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Clinical and economic burden of community-acquired pneumonia among adults in Europe

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ABSTRACT

It is difficult to determine the impact of community-acquired pneumonia (CAP) in Europe, because precise data are scarce. Mortality attributable to CAP varies widely between European countries and with the site of patient management. This review analysed the clinical and economic burden, aetiology and resistance patterns of CAP in European adults. All primary articles reporting studies in Europe published from January 1990 to December 2007 addressing the clinical and economic burden of CAP in adults were included. A total of 2606 records were used to identify primary studies. CAP incidence varied by country, age and gender, and was higher in individuals aged ≥65 years and in men. *Streptococcus pneumoniae* was the most common agent isolated. Mortality varied from <1% to 48% and was associated with advanced age, co-morbid conditions and CAP severity. Antibiotic resistance was seen in all pathogens associated with CAP. There was an increase in antibiotic-resistant strains, but resistance was not related to mortality. CAP was associated with high rates of hospitalisation and length of hospital stay. The review showed that the clinical and economic burden of CAP in Europe is high. CAP has considerable long-term effects on quality of life, and long-term prognosis is worse in patients with pneumococcal pneumonia.

Although data are available from a number of prospective studies and national databases, it is difficult to determine the clinical and economic impact of community-acquired pneumonia (CAP) in European adults for a number of reasons. For example, only Finland, Spain and the UK have precise epidemiological data on CAP. Mortality attributable to CAP varies widely between European countries and with the site of patient management.[1] The burden of CAP may be underestimated because a universally recognised definition of CAP is lacking. Other reasons include difficulties in obtaining samples for culture because of the lack of a productive cough and frequent use of antibiotics before diagnosis. Technical limitations of diagnostic tests may also prevent the accurate identification of a pathogen.[2] This, in turn, may result in empiric treatment of outpatients with antibiotics. Given that most patients are treated on an outpatient basis and a substantial proportion of studies are based on hospitalised patients, the true extent of CAP is not known.[3]

The risk of death from CAP is linked to increasing age. In a Finnish study, the incidence of CAP rose dramatically with age, with a sixfold increase in incidence between ages 30–44 years and ≥75 years.[3] In Portugal, case fatality rates were 4.5% for patients aged 18–50 years, 19.4% for those aged ≥50 years and 24.8% for those aged ≥75 years.[4] A UK study reported case-fatality rates of 5.6% in those aged <65 years and 47.2% for those aged ≥85 years. This study also found a 12-fold higher OR for death within 30 days of hospital admission for adults aged ≥85 years than for those aged <65 years.[5] With the projected increase of those aged ≥65 years to 20% of the adult population in developed regions of the world by 2025,[6] the burden of CAP will be felt even more acutely in the years to come.

Although many country-specific reports on CAP in Europe are available, a comprehensive assessment among adults has not been reported recently. We reviewed the published literature to define the clinical and economic burden of CAP in adults. Among the topics considered were incidence of morbidity and mortality, mortality-associated risk factors, quality of life, costs of care and duration of hospital stay. Our review also investigated current aetiology and patterns of antibiotic resistance across Europe.

METHODS

The most recent guidelines of the British Thoracic Society (2005) were used to define CAP: pneumonia should be suspected if a patient has an acute cough and one of the following signs or symptoms: new focal chest signs, dyspnoea, tachypnoea, fever lasting >4 days and a diagnosis confirmed by chest radiograph.[7]

Inclusion and exclusion criteria

All primary articles reporting studies from the European countries or regions listed below that addressed the clinical and economic burden of CAP among adults were included. Studies conducted prior to 1990 were included if they were published in 1990 or later. Studies with enrollees aged <18 years were excluded (figure 1).

The literature search was conducted in February 2008. MEDLINE and EMBASE databases were searched for literature published from January 1990 to December 2007 inclusive. The computer searches and reference lists of all of the retrieved articles were reviewed by investigators. There were no restrictions on language or publication type. The initial search terms used were 'adults' (men and women aged ≥18 years) and 'community-acquired pneumonia' or 'hospital-acquired pneumonia' or 'pneumococcal pneumonia'. The 2606 records retrieved by the search formed a database and were reviewed to identify primary studies conducted in Europe using the Boolean operator 'AND' to filter by geographical regions specific to Europe. As depicted in figure 1, additional filters narrowed the

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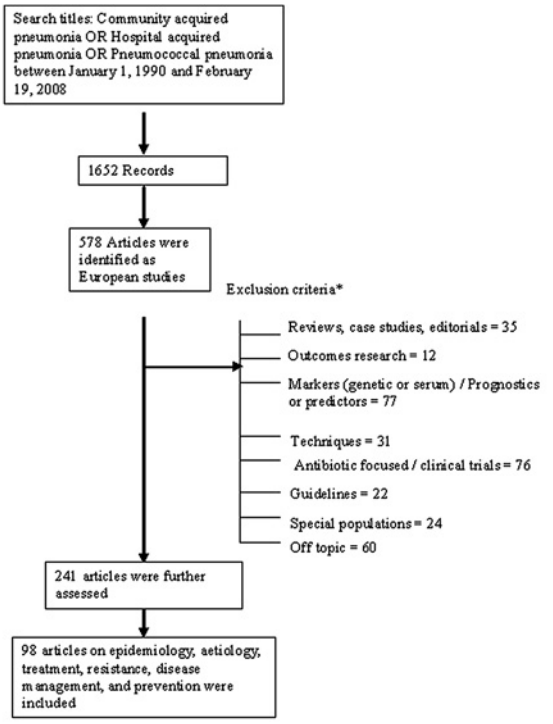

*Outcomes research included papers describing the creation or validation of questionnaires, etc; Markers included any serum or genetic marker analyses for prognostic or predictive purposes, or clinical signs to predict outcome or prognosis; Techniques included new techniques or papers focused on the interpretation of imaging or genetic or serum constituents, etc; Antibiotic-focused studies or clinical trials of specific antibiotics were excluded; Guidelines included papers on the use of, change in, or improvement to treatment guidelines; Special populations included papers focused on particular patient types or disease aetiologies ie, HIV/AIDs or COPD patients, etc; Off topic papers were focused on specific interventions such as vaccines, the consequences of pneumonia in relation to other diseases, etc.

Figure 1 Flow diagram of the literature search strategy.

number of records to 98. Of these, 46 primary articles dealt with aetiology, and the remaining focused on topics such as morbidity and mortality, antibiotic resistance and health-related quality-of-life issues.

The countries or regions included as keywords to identify articles specific to the European region as defined by the WHO were: Albania, Andorra, Austria, Belarus, Belgium, Bosnia, Bulgaria, Crete, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Greenland, Hungary, Iceland, Ireland, Italy, Kazakhstan, Kosovo, Latvia, Lichtenstein, Lithuania, Luxembourg, Macedonia, Malta, Moldova, Monaco, The Netherlands, Norway, Poland, Portugal, Romania, Russia, the Russian Federation, Sardinia, Scotland, Siberia, Sicily, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tajikistan, Turkmenistan, Ukraine, the UK, Uzbekistan, the Vatican, Wales and Yugoslavia.

The references listed in the primary articles that formed the database were reviewed to validate the accuracy of the database search and to identify articles that were missed in the initial search. The database was sorted by the keywords 'epidemiology', 'aetiology', 'incidence', 'mortality', 'morbidity', 'antibiotic resistance' and 'health-related quality-of-life (HRQOL)' to identify articles addressing these topics.

The literature search was updated on 15 April 2009. Fifty new studies published in 2008 and 2009 were identified using the terms 'community-acquired pneumonia' or 'hospital-acquired pneumonia' or 'pneumococcal pneumonia'.[1] When sorted according to keywords, two new studies[8 9] were selected.

RESULTS

Aetiology

Forty-six primary articles with the word 'aetiology' or 'etiology' in the title, abstract or keywords, or with a discussion of aetiology of CAP in the body of the article were identified and analysed.[2 5 10–53] Most of these were prospective studies conducted in a hospital setting. The studies included in this analysis were not weighted to correct for differences in sample size. The 46 studies were from the following European countries: Spain (19), France (7), Italy (3), The Netherlands (3), the UK (3), Denmark (2), Germany (2), Switzerland (2), Estonia (1), Finland (1), Ireland (1), Slovenia (1) and Turkey (1). The studies used a variety of techniques to detect aetiological agents, including microbial cultures (blood, sputum, pleural fluid, bronchoalveolar lavage, aspirates from transthoracic needle aspiration and homogenised lung biopsy samples), immunoassays (urine, sputum, serum and pleural fluid) and nucleic acid amplification techniques. Data are presented as percentage means from the included studies, as was done previously.[54] These studies confirmed that numerous microbial pathogens cause CAP, and the most frequently isolated pathogen in most European countries is *Streptococcus pneumoniae* (table 1, table 2,[55] figure 2).

Antibiotic resistance

Antibiotic resistance has important clinical and economic implications. The failure of empiric antibiotic treatment due to resistance can increase the cost of treatment if a more expensive class of antibiotics or longer hospitalisation time is required. The proliferation of resistant strains of *S pneumoniae* and other pathogens in the past 15 years threatens the successful

Table 1 Frequency of isolation of causative organisms of community-acquired pneumonia in Europe by country* [2 5 10–53 55]

	Percentage means of frequency of isolation in each country												
Pathogen	**Denmark**	**Estonia**	**Finland**	**France**	**Ireland**	**Italy**	**Slovenia**	**Spain**	**Switzerland**	**Netherlands**	**Turkey**	**UK**	**Germany**
Streptococcus pneumoniae	26.1	25.8	68.3	37.2	37	11.9	17.7	33.7	48.9	44.5	25.5	42.1	40
Haemophilus influenzae	10.7	2.4	6.6	10.3	18	5.1	2.9	5.3	14.6	12.3	44.9	12.3	8
Legionella spp.	4.3	0	0	2.0	0	4.9	2.9	12.9	8.6	6.7	0	9.1	3.1
Staphylococcus spp.	1.6	4.3	0	11.7	0	6.5	0	3.2	9.1	1.0	1.0	2.6	5
Moraxella catarrhalis	1.1	12.0	4.4	3.3	10	1.0	2.9	2.7	5.5	1.0	12.2	0.8	0
Gram-negative bacilli	2.7	41.6	0	16.8	0	24.3	1.5	7.9	4.7	9.4	4.1	2.6	7
Mycoplasma pneumoniae	9.5	6.2	16.34	0.7	1.3	7.0	32.4	8.4	9.7	14.0	0	5.3	5.6
Chlamydophila spp.	1.6	5.3	20.2	1	0	2.4	26.5	7.2	3.2	7.6	0	5.9	1.3
Coxiella burnetii	0	0	0	0.2	0	0.4	0	6.2	0	0.7	0	0.3	0
Viruses	6.3	0	15.9	1.7	0	11.6	0	5.9	0	16.5	0	18.6	9
No pathogen identified	59.8	52.4	39.8	35.6	39.4	67.3	39.8	56.8	67.1	35.3	40.6	38.4	NR

*Data are presented as percentage means of frequency of isolation of the respective pathogens from the studies included.
NR, not reported.

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Table 2 Aetiology of community-acquired pneumonia in Europe by treatment setting[2 5 10–53 55]

Pathogen	Percentage means		
	Outpatient	Hospital	Intensive care unit
S pneumoniae	38	27	28
M pneumoniae	8	5	2
H influenzae	13	6	7
Chlamydophila pneumoniae	21	11	4
Staphylococcus aureus	1.5	3	9
Enterobacteriaceae	0	4	9
Pseudomonas aeruginosa	1	3	4
Legionella spp.	0	5	12
C burnetii	1	4	7
Respiratory viruses	17	12	3
Unclear	50	41	45

treatment of CAP.[56] Several studies estimated the increase in antibiotic resistance among CAP-related pathogens in Europe (table 3).[33 41 46 57–67] Although many studies found no significant correlation between antibiotic resistance and mortality, half of the studies[59 60 62–64 66 67] documented appreciable increases in resistance to commonly used antibiotics. Three studies[57 59 63] following the evolution of *S pneumoniae* antibiotic resistance over time documented appreciable increases in resistance of *S pneumoniae* to commonly used antibiotics.

Bruinsma and colleagues investigated penicillin and erythromycin resistance in invasive *S pneumoniae* using data from the European Antimicrobial Resistance Surveillance System (EARSS) from 26 countries between 1999 and 2002.[56] Results showed that 10% of *S pneumoniae* isolates were penicillin non-susceptible (NS), 17% were erythromycin-NS and 6% were co-resistant. Twenty percent of penicillin-NS *S pneumoniae* and 33% of erythromycin-NS *S pneumoniae* occurred in children aged <5 years. Of the penicillin-NS *S pneumoniae* isolates, 78% had intermediate resistance to penicillin; 97% of isolates with reduced susceptibility to erythromycin were fully resistant.[56] Penicillin and erythromycin non-susceptibility varied greatly between countries. Overall,

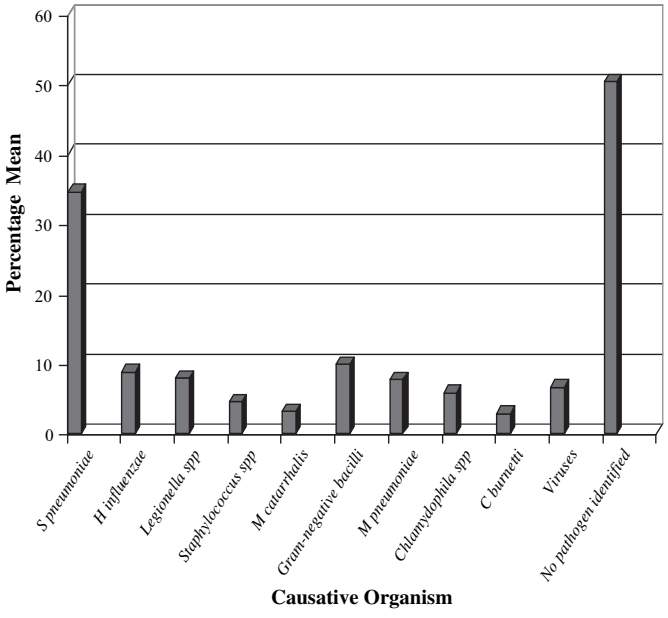

Figure 2 Frequency of causative organisms of community-acquired pneumonia (CAP) in Europe. Data are presented as percentage means of frequency of isolation of the respective pathogens from the studies included.

single penicillin non-susceptibility decreased and dual non-susceptibility increased, indicating a shift toward combined non-susceptibility with erythromycin. The highest percentage of penicillin non-susceptibility was in southern European countries and exceeded 30% in France, Israel and Spain. For both penicillin-NS and erythromycin-NS *S pneumoniae*, the highest percentage of resistance was in Mediterranean countries. Co-resistance was highest in Spain (18%) and Luxembourg (12%), followed by Belgium, Israel and Croatia with 10%. The highest percentages of fully resistant strains were in Bulgaria (11%), Spain (11%), Israel (6%) and Luxembourg (6%).[56]

Results showed an overall 5.3% annual decrease in single penicillin non-susceptibility. Single erythromycin non-susceptibility increased for all European countries included in the study (5.9%/year), except for the UK. Isolates with dual non-susceptibility increased by 7.6%/year. When analysed individually, no countries showed a significant increase in single penicillin non-susceptibility. However, countries with the lowest percentage of erythromycin and dual non-susceptibility in 1999 (eg, Finland) had the highest rates of increase. When the regression model for this study was extrapolated from 1999 to 2006, single penicillin non-susceptibility decreased from 4.8% to 3.6%; single erythromycin non-susceptibility increased from 14.6% to 20.4%; and dual non-susceptibility increased from 5.4% to 8.9%.[56] These results are consistent with data from another antibiotic resistance surveillance project.[68]

Clinical burden of disease: morbidity and mortality

Incidence

Studies[3–5 8 24 28 69–77] show that the incidence of CAP in Europe varies by country, age and gender (table 4). In all studies, the incidence increased sharply with age and was appreciably higher in men than in women. Trotter and colleagues also observed that the incidence of hospital admission increased between 1997–1998 and 2004–2005 across all age groups.[5] Although several outpatient and inpatient studies were conducted in different regions in Spain, no conclusions can be drawn about regional differences in incidence within a country because the studies were conducted during different time periods and may have had different designs.

Mortality and associated risk factors

Table 5[3–5 8 9 12–14 18 21 22 24 35 37–39 42–44 46 49 50 58 59 61–64 66 67 69–71 73 75 77–87] summarises mortality studies in patients with CAP. Mortality varied from <1% to 48% and was not related to antibiotic resistance. Some variables associated with mortality were age ≥65 years, female gender, use of oral corticosteroids, hospital-acquired lower respiratory tract superinfections, polymicrobial pneumonia, pleural effusion, intensive care unit (ICU) admission, atypical pneumonia, nosocomially acquired pneumonia, recent hospitalisation, serious underlying disease, acute renal failure, bacteraemic pneumonia, ineffective initial therapy, multilobar involvement, impaired alertness and septic shock. A long-term follow-up study (median=9.2 years) conducted in Finland found that elderly patients treated for CAP in both ambulatory and hospital settings had significantly higher risks of death and death related to pneumonia and cardiovascular conditions for several years following a diagnosis of pneumonia than the elderly without pneumonia.[88] The risk for pneumonia-related mortality was almost threefold higher if pneumonia was pneumococcal.

Effects of CAP on quality of life

Three studies documenting the effects of CAP on HRQOL were identified.[65 69 89] When measuring the time it took for patients

Table 3 Antibiotic resistance of *S pneumoniae* causing community-acquired pneumonia in Europe

Country	Reference	Period (years)	β-Lactams	Macrolides	Tetracyclines	Fluoroquinolones	Other
Estonia	Leesik *et al*[33]	1996–1998	PEN Benz 20.5% Amp 12.5% CSPN 50%	—	—	Cipro 40%	—
England and Wales	Johnson *et al*[57]	1990–1995	PEN 1.5% (1990); 3.9% (1995) CSPN Cftx 0.7% (1995) Cftr 0.3% (1995)	Ery 8% (1990); 8.6% (1995) Cln 0.6% (1990); 1.9% (1995)	5.0% (1990) 5.1% (1995)	—	—
France	Jehl *et al*[58]	1998–2000	—	Ery 46%	27%	—	SULF Cotr 37%
	Bonnard *et al*[59]	1995–2000	PEN 19% (1995)–50% (2000)	Ery 19% (1995); 46% (2000)	Dox 8% (1995)–18% (2000)	—	—
	Yu *et al*[60]	1998–2001	PEN 29%	—	—	—	—
Sweden	Yu *et al*[60]	1998–2001	PEN 7%	—	—	—	—
Spain	Yu *et al*[60]	1998–2001	PEN 28%	—	—	—	—
	Roson *et al*[46]	1995–2000	PEN 12% CSPN 5%	Ery 22%	—	Cipro 6.7%	—
	Nunez Fernandez *et al*[61]	1995–2000	PEN 31%	Ery 13%	—	Cipro 3%	SULF TMP-SMX 28%
	Valles *et al*[62]	1999–2002	PEN 34% CSPN Cftx 9%	Ery 33%	—	Cipro 1.5%	—
	Pallares *et al*[63]	1984–1993	PEN 1% (1984–1988)–4% (1989–1993) CSPN Cftr/Cftx 2% (1984–1988)–9% (1989–1993) CARB Imi: 6% (1984–1988)–18% (1989–1993)	Ery 7% (1984–1988)–13% (1989–1993)	44% (1984–1988)–33% (1989–1993)	—	SULF TMP-SMX 41% (1984–1988)–37% (1989–1993)
	Ewig *et al*[64]	1996–1998	PEN 14% IR, 30% R CSPN 19% IR, 10% R CARB Imi 23% IR	Ery 27% R	—	Cipro 14% IR, 2% R	—
	Carratala *et al*[65]	2000–2002	PEN 41%	Ery 35%	—	—	—
	Falco *et al*[66]	1997–2001	PEN 21% IR, 6% R CSPN Cftx 10% IR, 2% R	Ery 1% IR, 21% R	22% R	—	SULF Cotr 18% IR, 11% R
	Aspa *et al*[67]	1999–2000	PEN 26% IR, 10% R Amx 3% IR, 2% R CSPN Cftx 3% IR, 0.3% R Cfur 3% IR, 29% R CARB Imi 22% IR, 4% R	Ery 27% R	0.8% IR, 31% R	—	CHLOR18% R

Amp, ampicillin; Amx, amoxicillin; Benz, benzyl penicillin; CARB, carbapenem; Cftr, ceftriaxone; Cftx, cefotaxime; Cfur, cefuroxime; CHLOR, chloramphenicol; Cipro, ciprofloxacin; Cln, clindamycin; Cotr, cotrimoxazole; CSPN, ciclosporin; Dox, doxycycline; Ery, erythromycin; Imi, imipenem; IR, intermediately resistant; PEN, penicillin; R, resistant; SULF, sulfonamides; TMP-SMX, trimethoprim–sulfamethoxazole.

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Table 4 Incidence of community-acquired pneumonia in Europe

Country, investigator	Study period	Age	Annual incidence
Outpatient treatment			
Spain, Almirall *et al*[69] *	1993–1995	15–39	1.2♂; 1.0♀
		40–64	1.8♂; 1.4♀
		>64	5.2♂; 1.9♀
		All ages	1.6
Finland, Jokinen *et al*[3] *	1981–1982	15–29	4.2♂; 4.6♀
		30–44	5.6♂; 5.9♀
		45–59	9.8♂; 7.0♀
		60–74	25.0♂; 9.0♀
		≥75	65.2♂; 19.6♀
		≥60	33.0♂; 11.8♀
Spain, Gutierrez *et al*[28] †	1999–2001	15–44	0.8♂; 0.6♀
		45–64	1.4♂; 0.7♀
		65–74	3.2♂; 1.6♀
		≥75	8.7♂; 3.0♀
		All ages	1.6♂; 0.9♀
Spain, Ochoa-Gondar *et al*[70] ‡	2002–2005	65–74	3.0♂; 2.2♀
		75–84	5.3♂; 2.8♀
		≥85	10.0♂; 7.9♀
		All ages	4.2♂; 2.9♀
Spain, Vila-Corcoles *et al*[8] †	2002–2005	>65	3.5
Italy, Viegi *et al*[71] *	1999–2000	15–44	0.9
		45–64	1.6
		>64	3.3
		All ages	1.7♂; 1.7♀
Germany, Schnoor *et al*[72] *	2003	>18	8.7
Hospitalisation			
England and Wales, Melegaro *et al*[73] *	1995–2000	15–44	0.2
		45–64	0.5
		65–74	1.5
		≥75	4.0
England, Trotter *et al*[5] *	1997–2005	<65	0.65–0.84
		65–74	2.63–3.55
		75–84	6.8–8.8
		≥85	16.0–22.4
Italy, Rossi *et al*[24] *	1997–1999	<65	0.8
		≥65	4.8
		Overall	1.6
Portugal, Froes[4] *	1998–2000	≥15	2.7
		≥65	9.8
Spain, Carretero Gracia *et al*[74] *	1995–1996	Mean 68 (range 42–94); 43% >80	3.2
Spain, Gutierrez *et al*[28] *	1999–2001	All ages	0.9
Spain, Monge et al[75] *	1995–1996	All ages	1.6
		≥65	5.2
Spain, Ochoa-Gondar *et al*[70] ‡	2002–2005	65–74	11.1♂; 4.3♀
		75–84	19.9♂; 8.71♀
		≥85	29.0♂; 16.4♀
		All ages	15.1♂; 7.0♀
Spain, Vila-Corcoles *et al*[8] †	2002–2005	>65	10.5
Sweden, Hedlund *et al*[76] †	1987–1988	18–49	17
		50–64	69
		65–84	120
		≥85	242

*Cases per 1000 population.
†Cases per 1000 person-years.
‡Range between 1997–1998 and 2004–2005.

with CAP to return to full activity, results varied with the aetiology of the infection (viral 13–33 days; bacterial 7–43 days; mixed bacterial and viral 10–50 days).[69] A Spanish study measured HRQOL with the Medical Outcomes Study questionnaire (SF-36) given to ambulatory and hospitalised patients on day 7 and day 30 after they were diagnosed with pneumonia. Although the scores were not significantly different between the two groups, both groups were still subnormal compared with the general Spanish population.[65] A Dutch study found a positive correlation between HRQOL and CAP scores; after 18 months, patients with CAP had significantly lower scores on physical functioning and general health components of the SF-36 questionnaire than matched controls. Patients with co-morbidities had significantly greater HRQOL impairments in physical function, physical role function, general health and vitality than the Dutch controls.[89]

Economic burden of disease: costs of care

In Europe, pneumonia costs ~€10.1 billion annually, with inpatient care accounting for €5.7 billion, outpatient care €0.5 billion and drugs €0.2 billion.[1] The indirect costs of lost work days amount to €3.6 billion. The high cost of care for patients with CAP has resulted in the implementation of cost-saving measures, such as reduction in hospital length of stay (LOS), the use of less expensive antibiotics and stratification of patients by severity of disease to identify those who can be cared for as ambulatory patients.

The direct and indirect costs of treating CAP were the subject of several European studies. Analysis of hospital discharge data from the Spanish national surveillance system over a 2-year period showed that the cost of hospitalisation for CAP in Spain was €114.8 million in 2001.[75] Of this amount, the care of patients aged ≥65 years accounted for €66.8 million. A multicentre study in Italy estimated that the yearly costs for treating a patient with CAP, including healthcare costs during the follow-up period, were €1586.[90] A population-based study in Spain estimated that the mean direct costs of treatment of CAP in the ambulatory and hospital settings were €196 and €1553, respectively.[91] Although costs were higher for patients aged ≥65 years, the difference was statistically significant only when compared with patients aged <65 years who were ambulatory.[91] In a prospective study in 22 hospitals in Germany, the median cost of treatment of a hospitalised patient was €1201. Costs rose as pneumonia severity index (PSI) scores increased from I to III and dropped slightly for PSI classes IV and V. This was attributed, in part, to the shorter length of treatment in non-survivors, who were only in the latter two PSI classes.[92] Data from the Romanian national surveillance records show that the cost of treatment for bacteraemic and non-bacteraemic pneumococcal pneumonia in ambulatory and hospitalised patients in 2004 was €8.3 million.[93]

Hospital LOS

Hospital LOS is a significant cost factor in caring for patients with CAP. When a multiple regression model was used to analyse the factors influencing LOS, interhospital variability, PSI risk class, complications during hospitalisation, ICU admission, oxygen therapy and discharge to a nursing home were associated with increased LOS.[94] Another study found that low socioeconomic status independently prolonged LOS by 6 days (95% CI 2.2–9.5 days, p~0.003). This finding was not related to mortality, severity at presentation, number of co-morbid conditions or transfer to an ICU. Patients with low socioeconomic status were more likely to be addicted to alcohol, tobacco or drugs, and were more likely to have tuberculosis than patients with average socioeconomic status.[95]

A study of patients aged ≥65 years with CAP found statistically significant associations between LOS and higher fever, higher number of days with fever, greater co-morbidity, urinary catheterisation and urinary infections, higher erythrocyte

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Table 5 Mortality by country and setting due to community-acquired pneumonia in Europe

Setting	Investigator	Case-fatality rate
Community		
Finland	Jokinen *et al*[3]	4% overall; 11% ≥60 years; 0.6% 15–59 years; highest men ≥60 years
France	Fantin *et al*[78]	3.8%
Community and hospital		
Spain	Almirall *et al*[69]	5.0%
Italy	Viegi *et al*[71]	6.0%; hospitalised > outpatients
Spain	Vila-Corcoles *et al*[8]	12.7% overall; 2% outpatients, 15% hospitalised
Spain	Ochoa-Gondar *et al*[70] *	12.7%; increased with age
Germany	Kothe *et al*[9]	6.3% overall; 2.2% <65 years, 10.3% ≥65 years
Hospital		
England	Venkatesan *et al*[50]	33%
Denmark	Nielsen *et al*[77]	17%, all >65 years (range 21–92 years)
Spain	Rello *et al*[44]	22.4%
Denmark	Ostergaard and Andersen[39]	6.3%
The Netherlands	Bohte *et al*[13]	8%
Spain	Pallares *et al*[63]	28%
Switzerland	Janssens *et al*[79]	14%
Germany	Holtermann *et al*[80]	31%
Spain	Ewig *et al*[64]	11% immunocompetent; 9% immunosuppressed 15% antibiotic-resistant; 6% antibiotic-sensitive strains
France	Georges *et al*[22]	27.5%
Italy	Logroscino *et al*[81]	2.8%; mortality increased with disease severity according to Fine risk categories
Spain	Arancibia *et al*[82]	43%
Spain	Monge *et al*[75]	2.7% <65 years; 11.6% ≥65 years
Switzerland	Garbino *et al*[21]	8%
France	Jehl *et al*[58]	16.3%
Spain	Celis *et al*	6%
Spain	Nunez Fernandez *et al*[61]	Age <60 years: 6.6%; age ≥60 years: 15.7%; PSI score associated >140
Portugal	Froes[4]	14.0%; increased with age
Spain	Aspa *et al*[67]	14.4%
The Netherlands	Braun *et al*[12]	17.8%
Spain	Falco *et al*[66]	9.9–13.7%, related to antibiotic susceptibility
Italy	Rossi *et al*[24]	Overall: 11.2%; age ≥65 years: 13.8%
Spain	Martinez-Moragon *et al*[37]	11%; Fine severity score associated
Spain	Menendez *et al*[83]	5.6%
France	Paganin *et al*[42]	43%
Spain	Roson *et al*[46]	4% early treatment response; 27% early treatment failure
France	Bonnard *et al*[59]	32%; associated with PSI scores of 90 and 130
Ireland	Foley *et al*[84]	2% <65 years; 11.5% >65 years
Spain	Valles *et al*[62]	7%
England and Wales	Melegaro *et al*[73]	Range: 1–20% age related
England	Trotter *et al*[5]	Range: 24.8–28.2% related to year (1997–1998 to 2004–2005)
ICU		
England	Alkhayer *et al*[85]	28%
Spain	Torres *et al*[49]	22%
UK	BTS Research Committee[14]	48%
France (ICU and ID unit)	Leroy *et al*[35]	28.5%
France	Moine *et al*[38]	35%
France	Leroy *et al*[86]	19% <65 years; 30% ≥65 years (CAP attributable)
Spain	Rello *et al*[87]	11.1–44.7% related to antibiotic regimen
Spain	Rello *et al*[43]	23.5%; age associated

BTS, British Thoracic Society; CAP, community-acquired pneumonia; ICU, intensive care unit; ID, infectious disease; PSI, pneumonia severity index.
*Includes ICU.

sedimentation rate, dehydration and malnutrition.[96] An analysis of the influence of clinical parameters and hospital type on LOS found that hypoxaemia, low diastolic pressure, pleural effusion, multilobar pneumonia and hypoalbuminaemia were associated with increased LOS in patients in PSI risk classes III–V.[97] Hypoxaemia and pleural effusion were associated with prolonged LOS in patients in the low-risk classes I and II. A study evaluating the impact of empiric antibiotic regimens on the prognosis of CAP found no associations between choice of antibiotics and hospital LOS.[98]

A recent study of the impact on LOS of adherence to American Thoracic Society guidelines for the treatment and management of CAP found that hospital stay was significantly longer in patients who received treatment deviating from the guidelines (10.4 days mean duration) than patients receiving treatment adhering to the guidelines (7.6 days; 2.8 days difference; 95% CI 0.93 to 4.66, p=0.004).[99]

Two studies conducted in Europe showed no difference in LOS whether or not patients were treated in accordance with guidelines.[100 101] However, a study evaluating atypical pathogens in CAP worldwide found that antibiotic treatments that included coverage for atypical organisms led to a significantly shorter LOS; mortality rate was increased when atypicals were not covered.[102]

Treatment and prevention

As shown in a number of studies, the use of guidelines for treating CAP can significantly reduce morbidity and mortality.[103–105] Guidelines for treatment and prevention of lower respiratory tract infections (LRTIs)—including CAP—were established by a European Respiratory Society (ERS) task force in collaboration with the European Society for Clinical Microbiology and Infectious Diseases (ESCMID).[7] Recommendations for antibiotic treatment are based on illness severity, frequency of specific pathogens, local microbial resistance patterns and drug safety profiles. These guidelines also stress the possibility of a viral cause for pneumonia and offer recommendations for prevention of LRTI by vaccination and other methods.[7]

Empirical antibiotic coverage of atypical pathogens does not reduce mortality or improve clinical efficacy in hospitalised patients with CAP.[106] There is a higher level of *S pneumoniae* resistant to macrolides in Europe. For patients who cannot tolerate penicillins and macrolides, fluoroquinolones with Gram-positive coverage are recommended.[107] Adherence to CAP guidelines also allows identification of individuals who can be managed in the outpatient setting. In addition to eliminating all hospital costs, outpatient management can decrease the risk of death, thromboembolic events and infection with resistant nosocomial bacteria.[108]

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DISCUSSION

The studies reviewed here highlight the substantial clinical and economic burden of CAP in Europe. Many of these studies demonstrate appreciable increases in disease incidence and hospitalisation for CAP. They show that the elderly are disproportionately affected by CAP; moreover, death from CAP increases and HRQOL declines with advancing age. According to the WHO, in 2002 LRTIs outranked infectious diseases such as HIV/AIDS and tuberculosis as causes of mortality among European adults. The incidence of LRTIs in Europe in 2002 (25.8 million) was second only to diarrhoeal diseases (205.5 million) and was greater than diabetes mellitus (2.0 million) and all malignant neoplasms combined (2.4 million).[109]

With the increases projected in the elderly population by 2025, it is imperative that therapeutic interventions be developed to address the emergence of antibiotic-resistant bacterial strains causing CAP. Co-morbidities are more common among the elderly. Consequently, the clinical outcome of pneumococcal disease in elderly individuals with multiple co-morbidities can be significantly worse than in the younger population. Increases in resistance might be explained by certain patterns of antibiotic use, such as overuse for doubtful indications or low doses of oral β-lactams.[110] Because resistance to erythromycin tends to be clinically relevant,[68] it is more likely to lead to treatment failures and the resultant resistant strains. Although macrolides are generally a good alternative to β-lactams, treatment failures with macrolides are increasing.[56] Furthermore, macrolides select for co-resistance more frequently than β-lactams,[111] which would explain the increase in dual non-susceptibility to erythromycin and penicillin in countries where macrolides are preferred for children.

The ability of 23-valent pneumococcal polysaccharide vaccine (PPV) to prevent pneumonia in adults is limited. A recent meta-analysis of randomised, controlled trials pointed to the lack of evidence supporting the use of PPV to prevent all-cause pneumonia or mortality.[112] These observations suggested the need for improved vaccines for adults and prompted the development of new pneumococcal conjugate vaccines (PCVs). These investigational PCVs are likely to make significant contributions to reducing the burden of CAP in adults. A 13-valent PCV is currently in late-stage clinical trials for use in adults.

This review has several limitations. Only published data were analysed. Although these data are substantial, they provide incomplete information on the burden of CAP. Data from national surveillance databases and proprietary databases, to which we did not have access, may contain information that would alter our estimates. Estimates based on data from individual countries may not be applicable to the European continent as a whole, because of country-specific differences in disease management and hospital admission criteria. Additionally, data on epidemiology and disease resistance may be skewed towards Spain, since 19 of the 46 studies identified were conducted in this country. Studies included in the analysis were all weighted equally, rather than weighted by sample size, making it difficult to compare results across studies with different sample sizes. However, we believe that by reporting the frequency of isolation of aetiological agents as percentage means from the studies included and by combining the percentage means for each country (table 1), any bias attributed to different sample sizes in individual studies is effectively addressed, and the estimates reported are an accurate representation of the situation in each country.

Because of differences in the methods used to gather and report data, studies performed in different geographic locations may not be comparable. Despite these drawbacks, this review highlights the substantial effects of CAP on adults in Europe. Improvements in the sensitivity and specificity of diagnostic assays to detect pneumococcal pneumonia, further validation and widespread use of diagnostic assays for enhanced detection of pneumococcal pneumonia and routine use of standardised definitions to report disease burden will help provide a more accurate picture of the true burden of CAP in adults.

Although the clinical and economic burden of CAP among adults in Europe is significant, data on the incidence of CAP have been wanting. A recent study analysed the inpatient records of every hospitalised patient with CAP in Germany during 2005 and 2006 (388 406 patients).[113] Results showed that the incidence of hospitalised CAP in the German population was 2.75/1000/year in 2005 and 2.96/1000/year in 2006. The incidence was strongly age related, with an incidence of 7.65/1000/year in patients aged ≥60 years. Mortality was higher than had been reported in previous studies, with the highest risk of death occurring in the first days after hospital admission. These results confirm that CAP is a disease of the elderly. Undoubtedly, the incidence of CAP will increase in the next decade due to the ageing of the population and consequent increase of associated co-morbidities.[113]

For an update on the incidence, aetiology and antibiotic resistance among patients with CAP from the German Network for Community Acquired Pneumonia (CAPNETZ) registry and review data from several European countries, see the 2009 review by Welte and Kohnlein.[114] For an update on the effect of hospitalised CAP on the health outcomes and resources of the elderly, see information on the currently recruiting Costs Health Status and Outcomes of CAP (CHO-CAP) study (NCT00812084) at http//www.clinicaltrials.gov.[115]

CONCLUSIONS

The increasing numbers of older patients hospitalised with CAP will consume a large percentage of health resources in the future. These increases in morbidity and mortality in the elderly and the considerable cost of treatment support the need to prevent CAP with an effective vaccine. PCVs based on antigens common to 7, 10 or 13 pneumococcal serotypes are currently licenced and in late-stage clinical trials in adults. These vaccines may prevent a substantial proportion of the overall burden of CAP. Vaccination of young children may also aid in controlling antibiotic resistance in pneumococcal disease in Europe. Children are a reservoir for antibiotic-resistant pneumococci and are the most vulnerable to pneumococcal infections.[116] Vaccinating this age group with PCV may be an effective tool for preventing infections caused by drug-resistant strains. In addition to preventing disease, vaccine-induced immunity reduces transmission by preventing carriage, and subsequently may contain the spread of resistant strains.

Resistance is a growing problem in Europe and the diverse nature of resistance has rendered the current European CAP treatment guidelines inadequate. In order to provide optimal treatment, national guidelines must be formulated. The possibility of an increase in erythromycin resistance, with or without reduced susceptibility to penicillin, requires intervention. The prudent use of macrolides is important in areas where resistance to penicillin and erythromycin is common. Although appropriately dosed β-lactams for empirical therapy are still the treatment of choice, macrolides should be used judiciously.[56]

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