Epidemiology of community-acquired pneumonia in older adults: A population-based study

Angel Vila-Corcoles a,*, Olga Ochoa-Gondara a, Teresa Rodriguez-Blanco b, Xavier Raga-Luria c, Frederic Gomez-Bertomeu d, EPIVAC Study Group a

a Primary Care Service of Tarragona-Valls, Institut Català de la Salut, Prat de la Riba 39, Tarragona 43001, Spain
b Department of Statistics and Epidemiology, IDIAP Jordi Gol, Barcelona, Spain
c Department of Microbiology, Hospital Santa Tecla, Tarragona, Spain
d Department of Microbiology, Hospital Joan XXIII, Tarragona, Spain

Received 29 May 2008; accepted 8 August 2008
Available online 18 September 2008

KEYWORDS
Incidence;
Aetiology;
Clinical characteristics;
Community-acquired pneumonia;
Risk factors;
Elderly

Summary
Objective: This study assessed incidence, aetiology, clinical outcomes and risk factors for community-acquired pneumonia (CAP) in older adults.

Methods: This was a population-based cohort study that included 11,241 community-dwelling individuals aged 65 years or more, who were followed between 2002 and 2005 in the region of Tarragona, Spain. Primary endpoints were all-cause CAP (hospitalised and outpatient) and 30-day mortality after the diagnosis. All cases were radiographically proved and validated by checking clinical records.

Results: Incidence rate of overall CAP was 14 cases per 1000 person-years (10.5 and 3.5 for hospitalised and outpatient cases, respectively). Incidence was almost three-fold higher among immunocompromised patients (30.9 per 1000) than among immunocompetent subjects (11.6 per 1000). Maximum incidences were observed among patients with chronic lung disease and long-term corticosteroid therapy (46.5 and 40.1 cases per 1000 person-years, respectively). Overall 30-day case-fatality rate was 12.7% (2% in cases managed as outpatient and 15% in hospitalised patients). Among 358 patients with an aetiological work-up, a total of 142 pathogens were found (single pathogen in 121 cases and mixed pathogens in 10 cases). Streptococcus pneumoniae was the most common pathogen (49%), followed by Pseudomonas aeruginosa (15%), Chlamydia pneumoniae (9%) and Haemophilus influenzae (6%). In multivariable analysis, the variables most strongly associated with increasing risk of CAP were history of hospitalisation for CAP in the previous 2 years and presence of any chronic lung disease.

Conclusions: CAP remains a major cause of morbidity and mortality in older adults. Incidence rates in this study largely doubled prior rates reported in Southern European regions.

© 2008 Elsevier Ltd. All rights reserved.

* Corresponding author. Tel.: +34 977 240666; fax: +34 977 226411.
E-mail address: avila.tarte.ics@gencat.cat (A. Vila-Corcoles).
Introduction

Community-acquired pneumonia (CAP) remains an important cause of morbidity and mortality, especially in older adults and patients at-risk.1-4 Nowadays, CAP cases in older adults increase as a consequence of an overall increase in the elderly population (persons aged 65 years or older).4 In developed countries, almost one half of the total hospitalisations for pneumonia occurs in patients over 65 years and pneumonia is a leading cause of death among this age group.2,3,5-7

However, despite the recognised importance of CAP in the elderly, information on its epidemiology in this age group is limited. Most epidemiological data has been obtained from studies on CAP patients admitted in hospitals,5-11 and few studies focusing on the possible contribution of outpatient cases have been reported.12-15 Controversy about the epidemiology of CAP still exists and more epidemiological studies are needed.

In this study, we have assessed incidence, aetiology and clinical characteristics of CAP (hospitalised and outpatient cases) in a large cohort of 11,241 Spanish community-dwelling elderly individuals followed during a consecutive 40-month study period. This work is a part of the EVAN-65 Study, whose results evaluating pneumococcal vaccine effectiveness in elderly people have already been published.16

Methods

Design, setting and study population

This was a population-based cohort study focused on elderly people assigned to eight Primary Health Care Centres (PHCC) in the region of Tarragona, a mixed residential-industrial urban region on the Mediterranean coast of Catalonia, Spain.

The study cohort included all community-dwelling individuals assigned to the eight participating PHCCs, who were 65 years or older at the start of the study (an amount of 11,241 individuals with a mean age of 74.6 [SD:7.5] years-old at baseline). The study was approved by the ethical committee of the Catalonian Health Institute and was conducted in accordance with the general principles for observational studies set out by the institution.

Cohort members were followed from when the study started (January 1, 2002) until the occurrence of the first event, the enrolment from the PHCC ceased, death, or until the end of the study (April 30, 2005). Mean temperatures in the study area for summer and winter seasons throughout the study period were 23.2 °C (73.8 °F) and 9.8 °C (49.6 °F), respectively.

Sources of data

All participating PHCCs had a computerised clinical record system (working since 1999 or before) with registries of administrative data, medical conditions and diagnoses associated with outpatient visits coded according to the International Classification of Diseases, 9th Revision, Clinical modification (ICD-9). This electronic clinical record system was used to identify underlying conditions in cohort members and validate cases of outpatient CAP occurred during the survey. Additionally, the hospital discharge diagnoses database and the clinical medical records of the three participating reference hospitals in the study area (Joan XXIII, Santa Tecla, and Pius Hospital) were used to identify and validate hospitalisations for CAP in cohort members during the study period.

Outcome measure and definitions

Primary endpoints were CAP and death from CAP. Pneumonia was defined when a new radiological infiltrate was identified with one of major criteria (cough, expectoration or fever) or two of minor criteria (dyspncea, pleuritic pain, altered mental status, pulmonary consolidation on auscultation and leukocytosis). Death from pneumonia (case-fatality) was considered when the patient died (in-hospital or not) within the first 30 days after the diagnosis.17,18

Hospitalisations for CAP were identified on the basis of first-listed code in the hospitals discharge databases (ICD-9: 480-487). Outpatient CAP was a primary care or emergency visit with an ICD-9 code registered for pneumonia in the PHCCs databases. All pneumonia cases (hospitalised and outpatient) were radiographically confirmed and validated by checking clinical records with the use of a standardised data collection instrument (which included sociodemographical, clinical, exploratory, analytical and radiographical data at the time of diagnosis). Pneumonia Severity Index (PSI) was calculated according to criteria described in classical meta-analysis.17

Since the beginning of the study, conventional diagnostic work-ups to identify different microorganisms causing pneumonia included blood cultures, sputum cultures and serological testing of paired serum samples obtained at an interval of 3–8 weeks. Additionally, Streptococcus pneumoniae and Legionella urinary antigen tests could be used from May 2003. The aetiological diagnostic procedures used and the treatment administered depended on the attending physician. Similarly, patients were hospitalised or managed as outpatient according to the agreement of the patient of their family and the recommendation of the attending physician.

Covariates

Baseline covariates were age, sex, number of outpatient visits in previous 2 years, history of hospitalisation for pneumonia in previous 2 years, history of pneumococcal vaccination, receipt of influenza vaccine in prior autumn, smoking (current smoker or not smoker), chronic lung disease (chronic bronchitis, emphysema or asthma), chronic heart disease (congestive heart failure or coronary artery disease), diabetes mellitus, cancer (solid organ or haematological neoplasia), chronic nephropathy (nephrotic syndrome, renal failure, dialysis or transplantation), chronic liver disease (cirrhosis or alcoholic hepatitis), and long-term corticosteroid therapy.

Statistical analysis

Incidence rates of CAP were calculated as person-years, considering that in the denominator the total persons-time
for the study period was simply the sum of the person-time contributed to each individual during the study period. Event rates were based on the first episode of CAP occurring during the study period and they do not include multiple events per person. Chi-squared and Fisher's tests were used to calculate p-values in the comparison of categorical variables, whereas Student's test and one-way analysis of variance were used to compare continuous variables.

Multivariable Cox regression analysis with time-varying covariates was used to calculate hazards ratio (HR) and estimate the association between baseline conditions and the time to first outcome during the study period. We checked for confounders, interactions and multicollinearity among the independent variables. The final model was adjusted by all significant variables, as well as confounders and other baseline covariables judged of clinical importance. We assessed the proportional hazards assumptions adding the covariate by time interactions to the model and plot the scaled and smoothed Schoenfeld residuals. Statistical significance was set at p < 0.05. The analyses were performed using Stata/SE version 9.1 (Stata Corp.).

Results

Incidence rates

The 11,241 cohort members were observed for a total of 33,905 person-years. Overall, 43.5% of the subjects were male, 55.2% were 65–74 years old, 34.3% were 75–84 years old and 10.5% were aged 85 years or older at the beginning of the study. At baseline, the most prevalent co-morbidities were diabetes mellitus (23.6%), chronic heart disease (11.9%) and chronic lung disease (11.5%).

During the 40-month study period, a total of 512 individuals with a first episode of presumptive CAP (380 hospitalised and 132 outpatient) were initially identified according to ICD-9 codes, but only 473 cases (355 hospitalised and 132 outpatient) were finally included as radiologically confirmed CAP after clinical record review. Incidence rate was 14 cases per 1000 person-years (10.5 and 3.5 for clinically-confirmed CAP after clinical record review. Incidence rate was 14 cases per 1000 person-years (10.5 and 3.5 for hospitalised and 118 outpatient) were finally included as radiologically confirmed CAP after clinical record review. Incidence rate was 14 cases per 1000 person-years (10.5 and 3.5 for hospitalised and outpatient cases, respectively).

Mean incidences of CAP were 11.6 per 1000 among immunocompetent subjects and 30.9 per 1000 among immunocompromised patients. Maximum incidences were observed among patients with chronic lung disease and long-term corticosteroid therapy (46.5 and 40.1 cases per 1000 person-years, respectively). Table 1 shows time follow-up, absolute number of CAP cases, and overall incidence rates according to age, sex and main underlying conditions.

Microorganisms identified

An aetiological study was carried out in 358 (75.7%) of the total 473 CAP cases (see footnote a of Table 2). Of the 358 patients with any aetiological evaluation, 131 (36.6%) had an identifiable (definitive or probable) aetiology. A total of 142 pathogens were identified: a single pathogen in 121 patients, two pathogens in 9 patients and three pathogens in one patient. Streptococcus pneumoniae was the most common pathogen and accounted for 70 cases (49.3%), followed by Pseudomonas aeruginosa in 22 (15.5%), Chlamydia pneumoniae in 13 (9.2%) and Haemophilus influenzae in 8 (5.6%). Table 2 shows the distribution of the total 142 microorganisms identified and diagnostic methods used for their diagnosis.

Clinical characteristics

Seventy-five percent of CAP episodes were hospitalised and 25% were managed as outpatients. Percentages of CAP cases requiring hospitalisation did not significantly differ according to sex or age subgroups. The mean days of hospitalisation was 10.4 days (SD: 8.02). We did not observe significant differences in the mean length-stay according to sex or age groups. Twenty (5.6%) of 355 hospitalised CAP patients were admitted to the intensive care unit (ICU), with a mean stay of 10.6 days (SD: 9.9).

Of the total 473 CAP cases, 30 (6.3%) had pleural effusion, and 12 (2.5%) had multilobe pneumonia. Overall, cough was observed in 322 cases (68.1%), fever in 330 (69.8%), dyspnoea in 255 (53.9%), expectoration in 275 (58.1%), pleural pain in 224 (47.4%), and crepitations in 395 (83.5%). An acute altered mental state was observed in 67 patients (14.2%). The association of cough, expectoration and pleural pain was registered in 135 cases (28.5%).

Table 3 shows results on clinical, exploratory and analytical data used to estimate PSI. Overall, 73 (15.4%) patients were assigned to PSI class I–II, 160 (33.8%) were class III, 171 (36.2%) were class IV, and 69 (14.6%) were class V.

Considering 30-day mortality after the diagnosis, there were 60 deaths from CAP (9 cases due to pneumococcus, 13 due to other microorganisms and 38 caused by unknown aetiology). Two deaths occurred among CAP cases managed as outpatient, three deaths of patients in emergency unit before hospitalisation, and 55 deaths among hospitalised patients. This meant that the overall 30-day case-fatality rate reached 12.7% (2% for CAP cases managed as outpatient and 15% for CAP requiring hospitalisation). Of the 20 CAP admitted to the ICU, case-fatality rate was 40% (3 cases due to pneumococcus, 3 due to other pathogens, and 2 caused by unidentified microorganism). No 30-day case-fatality was observed in PSI class I–II, 11 (6.9%) in PSI class III, 28 (16.4%) in PSI class IV, and 21 (30.4%) in PSI class V.

Risk factors

In multivariable analysis, the variables most strongly associated with increasing risk of CAP were history of hospitalisation for CAP in previous 2 years (HR: 3.81; 95% confidence interval [CI]: 2.64–5.51) and presence of chronic lung disease (HR: 2.91; 95% CI: 2.35–3.61). Age, male sex, chronic heart disease, liver disease, cancer and corticosteroid therapy were also independently associated with increased risk of CAP. Prior pneumococcal vaccination was significantly associated with lower risk for CAP (HR: 0.79; 95% CI: 0.64–0.98). Table 4 shows multivariable Cox regression analysis assessing the association between the different baseline conditions and risk of CAP in the study population.
Discussion

CAP is generally considered a major cause of morbidity and mortality in older adults.2,3 However, because it is not a reportable illness and a considerable proportion of cases are managed as outpatient, information about its true epidemiology can only be obtained from community- or population-based studies.

In this community-based study, we have analysed the incidence and epidemiology of CAP among community-dwelling elderly people in a well-defined geographical area on the Mediterranean Coast of Spain between 2002 and 2005. To our knowledge, this is the first contemporary study that provides population-based assessment of incidence and risk factors for CAP specifically focused on elderly people in a European country.

The incidence rate of CAP observed in our population (14 cases per 1000 elderly person-years) is much higher than previously reported in Southern Europe,20–22 but it is, however, more similar with incidences reported for elderly persons in Northern Europe and America.5,9,12,23 In Europe, the reported incidence rates of CAP among the subgroup of people aged 65 years or older varied widely from approximately 3 cases per 1000 elderly person-years in Spanish and Italian individuals20–22 to 24 cases per 1000 reported among Finnish elderly people.23

There are several possible explanations for the different incidence rate of CAP found in the present study, compared to previous data from other European Mediterranean regions, including differences in the study design, study populations, geographical variations in frequency, and inclusion criteria of cases. Until now, the apparently low incidence of CAP in Southern Europe was often explained by climatic factors. However, mean temperatures that occurred during our study period were similar to temperatures described in prior studies in the Spanish Mediterranean regions,20,21 so this reason cannot explain the great difference in the reported incidences.

The large differences in the reported incidences of CAP are probably not due to true epidemiological differences; more likely they basically reflect methodological differences between the studies. In this study, hospitalisations for CAP were identified on the basis of first-listed hospital discharge database codes.

### Table 1

<table>
<thead>
<tr>
<th>Study population</th>
<th>No. of CAP cases</th>
<th>Overall CAP Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Person-years</td>
</tr>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–74 years</td>
<td>6205</td>
<td>19589</td>
</tr>
<tr>
<td>75–84 years</td>
<td>3859</td>
<td>11420</td>
</tr>
<tr>
<td>85 years or more</td>
<td>1176</td>
<td>2896</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4892</td>
<td>14550</td>
</tr>
<tr>
<td>Female</td>
<td>6348</td>
<td>19355</td>
</tr>
<tr>
<td><strong>Underlying conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>1298</td>
<td>3674</td>
</tr>
<tr>
<td>Chronic heart disease</td>
<td>1340</td>
<td>3884</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2650</td>
<td>8014</td>
</tr>
<tr>
<td>Smoking</td>
<td>930</td>
<td>2804</td>
</tr>
<tr>
<td>Cancer</td>
<td>304</td>
<td>821</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>215</td>
<td>607</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>410</td>
<td>1177</td>
</tr>
<tr>
<td>Corticosteroid therapy</td>
<td>692</td>
<td>1996</td>
</tr>
<tr>
<td><strong>Immunological status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunocompetents</td>
<td>9794</td>
<td>29760</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>1446</td>
<td>4145</td>
</tr>
<tr>
<td><strong>Overall total</strong></td>
<td>11240</td>
<td>33905</td>
</tr>
</tbody>
</table>

---

**Table 1** Study population, time followed, absolute number of events, and incidence rates of CAP according to age, sex and underlying conditions among elderly people in Tarragona, Spain (January 1, 2002 to April 30, 2005).

- **A** A total of 380 cohort members who had a presumptive episode of hospitalisation for CAP were identified on the basis of the hospital discharge databases; information on 369 of these events was available for clinical record review, of which 355 were finally validated as hospitalised CAP cases and 14 were excluded (nosocomial pneumonia or other diagnoses).
- **B** A total of 132 individuals with an episode of presumptive outpatient pneumonia were identified according to ICD-9 pneumonia codes from emergency or ambulatory visits, but only 118 cases were included as radiologically-confirmed outpatient CAP after review of the clinical records.
- **C** IR denotes incidence rate of overall CAP (including hospitalised and outpatient cases), and it is calculated per 1000 person-years.
- **D** CI denotes confidence interval.
- **E** Corticosteroid therapy was considered when the patient had received long-term (more than 14 days during 6 months prior study) corticosteroid therapy (20 mg/day of prednisone or equivalent) for respiratory-related diseases or another immunosuppressive medication for other illness.
- **F** Immune compromise was a composite variable defined by the presence of any of the following: cancer, immunodeficiency, renal disease, liver disease, or long-term corticosteroid therapy.
An aetiological study was carried out in 358 (75.7%) of the Diagnostic methods were: haemoculture (H), pleural fluid and all cases were radiographically proved and validated by checking clinical records, so an overestimation of incidence is unlikely. In addition, in the present study incidence rates were based on the first episode of CAP occurring during the study period and they do not include multiple events per person, so the total incidence was slightly underestimated considering that some high-risk persons could have suffered repeated episodes of CAP, which were not included in the analysis.

The high rate of hospital admission observed in this study may be explained by the characteristics of the study cohort (people over 65 years) and the characteristics of the "Tarragona region" where the study was conducted, particularly in relation to easy accessibility to the reference hospital, so that many patients sought medical care directly from the emergency service of the hospital rather than visiting a primary care physician.

In this study, an aetiological diagnosis was achieved only in 37% of 358 patients with an aetiological work-up, and this was relatively low as compared with other studies which found a causative pathogen in 40–60% of CAP cases. However, most of these studies were hospital case series and they did not include outpatient CAP (where aetiological procedures are uncommon).
Generally, Streptococcus pneumoniae is the most frequent microorganism identified in all-age CAP cases, followed by atypical microorganisms (mainly Mycoplasma pneumoniae and Chlamydia pneumoniae). In elderly patients, pneumococcus is also the most common aetiologic agent, but there are discrepancies in different studies regarding the true incidence of Pseudomonas aeruginosa and Gram-negative bacilli. In this study, pneumococcus caused almost 50% of those CAP cases with identified aetiology, whereas Pseudomonas aeruginosa and Chlamydia pneumoniae were responsible for 15% and 9% of cases, respectively.

Some recent studies have reported high frequencies of Pseudomonas aeruginosa causing CAP among older adults (especially COPD, immunocompromised and nursing-home patients). In our study, 19 of 22 cases involving Pseudomonas aeruginosa occurred in COPD patients, and eight were among patients admitted in the ICU (five of them were cases with more than one identified microorganism). Our result fits with data reported by Marin et al. in a large case series including 4543 American older adults with pneumonia, where the occurrence of Pseudomonas aeruginosa was 17.1% in the community-acquired pneumonia cases and 25.3% in the health care-associated pneumonia cases.

We emphasise that microbiological investigations were not consistently applied to all patients in our study but depended on the attending physician, so a possible bias linked to microbiological assessment cannot be completely excluded. In this way, two-paired serologies were performed only in 21% of overall CAP cases and this could explain why atypical microorganisms were not very frequent in this study.

Several studies have identified different viruses in 2–16% of patients with CAP. Its frequency depends on geographical variations and number of aetiologic diagnostic tests used to research them. In this observational study, no diagnostic tests for viruses were used and this was a limitation of this study.

Classically, the clinical presentation of CAP in older adults has been described as quite unspecific and subacute, with few respiratory symptoms, absence of fever in 40–50% of cases and a characteristic altered mental state in 20–40% of patients. Although this is the pre-recognised presentation, in the current study (likely related to the inclusion of outpatient CAP cases) respiratory symptoms and fever were found in most patients whereas a confused mental state was only found in 14% of patients.

Overall 30-day case-fatality rate was considerable (12.7%), but it appears in the low limit of case-fatality rates observed in older adults, where values ranging from 11% to 35% have been reported.

Regarding data sources, it is known that the quality of clinical databases is not always as good as desirable. If we consider indicators about quality of our database codifications, 92% of cases initially coded as CAP were later confirmed by checking clinical records. In addition, the registered prevalences of chronic diseases in the study population are in accordance with prevalences reported for Spanish elderly population, which supports the validity of our methods.

The availability of electronic clinical record system for all participating PHCCs allowed us to define the presence of underlying conditions among the study population. Thus, we were able to assess the independent association of baseline characteristics with risk of CAP in multivariable analysis. As previously reported among adults, we found that chronic lung disease, chronic cardiopathy and immunosuppressive medication were independently associated with increased risk. In addition, similar to data reported in community-dwelling elderly individuals in the USA, we also found that the presence of severe chronic liver disease, cancer and previous hospitalisations for pneumonia were also risk factors for CAP among elderly persons. As was already reported, prior pneumococcal vaccination was significantly associated with a low risk of CAP in the multivariable analysis.

Surprisingly, although incidence rates of CAP were 56% higher in smokers (20.7 cases per 1000) than in non-smokers (13.3 per 1000), smoking did not appear as a significant risk factor in the multivariable analysis. In the present authors’ opinion, the relatively low proportion of smokers registered in the clinical records of our elderly population could be a possible explanation for this unexpected finding. Our data point to an independent risk of CAP associated with being male. Nevertheless, it is possible that the observed differences in adjusted risks could be the result of confounding factors unmeasured in our study population.
Our study has several strengths. Study design was population-based, outcome measures and definitions were based on defined criteria in classical meta-analyses, and all cases of CAP were radiographically confirmed and validated by clinical record review. However, considering that case findings were primarily restricted to hospitalisations or outpatient visits recorded with an ICD-9 code 480–487 and a chest radiograph was needed to validate each case, one limitation of this study could be the possible under-identification of CAP events. This possible problem is likely to be more important for CAP treated on an outpatient basis than in hospitalised cases. It is possible that some ambulatory patients with mild symptoms were missed because they were not referred to the hospital or emergency unit for evaluation, because a chest radiograph was not ordered, or because pneumonia diagnosis code was not recorded in the primary care clinical record. In this way, the proportion of outpatient cases without aetiological diagnostic procedures was very great and this was also a limitation of the study. Finally, it must be mentioned that although our study cohort includes all community-dwelling elderly persons assigned to eight different PHCCs, the overall study population includes only persons living in a single geographical area, and the findings may not be extrapolated to the Spanish population as a whole. On other hand, given that the study population comprised community-dwelling individuals, our study cannot assess the issue of nursing home and health care-related pneumonia.

In the next years, population-based studies on the incidence and epidemiology of CAP in different settings and study populations will be needed (especially in high-risk groups such as elderly people) to clarify the true burden of the disease, to recognise changes in disease patterns, to assess preventive interventions and to allocate health care and research resources, which should be evaluated on the basis of actual surveillance and incidence data.

Conflict of interest statement

All the authors declare that they do not have conflicts of interests.

Funding

This study was supported by a grants from the “Fondo de Investigación Sanitaria” of the Spanish Health Ministry (expedients FIS PI-021117 and PI-050231) and Jordi Gol i Gurina Foundation.

Acknowledgements

The authors would like to thank all Health professionals of SAP Tarragona-Valles, Joan XXIII Hospital, Santa Tecla Hospital and Pius Hospital de Valls for their collaboration in this study. The authors also thank Timothy Bowring for their help in the production of this paper. A.V.-C. and O.O.-G. designed the study, assessed outcomes, and wrote and edited the paper; A.V.-C. coordinated the study; O.O.-G., X.R.-L. and F.G.-B. obtained the data; T.R.-B. did the statistical analysis.

References


