

The Incidence of Community-Acquired Pneumonia in the Elderly Population of the United States of America: A Systematic Review and Meta-Analysis

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Abstract

Current epidemiological data reports that adults aged 65 years and older comprise the most vulnerable age group with the highest proportion of CAP-attributable hospitalizations.

Pneumococcal vaccine efficacy (VE) has been shown to decrease over time, contributing to increasing incidence rates of CAP. A holistic evaluation of age, sex, seasonality, and VE are conducted in this systematic review and meta-analysis of 12 prospective and retrospective cohort studies. The findings suggest that incidence and age are positively associated and that incidence in females is more often reported to be higher in females than in males. In studies that observed seasonality of CAP, high seasons and low seasons were reported to be in winter and summer months, respectively. Lastly, studies that reviewed the effect of vaccination on incidence consistently found decreased observance of CAP in elderly adults following reception of PCV13 or PPSV23. However, one study suggested that such vaccinations may have decreased effectiveness in elderly populations and that research examining potential explanations for this require further investigation. Furthermore, distinct diagnostic and case ascertainment standards, descriptive measures, and methods of prevention and treatment of CAP used across the US are outlined in this review. Public health guidance such as encouraging the reception of pneumococcal vaccinations and mask-wearing during high seasons of CAP, and communicating the risks of not adhering to the aforementioned preventative measures can facilitate an effort to reduce the incidence of CAP and its associated adverse outcomes in the US elderly population.

Keywords

Community-acquired pneumonia; incidence; prophylaxis; pneumococcal; vaccination

List of abbreviations

BMI	body mass index
CAP	community-acquired pneumonia
COPD	chronic obstructive pulmonary disease
CT	computed tomography
CVD	cardiovascular diseases
HAP	hospital-acquired pneumonia
ICD-9CM	International Classification of Diseases, Ninth Revision, Clinical Modification
PCV13	13-valent pneumococcal conjugate vaccine
PPSV23	23-valent pneumococcal polysaccharide vaccine
PSI	pneumonia severity index
RSV	respiratory syncytial virus
SARS	severe acute respiratory syndrome
US(A)	United States (of America)
VAP	ventilator-acquired pneumonia
VE	vaccination efficacy

1. Introduction

With more than 1.5 million unique American adults hospitalized for community-acquired pneumonia (CAP) annually, CAP is the leading cause of infectious disease-related death in the US (Ramirez et al., 2017). Current epidemiological data report that adults aged 65 years and older comprise the most vulnerable age group, accounting for 60% of hospitalizations attributable to pneumococcal pneumonia (Wroe et al., 2012). From 2004 to 2040, as the US population increases by 38%, it is projected that there will be a 96% increase in CAP hospitalizations (Wroe et al., 2012). CAP occurs in all age groups, however, is most fatal and prevalent in the elderly, who possess senescent immune systems and have a higher rate of comorbidity (Brown et al., 2018). In comparison to other existing reviews, this review focuses on CAP incidence specifically within the elderly population of the US. The aim of this review is to provide a critical evaluation of studies focused on the epidemiology and incidence of elderly CAP and to inform current and future public health interventions when planning prevention measures.

1.1 Population of interest

The population of interest in this review is elderly adults living in the US. Elderly adults will be defined as people aged 65 years or older, while any reference to non-elderly adults refers to people between 19 and 65 years of age. CAP hospitalizations for the elderly occurs at a notably higher rate compared to that for non-elderly adults (Ramirez et al., 2017). Increased utilization of prophylactic measures and standardization of laboratory and radiographic diagnostic criteria serve as options for the mediation of CAP and increasing accuracy of incidence estimates.

1.2 Case definition and criteria for CAP diagnosis

CAP is a lower respiratory tract infection that may be caused by the inhalation of a variety of pathogens including bacteria, viruses, and fungi in a non-clinical setting (Mayo Clinic, 2020). Pneumonia is defined as an infection of the alveoli in either or both lungs, consequently causing the build-up of purulent material in the alveoli (American Lung Association [ALA], 2020). Such physiological changes limit the exchange of oxygen and carbon dioxide at the alveolar-capillary membrane, leading to physiological changes such as respiratory acidosis and symptoms including but not limited to shortness of breath, expectoration of phlegm, fever, and, in particular for the elderly, lowered body temperature, and changes in mental awareness (ALA, 2020; Mayo Clinic, 2020). This review focuses on geriatric cases that are clinically severe, defined as elderly patients who require hospitalization for infection treatment.

1.3 Meaningful measures of disease frequency

The studies included in this review utilize incidence as the most meaningful measure of disease frequency. Incidence will be defined here as the number of new CAP cases per 1,000 person-years.

2. METHODS

A systematic review and meta-analysis using PRISMA methodology was implemented to investigate the incidence of CAP amongst the US elderly population, using three electronic databases: Web of Science, PubMed, and Scopus.

2.1 Literature search

Systematic search methods were performed using Global Health, PubMed, and Scopus using MeSH terms as appropriate. Pilot examination of studies was carried out in order to identify key MeSH terms used in relevant literature. Search filters were not used when selecting studies to avoid the exclusion of potentially admissible studies. The terms utilized in literature searches are detailed in Table 1.

Table 1 — Databases and terms used for literature search

Web of Science (elderly OR senior OR geriatric) AND (“community-acquired pneumonia” OR pneumonitis) AND (epidemiolog* OR aetiolog OR incidence OR cross-section*) AND (“United States of America” OR American)
PubMed ((elderly OR senior OR geriatric) AND (“community-acquired pneumonia” OR pneumonitis) AND (epidemiolog* OR aetiolog OR incidence OR cross-section*) AND (“United States of America” OR American)) OR (pneumonia [MeSH]) AND (elderly [MeSH]) AND (“United States of America” [MeSH]))
Scopus (elderly OR senior OR geriatric) AND (“community-acquired pneumonia” OR pneumonitis) AND (epidemiolog* OR aetiolog OR incidence OR cross-section*) AND (“United States of America” OR American)

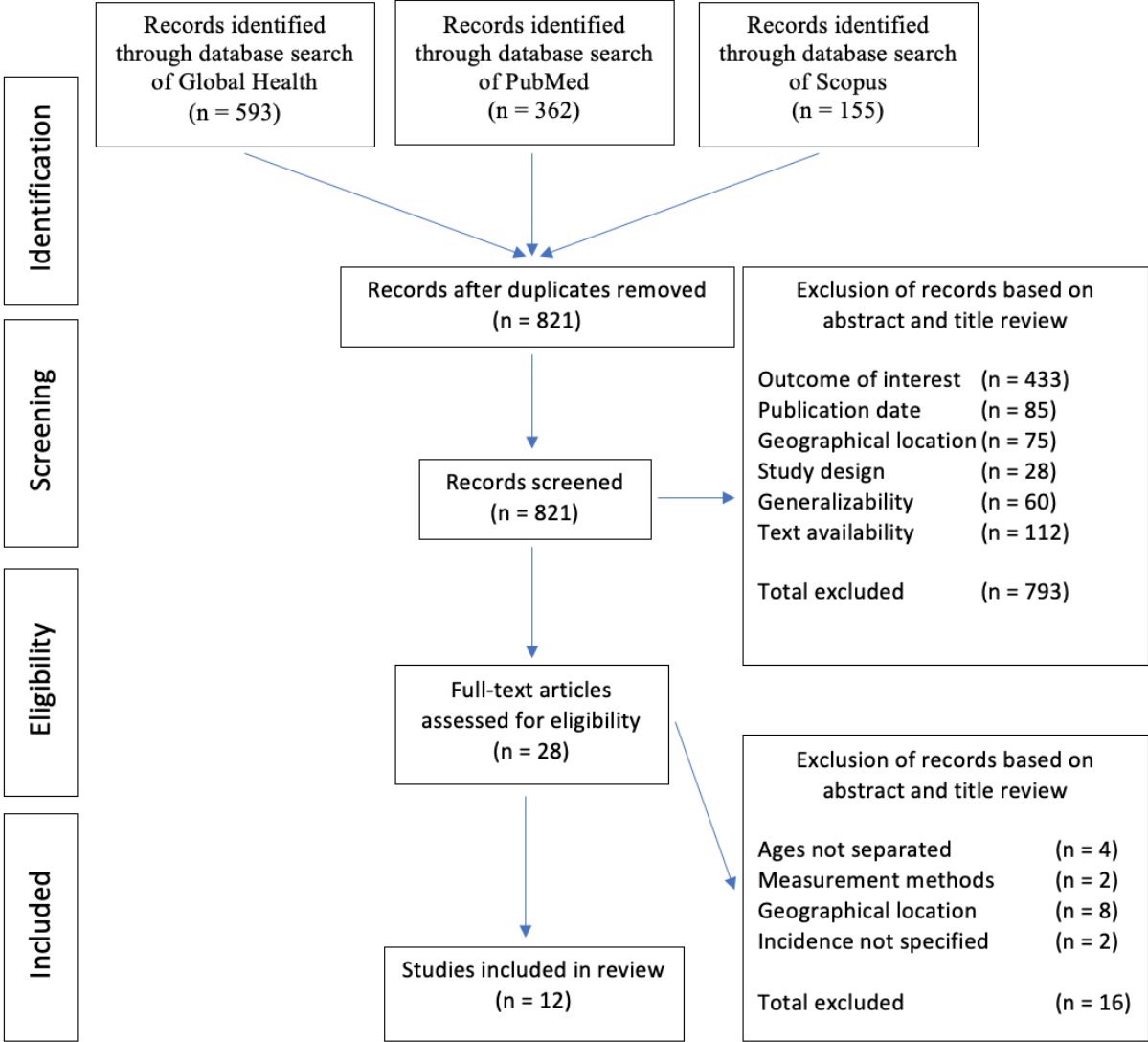
2.2 Selection of studies

A list of 1,110 studies were initially gathered using the search terms detailed in table 1 in their designated databases. The studies were imported to Mendeley and duplicate literature was discarded, leaving 821 records for assessment. The remaining records were screened by title-abstract review according to the inclusion and exclusion outlined in Table 2. Of the 821 records, 28 titles and abstracts were chosen for full-text evaluation. Following the completion of full-text evaluation and further consideration of inclusion-exclusion criteria, 12 studies were deemed eligible for inclusion. Figure 1 illustrates the methodology used for the identification, screening, and eligibility-determination of included publications.

Table 2 — Inclusion and exclusion criteria used to screen preliminary publications collected from literature search

Inclusion Criteria
Community-acquired pneumonia (CAP) is the main outcome of interest
Study focuses on the US as the only geographic location of interest
Study focuses on American elderly adults, ages 65 or older, as the population of interest
Study was either of prospective or retrospective cohort design
Data collected on incidence of CAP
Peer-reviewed and original data
Language of study is in English
Study includes exclusively human data
Exclusion Criteria
Study exclusively reports hospital-acquired or ventilator-acquired pneumonia data
Study does not define community-acquired pneumonia
CAP incidence data not provided
Study was deemed a systematic review or meta-analysis
Study considers geographic locations that are not considered as part of the US
Study did not provide CAP incidence data broken down by age band
Data 35 years or older was used
Studies that exclusively report CAP infections that did not require hospitalization
Language of study is not in English
Study does not include elderly-aged patients or focuses on foreign-born Americans
Study includes non-human data

Figure 1 — Identification and selection of reports for inclusion into the review



3. RESULTS

3.1 Overview of included studies

12 studies were deemed eligible and included in this review. The total sample of this review constituted 14,949,946 participants. Six studies used national databases to select for elderly participants who developed CAP and met specified inclusion-exclusion criteria for the respective study (Brown et al., 2018; Fry et al., 2005; Kaplan et al., 2002; McLaughlin et al., 2015; Self et al., 2016; Waterer et al., 2018). The remaining six studies selected sample populations from single city- (Isturiz et al., 2019; Jain et al., 2015; Kollef et al., 2005; McLaughlin et al., 2018; Ramirez et al., 2017) and state- (Jackson et al., 2006) wide databases. Eight of the included studies used prospective cohort designs, while four used retrospective cohorts as summarized in Table 3. Six studies assessed CAP incidence in participants whose ages ranged broadly from five to greater than 85 years (Isturiz et al., 2019; Jain et al., 2015; McLaughlin et al., 2015; Ramirez et al., 2017; Self et al., 2016; Waterer et al., 2018). The remaining six studies used cohorts comprised exclusively of elderly patients, aged 65 years and old (Brown et al., 2018; Fry et al., 2005; Jackson et al., 2006; Kaplan et al., 2002; Kollef et al., 2005; McLaughlin et al., 2018;). Important characteristics from each study are summarized by Table 3.

Table 3 — Studies included in this review

Authors	Study period	Data Source	Study Design	Mean Age (SD)	Median Age	Percent Female Sex	Sample size	Epidemiological estimates and descriptive measures
Ramirez 2017 (1)	2014-2016	The University of Louisville Pneumonia Study	Prospective cohort	NR	68	53.8%	587,499	Incidence (age, sex), year, race, medical and social history, physical examination findings, severity of disease
Self 2016 (3)	2010-2012	Etiology of Pneumonia in the Community (EPIC) study, Centers for Disease Control and Prevention (CDC)	Prospective cohort	56.3 (21.1)	57	51.1%	2,259	Incidence (age), year, race, comorbidity, hospitalization, pathogen type, radiographic findings, pneumonia severity index (PSI) score
Jain 2015 (4)	2010-2012	Patient databases from John H. Stroger, Jr., Hospital of Cook County, Northwestern Memorial Hospital, and Rush University Medical Center	Prospective cohort	56.5 (20.9)	57	NR	2,488	Incidence (age), race, comorbidity, receipt of vaccine or treatment, radiographic finding

Authors	Study period	Data Source	Study Design	Mean Age (SD)	Median Age	Percent Female Sex	Sample size	Epidemiological estimates and descriptive measures
Brown 2018 (5)	2014-2015	National Hospital Discharge Survey, Optum Clinformatics™ Data Mart	Retrospective cohort	75.8 (8.02)	NR	57.8%	1,949,352	Incidence (age-adjusted), year, sex, hospitalization rate, mortality rate
Fry 2005 (6)	1988-2002	National Hospital Discharge Survey	Prospective cohort	78.0 (7.86)	NR	52.9%	3,892,591	Incidence (age-adjusted), comorbidity history, number of hospitalizations, previous pneumonia diagnosis, mortality ratio, risk ratio
Kaplan 2002 (7)	1997	Medicare Provider Analysis and Review hospital discharge database (MedPAR), Centers for Medicare and Medicaid Services (CMS)	Prospective cohort	78.7 (8.14)	NR	53.6%	623,718	Incidence (age-, location-, comorbidity-adjusted), sex, etiology, hospitalization, mean hospital length of stay
Jackson 2004 (13)	1998-2001	Group Health Cooperative (GHC) administration database – GHC is a health maintenance organization in Washington State	Retrospective cohort	74.7 (8.85)	NR	57.8%	46,237	Incidence (age), sex, smoking status, comorbidity, outpatient visits, number of hospitalizations

Authors	Study period	Data Source	Study Design	Mean Age (SD)	Median Age	Percent Female Sex	Sample size	Epidemiological estimates and descriptive measures
McLaughlin 2018 (15)	2013-2016	9 acute-care hospitals from Louisville, Kentucky (names of hospitals not provided in the study)	Prospective cohort	74.8 (5.89)	76	50.7%	2,034	Incidence (age-adjusted) race, ethnicity, incidence seasonality, risk level, BMI category, vaccination history
Kollef 2005 (16)	2002-2003	Cardinal Health-Atlas Research Database and Cardinal Health Clinical Knowledge Services	Retrospective cohort	70.5 (4.88)	74	41.8%	4,543	Incidence (age-adjusted) race, comorbidity, insurance type, risk-adjusted severity
Isturiz 2019 (17)	2013-2019	Acute care hospital across 10 cities (Akron, OH, Chicago IL, Detroit, MI, Louisville, KY, Nashville, TN, Norfolk, VA, Houston, TX, Las Vegas, NV, San Diego, CA, Worcester, MA)	Prospective cohort	64.1 (16.6)	65	50.5%	12,055	Incidence (age), sex, race, ethnicity, height, weight, BMI, location of residence, PSI score, radiographically confirmed CAP

Authors	Study period	Data Source	Study Design	Mean Age (SD)	Median Age	Percent Female Sex	Sample size	Epidemiological estimates and descriptive measures
McLaughlin 2015 (18)	2011	US Veterans Health Administration (VHA) patient database	Retrospective cohort	58.2 (20.6)	65	5.00%	7,824,850	Incidence (age), race, hospitalization, mortality, 30-day readmission, comorbidity, immunocompetence
Waterer 2018 (19)	2010-2012	Etiology of Pneumonia in the Community (EPIC) study, CDC	Prospective Cohort	56.4 (21.0)	57	51.3%	2,320	Incidence (age), sex, comorbidity, vaccination history, PSI score, hospitalization, cause of death

SD: Standard Deviation, NR: Not reported, EPIC: Etiology of Pneumonia in the Community, CDC: Centers for Disease Control and Prevention, MedPAR: Medicare Provider Analysis and Review, CMS: Centers for Medicare and Medicaid Services, GHC: Group Health Cooperative, PSI: Pneumonia Severity Index, BMI: Body Mass Index, CAP: Community-Acquired Pneumonia, VHA: Veterans Health Administration.

3.1.1 Diagnostic standards and case ascertainment

Out of the 12 included studies, eight studies applied computed Tomography (CT) radiography of the chest as a diagnostic tool (Isutriz et al., 2019; Jackson et al., 2006; Jain et al., 2015; McLaughlin et al., 2015; McLaughlin et al., 2018; Ramirez et al., 2017; Self et al., 2016; Waterer et al., 2018). One study identified several hallmarks of pneumonia infection on radiographic images, including parenchymal scarring, bronchial wall thickening, pleural thickening, and trapped lung (Eslamy et al., 2011). In two studies, clinical criteria used to diagnose CAP, via lung infiltrate on chest radiography as a reference standard, included asymmetric chest expansion and oxygen saturation $<95\%$ (Self et al., 2016; Hunton, 2019). However, microbiological and hematological evaluations are also important for the differential diagnosis of CAP (Bartlett, 2011; File, 2020; Muller et al., 2005). In one study, laboratory measurements at the time of hospitalization for elevated lymphocyte, neutrophil, creatine kinase, and serum calcium were considered alongside radiographic results to confirm CAP diagnosis (Muller et al., 2005). Another study detailed common microbiological diagnostic tests used, which include sputum gram stain and culture, respiratory viral panel, and blood cultures (File, 2020). Six out of the 12 studies included hematological diagnostic standards (Isturiz et al., 2019; Jain et al., 2015; Kaplan et al., 2002; Kollef et al., 2005; Muller et al., 2005; Ramirez et al., 2017). For hematological tests, elevated levels of immune cells, including lymphocytes and neutrophils, and certain metabolic intermediates within gold-standard ranges allow for clinicians to differentiate CAP from other respiratory infections. If such cumulative radiographic, microbiologic, hematologic findings are discovered ≤ 48 hours after hospital admission or endotracheal intubation, the patient will likely be diagnosed with CAP (Ramirez, 2020).

The studies included in this review used symptomatic abnormalities, laboratory evidence, and radiographic approaches to diagnose cases of CAP. The methods used for case ascertainment vary between reports due to differing diagnostic criteria. Six studies reported cough, sputum production, fever, chills, hypothermia, chest pain, dyspnea, and tachypnea as potential symptomatic indicators of CAP (Isturiz et al., 2019; Jain et al., 2015; Kaplan et al., 2002; McLaughlin et al., 2018; Ramirez et al., 2017; Self et al., 2016). Additional indicators, though less frequently specified, include rash, confusion, wheezing, hemoptysis, shortness of breath, effusion, and respiratory failure. Radiographic approaches for CAP screening prioritize chest X-rays, which appeared consistent with the findings of this review as the majority of the included studies used CT scans for case ascertainment. The most common laboratory tests reported for case ascertainment include sputum, blood culture, pleural fluid, and microbiological cultures as well as urinary antigen detection (UAD). Bronchoalveolar lavage (BAL) specimen analysis was also reported, however less frequently, by three of the included studies (Jain et al., 2015; Kaplan et al., 2002; Self et al., 2016). Other methods of case ascertainment primarily consisted of the use of *ICD-9-CM* codes to verify patient symptoms with accepted criteria. Table 4 provides an overview on the determinants for each of the included studies.

Table 4 — Case definition and case ascertainment used in included studies

Reference	Case definition; symptomatic indicators included as diagnostic criteria if specified	Laboratory test and/or radiographic imaging? If yes: type of test and/or imaging	Other methods of case ascertainment; additional data sources
Ramirez 2017 (1)	CAP; new cough, increased cough or sputum production, fever >37.8°C or hypothermia <35.6°C	Yes, sputum culture, CT scan, blood culture with leukocytosis: >11,000 cells/ μ L	Elderly with discharge diagnoses of CAP <i>ICD-9-CM</i> coded (code J18.9) were included as cases
Self 2016 (3)	<i>Staphylococcus aureus</i> CAP; fever, cough with sputum production, hemoptysis, shortness of breath, chest pain, rash, confusion, wheezing	Yes, chest CT scan, blood culture, sputum culture, urinary antigen test, RT-PCR, endotracheal aspirates, pleural fluid, BAL, and hematocrit	Patient characteristics, antibiotics administered, and clinical outcomes were ascertained via patient interviews; the use of antibiotics was defined as administration of ≥ 1 dose of vancomycin or linezolid during the first 3 days of hospitalization
Jain 2015 (4)	CAP; fever or hypothermia, chills, new cough, sputum production, chest pain, dyspnea, tachypnea, and respiratory failure	Yes, chest CT scan, blood sample, urine sample, sputum culture, endotracheal aspirate, BAL specimen, and convalescent-phase serum collection	Participants underwent phone interviews to provide information regarding whether fever or respiratory symptoms were experienced 14 days before and after enrollment or whether a live attenuated influenza vaccination was received seven days before enrollment
Brown 2018 (5)	CAP, myocardial infarction (MI), and osteoporotic fractures (OF)	No	The study only considered primary hospital diagnoses of CAP; CAP cases were identified in medical claims using diagnosis codes (unspecified)
Fry 2005 (6)	Pneumonia	No	Hospitalization for pneumonia was defined according to <i>ICD-9-CM</i> codes 480 to 486 or 487.0 for pneumonia among any one of up to seven discharge diagnoses.

Reference	Case definition; symptomatic indicators included as diagnostic criteria if specified	Laboratory test and/or radiographic imaging? If yes: type of test and/or imaging	Other methods of case ascertainment; additional data sources
Kaplan 2002 (7)	CAP; hemoptysis, effusion, atelectasis, pneumothorax, and lung abscess	Yes, BAL specimen	CAP was defined as bacterial pneumonia (<i>ICD-9-CM</i> codes 481, 482, 485, or 486), listed both as the admission diagnosis and discharge diagnosis, or bacterial pneumonia listed as a discharge diagnosis coupled with a pulmonary complaint at admission
Jackson 2004 (13)	CAP	Yes; radiographic tests (not specified)	Participating hospitals assigned discharge diagnosis of pneumonia (<i>ICD-9-CM</i> codes 480-487.0) or streptococcal or pneumococcal bacteremia (<i>ICD-9-CM</i> codes 038.0, 038.2, 041.0, 041.2, and 320.1) were selected for chart review; cases of pneumonia in which symptoms developed after hospitalization or in which the patient had been hospitalized in the previous seven days, were excluded
McLaughlin 2018 (15)	CAP; clinical evidence of ≥ 2 of the following: fever, hypothermia, chills or rigors, pleuritic chest pain, cough, sputum production, dyspnea, tachypnea, or abnormal auscultatory findings	Yes, chest radiograph and/or CT image, sputum/respiratory and pleural fluid cultures, and serotype-specific UAD assay	Patients who did not provide a urine sample or did not have a final diagnosis of pneumonia at discharge were excluded; Patients could contribute >1 CAP hospitalization event if a subsequent CAP hospitalization for the same patient occurred >30 days after the previous hospitalization
Kollef 2005 (16)	Culture-positive pneumonia	Yes, sputum/respiratory and pleural fluid cultures	Elderly with discharge diagnoses of CAP <i>ICD-9-CM</i> coded (code J18.9) were included as cases
Isturiz 2019 (17)	CAP; clinical evidence of ≥ 2 of the following: fever or hypothermia within 24 hours of enrollment, chills or rigors, pleuritic chest pain, cough, sputum production, and abnormal auscultatory findings	Yes, Chest CT, sputum/respiratory and pleural fluid cultures, and microbiology culture	Cases of pneumonia contracted no more than 72 hours prior to study enrollment were confirmed by radiologists; participants were excluded if they had any other category of pneumonia except CAP

Reference	Case definition; symptomatic indicators included as diagnostic criteria if specified	Laboratory test and/or radiographic imaging? If yes: type of test and/or imaging	Other methods of case ascertainment; additional data sources
McLaughlin 2015 (18)	CAP	Yes, Chest CT and microbiology culture	Cases of pneumonia had to have a medical claim (<i>ICD-9</i> : 480-486, 487.0)) with a procedure code for a chest X-ray (CPT code 71010-71035 – <i>ICD-9-CM</i> 87.4x) within 14 days before or after initial diagnosis of pneumonia; cases were defined by risk-level of patient
Waterer 2018 (19)	CAP	Yes, chest radiograph or CT scan blood, urine, and respiratory specimens for microbiologic testing	IRB approval was obtained for each of the participating hospitals prior to case ascertainment; cases of CAP for which the patient was recently hospitalized (< 28 days for immunocompetent patients and < 90 days for immunosuppressed patients were excluded from the study

CAP: Community-acquired Pneumonia, CT: Computed Tomography, ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification, RT-PCR: Reverse Transcription Polymerase Chain Reaction, BAL: Bronchoalveolar Lavage, MI: Myocardial Infarction, OF: Osteoporotic Fractures, NHDS: National Hospital Discharge Survey, UAD: Urinary Antigen Detection, PCV13: 13-Valent Pneumococcal Conjugate, IRB: Institutional Review Board.

3.1.2 CAP Prophylaxis and Antibiotic Treatment

Current US strategies to prevent pneumonia among elderly adults include immunization with pneumococcal polysaccharide, conjugate, and annual influenza vaccinations (Fry et al., 2005). The majority of the studies included in this review reported the use of either 23-valent pneumococcal polysaccharide (PPSV23) or 13-valent pneumococcal conjugate (PCV13) vaccines for the immunization of adults ≥ 65 years. Administration of influenza vaccinations was reported by three of the included studies as an additional prophylactic measure (Brown et al., 2018; Fry et al., 2005; Jackson et al., 2006). Antibiotic treatments were employed if methicillin-resistant *Staphylococcus aureus* (MRSA) CAP is clinically suspected (Self et al., 2016). Table 5 presents an overview of CAP prophylactic and antibiotic treatment measures provided in the included studies. Vaccine effectiveness (VE) decreases over time and with comorbid conditions, resulting in disproportionately high levels of CAP incidence in older age groups despite routine immunization programs; *Isturiz 2019 (17)* reported a decline in PCV13 serotypes among elderly adults who received pneumococcal vaccination more than 30 days prior to study enrollment, providing further evidence for diminishing VE. The results of this review suggest that the burden of CAP may be potentially reduced by broadening the immunization capability of current vaccines to account for additional pathogens and variants, including human metapneumovirus or respiratory syncytial virus (Jackson et al., 2006). Additionally, the implementation of vaccination programs for household contacts and caregivers could serve to reduce the likelihood of communicable transfer of CAP-causing pathogens to elderly adults.

Table 5 — Use of CAP-prophylaxis and treatment in the study populations

Reference	Available information on use of CAP-prophylaxis (PCV13, PPSV23, or influenza) and treatment (antibiotics)
Ramirez 2017 (1)	No information provided
Self 2016 (3)	Addition of vancomycin or linezolid as a standard antibiotic therapy was recommended if methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) pneumonia is clinically suspected – elderly risk groups likely received antibiotic treatment
Jain 2015 (4)	Reception of a live attenuated influenza vaccination within seven days before enrollment constituted an exclusion criteria; elderly adults who received PCV13 led to a lower observance of CAP in this study compared to prior studies
Brown 2018 (5)	The study includes data on PCV13, PPSV23, and influenza vaccinations as prophylactic measures against CAP hospitalizations for the following age groups: 65-69, 70-74, 75-79, 80-84, 85-89
Fry 2005 (6)	Data supporting the proportion of individuals aged ≥ 65 years reporting receipt of annual influenza vaccine has increased from 30.4% in 1989 to 65.6% in 2002; reported that it was not possible to estimate the effect of influenza vaccination on hospitalization trends for pneumonia during the study period
Kaplan 2002 (7)	No information provided
Jackson 2004 (13)	Despite the fact that vaccination rates for both influenza and pneumococcal polysaccharide vaccines were high in the elderly study population ($>75\%$ and $>70\%$, respectively), rates of CAP were high, especially among those aged ≥ 85 years; the study reported a correlation between influenza virus circulation and CAP incidence
McLaughlin 2018 (15)	Study participants who were diagnosed with CAP were less likely to have received PCV13 than controls (3/68 [4.4%] vs 285/1966 [14.5%]; unadjusted VE, 72.8% [95% confidence interval, 12.8%–91.5%]); study is the first to demonstrate the real-world effectiveness of PCV13 against vaccine-type CAP in adults aged ≥ 65 years following introduction into a national immunization program
Kollef 2005 (16)	Approximately 50% of hospitalized elderly patients with pneumonia had CAP, with <i>Staphylococcus aureus</i> as the major pathogen – study participants received antibiotic treatment (regimen not specified)
Isturiz 2019 (17)	Only patients who met study eligibility criteria, had a final diagnosis of CAP confirmed by chest X-rays, and did not receive pneumococcal vaccination within 30-days of study enrollment were included in the primary analysis population; a decline in PCV13 serotypes was reported in the study, which may reflect the decreased effectiveness of vaccination among elderly adults

Reference	Available information on use of CAP-prophylaxis (PCV13, PPSV23, or influenza) and treatment (antibiotics)
McLaughlin 2015 (18)	At the time of the study, only PPSV23 was approved for routine use in adults; the study reported a significant burden of CAP in the veteran population (median age 65 years) despite VHA patients having better PPSV23 coverage than the general, non-VA population
Waterer 2018 (19)	Patient reports of pneumococcal vaccination in adults \geq 65 years detailed in the study; 20/33 (60.6%) of hospitalized CAP patients who died in the study were vaccinated, while 482/799 (60.3%) of hospitalized CAP patients who survived were vaccinated

CAP: Community-acquired Pneumonia, MRSA: Methicillin-resistant *Staphylococcus* Aureus, PCV13: 13-Valent Pneumococcal Conjugate Vaccine, PPSV23: 23-Valent Pneumococcal Polysaccharide Vaccine.

3.1.3 Quality of studies

Depending on the design and methods of a particular study, different limitations to reported results may exist. In an effort to account for such limitations, Table 6 summarizes key limitations, biases (if present), and strengths of the studies included in this review.

Table 6 — Quality of included studies

Reference	Main Objective	Limitations regarding external validity	Limitations due to case definition / diagnostic methods / further issues	Strengths
Ramirez 2017 (1)	To define the incidence and mortality of adult patients hospitalized with CAP in the city of Louisville, and the burden of CAP in the US adult population	Cohort consisted of patients limited to the city of Louisville; Only patients who had consecutive hospitalizations were enrolled in the study	Laboratory findings without inclusion of radiographic confirmation; no specification as to pathogenic cause of documented CAP infections	Geospatial epidemiology was used to define ecological associations among CAP and income level, race, and age
Self 2016 (3)	To increase understanding of the incidence of <i>Staphylococcus aureus</i> CAP and provide guidance on antibiotic selection	Representative of Chicago, Illinois and Nashville, Tennessee but not for the whole of the US	Patient characteristics were ascertained via patient interviews – such data is prone to reporting bias; assessment of pathogen-specific outcomes, besides that of <i>Staphylococcus aureus</i> , is unavailable	Broad clinical assessment for bacterial-, viral-, and fungal-induced CAP
Jain 2015 (4)	To provide incidence estimates of CAP incidence that is confirmed radiographically and with laboratory diagnostic tests	Representative of Chicago, Illinois and Nashville, Tennessee but not for the whole of the US	Patients provided their own demographic and medical data – reporting bias may have occurred, such as lack of reporting full details of medical history	Broad clinical assessment: blood, urine, and respiratory specimens were collected for laboratory testing and radiologists reviewed chest radiographs
Brown 2018 (5)	To compare the burden of illness and cost of preventing CAP	Only adults ≥65 years enrolled in a Medicare Advantage insurance plan were included – excludes patients enrolled in an Original Medicare	Only primary diagnoses of CAP were included in the study – underestimation if patients present comorbidities in addition to CAP	Large population-based study with good predictiveness

Reference	Main Objective	Limitations regarding external validity	Limitations due to case definition / diagnostic methods / further issues	Strengths
Fry 2005 (6)	To examine trends in hospitalizations for pneumonia among people aged 65 years or older and to compare outcomes	The data source for patient records only takes into account data from nonfederal general hospitals. The study excludes data from federal military and VA hospitals	Data was collected from 1988 through 2002, thus different diagnosis standards and <i>ICD-9-CM</i> codes may distort the analysis	Hospital discharge data is collected from a large representative sample from approximately 500 hospitals across the US. Discharge data are collected monthly for 270,000 inpatient records
Kaplan 2002 (7)	To assess the incidence, patterns of care, and outcome of hospitalized CAP in the elderly US population and to determine differences by age and sex	Study was conducted in 1997: incidence, patterns of care, and outcome of hospitalized CAP in the elderly population are likely different due to development of prophylactic, diagnostic, and treatment options	Diagnostic methods for CAP are limited to laboratory findings without inclusion of radiographic confirmation; no controlling for CAP main vs. co-infection	Data sources include all elderly patients enrolled in mandatory government-funded health insurance programs; microbiological etiology was detailed – allows for comparison of CAP outcome given pathogen type
Jackson 2004 (13)	To estimate rates of CAP and to identify risk factors using a population-based cohort of persons aged ≥ 65 years that included both hospitalizations and outpatient visits	The study population is limited to elderly patients who are members of the GHC in the state of Washington – excludes elderly patients outside of this particular group	Information on smoking status was missing for 12% of study subjects (approximately 5,553 patients) – decreased accuracy in allocation of subjects into smoking and non-smoking subgroups	Study ensures ensures data for HAP and VAP cases are independent to those of CAP
McLaughlin 2018 (15)	To conduct an evaluation of PCV13 vaccine effectiveness against hospitalized vaccine-type CAP in the US in adults aged ≥ 65 years	The study population is restricted to elderly adults residing in Louisville, Kentucky, limiting generalizability; cohort limited to those who provided their pneumococcal vaccination history	Aspects of the study rely on observational data and thus is not immune to selection bias	The test-negative method is good for evaluating vaccine effectiveness against infectious respiratory diseases; laboratory and radiographic data were used to define CAP
Kollef 2005 (16)	To characterize the microbiology and outcomes among patients with culture-positive CAP, HCAP, HAP, and VAP	A cohort of 4,543 patients with culture-positive pneumonia were included in the study – underestimation of incidence as blood cultures show poor sensitivity in pneumonia: results often present false negatives (Gamache, 2020)	Diagnostic methods for CAP are limited to laboratory findings without inclusion of radiographic confirmation	Study uses a large US inpatient database consisting of 59 acute-care hospitals across the country – strengthens external validity

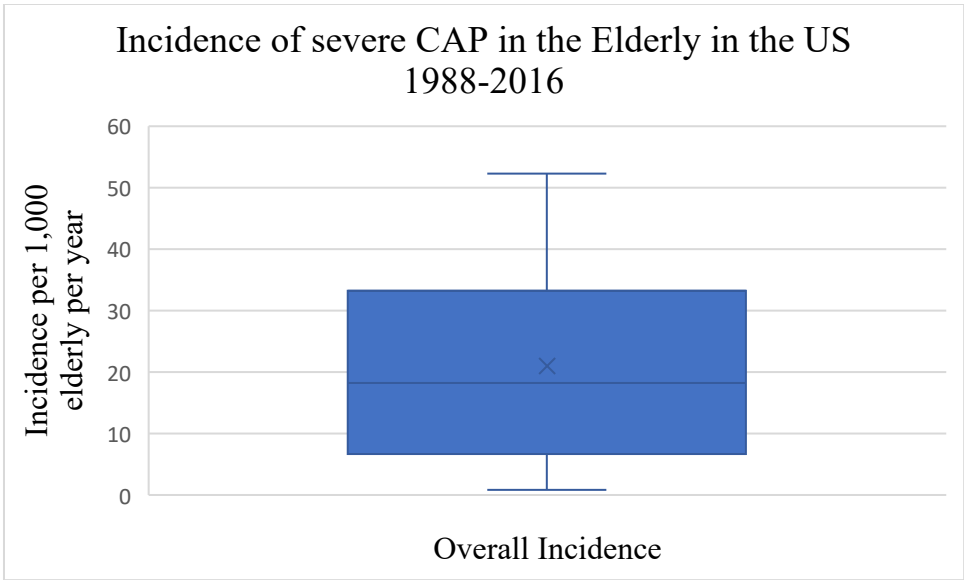
Reference	Main Objective	Limitations regarding external validity	Limitations due to case definition / diagnostic methods / further issues	Strengths
Isturiz 2019 (17)	To measure the proportion of radiographically confirmed (CXR+) CAP caused by PCV13 serotypes in hospitalized US adults	High proportion (80%) of participants were from Louisville hospitals, limiting generalizability of the results	Study start-up was staggered, and recruitment varied considerably among sites and over time	Study subjects were recruited from 21 hospitals across 10 geographically-dispersed cities in the US over a three-year period – strengthens external validity; laboratory and radiographic methods were used to confirm CAP diagnosis
McLaughlin 2018 (18)	To describe the burden of CAP in the US VHA by hospitalization, mortality, and medical expenditure rates	Study’s definition of CAP excludes patients that had any inpatient encounters in the prior 90 days – underestimates the incidence of CAP due to conservative approach; no clear method was used to distinguish between CAP and HAP	Diagnosis of CAP was defined was based on an algorithm of diagnostic and procedural claims, the codes of which are not always accurate	For all statistical models used, each justifiable interaction term was tested for statistical significance – increases confidence in validity of study conclusions including odds ratio and relative risk values
Waterer 2018 (19)	Review all in-hospital deaths in a large prospective CAP study to assess the cause of each death and assess the extent of preventable mortality	Participants hospitalized with CAP were from Chicago and Nashville hospitals, limiting generalizability of the results	Determining cases of CAP that are preventable is vulnerable to subjective interpretation	Controlling for CAP main vs. co-infection; blood, urine, respiratory specimens, and time of CAP development were used to confirm CAP diagnosis

CAP: Community-acquired Pneumonia, HAP: Hospital-acquired Pneumonia, VAP: Ventilator-acquired Pneumonia, VA: Veterans Administration, GHC: Group Health Cooperative, PCV13: 13-Valent Pneumococcal Conjugate Vaccine, ACIP: Advisory Committee on Immunization Practices, CXR: Chest X-ray, UAD: Urinary Antigen Detection , VHA: Veterans Health Administration.

3.2 Incidence

Amongst the 12 included studies, eight reported incidence estimates for CAP in the US elderly population (Brown et al., 2018; Fry et al., 2005; Isturiz et al., 2019; Jackson et al., 2006; Jain et al., 2015; Kaplan et al., 2002; McLaughlin et al., 2015; Ramirez et al., 2017). The median incidence of clinically severe CAP requiring hospitalization in elderly patients ages 65 years and older between 1988 and 2016 was 18.2 per 1,000 elderly per year, with a total range of 1.21 to 52.3. The Q1-Q3 quartile range, presented in Figure 2, was 26.5 per 1,000 elderly per year (see Figure 2 below). The mean of the estimates was 21.0 per 1,000 elderly per year. Incidence estimates depended largely on how cohort age bands were specified by their respective authors. In addition to the variation caused by differing age band specifications between studies, as summarized in Table 7, estimates varied notably with regards to sex, seasonality, and vaccination history.

Figure 2 — Overall incidence reported in studies included in the review.



Sources: *Brown et al., 2018; Fry et al., 2005; Isturiz et al., 2019; Jackson et al., 2004; Jain et al., 2015; Kaplan et al., 2002; McLaughlin et al., 2015 Ramirez et al., 2017*

Table 7 — Incidence of CAP in the US by age, sex, and year of data collection

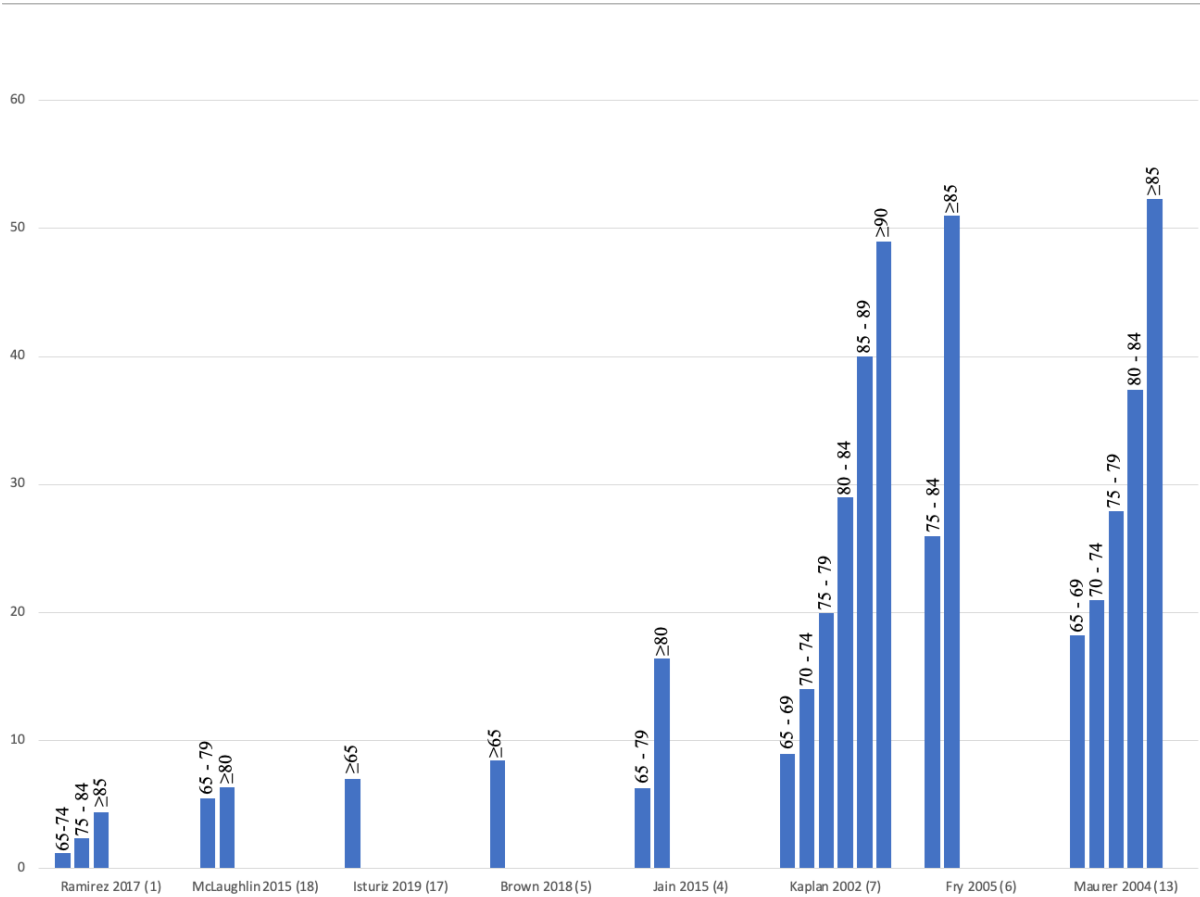
Reference	Most recent year data collected	Incidence as new CAP cases / 1,000 person-years (age band in years)	Incidence in males as new CAP cases / 1,000 person-years	Incidence in females as new CAP cases / 1,000 person-years	% of male participants diagnosed with CAP	% of female participants diagnosed with CAP
Ramirez 2017 (1)	2016	1.21 (65-74) 2.40 (75-84) 4.40 (≥85)	2.93	3.41	46.2%	53.8%
Jain 2015 (4)	2012	6.30 (65 - 79) 16.4 (≥80)	NR	NR	NR	NR
Brown 2018 (5)	2015	8.47 (≥65)	3.57	4.90	42.2%	57.8%
Fry 2005 (6)	2002	26.0 (75-84) 51.0 (≥85)	NR	NR	NR	NR
Kaplan 2002 (7)	1997	9.00 (65-69) 14.0 (70-74) 20.0 (75-79) 29.0 (80-84) 40.0 (85-89) 49.0 (≥90)	11.9	13.7	46.4%	53.6%
Jackson 2004 (13)	2001	18.2 (65-69) 21.0 (70-74) 27.9 (75-79) 37.4 (80-84) 52.3 (≥85)	32.2	25.6	42%	58%
Isturiz 2019 (17)	2016	7.00 (≥65)	3.47	3.54	49.5%	50.5%
McLaughlin 2015 (18)	2011	5.49 (65-79) 6.40 (≥80)	NR	NR	95.0%	5.00%

NR: Not Reported

3.2.1 Age

Age constitutes an established risk factor for CAP infections in the elderly. Figure 3 compares the incidences reported for elderly cohorts within varying age bands. The median and mean incidences for elderly patients between the ages of 65 to 74 were 8.5 and 10.1, respectively, with a total range of 1.21 to 21.0 (Brown et al., 2018; Isturiz et al., 2019; Jackson et al., 2006; Jain et al., 2015; Kaplan et al., 2002; McLaughlin et al., 2015; Ramirez et al., 2017). The median and mean incidences for elderly patients between the ages of 75 to 85 were 18.2 and 18.1, respectively, with a total range of 2.40 to 37.4 (Brown et al., 2018; Fry et al., 2005; Jackson et al., 2006; Kaplan et al., 2002; Ramirez et al., 2017). The median and mean incidences for elderly patients greater than 85 years of age were 28.2 and 28.5, respectively, with a total range of 4.40 to 52.3 (Brown et al., 2018; Fry et al., 2005; Jackson et al., 2006; Kaplan et al., 2002; Ramirez et al., 2017). After summarizing the estimates from each study, a positive association was identified between age and CAP incidence. Studies ranged from providing a single age band (Brown et al., 2018: ≥ 65) to providing six age bands (Kaplan et al., 2002: 65-69, 70-74, 75-79, 80-84, 85-90, ≥ 90)^{5,7}. Because factors including comorbidity and immunocompetence differ between elderly adults of different ages, precise comparisons between studies with regards to age are limited.

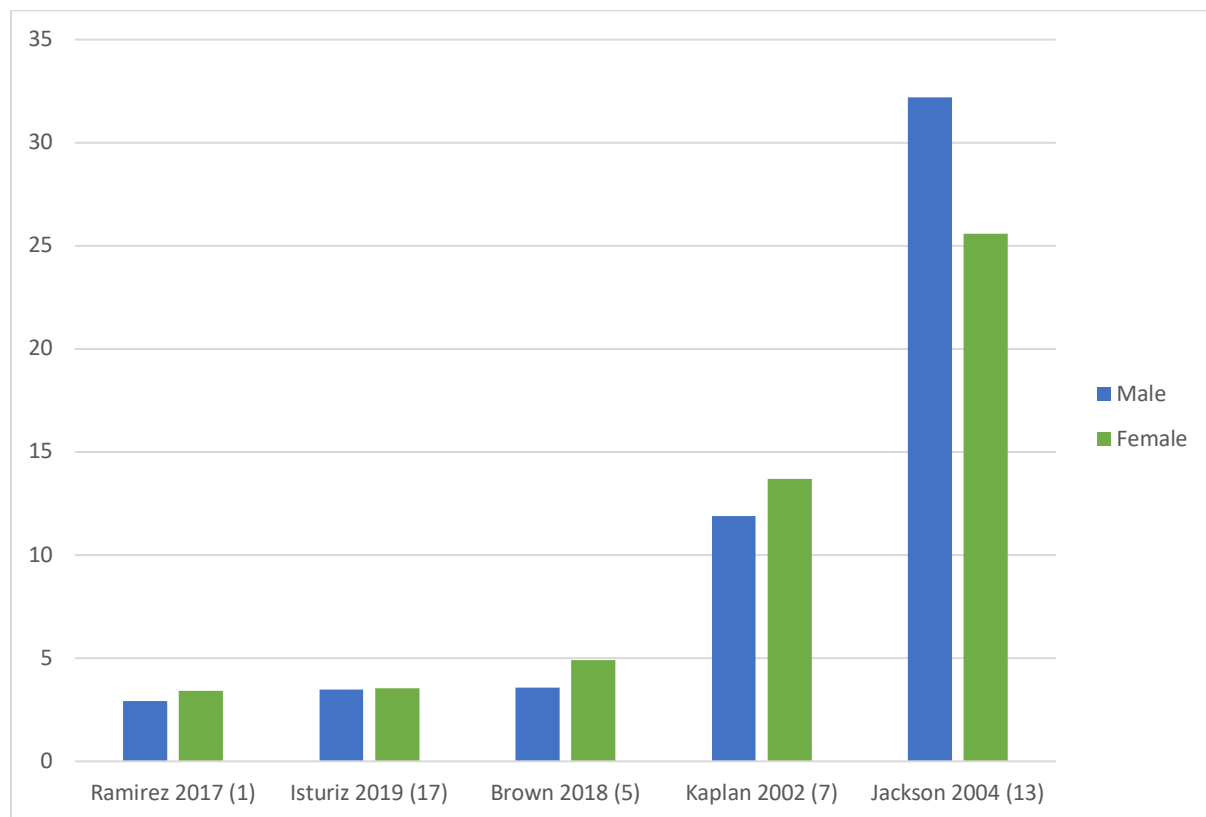
Figure 3 — Overall incidence (new cases / 1,000 person-years) of CAP for specified age bands reported by included studies



3.2.2 Sex

Differences between incidence estimates for males and females were reported in five of the 12 included studies detailed in Figure 4. In four out of five of the studies, overall incidence of CAP infection was greater in females than in males (Brown et al., 2018; Isturiz et al., 2019; Kaplan et al., 2002; Ramirez et al., 2017). Such findings seem contrary to the findings presented in Jackson et al., 2004, which states that men were more likely to be hospitalized with CAP, more likely to receive intensive care or life support. However, failure to report unique cases, sex bias in the hospital admission decision, and differences in CAP diagnosis methodologies between the included studies limit precise sex-adjusted comparisons. Overall incidence values include combined sex-adjusted estimates across different age bands and years of data collection. The results are summarized in Figure 4.

Figure 4 — Overall incidence of CAP in males and females in included studies (if reported)



3.2.3 Seasonality

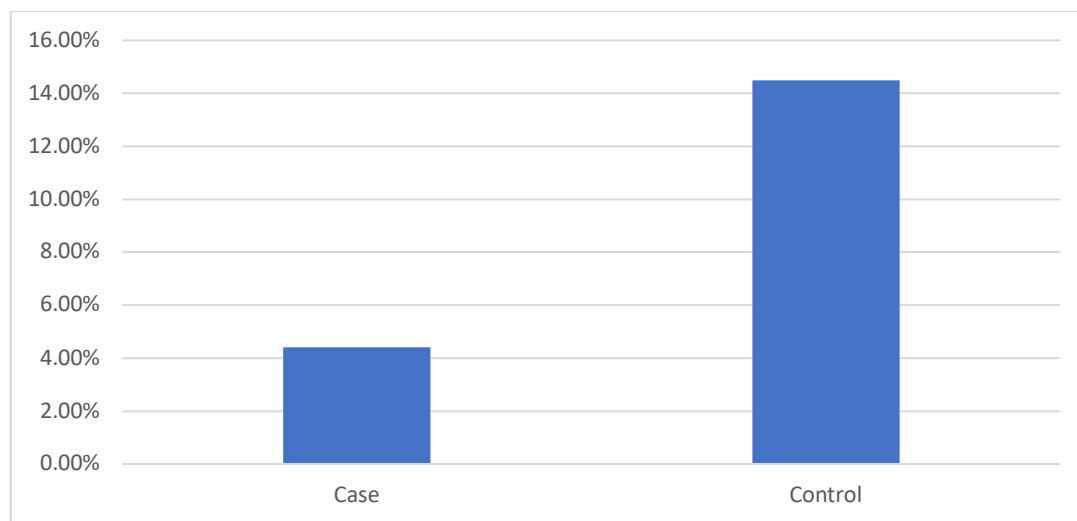
Winter months constitute the high season for CAP infections, whereas fewer events are presented during the summer months (Jackson et al., 2006). A multicenter, prospective surveillance study of US adults hospitalized with CAP identified three notable peaks of *Staphylococcus aureus* CAP from December 2010 to February 2011, May 2011, and January to March 2012 (Self et al., 2016). The peaks beginning in December 2010 and March 2012 coincided with increased number of influenza CAP suggesting a potential co-seasonality of *staphylococcus aureus* and influenza CAP cases. The frequency of CAP and influenza mortality shows a similar seasonal pattern as CAP incidence, with winter months constituting high season and summer months constituting low season. A population-based surveillance for CAP requiring hospitalization among US adults in Chicago and Nashville, provided further evidence that several pathogens are responsible for peaks of CAP during winter months (Jain

et al., 2015). Such pathogens include: HMPV, influenza A and B viruses, *Staphylococcus aureus*, *Staphylococcus pneumoniae*, and RSV. Conversely, a lower circulation of respiratory viruses, which was observed during the 2011 to 2012 winter months contributed to a lower incidence of CAP in that year as supported by the national surveillance data (Jain et al., 2015). The mean peak incidence during the high season (winter months) was 51.7 (range: 38-50) and the mean trough incidence during the low season (summer months) was 13.7 (range: 11-15) cases per 1,000 elderly per year, respectively (Jackson et al., 2006).

3.2.4 Vaccination

In five out of the 12 included studies, vaccine efficacy (VE) with 13-valent pneumococcal conjugate vaccine (PCV13) or 23-valent pneumococcal polysaccharide vaccine (PPSV23) was examined. McLaughlin et al., 2018 reported that patients who developed CAP were less likely to have received PCV13 compared to those who did not develop CAP (3/68 [4.4%] vs. 285/1,966 [14.5%]), indicating that PCV13 may result in some degree of immunity against its 13 pneumococcal bacteria targets (McLaughlin et al., 2018). After adjusting for patient characteristics, including BMI, immunocompromised status, and history of influenza and PCV13 vaccination, a VE of 72.8% (95% confidence interval, 71.1% to 73.3%) was reported. Three studies reported vaccination with PCV13 or PPSV23 in elderly adults led to a lower observance of CAP (Brown et al., 2018; Fry et al., 2005; Jain et al., 2015). One study reported a decline in PCV13 serotypes in elderly patients in the US, which may reflect a decreased effectiveness of vaccination in this vulnerable population (Isturiz et al., 2019). Figure 5 summarizes the rate of infection for vaccinated and unvaccinated participants included in McLaughlin et al., 2018.

Figure 5 — Percentage of elderly cases (patients who developed CAP) and controls (patients who did not develop CAP) who received PCV13 within five years prior to the study



4. Discussion

4.1 Synthesis of results and discussion of findings

In this review, the incidence of CAP among elderly adults in the US was examined. The 12 included studies suggested that incidence and age are positively associated and that incidence in females was reported to be higher more often in females than in males with one study reporting the opposite findings. In studies that observed seasonality of CAP, high seasons and low seasons were reported to be in winter and summer months, respectively. Lastly, studies that reviewed the effect of vaccination on incidence consistently found decreased observance of CAP in elderly adults following reception of PCV13 or PPSV23. However, one study suggested that such vaccinations may have decreased effectiveness in elderly populations and that research examining potential explanations for this require further investigation.

4.2 Limitations of this review and meta-analysis

Although sample sizes were sufficiently large, some cohorts consisted of patients limited to one or multiple cities within a specified geographic region of the US, which limits generalizability of the results. Additional limitations to generalizability include limiting cohort sampling to acute care hospitals and excluding patients from federal and long-term care hospitals, limiting CAP incidence estimates to an uncomprehensive range of causative pathogens rather than considering the array of causative agents, and a lack of consideration of race and ethnicity in particular studies when determining incidence.

A lack of uniformity of diagnostic criteria methodologies creates challenges for comparing studies. Some studies limit CAP diagnosis to laboratory findings while others require both laboratory and radiographic evidence to diagnose cases. Radiographic confirmation of laboratory results is the standard procedure used by clinicians to diagnose CAP and a lack of such evidence can lead to overestimation or underestimation if laboratory results provide false positive or false negative data, respectively. Furthermore, because incidence data from over two decades ago was used by three of the included studies, changes in *ICD-9-CM* coding and less advanced diagnostic methods during their respective study periods likely led to less precise incidence estimates.

In addition to the aforementioned limitations, inconsistency of age band designations between the included studies presented additional challenges in comparing age-specific incidence estimates.

4.3 Implications of findings

The limitations identified in this review indicate a need for uniform utilization of age band designations and diagnostic standards when providing epidemiological estimates for a particular disease. Additionally, if researchers seek to provide national estimates of incidence, generalizability, in terms of geographic breadth of study, the inclusion of different types of relevant hospitals treating the disease of interest, and consideration of relevant demographic data and medical history should be included to maximize external validity. Beginning with increased application of vaccinations and standardization of reliable laboratory and radiographic diagnostic criteria, the US must tend to the healthcare needs of its growing elderly population.

5. Conclusions

This review and meta-analysis provides evidence of increasing incidence of CAP with progressing age in the US elderly population. Additionally, it presents an argument for differences in gender-specific incidence of CAP as more studies found higher rates in females than in males. After adjusting for BMI and immunocompromised status, the included studies demonstrate the effectiveness of pneumococcal vaccinations, highlighting a need to ensure that elderly patients establish and maintain their immunity. Due to findings of decreasing vaccination serotypes in elderly patients over time, booster shot administration is important to decrease the likelihood of adverse outcomes. This review delineates that the elderly population is particularly vulnerable to CAP during the winter months, and so mask wearing policies and patient recommendations should be considered to initiate protective behavior changes. Lastly, wide-ranging diagnostic and case ascertainment standards of CAP across the US signal a need for nation-wide standardization so that methods of reporting CAP incidence are consistent.

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