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MAJOR ARTICLE

Adults Hospitalized With Pneumonia in the United States: Incidence, Epidemiology, and Mortality

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Background. Understanding the burden of community-acquired pneumonia (CAP) is critical to allocate resources for prevention, management, and research. The objectives of this study were to define incidence, epidemiology, and mortality of adult patients hospitalized with CAP in the city of Louisville, and to estimate burden of CAP in the US adult population.

Methods. This was a prospective population-based cohort study of adult residents in Louisville, Kentucky, from 1 June 2014 to 31 May 2016. Consecutive hospitalized patients with CAP were enrolled at all adult hospitals in Louisville. The annual population-based CAP incidence was calculated. Geospatial epidemiology was used to define ecological associations among CAP and income level, race, and age. Mortality was evaluated during hospitalization and at 30 days, 6 months, and 1 year after hospitalization.

Results. During the 2-year study, from a Louisville population of 587 499 adults, 186 384 hospitalizations occurred. A total of 7449 unique patients hospitalized with CAP were documented. The annual age-adjusted incidence was 649 patients hospitalized with CAP per 100 000 adults (95% confidence interval, 628.2–669.8), corresponding to 1 591 825 annual adult CAP hospitalizations in the United States. Clusters of CAP cases were found in areas with low-income and black/African American populations. Mortality during hospitalization was 6.5%, corresponding to 102 821 annual deaths in the United States. Mortality at 30 days, 6 months, and 1 year was 13.0%, 23.4%, and 30.6%, respectively.

Conclusions. The estimated US burden of CAP is substantial, with >1.5 million unique adults being hospitalized annually, 100 000 deaths occurring during hospitalization, and approximately 1 of 3 patients hospitalized with CAP dying within 1 year.

Keywords. community-acquired pneumonia; incidence; epidemiology; mortality.

Community-acquired pneumonia (CAP) is the leading cause of infectious disease–related death in the United States, with mortality occurring largely in patients requiring hospitalization [1, 2]. Current assessment of the incidence, epidemiology, and clinical outcomes of patients hospitalized with CAP is important to guide appropriate allocation of resources for prevention, management, and research. CAP is not a reportable infection in the United States; therefore, data regarding the burden of disease are primarily obtained through clinical investigations or through use of administrative datasets [3–5]. These population-based studies are challenging, as researchers must enroll and follow all hospitalized patients with CAP in a clearly defined at-risk population. Considering these challenges, we created the University of Louisville Pneumonia Study Group, a multidisciplinary research collaboration including investigators from University of Louisville Infectious Diseases, Pulmonary Medicine, and Pathology, as well as investigators from the Louisville Department of Public Health and the Kentucky Office of Vital Statistics. The University of Louisville Pneumonia Study Group is an expansion of our already existing clinical research organizational structure initiated in the year 2000 through the Community-Acquired Pneumonia Organization (CAPO) [6] (http://caposite.com/).

The objectives of this study were (1) to define the current incidence, epidemiology, and mortality of adult patients hospitalized with CAP in Louisville, Kentucky, and (2) to estimate the burden of CAP in the US adult population.

METHODS

Study Design and Subjects

The University of Louisville Pneumonia Study was a prospective population-based cohort study of all hospitalized adults with CAP who were residents in the city of Louisville, Kentucky, from 1 June 2014 to 31 May 2016. All hospitalized adult patients in Louisville underwent screening for participation in the study. Information on each participating hospital and criteria used to screen all adult hospitalized patients can be found in the Supplementary Materials.

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Inclusion Criteria

A patient was defined as having CAP when the following 3 criteria were met: (1) presence of a new pulmonary infiltrate on chest radiograph and/or chest computed tomography scan at the time of hospitalization, defined by a board-certified radiologist's reading; (2) at least 1 of the following: (a) new cough or increased cough or sputum production, (b) fever >37.8°C (100.0°F) or hypothermia <35.6°C (96.0°F), (c) changes in leukocyte count (leukocytosis: >11 000 cells/μL; left shift: >10% band forms/mL; or leukopenia: <4000 cells/μL); and (3) no alternative diagnosis at the time of hospital discharge that justified the presence of criteria 1 and 2. These criteria were adapted from prior CAPO investigations [7, 8].

Exclusion Criteria

With the intent to enroll only hospitalized patients with CAP who lived in Louisville, Kentucky, and who were counted in the 2010 US Census, patients were excluded from analysis if they did not have a permanent or valid Louisville address based on US Census Bureau data, did not have a valid Social Security number (SSN), or were in the correctional system.

Unique Patients Hospitalized With Community-Acquired Pneumonia

A unique patient hospitalized with CAP was counted as the first hospitalization during each study year. A rehospitalization due to a new episode of CAP was identified by a repeat of the same SSN in the same study year.

Incidence Calculations

The annual adult CAP incidence rates per 100 000 adults were estimated for unique patients (unadjusted and age-adjusted), total hospitalizations, unique patients by various age groups, and unique patients by comorbid conditions and smoking status, as well as for white and black/African American races. The estimated number of CAP cases in the United States was calculated by multiplying the Louisville incidence rate by the estimated 2014 US adult population obtained from the US Bureau. A normal approximation was used to calculate 95% confidence intervals (CIs) for all rates. Complete descriptions of the incidence calculations can be found in the Supplementary Materials.

Geospatial Epidemiology

The geomasked location of the home address of each patient who was enrolled in the study was obtained through the US Census Bureau website [9]. A kernel density heatmap was created using each unique patient's home location at the time of first hospitalization during the first year of the study. Kuldorff spatial scan statistic was used to calculate significant areas of risk for hospitalization due to CAP. Choropleth maps were created to compare census tract–level demographics and the spatial distribution of CAP cases. A complete description of the geospatial methods can be found in the Supplementary Materials.

Mortality

All-cause mortality for all unique hospitalized patients with CAP was evaluated during hospitalization and at 30 days, 6 months, and 1 year after hospitalization. To ensure appropriate 1-year follow-up, mortality was evaluated for patients enrolled in the first year of the study. After discharge, mortality was evaluated by reviewing medical records and by matching patients' SSNs with mortality data obtained from the Kentucky Department for Public Health Office of Vital Statistics. Mortality data from Louisville were extrapolated to the US population hospitalized with CAP. Full methodologic descriptions can be found in the Supplementary Materials.

Human Subjects Protection

The study was approved by the Institutional Review Board (IRB) at the University of Louisville Human Subjects Research Protection Program Office (IRB number 11.0613) and by the research offices at each participating hospital. The study was exempt from informed consent.

Study Coordinating Center

The study coordinating center, located at the University of Louisville Division of Infectious Diseases, directed all operational and data aspects of the study. A description of the center and its primary activities can be found in the Supplementary Materials.

RESULTS

Study Population

The US Census indicated an estimated 587 499 adult residents in the city of Louisville in 2014. During the 2-year study period, there were a total of 186 384 adults hospitalized in Louisville. A total of 8284 hospitalizations were due to CAP. Rehospitalizations due to CAP were documented in 9% of these patients. The total number of unique patients hospitalized with CAP during the 2-year study period was 7449. A flowchart describing the study patients for years 1 and 2 of enrollment is depicted in Figure 1. The clinical and laboratory characteristics of the study population are outlined in Table 1. A comparison of the Louisville population with the US population can be found in Supplementary Table 1.

Incidence of Unique Patients Hospitalized With Community-Acquired Pneumonia

The annual incidence of unique patients hospitalized with CAP was 634 (95% CI, 613.6–654.4) per 100 000 adults. The age-adjusted annual incidence was 649 (95% CI, 628.2–669.8) per 100 000 adults. The unadjusted and age-adjusted estimated number of patients hospitalized with CAP in the United States was 1 555 034 and 1 591 825 adults per year, respectively.

The annual incidence for patients 18–64 years old was 327 (95% CI, 310.9–343.1) cases per 100 000, and for patients aged

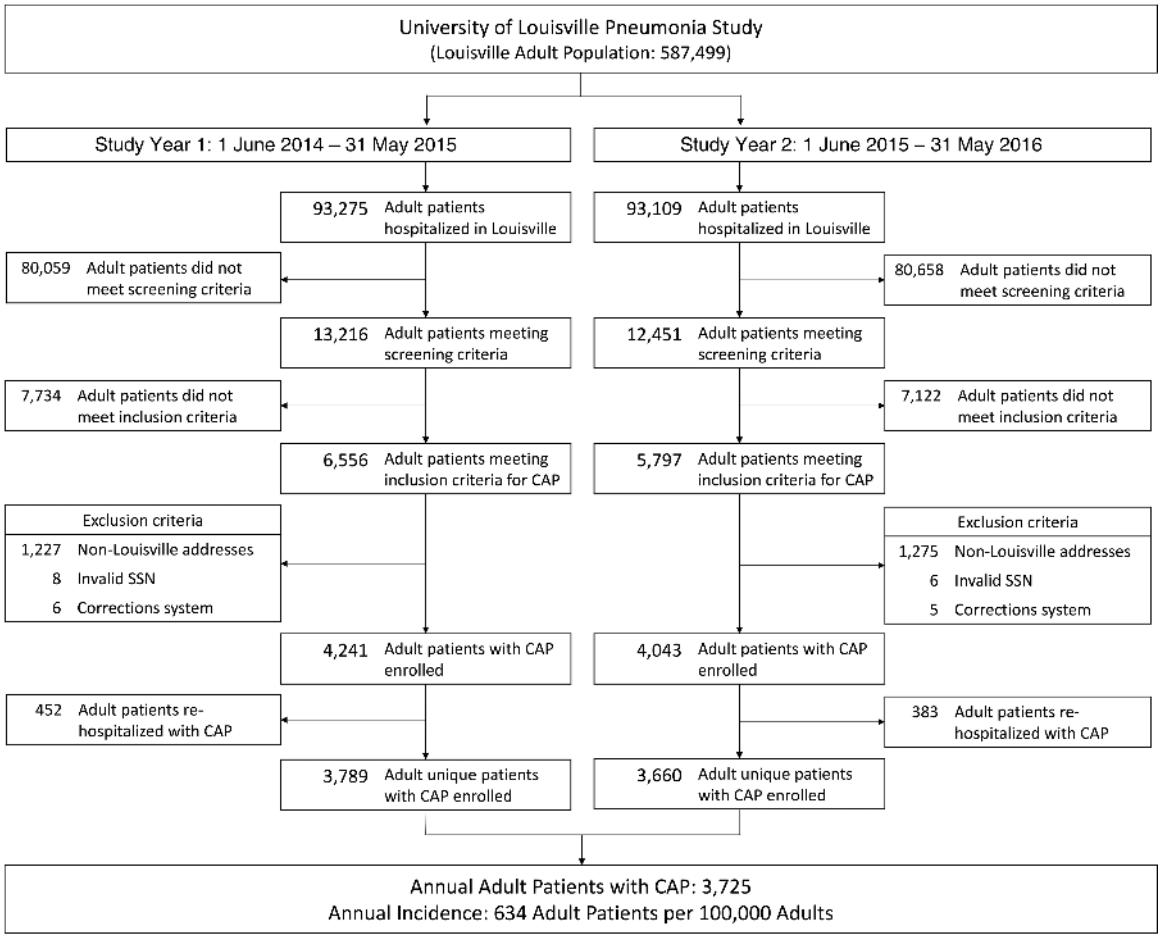

Figure 1. Study flowchart. Abbreviations: CAP, community-acquired pneumonia; SSN, Social Security number.

≥65 years was 2093 (95% CI, 2000.4–2187.7) cases per 100 000. The incidence rate for whites and black/African Americans were 667 (95% CI, 642.9–691.1) and 663 (95% CI, 615.1–710.9) cases, respectively, per 100 000 race-specific adults.

Incidence of Hospitalizations due to Community-Acquired Pneumonia

The annual incidence of hospitalizations due to CAP was 706 (95% CI, 684.5–727.5) cases per 100 000 adults. The estimated number of hospitalizations due to CAP in the United States was 1 731 121 adults per year.

Older age patients had a higher incidence of hospitalization due to CAP (Figure 2). Chronic obstructive pulmonary disease (COPD) was the comorbid condition associated with the highest incidence of hospitalization due to CAP (Figure 3).

Geospatial Epidemiology

The heatmap of unique patients with CAP in the city of Louisville during the first year of the study is depicted in Figure 4A. A zone of high risk for hospitalization due to CAP was identified in the western section of the city (risk ratio, 1.6; $P < .001$). The clustering of CAP in the western section of the city correlated with the census tract level where the average population has low annual income (Figure 4B) and is of black/African American race (Figure 4C). Census tracts with the highest percentage of elderly population were located in the eastern section of the city (Figure 4D).

Mortality

The all-cause mortality for the 3789 hospitalized adult patients with CAP in the city of Louisville for the first year of the study was 6.5% during hospitalization, 13% at 30 days, 23.4% at 6 months, and 30.6% at 1 year. During the same first year of study, the estimated number of patients hospitalized with CAP in the United States was 1 581 860. Extrapolating Louisville mortality data to the patients hospitalized with CAP in the United States, the number of deaths in the US population will be 102 821 during hospitalization, 205 642 at 30 days, 370 156 at 6 months, and 484 050 at 1 year.

DISCUSSION

This study indicates that the annual incidence of unique adult patients hospitalized with CAP in the city of Louisville is 634 (95% CI, 613.6–654.4) per 100 000 adults. When adjusted for

Table 1. Characteristics of Unique Hospitalized Patients With Community-Acquired Pneumonia Enrolled in the University of Louisville Pneumonia Study

Variable	Value
Demographics	
Age, y, median (IQR)	68 (24)
Male sex	3443 (46.2)
Black/African American race	1475 (19.8)
Medical and social history	
Obese	2615 (35.1)
HIV disease	110 (1.5)
Neoplastic disease (active or within the last year)	990 (13.3)
Renal disease	2185 (29.3)
Chronic renal failure	604 (8.1)
Congestive heart failure	2124 (28.5)
Chronic obstructive pulmonary disease	3475 (46.7)
Stroke	956 (12.8)
Current smoker	2343 (31.5)
Diabetes mellitus	2433 (32.7)
Physical examination findings	
Temperature, °C, median (IQR)	37.2 (1.1)
Respiratory rate, breaths/min, median (IQR)	22 (7)
Systolic blood pressure, mm Hg, median (IQR)	116 (36)
Diastolic blood pressure, mm Hg, median (IQR)	57 (19)
Heart rate, beats/min, median (IQR)	105 (28)
Laboratory findings	
Blood urea nitrogen, mg/dL, median (IQR)	19 (16)
Serum glucose, mg/dL, median (IQR)	141 (81)
Hematocrit, %, median (IQR)	35.7 (8.4)
Serum sodium, mEq/L, median (IQR)	137 (6)
Severity of disease	
ICU admission	1275 (17.1)
Altered mental status on admission	1407 (18.9)
Vasopressors on admission	213 (2.9)
Ventilatory support on admission	987 (13.3)
Pneumonia severity index, median (IQR)	101 (56)
PSI risk class IV or V	4502 (60.4)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: HIV, human immunodeficiency virus; ICU, intensive care unit; IQR, interquartile range; PSI, Pneumonia Severity Index.

age, the incidence is 649 (95% CI, 628.2–669.8) per 100 000 adults. This translates into approximately 1.5 million unique adult hospitalizations in the United States. To our knowledge, this is the first population-based study evaluating data on the number of unique patients requiring hospitalization for CAP in the United States. We were able to identify individual patients with CAP by using each patient's SSN as a unique identifier. Nearly 9% of the patients hospitalized with CAP will be rehospitalized due to a new episode of CAP during the same year, producing an annual incidence of hospitalizations due to CAP in the city of Louisville of 706 (95% CI, 684.5–727.5) per 100 000 adults. This translates into >1.7 million total annual hospitalizations for CAP in the United States.

Two recent studies estimated the incidence of hospitalizations due to CAP in the United States [4, 5]. Griffin et al reported annual rates of hospitalization for CAP using the Agency for Healthcare Research and Quality Nationwide Inpatient Sample (NIS) data, including approximately 20% of US hospitals [4]. The reported incidence of annual hospitalizations in elderly adults per 100 000 population for the years 2007–2009 was 1208 for 65–74 years of age, 2398 for 75–84 years of age, and 4396 for ≥85 years of age. The annual incidence of hospitalizations in adults per 100 000 population for the years 2014–2015 in Louisville calculated for the same age groups were 1699 for 65–74 years of age, 2452 for 75–84 years of age, and 4313 for ≥85 years of age. These 2 studies have remarkably similar incidence data for elderly adult hospitalizations in the United States. The NIS data included approximately 8 million annual hospitalizations and defined CAP using the *International Classification of Diseases, Ninth Revision* (*ICD-9*). We evaluated >186 000 hospitalizations and defined CAP using clinical and radiographic criteria. These 2 studies suggest that *ICD-9*–based diagnosis for CAP, when used in a large number of patients, may approximate the diagnosis of CAP based on clinical and radiographic criteria. The second recent study evaluating hospitalizations in US adults was the Etiology of Pneumonia in

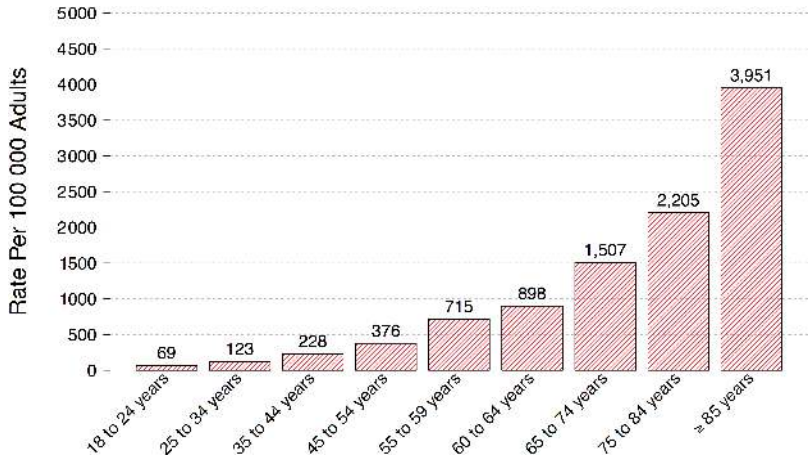

Figure 2. The impact of age on the incidence of patients hospitalized with community-acquired pneumonia.

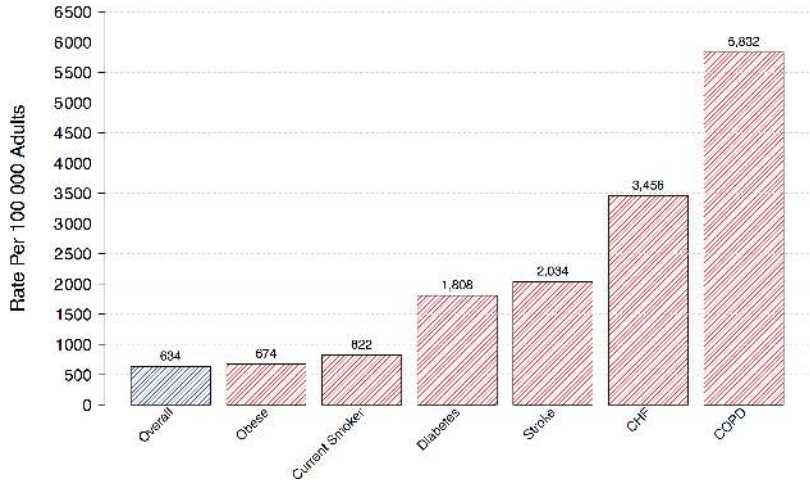

Figure 3. The impact of comorbid conditions on the incidence of patients hospitalized with community-acquired pneumonia. Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

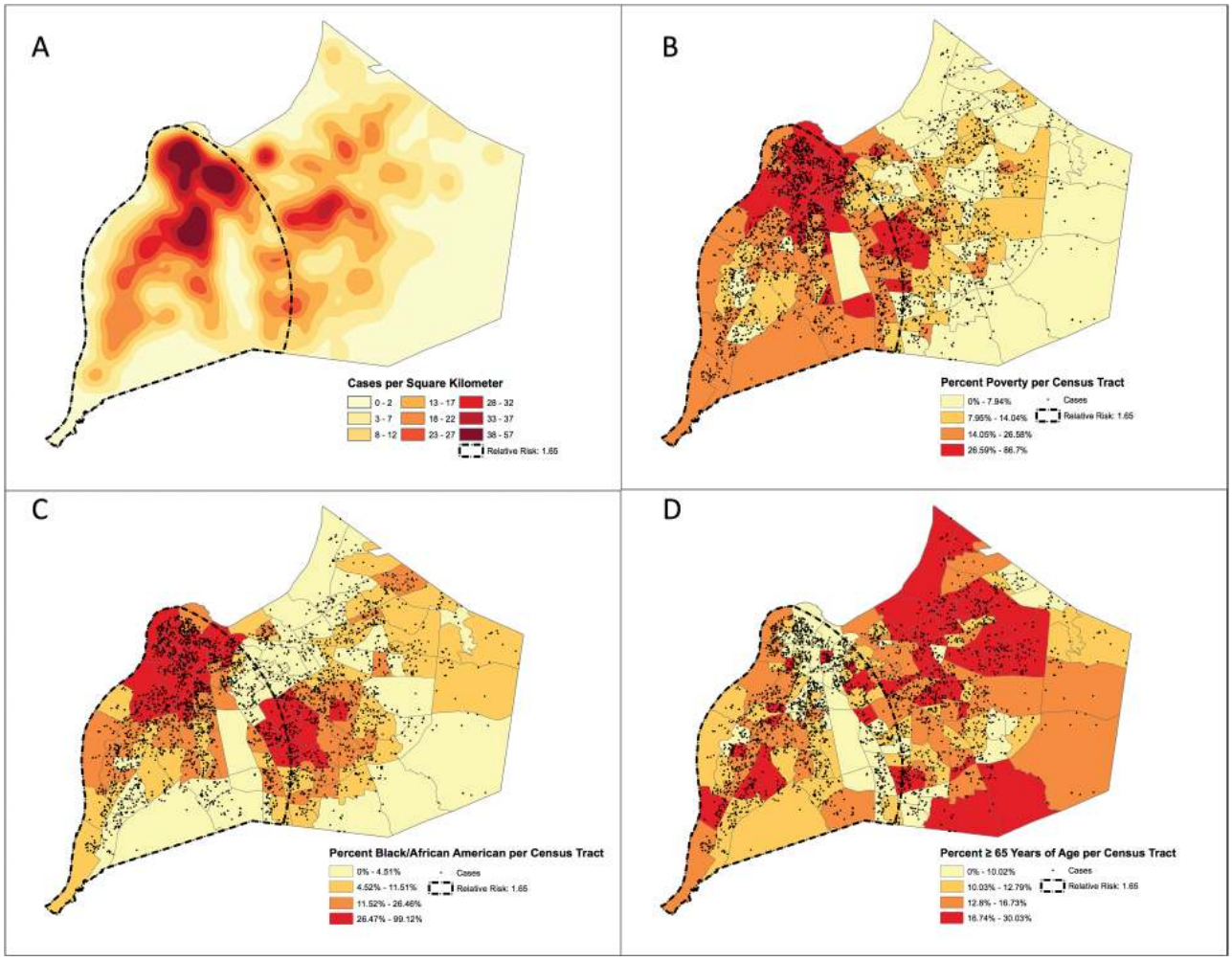

Figure 4. The heatmap distribution of unique hospitalized patients with community-acquired pneumonia (CAP) in the city of Louisville (*A*), and the associations of CAP clustering with income level (*B*), black/African American race (*C*), and population age (*D*).

the Community (EPIC) study [5]. The authors found an annual incidence of hospitalizations due to CAP in the United States of 248 per 100 000 adults; substantially lower than the NIS rates, as well as those in our study. As the primary objective of the EPIC study was to define the etiologic agents in patients with CAP, patients with risk factors for non-community-acquired respiratory pathogens were excluded. Applying the EPIC exclusion criteria available in the Louisville database, such as patients with immunosuppression, recent hospitalization, nursing home residents, and human immunodeficiency virus patients with CD4 count <200 cells/μL, the incidence rate of hospitalizations due to CAP in Louisville (271 [95% CI, 258–284] per 100 000 adults) was not statistically different than the EPIC rate (248 [95% CI, 235–261] per 100 000 adults).

In accordance with prior investigations [3–5], we documented that elderly patients had a substantially higher rate of hospitalization due to CAP compared with nonelderly adults (2093 per 100 000 vs 327 per 100 000, respectively). Several comorbid conditions place patients at increased risk for CAP, but our data suggest that the risk varies according to the condition. In our study, the highest risk appeared to be for patients with COPD, with an annual incidence of 5794 per 100 000 adults with COPD.

Approximately 1 of 10 patients hospitalized with CAP required a second hospitalization due to a new episode of CAP during the same study year. A patient hospitalized with CAP should be considered at high risk for rehospitalization due to a new episode of CAP and targeted for prevention interventions.

Geospatial epidemiology indicates that areas in Louisville with a high CAP incidence are associated with census tracts where both a high proportion of impoverished individuals and black/African American individuals reside. These data are in accordance with a prior Centers for Disease Control and Prevention (CDC) study evaluating socioeconomic and racial disparities in 4870 adults with bacteremic pneumococcal pneumonia [10]. We found similar CAP incidence rates for whites and blacks/African Americans in Louisville, suggesting that race may not be a direct risk factor for the development of CAP. Finding a race-specific genetic predisposition to CAP may be unlikely considering that race taxonomy has provided limited ability to detect genetic differences among humans [11]. Poverty is a marker of several factors such as poor nutrition, poor housing conditions, poor air quality, increased rates of smoking, lack of medical insurance, and suboptimal access to medical care and preventive medicine, each of which may increase the risk for respiratory infection [12]. Future studies are necessary to better delineate the role of race and socioeconomic disparities as risk factors for CAP.

The estimated annual number of all-cause deaths in hospitalized patients with CAP in the United States was 102 821 for in-hospital mortality and 205 642 for 30-day mortality. However, data from the 2013 CDC National Vital Statistics System indicate a total of 56 979 annual deaths due to pneumonia in the United States [1]. In our study we report all-cause mortality, counting deaths due to any reason in a hospitalized patient with CAP. The National Vital Statistics System calculates mortality for a particular disease counting only the underlying cause of death reported by physicians on death certificates. Underlying cause of death is defined as "the disease or injury, which initiated the train of events leading directly to death" [13]. A hospitalized patient with CAP may have heart disease documented as the underlying cause of death if the patient dies due to cardiovascular complications. This scenario may be common, as studies have documented that cardiovascular events such as acute myocardial infarction are frequent complications in hospitalized patients with CAP [14–16]. It can be argued that in the majority of hospitalized patients with CAP who die due to other medical complications, CAP should be considered the disease that initiated the chain of events leading to death.

Our data indicate that 1 year after hospitalization for CAP, approximately 450 000 patients will die in the United States. We, and other investigators, have reported an excess death after hospital discharge for patients admitted with CAP when compared to controls [17–22]. Future studies are necessary to determine if a hospitalization due to CAP is only a marker for severe underlying conditions, or if a causal relationship exists between CAP and late patient mortality. Chronic inflammation has been associated to accelerate aging and early death, a phenomenon describe as inflammaging [23]. Systemic inflammation has been documented in patients with CAP after a clinical resolution of infection [24]. Persistent inflammation after an episode of CAP may play a role in the premature death observed in these patients.

This study has several limitations, the primary one being the lack of a gold standard diagnostic test to define a patient as having CAP. In our study, patients hospitalized with signs and symptoms of a respiratory infection, with a new pulmonary infiltrate, and no clear alternative diagnosis were classified as having CAP. The sensitivity and specificity of our definition is unknown due to the lack of a gold standard. We used 1 or more symptoms consistent with CAP as an inclusion criterion, but many other studies required 2 or more. This may have led to an overestimate of the number of CAP cases. On the other hand, we added a criterion that no alternative diagnosis was present at the time of discharge, in an attempt to reduce the likelihood of overdiagnosis. Furthermore, if a patient residing in the city of Louisville was hospitalized for CAP at a hospital outside Louisville, they would not have been included in our study, reducing the numerator and leading to an underestimated incidence rate. Another important limitation is that we define incidence of CAP and mortality associated with CAP for hospitalized patients in the city of Louisville. We extrapolated these data to generate data for the US population. Because some demographic characteristics of the Louisville population do not

correlate with those of the US population, our generalization of incidence and mortality to the United States should be considered only an estimate. Our study has several strengths. First we were able to evaluate and enroll all adult hospitalizations in the city of Louisville for 2 consecutive years. Second, we were able to identify cases of CAP that were also included in our defined geographic area through the US Census Bureau using the patients' home address. Third, we were able to define the number of unique patients hospitalized with CAP using SSNs.

In conclusion, we documented in the city of Louisville an annual incidence of 649 adults hospitalized with CAP per 100 000 adults. We estimated a substantial burden of CAP in the US adult population. More than 1.5 million unique adults will be hospitalized in the United States each year due to CAP, and approximately 100 000 adults will die during their hospitalization. One year after a hospitalization due to CAP, death will occur in nearly 1 of 3 adults. Efforts to advance prevention strategies and treatment modalities are needed.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. J. A. R. designed the study, performed analysis and interpretation of data, and drafted the study manuscript. T. L. W., P. P., F. W. A., R. K., and W. A. M. participated in the design of the study, data analysis and interpretation, and collaborated with the development of the manuscript.

R. N., S. P., B. E. G., S. P. F., A. K. P., A. R., F. F., L. B., R. B., R. F.-B., R. C., J. B., C. V., J. S., and R. M. C. participated in the interpretation of the data and performed a critical review of the manuscript for important intellectual content. All authors approved the final version of the manuscript and are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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