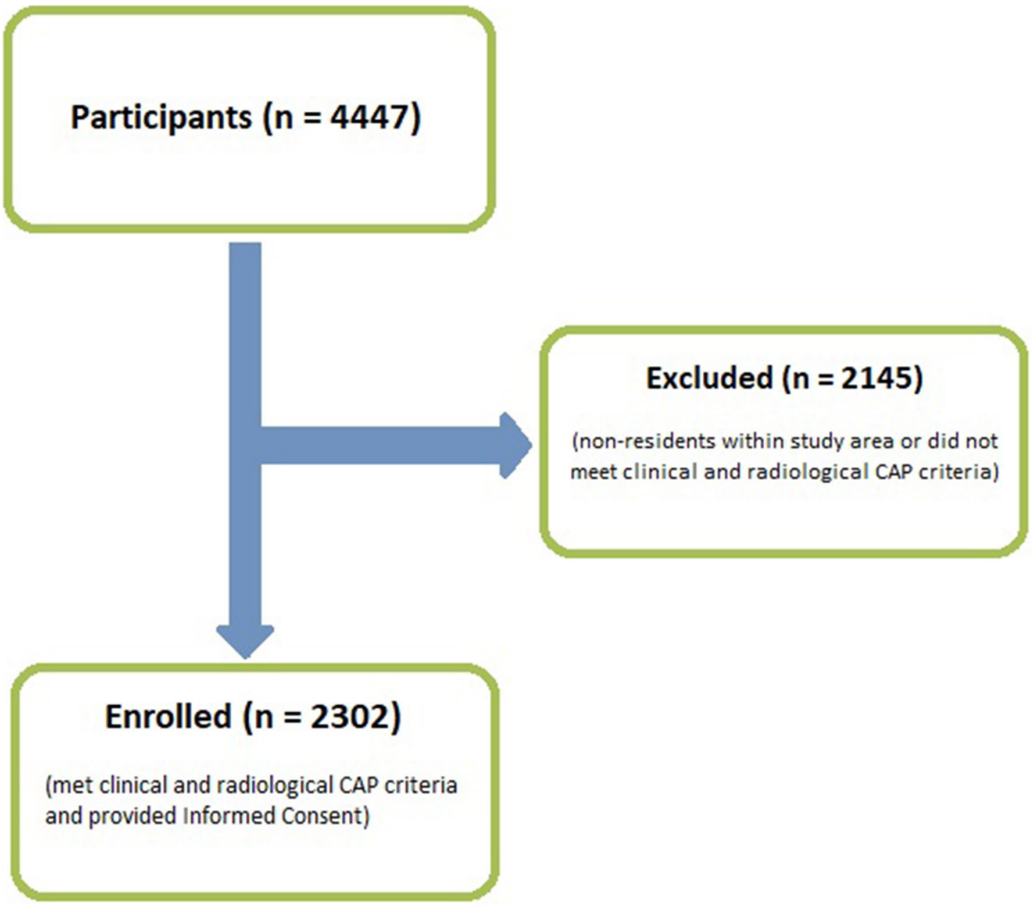

Figure 1 Eligibility and enrolment of participants with community-acquired pneumonia (CAP). The 2145 non-enrolled subjects consulted for respiratory symptoms but did not meet the clinical and radiological criteria established by the study to define CAP.

pneumococcal antigen testing (BinaxNOW *Streptococcus pneumoniae*, Alere, USA).

The second on-site visit was carried out 14 days later (±7 days) to assess the impact of CAP on daily activities based on the number of days during which participants were unable to carry out routine activities due to illness, and to determine 14-day mortality.

The third and final contact (telephone call) was conducted after 1 year, with the sole objective of determining 1-year mortality. Study follow-up ended 12 months after last enrolment. During the study, auditors visited study sites two times in a year to assess study protocol compliance.

Because NACREG1 was an observational study, research team members were not involved in patient care (management and/or treatment decisions were at the discretion of the clinician or GP), nor were microbiological assessments requested other than the BinaxNow test.

This observational study was designed to last 3 years in order to reduce the impact on CAP burden resulting from annual variations in circulating respiratory viruses.

Outcomes

The primary outcome of interest was incidence rate of CAP in adults, which was defined as the number of episodes of CAP in individuals 18 years of age or older residing in the surveillance area, divided by the total population at risk during a 3-year period. As the annual incidence rate of CAP depends on age, participants were stratified into three separate age groups: 18–49 years, 50–64 years and 65 years or older. We also evaluated mortality rate from CAP at 14 days and at 1-year follow-up. Several multivariate analyses were performed in order to assess factors predicting 14-day and 1-year mortality, including demographical conditions, HCAP criteria and comorbidities. Only relevant comorbidities were considered to be reported in this observational study.

Statistical analysis

We performed a descriptive analysis of demographics and predisposing conditions for CAP; data were expressed as percentages for categorical variables and as median (IQR) for continuous variables. Incidence rates of CAP were expressed as cases per 1000 person-years and were calculated by dividing the number of CAP cases during the 3-year period by the person-years of disease-free exposure time, which was obtained from population of the last census and assuming that CAP episodes were developed at a half-way point between follow-ups. A multivariate analysis of factors predicting 14-day mortality was performed by applying a binary logistic regression model (p values, OR and 95% CI). P values were two tailed and values less

Table 1 Demographics and clinical characteristics of participants with CAP by age groups

Characteristics	Age group (years)			
	Total	18–49	50–64	≥65
Participants (%)	2302	557 (24.2)	508 (22.1)	1237 (53.7)
Age (years), median (IQR)	66 (50–79)	36 (28–43)	58 (54–61)	78 (72–84)
Gender				
Male (%)	1069 (46.4)	237 (42.5)	242 (47.6)	590 (47.7)
Female (%)	1233 (53.6)	320 (57.5)	266 (52.4)	647 (52.3)
Clinical signs				
Cough (%)	2156 (93.6)	521 (93.5)	481 (94.7)	1154 (93.3)
Dyspnoea, tachypnoea or hypoxaemia (%)	1759 (76.4)	383 (68.8)	387 (76.2)	989 (80.0)
Fever or hypothermia (%)	1498 (65.0)	451 (81.0)	345 (67.9)	702 (56.8)
Comorbidity				
COPD (%)	345 (15.0)	31 (5.6)	83 (16.3)	231 (18.7)
Heart disease (%)	987 (42.9)	45 (8.1)	191 (37.6)	751 (60.7)
Diabetes mellitus (%)	362 (15.7)	27 (4.8)	90 (17.7)	245 (19.8)
Immunosuppression (%)	139 (6.0)	18 (3.2)	49 (9.6)	72 (5.8)
Malignancy (%)	119 (5.2)	9 (1.6)	23 (4.5)	87 (7.0)
CBVD (%)	160 (6.9)	4 (0.7)	20 (3.9)	136 (11.0)
Kidney disease (%)	157 (6.8)	13 (2.3)	39 (7.7)	105 (8.5)
Liver disease (%)	59 (2.6)	10 (1.8)	24 (4.7)	25 (2.0)
Intravenous drug use (%)	10 (0.4)	6 (1.1)	1 (0.2)	3 (0.2)
Alcoholism (%)	138 (6.0)	35 (6.3)	48 (9.4)	55 (4.4)
Neurological/psychiatric disorder (%)	342 (14.8)	43 (7.7)	37 (7.3)	262 (21.2)
Suspected aspiration (%)	59 (2.6)	7 (1.2)	11 (2.2)	41 (3.3)
Hospitalisation due to CAP in previous year (%)	289 (12.5)	28 (5.0)	52 (10.2)	209 (16.9)
Overcrowding (%)	52 (2.2)	22 (3.9)	11 (2.2)	19 (1.5)
Smoking* (%)	844 (36.7)	233 (41.8)	254 (50.0)	357 (28.9)
Multimorbidity† (%)	1086 (47.2)	97 (17.4)	267 (52.5)	722 (58.4)

IQR: 25%–75%.
*Former or current smoker.
†At least two comorbidities from: COPD, heart disease, diabetes mellitus, immunosuppression, malignancy, CBVD, kidney disease, alcoholism, neurological/psychiatric disorder, smoking.
CAP, community-acquired pneumonia; CBVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease.

than 0.05 were considered statistically significant. Statistical analyses were conducted using SPSS software V.15.0 (SPSS).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design or implementation of this study. There are no plans to involve patients in the dissemination of results.

RESULTS

Of the 4447 participants assessed for symptoms suggestive of CAP, 2302 (52%) met clinical and radiological criteria for CAP diagnosis and were enrolled (figure 1). The 2145 non-enrolled subjects consulted for respiratory symptoms but did not meet the clinical and radiological criteria established by the study to define CAP.

Distribution for each city was as follows: General Roca, 1213 participants enrolled between 2 January 2012 and 31 December 2014; Rivera, 845 participants enrolled between 1 April 2012 and 31 March 2015, and Concepción, 244 participants enrolled between 1 March 2012 and 28 February 2015.

Median age of participants diagnosed with CAP was 66 years (IQR 50–70, range 18–102); 46.44% were men. Cough, dyspnoea, tachypnoea or hypoxaemia and fever or hypothermia were the most common clinical findings (table 1).

During the 3-year surveillance period, the annual incidence rate of CAP was 7.03 (95% CI 6.64 to 7.44) per 1000 person-years in General Roca, 6.33 (95% CI 5.92

Table 2 Incidence rates of CAP in three cities from 2012 to 2014—number of cases per 1000 person-years

City	Age group	Incidence rate*	95% CI †	Overall n	2012 n	2013 n	2014 n
General Roca							
(N=42 328)	18–49 years old	2.28	2.03 to 2.57	288	133	101	54
(N=8031)	50–64 years old	11.00	9.72 to 12.43	259	108	86	65
(N=7991)	≥65 years old	29.49	27.34 to 31.80	666	290	203	173
(N=58 350)	All ages	7.03	6.64 to 7.44	1213	531	390	292
Rivera							
(N=27 016)	18–49 years old	2.70	2.36 to 3.09	218	81	78	59
(N=10 317)	50–64 years old	6.12	5.29 to 7.07	187	74	65	48
(N=7707)	≥65 years old	19.81	18.04 to 21.75	440	163	175	102
(N=45 040)	All ages	6.33	5.92 to 6.78	845	318	318	209
Concepción							
(N=35 093)	18–49 years old	0.48	0.36 to 0.64	51	32	13	6
(N=7104)	50–64 years old	2.93	2.26 to 3.78	62	32	17	13
(N=4098)	≥65 years old	10.90	9.16 to 12.97	131	62	45	24
(N=46 295)	All ages	1.76	1.55 to 2.00	244	126	75	43

Exposure time=2012–2014.
n, CAP cases.
N, total population.
*Incidence rate=(overall n/person-years of disease-free exposure time‡)x1000.
†Wilson score method without continuity correction.
‡Person-years of disease-free exposure time=n of 2012×0.5+n of 2013×1+n of 2014×1.5+(N-overall n)x3.
CAP, community-acquired pneumonia.

to 6.78) per 1000 person-years in Rivera and 1.76 (95% CI 1.55 to 2.00) per 1000 person-years in Concepción. Overall, CAP incidence rate was highest in the older age group and lowest in the younger age group (table 2).

At least one predisposing condition was present in 82.4% of participants with CAP, and two or more (multimorbidity) in 48%. CVD was the most common predisposing condition (43.6%), followed by smoking (37.3%), diabetes mellitus (16%) and COPD (15.2%); 12.8% of participants suffered CAP in the previous year (table 1).

Of 2302 adults with CAP, 737 (32%) were managed as outpatients, 1565 (68%) were hospitalised and 322 (14%) were admitted to the ICU. 30.8% of participants had been immunised against influenza during the last influenza season and 17.5% had received 23-valent pneumococcal polysaccharide vaccine (PPV23) on at least one occasion.

CRB-65 was calculated for 2097 episodes of CAP: 24.5% 0 point, 43.7% 1 point, 22.8% 2 points, 8% 3 points and 1% 4 points.

The request for studies by GPs in order to establish the aetiological agent of the CAP episode was scarce. Pneumococcal urinary antigen test (BinaxNOW) was performed for 1999 (86.8%) CAP episodes, of which 122 (6.1%) were positive. The proportion of positive urine tests increased as severity of episodes worsened, 4.6% positivity in participants managed as outpatients, 6.4% in participants hospitalised in a general ward and 10.5% in those admitted to the ICU.

Overall, 18.1% of episodes of pneumonias accomplished the definition of HCAP. The most common risk factors for HCAP were previous hospitalisation in an acute care hospital for 2 or more days within 90 days (10.25%), having received recent intravenous antibiotic therapy, chemotherapy or wound care within the past 30 days (8.86%) and being resident in a nursing home or long-term care facility (4.7%).

A second visit was performed by 2173 (94.4%) patients and a third contact was done in 1914 (83.1%) patients. The second visit showed that the loss of daily activities was 13.28 days (95% CI 12.78 to 13.78). Overall, 14-day and 1-year mortality rates were 12.1% and 24.9%, respectively, with variations between age groups, 3.6% and 5.9% for the youngest group, 5.1% and 11.8% for those aged 50–64 years, 18.8% and 35.9% for the oldest group. The risk of death at 14 days was fivefold higher in participants with a pre-existent malignancy and twofold to threefold higher in patients with CBVD, kidney disease, alcoholism, neurological/psychiatric or multimorbidity than in those without said conditions (table 3).

DISCUSSION

Incidence rate of CAP in adults estimated over the 3-year study period was 7.03 (95% CI 6.64 to 7.44)/1000 person-years in General Roca, 6.33 (95% CI 5.92 to 6.78)/1000 person-years in Rivera and was substantially lower in

Table 3 Multivariate analysis of factors predicting mortality in patients with CAP

	14-day mortality*	
Condition (yes/no)	P values†	OR (95% CI)
COPD	0.698	1.09 (0.69 to 1.73)
Heart disease	<0.01	1.69 (1.17 to 2.44)
Diabetes mellitus	0.513	0.86 (0.55 to 1.34)
Immunosuppression	0.673	1.14 (0.62 to 2.08)
Malignancy	<0.01	5.59 (3.37 to 9.29)
CBVD	<0.01	2.20 (1.35 to 3.58)
Kidney disease	<0.01	2.62 (1.63 to 4.21)
Alcoholism	<0.01	2.95 (1.65 to 5.25)
Neurological/psychiatric	<0.01	3.01 (2.06 to 4.40)
Smoking‡	0.028	1.53 (1.05 to 2.25)
Multimorbidity§	<0.01	2.42 (1.98 to 2.96)

*Binary logistic regression.
†P values derived from Wald tests.
‡Current or former smoker.
§At least two comorbidities from: COPD, heart disease, diabetes mellitus, immunosuppression, malignancy, CBVD, kidney disease, alcoholism, neurological/psychiatric disorder, smoking.
CAP, community-acquired pneumonia; CBVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease.

Concepción 1.76 (95% CI 1.55 to 2.00)/1000 person-years. Our results are different from incidence rates reported by others in the literature. In a review of 60 publications from European countries, namely Denmark, France, Germany, Greece, Italy, The Netherlands, Spain and the UK, overall annual CAP incidence rate in adults ranged between 1.07 and 1.7 per 1000 population.[11] Two studies exploring CAP incidence rate were conducted in primary care settings, one in the UK, which reported an annual CAP incidence rate of 2.33/1000 persons,[27] and a second retrospective observational study in Spain which reported a CAP incidence rate of 4.63/1000 person-years[28]. In the USA, Jain *et al* reported an incidence rate of 2.48 per 1000 population.[29]

In General Roca, global incidence rate of CAP in adults was higher than the incidence rate reported by the National Argentine Surveillance Program in which CAP rates for all ages (including infants in whom incidence rates are highest) was 1.28/1000 person-years from 2011 to 2016.[30]

The wide variation in incidence rate between cities in our study cannot be explained by the design of the study since inclusion criteria, study procedures, community awareness and monitoring processes were implemented in the same manner in the three cities.

Several studies have shown an association between climate, risk of developing respiratory tract infections and risk of death.[31 32] Carreras *et al* found that temperature range is a risk factor for hospitalisations due to both upper and lower respiratory infections, particularly among the elderly.[32] The cities selected for this study are located in different climate zones, General Roca is in Patagonia which has a cold windy climate, whereas Rivera and Concepcion are located in subtropical areas. Although situated in different climate regions, CAP incidence rates were similar in General Roca and Rivera, and markedly different in Rivera and in Concepcion, cities which share similar weather conditions.

Differences in vaccination coverage for influenza and pneumococcal vaccines could help explain differences in CAP incidence rates. However, vaccination coverage in adults was quite low in all three study populations. Although both vaccines are recommended for the elderly and for people with risk factors, only 30.8% of participants had received influenza vaccine during the past influenza season and 17.5% had received PPV23 at least once. 13-valent pneumococcal conjugate vaccine (PCV-13) is licensed in all three countries but was not included in routine immunisation programmes for adults at the time of the study.

Universal pneumococcal immunisation in infants reduces the incidence of pneumococcal diseases in adults through herd protection.[33] It is important to clarify that routine childhood pneumococcal immunisation schedules differ in each country. In Uruguay (city of Rivera) PCV7 was introduced into the national immunisation programme in 2008 and changed to PCV13 in 2010. Paraguay (city of Concepción) incorporated PCV10 in 2010 and Argentina (city of General Roca) incorporated PCV13 in 2012. The herd protection that vaccination in children could have offered to adults could have had a different impact in the three participating cities. Our hypothesis was that the lower CAP incidence rate in adults in Concepción compared with General Roca and Rivera might reflect differences in local medical practices such as patient self-medication, underuse of chest radiography for CAP diagnosis by treating physicians among others. Not in line with this hypothesis is the fact that, in Concepcion, were fewer CAP cases enrolled in the ambulatory setting, and hospitalisations due to CAP were markedly lower. This discrepancy underscores the importance of active surveillance in selected populations.

The high incidence rates observed in our study may be explained by the active and prospective surveillance. The methodology used in surveillance has probably been very successful in capturing episodes of hospitalised CAP and not so much to capture episodes treated on an outpatient basis. This hypothesis is reinforced by the high percentage of episodes that were hospitalised, representing 68% of the total episodes despite 68.2% of CAP episodes had a CRB-65 of 0 and 1 point. Furthermore, it is probable that some patients with CAP were not included, for example, those starting antimicrobial treatment without a prior diagnostic chest radiograph and therefore not eligible for enrolment, making overall CAP incidence rate probably higher than the incidence we report. Episodes that were not captured by the surveillance system could explain to some extent the differences in incidence rates between participating cities.

Age group-specific incidence rates increased with advancing age in all three cities, ranging from 0.48 (95% CI 0.36 to 0.64) per 1000 person-years in people aged 18–49 years in Concepcion to 29.49 (95% CI 27.34 to 31.80) per 1000 person-years in those aged 65 years and older in General Roca. These findings are in line with similar age-dependent trends reported by other authors.[2 34] In the Spanish study by Rivero-Calle, CAP incidence rates increased progressively with age ranging from 1.98 per 1000 person-years at 18–20 years, to 23.74 per 1000 person-years in patients over 90 years of age.[28] In our study, 53.7% of all CAP episodes occurred in individuals aged over 65 years and 75.7% in those 50 years of age and older, reflecting high burden of CAP in older adults in the region.

In our study, 82% of all CAP episodes occurred in participants with at least one predisposing factor of which CVD, smoking, diabetes mellitus and COPD were the most common. Multimorbidity, defined as two or more predisposing conditions, was present in 48% of episodes. Comorbidity profile was in agreement with the observations published by Torres *et al* who found 9.4%–62% of patients with CAP presented COPD, 10%–47.2% chronic heart disease and 4.9%–33% diabetes.[11] We were not able to analyse whether the risk of CAP was higher in persons presenting predisposing conditions because we lacked a risk factor database for the entire adult population in all three cities. This fact notwithstanding, risk factors and comorbidities were present in more than three-quarters of CAP episodes.

High prevalence of predisposing conditions in patients diagnosed with CAP in our study highlights the need for prevention programmes and adequate management to help reduce the risk of CAP. Smoking and excessive alcohol consumption lead to increased health risks, these lifestyle habits must therefore become targets for interventions to reduce the global CAP burden.[35 36] In addition, more effective strategies are needed to improve vaccination coverage since less than one-third of the population at risk in our study had received influenza and/or pneumococcal vaccines even though these are recommended by local scientific societies. Both vaccines are available free of charge in General Roca, and influenza vaccine is available free in Rivera.

In our study, more than two-thirds of CAP episodes required hospitalisation and almost 14% of all episodes were admitted to the ICU. Hospitalisation rates were higher than those found in the literature.[33 37] A high percentage of episodes of CAP was hospitalised despite a low CRB-65 score. We were not able to analyse the reasons that justified hospitalisation in these patients. In Greece, Bertsias *et al* reported admission rates of over 32.3%.[38] In the USA, Nelson *et al* studied the impact of the introduction of PCV on CAP rates in children and adults, hospitalisation rate in adults was 26.5%.[33] Study design and implementation may in part explain the high rates of hospitalisation. The low number of hospitals in each of the three cities allowed for daily visits by the research team favouring identification and enrolment of most hospitalised CAP episodes. Enrolment of ambulatory episodes was more difficult and probably less successful.

Detection of *S pneumoniae* antigen in urine can be used for diagnosis of pneumococcal pneumonia. The BinaxNOW *S pneumoniae* is a rapid urinary antigen assay that produces results in approximately 15 min. In our study, the test was positive in 6.1% of all CAP cases, positive results were more frequent in participants with more severe illness (10.5% of participants in the ICU, 6.4% of participants admitted to a general ward and 4.6% of those managed as outpatients). In a review of 35 studies, Said *et al* reported positivity rates between 20% and 23.9%.[39] The positivity of the test varies with the population and with severity of disease. Cost benefit of performing BinaxNOW as a standard diagnostic procedure in all patients with CAP should be reconsidered, particularly in resource-limited settings.

We found that CAP had a considerable impact on daily activities of subjects with CAP, with a mean period of limited activity of 13.28 days (95% CI 12.78 to 13.78).

CAP mortality rate was similar to other published studies.[20 21] We observed substantially increased mortality among participants over 65 years of age and among those with two or more risk conditions. We also observed 'risk stacking', a phenomenon whereby risk of disease increases with increasing numbers of risk factors, linked to increased risk of mortality.[40]

The observed CAP incidence rate in two out of the three participant cities was higher than those reported by the majority of authors. Nevertheless, our findings are in accordance with results recently published by Ramirez *et al*[41] through a prospective population-based cohort study of adult residents in Louisville, Kentucky. This similarity suggests that our findings could be applied to different settings.

The main strength of this study lies in its methodological design. It was an active, prospective, population-based study conducted over a period of 3 years in order to reduce the impact on CAP burden resulting from annual variations in circulating respiratory viruses. In addition, likelihood of including non-pneumonia lower respiratory tract infections was decreased by applying a more stringent definition of pneumonia involving both clinical findings and radiological confirmation, compared with other studies defining CAP-based solely on either clinical or radiological findings.

The study does, however, present limitations. One is a potential underestimation of CAP incidence rate. Due to the design of the study, we believe that the surveillance strategy was very successful in enrolling hospitalised participants with CAP. However, it is possible that a considerable number of ambulatory CAP episodes went unreported by GPs and clinicians or received empirical antimicrobial treatment before completing diagnostic tests. Another limitation concerns the design of the study as microbiological diagnosis only included detection of *S pneumoniae* urinary antigen. Use of extensive

microbiological testing could have afforded a better understanding of CAP epidemiology and helped explain differences in incidence rates between cities.

In conclusion, we found a high incidence rate of CAP in adults, ranging from 1.76 to 7.03 per 1000 person-years, in three cities in South America, disclosing the high burden of disease in the region. Efforts to improve prevention strategies are needed, particularly in the elderly and in individuals with underlying comorbid conditions.

Collaborators Pablo Luchetti, Cynthia Vartalitis.

Contributors All authors involved in this study played a significant role and abided to the ICMJE guidelines. They all had substantial contributions to conception and design, acquisition of data and analysis and interpretation of data; drafting the article and revising it critically for important intellectual content and final approval of the version to be published. GDL, DF and DS were responsible for the study design, statistical analysis, interpretation of data and drafting the manuscript. ER, DG, HA, HB and MS were responsible for data collection, analysis and final approval. AL participated in the study as coordinator and reviewed the manuscript. All authors contributed to the critical revision of the manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. GDL is the guarantor.

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Competing interests GDL and DS have received travel expenses and have been paid for delivering educational presentations for Pfizer; HA has received travel expenses from Pfizer.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Ethics approval This study was approved by the institutional review board at FUNCEI.

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