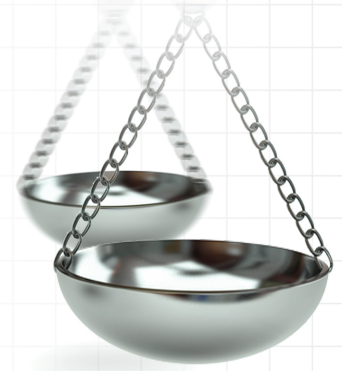




The 1-year economic burden of community-acquired pneumonia (CAP) initially managed in the outpatient setting in the USA

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Aim: To assess the annual economic burden of community-acquired pneumonia (CAP) initially managed in the outpatient setting. **Patients & methods:** Patients with an outpatient diagnosis of CAP between January 2012 and December 2016 were identified from the IQVIA (Danbury, CT & Durham, NC, USA) Real-World Data Adjudicated Claims – US Database. All-cause and CAP-related healthcare resource utilization and costs were assessed over the 1-year follow-up. Generalized linear model examined adjusted total cost. **Results:** Among 256,916 patients with outpatient CAP, a tenth (10.6%) had ≥ 1 hospitalization and, of these, 18.7% had ≥ 1 CAP-related hospitalization. The mean total cost per patient was US\$14,372; 10.9% was CAP-related and 26.1% was due to inpatient care. The adjusted mean total all-cause cost was US\$13,788. **Conclusion:** Patients with outpatient CAP incurred a substantial annual economic burden.

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Pneumonia, a common type of lower respiratory tract infection, is a leading cause of morbidity and mortality in the USA [1]. In 2017, pneumonia and influenza together were ranked as the eighth leading cause of death among adults, with an age-adjusted death rate of 14.3 deaths per 100,000 adults [2]. Community-acquired pneumonia (CAP) refers to pneumonia acquired outside of a hospital or long-term care setting. Each year in the USA, CAP affects approximately 6 million patients, resulting in more than 4 million ambulatory care visits [3].

The incidence of CAP is highest among the very young and the elderly [4]. As many patients with CAP tend to be older and have multiple comorbidities, both factors can increase the risk of poor outcomes and consequently contribute to the excessive healthcare resource utilization (HCRU) and cost [4–6]. However, the burden of CAP is still high among non-elderly adults. A study by Broulette *et al.* reported that CAP is common among commercially-insured working-age adults, with an overall incidence of 10.6 per 1000 person-years [7]. It is also costly, with mean annual costs of US\$20,961 for CAP versus US\$3783 for non-CAP patients.

The most common causes of CAP are bacterial and/or viral pathogens [8]; *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* are the most commonly identified pathogens [9]. Yet, the etiology of CAP remains unknown in up to 50% of patients in an outpatient setting, related to difficulty in obtaining an adequate sputum sample or diagnostic tests as well as infrequency of testing [10,11]. Treatment guidelines from the Infectious Diseases Society of America and American Thoracic Society recommend empiric treatment which targets the most likely pathogens based on clinical and epidemiologic risk factors and conditions [10]. In the outpatient setting, monotherapy with a macrolide is suggested for previously healthy patients with no risk of drug-resistant *S. pneumoniae* (DRSP). Monotherapy with a respiratory fluoroquinolone or combination therapy with a beta-lactam plus a macrolide is

suggested in the presence of certain comorbidities, immunosuppressing conditions or other risks for DRSP infection. The recommended empiric regimens adequately treat infections due to most CAP pathogens, but there are exceptions (e.g., methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*). Drug resistance to commonly used antibiotics for CAP is an increasing problem and will only continue to increase the clinical and economic burden of CAP [12–14]. Adverse events associated with these therapies (e.g., nausea, diarrhea, headache, dizziness) are also an important consideration [15].

As adequate treatment and management of CAP remain a significant public health issue, prior studies have examined the economic burden of CAP in the USA [7,16–20]. Most of the existing studies have reported the cost burden among patients diagnosed with CAP overall, combining patients managed in either the inpatient or outpatient setting [7,17,19]. Furthermore, other studies have only reported costs for an outpatient cohort using an episodic approach [16,18,20]. The majority of CAP episodes are treated in the outpatient setting [18,20] and CAP may have very different outcomes and associated economic burden based on the setting of care. To the best of the authors' knowledge, no studies have examined the direct annual economic burden among CAP patients managed in the outpatient setting. Such an analysis is necessary to provide a comprehensive assessment on the impact of outpatient CAP on the entire healthcare system. Understanding the economic burden of CAP specific to the outpatient setting can help to inform evidence-based targeted treatment and resource allocation, as well as help to identify 'high-cost' or 'high-need' patients.

The primary objective of this study was to examine the 1-year economic burden, in terms of all-cause and CAP-related HCRU and costs, among adults initially diagnosed with CAP and managed in the outpatient setting. Secondary objectives were to assess baseline patient characteristics, and to compare baseline characteristics and economic outcomes between patients treated with empiric monotherapy (EM) or empiric combination (EC) therapy.

Patients & methods

Study overview

This retrospective observational cohort study was conducted using data from July 2011 to December 2017. Patients with a diagnosis for CAP on an outpatient medical claim were identified from the IQVIA (Danbury, CT, and Durham, NC, USA) Real-World Data (RWD) Adjudicated Claims – US Database. Institutional review board approval was not required because this was a retrospective analysis of secondary data using only de-identified patient records.

Data source

The IQVIA RWD Adjudicated Claims is one of the largest US health plan claims databases, comprised of 150 million unique enrollees. The database is considered representative of the national, commercially insured population in terms of age (for those under 65) and gender. The database includes information on demographics, payer type, health plan enrollment dates, inpatient and outpatient diagnoses and procedures, retail and mail-order prescription records and payments. All data from the IQVIA RWD Adjudicated Claims are de-identified and compliant with the Health Insurance Portability and Accountability Act to protect patient's privacy.

Patient selection

Enrollees with ≥ 1 diagnosis code for CAP (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] 480.x–486.x, 487.0, 488.11, 488.81, and International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM] A22.1, A37.01, A37.11, A37.81, A37.91, A48.1, B25.0, B44.0, J09.X1, J10.0x, J11.0x, J12.x–J18.x) on a confirmatory outpatient medical claim in any diagnosis position between 1 January 2012 and 31 December 2016 (the 'selection window'; Figure 1) were selected; date of the first claim was termed as 'index date'. The study period began 1 July 2011 and ended 31 December 2017, allowing for a 6-month pre-index period and a 1-year follow-up period. CAP diagnoses included pneumonias due to bacteria, viruses or unspecified organisms, but did not include other types of pneumonia, such as ventilator-associated pneumonia, pneumonia in systemic infections or aspiration pneumonia. Additional patient inclusion criteria were as follows: 1) adults (≥ 18 years old at index) with a claim for an antimicrobial of interest on the index date or the day after the index date with minimum days' supply of > 1 day for oral prescriptions. Antimicrobials included drugs from the following classes: aminoglycosides, antifungals, beta-lactams, fluoroquinolones, folate pathway inhibitors, glycopeptides, macrolides, oxazolidinone, polymyxins and tetracyclines. The initiated antimicrobial(s) determined

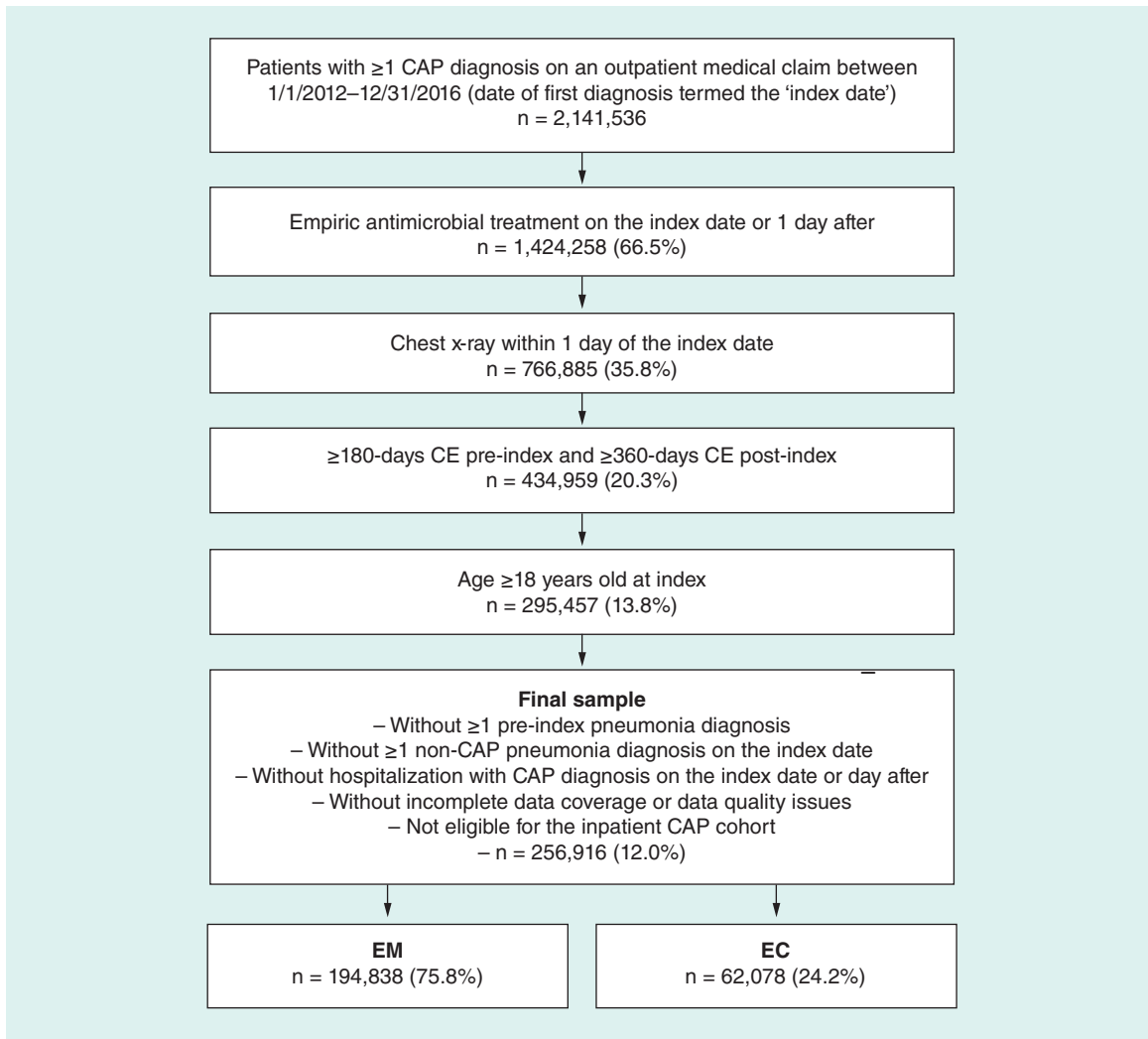


Figure 1. Patient selection.

CAP: Community-acquired pneumonia; CE: Continuous enrollment; EC: Empiric combination therapy; EM: Empiric monotherapy.

the index therapy class and index treatment type (EM or EC); 2) chest x-ray within 1 day of the index date; 3) continuous enrollment ≥ 180 days prior to the index date (the '6-month pre-index period') and ≥ 360 days continuous enrollment following (and including) the index date (the '1-year follow-up').

Patients were excluded if they had ≥ 1 diagnosis code for pneumonia (CAP or non-CAP) in the 6-month pre-index period or ≥ 1 diagnosis code for non-CAP pneumonia on the index date. Additionally, patients having an inpatient hospitalization with diagnosis of CAP (in any position) on the index date or the day after the index date were excluded from the study cohort. This was done to exclude CAP that was initially diagnosed in the outpatient setting but then rapidly progressed to requiring inpatient care. Those with incomplete data, data quality issues or those identified as an eligible patient for a parallel inpatient CAP economic burden study conducted by the authors, and with inpatient date of admission prior to or up to 1 day after the outpatient index date, were also excluded.

Study measures

Baseline demographic characteristics were assessed at the index date, including age, gender, geographic region, health plan type and payer type, and index year. Clinical characteristics were measured during the 6-month pre-index period (not including the index date unless otherwise specified). Clinical characteristics included index therapy class and index treatment type (EM or EC), physician specialty associated with the index date, and baseline Charlson

Comorbidity Index (CCI) score (Dartmouth–Manitoba adaptation) [21]. Presence of respiratory conditions (respiratory failure, respiratory acute infection, respiratory – other disease, respiratory – chronic condition) [16], pre-index comorbidities, and index CAP type were also assessed. Index CAP type was classified as healthcare-associated pneumonia (HCAP) or community-onset pneumonia (COP). A patient was classified as having HCAP if one of the following factors were presented: 1) prior hospitalization within 90 days of the index date, 2) hemodialysis in the 6-month pre-index period, or 3) immune suppression in the 6-month pre-index period (based on: ≥ 1 diagnosis code for encounter for chemotherapy and immunotherapy for neoplastic conditions, personal history of irradiation, or organ or tissue replaced by transplant, or ≥ 1 claim for a corticosteroid) [22]. Any patient not meeting the HCAP definition was considered to have COP. Total all-cause pre-index healthcare cost during the baseline period was also measured.

The primary outcomes were all-cause and CAP-related HCRU and costs over the 1-year follow-up period. CAP-related HCRU and costs were identified based on outpatient medical claims with a CAP diagnosis, CAP-related hospitalization or claims for antimicrobials used in the treatment of CAP. CAP-related hospitalization was defined as an inpatient hospitalization meeting any of the following criteria: admitting diagnosis of CAP, primary discharge of CAP or secondary discharge diagnosis of CAP if the primary discharge diagnosis was for sepsis or respiratory failure. HCRU and costs were expressed as both the proportion of patients with such utilization as well as per-patient mean, standard deviation (SD) and median for cost and utilization. Utilization and costs were calculated on a per patient basis, averaged across the cohort (unless otherwise specified). Thus, the denominator included all patients in a cohort. Direct healthcare cost was determined using the ‘allowed’ amount field, which represents the amount paid by payers combined with the patient out-of-pocket cost (e.g., copay, co-insurance). Cost was converted to 2017 US dollar using the medical component of the Consumer Price Index. HCRU and cost were measured and reported for the following mutually exclusive categories: outpatient pharmacy, inpatient hospitalizations and outpatient medical. Outpatient medical comprised the following mutually exclusive categories: emergency room (ER) visits, physician office visits, outpatient surgery, lab/pathology, radiology and all other outpatient services (outpatient ancillary and Healthcare Common Procedure Coding System drugs).

Statistical analyses

Descriptive statistics were reported for all relevant study measures described above for the overall cohort. For categorical measures, data reporting included frequency and percentage of total study patients observed in each category. For continuous and count variables, findings were presented as the mean, SD and median (and intervals as relevant). As a secondary analysis, study outcomes were compared by index treatment type (EM vs EC) using the parametric t-test for continuous variables and the Chi-square test for categorical variables.

Generalized linear models with log link and gamma distribution were used to estimate adjusted mean all-cause costs (inpatient, outpatient medical, outpatient pharmacy and total) over the 1-year follow-up and to identify patient characteristics associated with total all-cause cost. Because inpatient hospitalizations were infrequent, mean adjusted inpatient cost was calculated by subtracting mean adjusted outpatient medical and pharmacy cost from mean adjusted total cost. Baseline characteristics were considered for adjustment. Collinearity was evaluated during model development and a stepwise model-building approach was utilized ($p < 0.10$ for inclusion and retention). A p -value of < 0.05 was considered statistically significant. All analyses were conducted using SAS 9.4 (SAS Institute Inc., NC, USA).

Results

Sample description

A total of 2,141,536 patients were identified with an outpatient medical claim for CAP during the selection window. The final eligible sample comprised 256,916 patients (12.0% of the starting sample; [Figure 1](#)). The mean age of the study sample was 45.7 years and half or more were female (133,698 [52.0%]) and commercially insured (150,880 [58.7%]). Patients using EM and EC appeared similar in terms of demographic characteristics; although, there was some variation in geographical region of residence. For example, a lower proportion of EM patients resided in the South compared with EC patients (70,559 [36.2%] vs 37,883 [61.0%]; [Supplementary Table 1](#)) [Table 1](#).

[Table 2](#) summarizes the baseline clinical characteristics of the study sample. At index, the majority of patients were treated with EM (194,838 [75.8%]); the most common index therapies (mutually exclusive) were fluoroquinolones (80,165 [31.2%]), macrolides (72,132 [28.1%]), and beta-lactams ([28,966] 11.3%). Approximately half the patients (132,579 [51.6%]) saw a primary care physician at the index date. The majority (185,165 [72.1%]) were

Table 1. Baseline patient demographic characteristics.

Characteristic	Overall N = 256,916
Mean (SD; years)	45.7 (12.9)
Age group (%)	
– 18–34 years	21.3
– 35–44 years	21.6
– 45–54 years	26.6
– 55–64 years	29.3
– ≥65 years	1.1
Female (%)	52.0
Geographic region (%)	
– Northeast	19.0
– Midwest	26.9
– South	42.2
– West	11.9
Health plan type (%)	
– PPO	79.6
– HMO	12.5
– POS	5.2
– Other/unknown	2.7
Payer type (%)	
– Commercial	58.7
– Self-insured	34.9
– Other/unknown	6.4
Index year (%)	
– 2012	22.2
– 2013	18.8
– 2014	18.3
– 2015	20.8
– 2016	20.0

HMO: Health maintenance organization; POS: Point-of-service; PPO: Preferred provider organization; SD: Standard deviation.

identified as having COP while 27.9% (71,751) were identified with HCAP; approximately one-fourth (67,521 [26.3%]) used a corticosteroid in the 6-month baseline period. In the 6-month baseline period, the mean CCI score was 0.5. About a third (78,149 [30.4%]) had a respiratory acute infection. Common chronic conditions in the 6-month baseline period included asthma (19,324 [7.5%]), COPD (9739 [3.8%]) and diabetes (24,588 [9.6%]). In the 6-month baseline period, 43,249 patients (16.8%) used an inhaler for lung disease while 108,877 (42.4%) used an antimicrobial of interest. Only 3102 patients (1.2%) received pneumococcal vaccine in the 6-month pre-index period. The mean total all-cause cost in the 6-month baseline period was US\$5036 (SD = US\$16,508). Patients using EM and EC appeared similar in terms of baseline clinical characteristics (Supplementary Table 2).

All-cause HCRU & cost

Overall, 113,166 patients (44.0%) had ≥1 all-cause ER visit and 27,209 (10.6%) had ≥1 all-cause hospitalization over the 1-year follow-up, with mean length of stay (LOS) for the first hospitalization of 5.3 days (Figure 2A). Patients had a mean of 11.2 all-cause physician office visits and 14.6 all-cause lab/pathology tests over the 1-year follow-up (Figure 2B). All-cause HCRU appeared similar between EM and EC patients (Supplementary Table 3).

The mean total all-cause cost per patient over the 1-year follow-up was US\$14,372 (SD = US\$41,521), with inpatient care being the primary cost component (26.1%), followed by all other outpatient services (19.9%) and outpatient pharmacy (18.5%; Figure 3). Among patients with ≥1 all-cause hospitalization, mean total cost of the first hospitalization was US\$21,775 (SD = US\$32,373). Mean total all-cause cost per patient over the 1-year follow-

Table 2. Baseline patient clinical characteristics.

Characteristic	Overall N = 256,916
Index therapy class ($\geq 5\%$; not mutually exclusive)	
– Beta-lactams	33.9
– Fluoroquinolones	42.7
– Macrolides	40.4
– Tetracyclines	6.8
Index therapy class ($\geq 5\%$; mutually exclusive)	
<i>Monotherapy</i>	75.8
– Beta-lactams	11.3
– Fluoroquinolones	31.2
– Macrolides	28.1
<i>Combination therapy (%)</i>	24.2
– Top 5 most frequent combinations	
– Beta-lactams + macrolides	10.5
– Beta-lactams + fluoroquinolones	9.5
Physician specialty at index (%)	
– Primary care (GP/FM/IM/NP/PA)	51.6
– Emergency medicine	11.6
– Other	44.0
– Unknown/not available	8.8
Index CAP type (%)	
– HCAP ($\geq 5\%$)	27.9
– Pre-index immune suppression	26.6
– Received any claim for a corticosteroid	26.3
– COP	72.1
Mean (SD) CCI score	0.5 (1.0)
Respiratory conditions (%)	
– Respiratory acute infection	30.4
– Respiratory – other disease	11.1
– Respiratory – chronic condition	13.4
Pre-index comorbid conditions ($\geq 5\%$)	
– Cardiac arrhythmia	5.4
– Chronic pain/fibromyalgia	6.2
– Depression	8.8
– Dyslipidemia	19.5
– Hypertension	22.6
– Osteoarthritis	8.3
– Sleep disorders	8.1
– Smoking	7.5
– Thyroid disease	8.1
Pre-index medications ($\geq 5\%$)	
– Inhalers for lung disease	16.8
– Antibiotics of interest	42.4
– Beta-lactams	21.3
– Fluoroquinolones	9.5
– Macrolides	17.4
Mean (SD) total all-cause pre-index healthcare costs	US\$5036 (US\$16,508)
CAP: Community-acquired pneumonia; CCI: Charlson Comorbidity Index; COP: Community-onset pneumonia; COPD: Chronic obstructive pulmonary disease; FM: Family practice; GP: General practice; HCAP: Healthcare-associated pneumonia; IM: Internal medicine; NP: Nurse practitioner; PA: Physician assistant; SD: Standard deviation.	

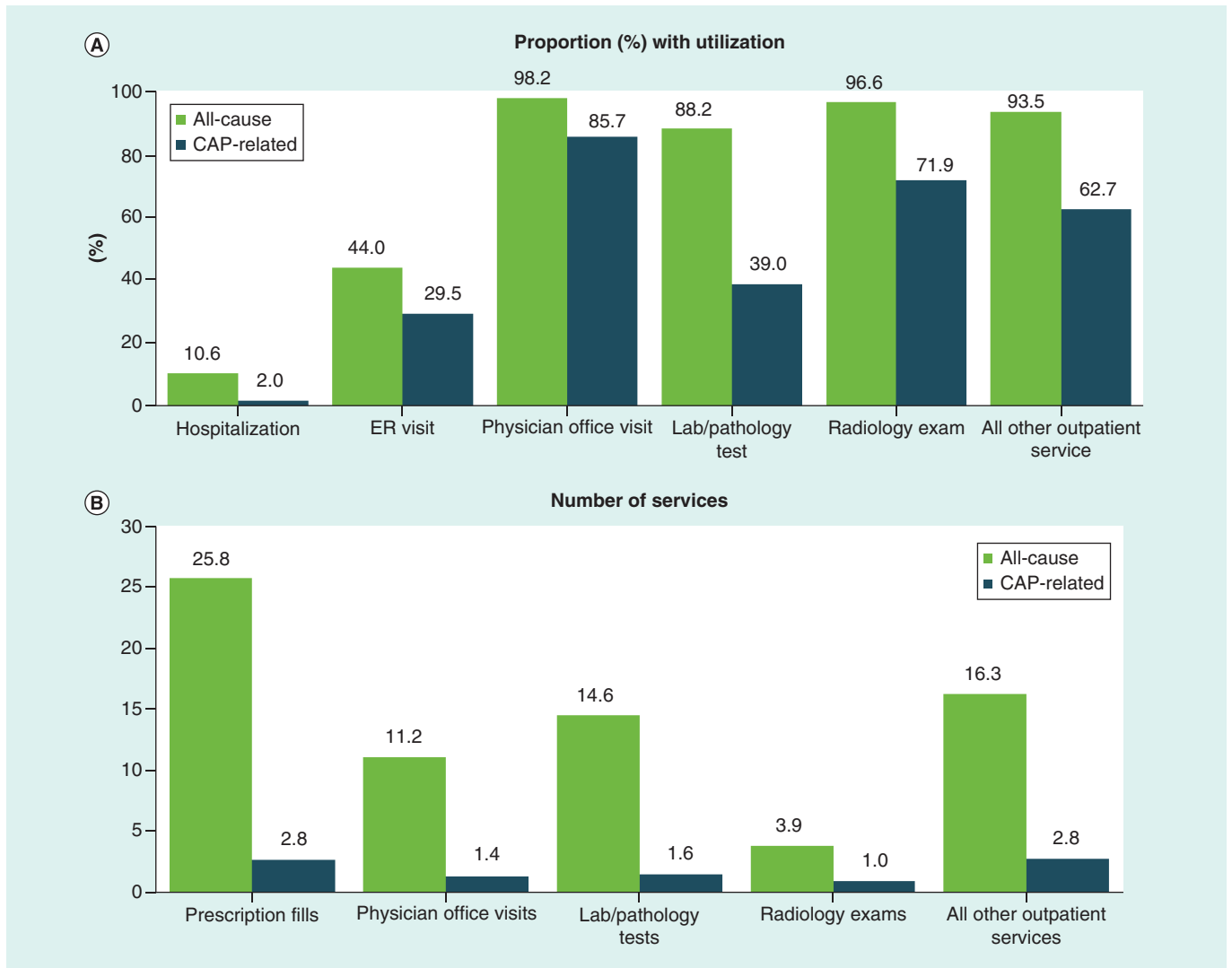


Figure 2. Healthcare resource utilization over the 1-year follow-up. (A) HCRU – proportion with utilization over the 1-year follow-up. **(B)** HCRU – mean number of services per patient over the 1-year follow-up. All other outpatient = outpatient ancillary and HCPCS drugs. CAP: Community-acquired pneumonia; ER, Emergency room; HCRU: Healthcare resource utilization.

up was higher among EC as compared with EM patients (US\$14,944 vs US\$14,189; $p < 0.0001$; [Supplementary Table 4](#)).

CAP-related HCRU & costs

Overall, 75,876 patients (29.5%) had ≥ 1 CAP-related ER visit and 220,122 (85.7%) had ≥ 1 CAP-related physician office visit over the 1-year follow-up ([Figure 2A](#)). A total of 5100 (2.0%) had ≥ 1 CAP-related hospitalization over the 1-year follow-up; the mean LOS for the first hospitalization was 5.8 days. Patients had a mean of 1.4 CAP-related physician office visits and 1.6 CAP-related laboratory/pathology tests over the 1-year follow-up ([Figure 2B](#)). CAP-related HCRU over the 1-year follow-up was generally similar between EM and EC patients with a few exceptions ([Supplementary Table 3](#)). A higher percentage of patients using EC had ≥ 1 CAP-related lab/pathology test (30,037 [48.4%] vs 70,040 [35.9%]), ≥ 1 CAP-related radiology exam (48,623 [78.3%] vs 135,995 [69.8%]), and ≥ 1 CAP-related all other outpatient service (54,887 [88.4%] vs 106,077 [54.4%]) than EM patients (all $p < 0.0001$).

The mean total CAP-related cost per patient over the 1-year follow-up was US\$1561 (SD = US\$7237; [Table 3](#)); together, inpatient care and ER visits accounted for more than half of CAP-related total cost (28.7 and 28.2%,

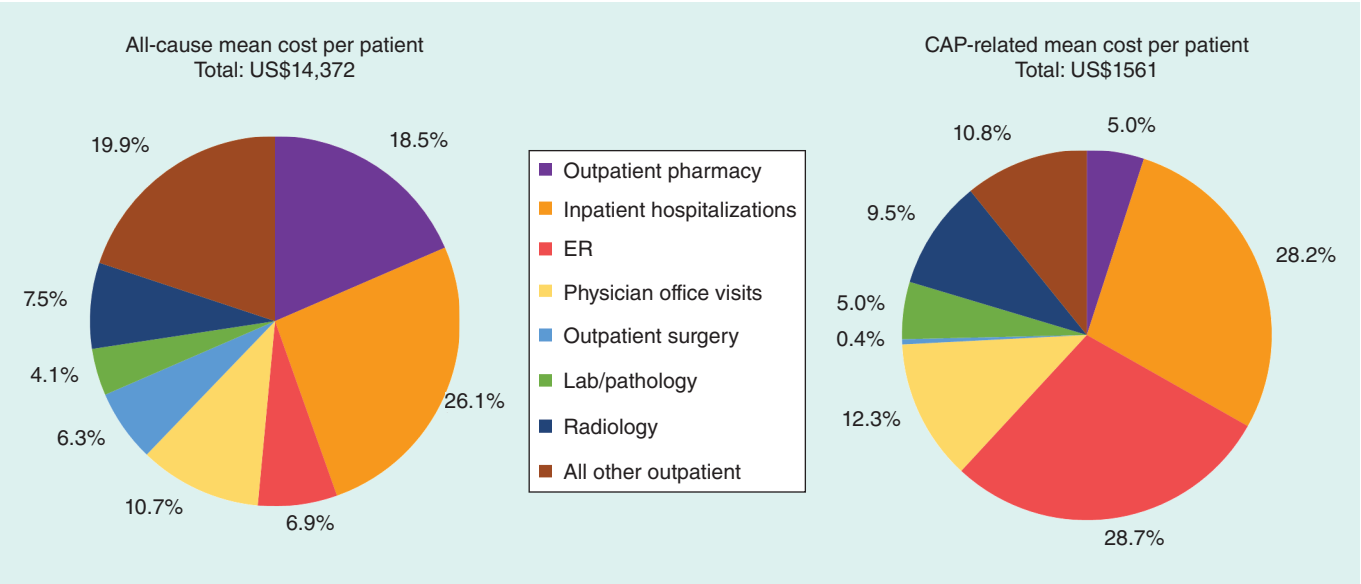


Figure 3. Mean healthcare cost over the 1-year follow-up by cost category. All other outpatient = outpatient ancillary and Healthcare Common Procedure Coding System drugs. CAP: Community-acquired pneumonia; ER: Emergency room.

Table 3. All-cause and community-acquired pneumonia-related healthcare cost over the 1-year follow-up.						
Cost (2017 US dollar) per patient		Overall N = 256,916				
Mean	SD	All-cause		SD	CAP-related	
		Median	Mean		Median	Mean
Total	US\$14,372	US\$41,521	US\$4590	US\$1561	US\$7237	US\$401
Outpatient pharmacy	US\$2659	US\$9749	US\$500	US\$78	US\$593	US\$27
Inpatient hospitalizations	US\$3746	US\$15,145	US\$0	US\$440	US\$6647	US\$0
Outpatient medical	US\$7967	US\$24,683	US\$3059	US\$1043	US\$2214	US\$335
ER	US\$995	US\$3281	US\$0	US\$448	US\$1333	US\$0
Physician office visits	US\$1537	US\$9776	US\$827	US\$192	US\$307	US\$142
Outpatient surgery	US\$906	US\$3148	US\$0	US\$7	US\$194	US\$0
Lab/pathology	US\$590	US\$1879	US\$196	US\$78	US\$279	US\$0
Radiology	US\$1079	US\$4368	US\$235	US\$149	US\$467	US\$45
All other outpatient	US\$2859	US\$15,866	US\$358	US\$169	US\$1094	US\$12
All other outpatient = outpatient ancillary and HCPCS drugs.						
CAP: Community-acquired pneumonia; ER: Emergency room; HCPCS: Healthcare Common Procedure Coding System; SD: Standard deviation.						

respectively; Figure 3). Among patients with ≥1 CAP-related hospitalization, mean total cost of the first hospitalization was US\$18,649 (SD US\$29,500). Mean total CAP-related cost per patient over the 1-year follow-up was significantly higher among patients using EC as compared with those using EM (US\$1801 vs US\$1484; $p < 0.0001$; Supplementary Table 4).

Adjusted all-cause total cost

The unadjusted and adjusted mean total all-cause costs over the 1-year follow-up were similar (Figure 4). Table 4 summarizes the baseline variables that were significantly associated ($p < 0.0001$) with all-cause total cost over the 1-year follow-up. Older age (55+ years at index; reference: 18–34 years of age) was associated with 90.7% higher cost. Those with HCAP at index incurred 55.4% higher cost as compared with those with COP. Presence of several comorbidities at baseline was associated with higher cost: diabetes was associated with 71.8% higher cost, cardiac arrhythmia was associated with 60.5% higher cost, chronic pain/fibromyalgia was associated with 42.4%

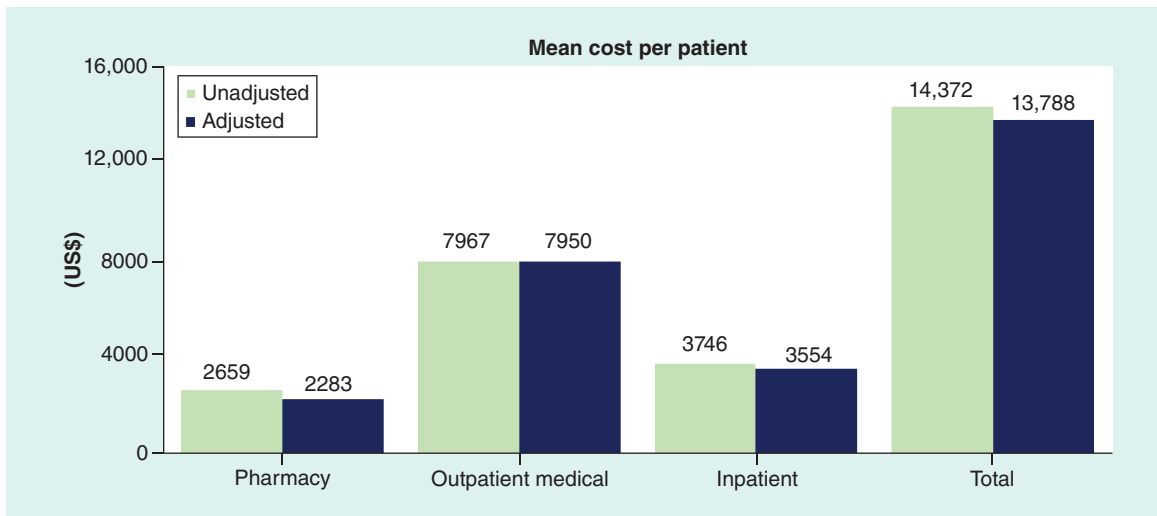


Figure 4. Unadjusted and adjusted mean healthcare cost over the 1-year follow-up. Outpatient medical = emergency room, physician office visits, outpatient surgery, lab/pathology, radiology, all other medical.

higher cost, depression was associated with 34.8% higher cost, and smoking was associated with 32.6% higher cost. Fluoroquinolone use was associated with 34.4% higher cost.

Discussion

This real-world retrospective database study evaluated 256,916 patients with CAP initially managed in the outpatient setting using the IQVIA RWD Adjudicated Claims – US Database. The majority (72.1%) of CAP was community-onset and treated with EM (75.8%). Patients incurred a substantial burden in the 1-year follow-up period. A tenth (10.6%) had ≥ 1 all-cause hospitalization, and of these, 18.7% had ≥ 1 CAP-related hospitalization. CAP-related hospitalizations were costly, and the first CAP-related hospitalization was associated with a mean cost of US\$18,649. The mean unadjusted total all-cause cost in the 1-year follow-up was US\$14,371. CAP-related costs represented only 10.9% of all-cause total costs; it is unknown whether this is related to potential miscoding in the claims data. CAP can also have broader and longer lasting impacts as CAP can cause exacerbations of pre-existing conditions or even increase the risk of incident cardiovascular disease [23,24]. Nevertheless, our cohort definition identified a population associated with high resource use and cost over the 1-year follow-up. Inpatient and ER care were important cost drivers. Inpatient care accounted for a quarter of total all-cause cost, while inpatient care and ER visits each accounted for a quarter of total CAP-related cost. In adjusted analyses, mean total all-cause cost was US\$13,798. Older age, index HCAP, baseline fluoroquinolone use and several baseline comorbidities were associated with significantly higher cost. In addition to quantifying the overall economic burden, the current study provides valuable insights on the association of initial treatment with EM or EC with the economic burden of CAP. EC patients had higher all-cause and CAP-related total costs compared with EM patients.

To the best of the authors' knowledge, this is the first retrospective real-world database study to quantify the direct economic burden of CAP initially diagnosed and managed in the outpatient setting over a 1-year follow-up period. While a number of studies have assessed the economic burden of CAP, including in the outpatient setting [7,16–18], differences in the study design, patient selection (e.g., length of follow-up, cohort definition, study population [e.g., Medicare, elderly], time periods, treatment and chest x-ray requirements, allowing prior hospitalization, etc.) limit direct comparisons. Furthermore, the majority of these studies have reported the overall cost of CAP (i.e., cost among patients diagnosed in either the inpatient or outpatient setting) [7,17,19], suggesting a lack of current data on the annual economic burden subsequent to CAP in the outpatient setting. A previous study by Bonafede *et al.* found a mean annualized total cost of US\$14,038 among patients diagnosed with CAP in either the inpatient or outpatient setting using a large administrative claims dataset of working-age adults (active employees or adult dependents) [17]. Their cost estimate was close to the annual cost estimate identified from our study, although it is important to note that the study by Bonafede *et al.* did not specifically report the annual burden of outpatient CAP. They also did not specify the number of patients diagnosed with outpatient CAP, but other research has found the

Table 4. Generalized linear model for total all-cause healthcare cost over the 1-year follow-up.

Independent variables	Exponentiated parameter estimate	95% CI		p-value
		Lower limit	Upper limit	
Dependent variable – all-cause total cost over the 1-year follow-up				
Age group (vs 18–34 years)				
– 35–44 years	1.104	0.084	0.113	<0.0001
– 45–54 years	1.477	0.376	0.404	<0.0001
– 55+ years	1.907	0.632	0.659	<0.0001
– Combination therapy (vs monotherapy)	1.067	0.054	0.076	<0.0001
– HCAP (vs COP)	1.554	0.429	0.452	<0.0001
Region (vs northeast)				
– Midwest	1.059	0.043	0.072	<0.0001
– South	0.942	-0.073	-0.046	<0.0001
– West	1.271	0.222	0.258	<0.0001
Payer type (vs. commercial)				
– Medicaid/Medicare Risk/Unknown	0.837	-0.199	-0.157	<0.0001
– Self-insured	0.981	-0.030	-0.009	0.000
Index therapy class (not mutually exclusive)				
– Macrolides	0.864	-0.157	-0.136	<0.0001
– Tetracyclines	0.889	-0.137	-0.098	<0.0001
– Emergency medicine specialist at index (vs primary care)	1.275	0.228	0.258	<0.0001
Respiratory conditions				
– Respiratory – other disease	1.043	0.027	0.058	<0.0001
Baseline comorbidities				
– Asthma	1.127	0.101	0.138	<0.0001
– Cardiac arrhythmia	1.605	0.452	0.494	<0.0001
– Chronic pain/fibromyalgia	1.424	0.333	0.373	<0.0001
– Depression	1.348	0.282	0.316	<0.0001
– Diabetes	1.718	0.525	0.558	<0.0001
– Osteoarthritis	1.280	0.229	0.265	<0.0001
– Sleep disorders	1.288	0.236	0.271	<0.0001
– Smoking	1.326	0.264	0.300	<0.0001
– Thyroid disease	1.151	0.123	0.158	<0.0001
Pre-index medications of interest				
– Antifungals	1.161	0.125	0.174	<0.0001
– Beta-lactams	1.050	0.037	0.061	<0.0001
– Fluoroquinolones	1.344	0.279	0.312	<0.0001
– Folate pathway inhibitors	1.285	0.227	0.274	<0.0001
– Macrolides	1.036	0.022	0.048	<0.0001
– Tetracyclines	1.164	0.129	0.175	<0.0001
Table reduced to significant covariates (p < 0.0001). COP: Community-onset pneumonia; HCAP: Healthcare-associated pneumonia.				

Table reduced to significant covariates ($p < 0.0001$).

COP: Community-onset pneumonia; HCAP: Healthcare-associated pneumonia.

majority of CAP cases to originate in the outpatient setting [18,20]. Other differences limiting comparisons to the study by Bonafede *et al.* include the use of older data (2003–2007) and lack of requirements for antimicrobial use or chest x-ray. Nevertheless, our findings confirm the results of previous studies that suggest that the direct costs associated with CAP are substantial among adults [7,17–20].

Several studies have used an episodic approach to evaluate the cost of outpatient CAP but did not require the patient eligibility criteria of empiric antimicrobial treatment and/or chest x-ray [16,18,20], and also studied elderly or older adults, limiting any direct comparisons. The reported mean cost of a CAP outpatient episode ranged from US\$2212 to US\$2394, with mean length of 10.2–12.4 days [18,20]. These findings suggest a substantial economic burden associated with the initial CAP outpatient episode.

Our study identified inpatient and ER-related care as the major drivers of total cost. Overall, a tenth (10.6%) of patients had ≥ 1 all-cause hospitalization, and, of these, 18.7% had ≥ 1 CAP-related hospitalization. These hospitalizations for a minority of patients were associated with high inpatient costs. For the overall sample, inpatient care accounted for a quarter of total all-cause cost, while inpatient care and ER visits each accounted for a quarter of total CAP-related cost. A previous study by Llop *et al.* reported that among patients with outpatient CAP treated with monotherapy (any oral fluoroquinolone, macrolide or beta-lactam monotherapy), the mean 30-day cost post-treatment initiation was substantially higher among patients with a hospitalization compared with those without a hospitalization (US\$13,204 vs US\$1508) [16]. Site-of-care (inpatient or outpatient) is an important decision in the management of CAP [10]. Although patients treated in the inpatient or ER setting may be high risk and require more intensive care, previous research suggests that many low-risk patients (26–31%) who could be good candidates for outpatient care are instead admitted to the inpatient setting [25,26]. This can amplify the economic burden of CAP, and adequate management of this group of patients can potentially lead to cost savings.

In the current study, more than a fourth of the sample (27.9%) was found to have HCAP. Index HCAP was found to be one of the risk factors associated with higher total healthcare costs. HCAP represents a distinct syndrome because highly resistant pathogens such as methicillin-resistant *S. aureus* are commonly seen in HCAP [27]. The high rates of HCAP among patients with CAP warrant more effective treatments for treating probable resistant pathogens. Another factor that was associated with higher adjusted healthcare cost was baseline fluoroquinolone use. Although this study did not evaluate antimicrobial-related adverse events, it is important to note that fluoroquinolones are associated with a number of severe adverse events, some of which are disabling and potentially irreversible, for which the US FDA has issued ‘black-box’ warnings (e.g., tendon rupture, tendinitis, central nervous system effects, etc.) [28–30]. In fact, the EMA has restricted the use of fluoroquinolones, where other antibiotics may be used [31]. In our study, 10% of patients had fluoroquinolone use at baseline, and at index, 31% were treated with fluoroquinolone monotherapy and another 12% received combination therapy including a fluoroquinolone. Future research is warranted to understand the association of fluoroquinolones with higher economic burden in light of the potential for severe adverse events. Other factors that were associated with higher total cost included older age and presence of certain baseline comorbidities. In our study, older age (>55 years) was associated with 90.7% higher cost as compared with those who were 18–34 years old. It is well-established that older adults carry a disproportionately higher epidemiologic burden of CAP due to higher risk of incidence, higher number of chronic conditions, and risk of hospitalization [18,32]. This highlights the need for better treatment strategies for older adults, especially those with multiple comorbidities who may be at higher risk for complications and adverse events related to CAP.

The study has limitations inherent to retrospective database studies, as well as to the data source and study design. First, results from retrospective studies must be interpreted with caution, and in context of results from similar studies, because they can only establish associations and not causal relationships. Second, administrative claims data do not provide as much clinical detail as medical records as they are primarily collected for the purposes of payment. Therefore, there is a potential for miscoding or misclassification in the identification of our cohort as well as in the measurement of CAP-related HCRU and cost. Third, our study only captures direct costs as measured by administrative claims data. The data does not provide any insight into indirect costs of CAP such as loss of productivity, sick time or short-term disability. It is also a limitation of the cost data that rebates or discounts may not be captured. It is unknown whether the allowed amount reflects any such discount, as this may vary from plan to plan. Therefore, it is possible that we overestimate the cost burden in some cases. Finally, since the study sample employed was largely commercially- or self-insured, these findings may not be representative of the uninsured, Medicare or Medicaid populations or the over 65 population in general. Despite these limitations, our study is the first to report estimates of the 1-year economic burden among patients with CAP initially diagnosed and managed in the outpatient setting.

Conclusion

This retrospective real-world study documents the annual direct costs among adults with CAP initially diagnosed and managed in the outpatient setting. Patients had a substantial 1-year economic burden in both unadjusted and adjusted analyses. At initial CAP diagnosis, nearly two-thirds of patients (76%) were treated with EM antimicrobials, most frequently fluoroquinolones (31%); one-quarter (24%) were treated with EC therapy. Inpatient care accounted for one-quarter (26%) of total all-cause costs and ER visits and inpatient care accounted for more than half (57%) of total CAP-related costs. Additionally, patients receiving EC had higher all-cause and CAP-related total costs

compared with patients receiving EM. Given these findings, efforts for cost-effective monotherapy treatment strategies for CAP are warranted in the outpatient setting, especially for high-risk and high-cost groups.

Summary points

- Community-acquired pneumonia is a leading infectious cause of morbidity and mortality. Each year in the USA, approximately 6 million cases of CAP are reported, resulting in more than 4 million ambulatory care visits [3].
- No previous studies have evaluated the annual economic burden of outpatient CAP. Prior studies have reported the cost burden among patients diagnosed with CAP overall, combining patients managed in either the inpatient or outpatient setting [7,17,19] or only reported costs for an outpatient cohort using an episodic approach [16,18,20].
- This large, US claims-based study evaluated healthcare resource utilization and costs over a 1-year follow-up period among 256,916 patients initially diagnosed with CAP and managed in the outpatient setting between 2012 and 2016.
- For the index CAP episode, two-thirds of patients (76%) were treated with empiric monotherapy antimicrobials, most frequently fluoroquinolones (31%); a quarter (24%) were treated with empiric combination therapy.
- Patients had a substantial 1-year economic burden. The mean unadjusted total all-cause cost in the 1-year follow-up was US\$14,371, 10.9% of which was CAP related (US\$1561).
- A tenth (11.6%) had ≥ 1 all-cause hospitalization, and of these, 18.7% had ≥ 1 CAP-related hospitalization. CAP-related hospitalizations were costly, and the first CAP-related hospitalization was associated with a mean cost of US\$18,649 and length of stay of 5.8 days.
- Inpatient and emergency room care were important cost drivers. Inpatient care accounted for a quarter (26%) of total all-cause costs. Emergency room visits and inpatient care accounted for more than half (57%) of total CAP-related costs.
- The adjusted mean total all-cause cost was US\$13,788. Baseline characteristics associated with higher costs included older age, diabetes, cardiac arrhythmia, chronic pain/fibromyalgia, depression, smoking and fluoroquinolone use.

Author contributions

V Divino, M DeKoven, M Jiang, J Schranz and H Shah were involved in study conception and design. V Divino, M DeKoven and M Jiang were involved in the analysis. All authors were involved in the interpretation of data. V Divino was involved in drafting the manuscript, and all authors revised the paper critically for intellectual content. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

Data records were de-identified and fully compliant with patient confidentiality requirements of the Health Insurance Portability and Accountability Act. Ethics approval was not required because this was a retrospective analysis of secondary data using only de-identified patient records.

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