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Pneumococcal infection in adults: burden of disease

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Abstract

To overview the present global burden of pneumococcal disease is important because new preventive measures such as the pneumococcal conjugate vaccine 13 are currently being evaluated. Pneumococcal disease is roughly divided into non-invasive and invasive disease. The burden of non-invasive pneumococcal disease in adults is mainly determined by community-acquired pneumonia. Pneumococcal pneumonia has high incidence rates and carries a high mortality risk, especially in the elderly. Within the cluster of invasive pneumococcal diseases, pneumonia also represents the most common infectious source. Incidence and mortality rates of both non-invasive and invasive disease have changed as a result of pneumococcal vaccination in children. However, especially elderly patients with comorbidities remain vulnerable to morbidity and mortality caused by pneumococcal disease. The current review summarizes the current knowledge on the epidemiology including outcome of the main clinical forms of pneumococcal disease, with a special focus on elderly patients. Furthermore, the economic burden and future vaccine strategies are briefly discussed.

Keywords: Community-acquired pneumonia, disease burden, elderly, incidence, invasive pneumococcal disease, outcome, pneumococcal conjugate vaccine, pneumococcal pneumonia, *Streptococcus pneumoniae*
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Introduction

Pneumococcal disease (PD) can be divided into non-invasive and invasive disease (Fig. 1) [1]. Considering the global burden of PD is especially important, because new preventive measures such as the pneumococcal conjugate vaccine (PCV)13 are currently being evaluated. To assess future effects, we aim to give an extensive overview of the current burden of PD in adults. From that perspective, incidence and mortality rates are described in pneumococcal pneumonia (PP) and invasive pneumococcal disease (IPD). Effects of the introduction of PCV7 vaccination in children on these rates are also illustrated. Subsequently, because the PD burden is especially high in the elderly, this age group will be highlighted separately. Finally, the economic burden of PD is described and future vaccine strategies are briefly discussed.

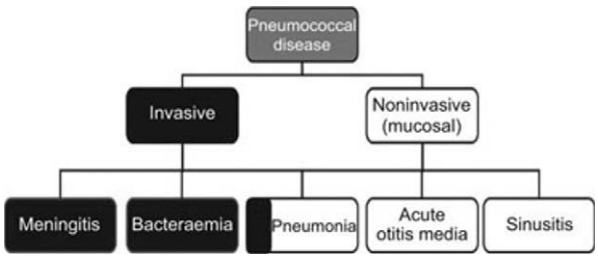

FIG. 1. Classification of pneumococcal disease [1].

Non-invasive Pneumococcal Disease

Non-invasive PD can principally be divided into sinusitis, acute otitis media and community-acquired pneumonia (CAP). As the burden of disease in adults is mainly determined by CAP, we will focus on CAP in this review.

Aetiology of CAP

In daily practice, a microbiological diagnosis is made in only about 20% of CAP. This can rise up to 60% when extensive and costly diagnostic testing is performed [2].

Aetiological fractions of the most common pathogens in CAP are summarized in Fig. 2 [3]. Accordingly, in a large European review, *Streptococcus pneumoniae* was the most frequently isolated pathogen in CAP (35% overall, ranging from 12 to 68% between various countries) [4]. This was true for all settings, including outpatients, hospital-treated patients and intensive care unit-treated patients [4]. Both European and worldwide meta-analyses generally confirmed these findings and estimated the prevalence of *S. pneumoniae* in CAP to be 19.3% and 27.3%, respectively. [5, 6]. A recent study specifically investigated CAP in outpatients and also found that *S. pneumoniae* was the most frequent pathogen (35.1% of cases with an established aetiological diagnosis) [7]. Similarly, *S. pneumoniae* was the most frequent pathogen causing CAP in younger patients (18–65 years) and patients with nursing-home-acquired-pneumonia [8,9].

In conclusion, *S. pneumoniae* is the most important pathogen in CAP in various different settings, indicating that epidemiological data on CAP in many cases mirror the situation in PP.

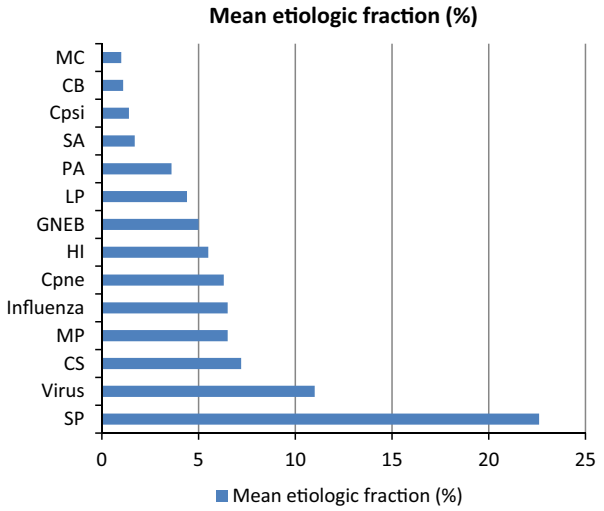

FIG. 2. Mean aetiological fraction of community-acquired pneumonia pathogens in adults admitted to the hospital. Abstracted and modified from European Respiratory Society guidelines on lower respiratory tract infections [3]. SP, *Streptococcus pneumoniae*; HI, *Haemophilus influenzae*; LP, *Legionella pneumophila*; MC, *Moraxella catarrhalis*; SA, *Staphylococcus aureus*; GNEB, Gram-negative enteric bacilli; PA, *Pseudomonas aeruginosa*; MP, *Mycoplasma pneumoniae*; CS, *Chlamydia* species (all); CPne, *Chlamydophila pneumoniae*; CPsi, *Chlamydophila psittaci*; CB, *Coxiella burnetii*.

Incidence of CAP

In Europe, incidence rates for CAP range from 1.6 per 1000 in Spain to 11.6 per 1000 in Finland [10,11]. Reports from England and Germany show intermediate rates (2.0 and 3.7–10.1 per 1000, respectively) [12,13]. It is not known whether these differences are related to study design or to actual differences between populations. In the USA, incidence rates for CAP requiring hospitalization were estimated to be 2.7 per 1000 in a large cohort [14]. Reliable data on incidence rates of CAP in other parts of the world are scarce. The few studies from the Asian-Pacific region report incidence rates from 0.2 to 0.9 per 1000, but these are probably underestimated [15].

Some recently published studies report an increase of hospital admissions due to CAP of about 30% in the last decade, suggesting that the annual incidence rates might have increased [12,16]. On the other hand, a study from the USA presented opposing findings, with the number of CAP hospitalizations declining by 54.8 per 100 000 annually after the initiation of PCV7 vaccination, leading to 168 000 fewer hospitalizations per year [17].

Outcome of CAP

In the USA, pneumonia was the eighth leading cause of death in 2004 and caused 1.3 million hospitalizations in 2005 [18].

Roughly, mortality rates can be divided into short-term (in-hospital or 30-day mortality) and longer-term mortality.

Short-term mortality. Risk factors for short-term mortality in CAP are shown in Table 1 [19–21]. In Europe, reported short-term mortality of CAP varied between <1% and 48% [4]. This great variability depends on multiple factors, including demographic differences, comorbid conditions, ambulatory versus hospitalized patients and time to follow up.

The mean short-term mortality in CAPNETZ, a large German competence network for CAP, was 8.6% (varying from 0.8% in outpatients to 12.2% in hospitalized patients)

TABLE 1. Risk factors for short-term mortality in community-acquired pneumonia (CAP) and invasive pneumococcal disease [19–21].

Community-acquired pneumonia	Invasive pneumococcal disease
Male gender	Male gender
Neoplastic disease	Solid malignancy
Neurological disease	Increasing age
Bacteraemia	Liver disease
Leucopenia	Renal disease
Multilobar infiltrate	Chronic pulmonary disease
Pleuritic chest pain	Higher Charlson Index
Hypothermia	Nursing home residence
Systolic hypotension	High acute physiology score
Tachypnoea	Mechanical ventilation
Diabetes mellitus	Alcohol abuse
	Smoking

[22]. In Germany, overall in-hospital mortality for CAP was 14% in 2005–2006. Mortality started to increase significantly with age in patients older than 40 years. [23].

Examining in-hospital mortality differences between world regions, the highest mortality was found in Latin America (13.3%) followed by Europe (9.1%) and North America (7.3%) [24].

Trends in in-hospital mortality between 1993 and 2005 were examined in the USA and decreased from 8.9% to 4.1%, showing that mortality rates in CAP are changing [25].

Long-term mortality. The excess mortality after surviving the initial CAP episode can be as high as 50% within 5 years [26]. A Dutch cohort estimated cause-specific long-term mortality (7 years) and found mortality rates more than three times as high as in the general population. Malignancy (27%), chronic obstructive pulmonary disease (19%) and cardiovascular disease (16%) were the most frequent causes of death [27]. Similarly, in a general practice population in the UK, 30-day and 3-year mortality in CAP patients were 18.5% and 30.8%, respectively, versus 0.4% and 10.3% in controls [28].

Invasive Pneumococcal Disease

Invasive pneumococcal disease is defined as an infection confirmed by the isolation of *S. pneumoniae* from a normally sterile site, such as blood or cerebrospinal fluid. The IPD burden is mainly determined by pneumococcal meningitis, bacteraemic PP and pneumococcal bacteraemia without a primary focus.

In a description of almost 16 000 IPD cases in adults in the USA, the origin of infection was pneumonia in 53% and meningitis in 5%. In 40%, bacteraemia was diagnosed without a focus [29].

Incidence of IPD

Invasive pneumococcal disease accounted for over 36 000 cases in the USA in 2011. The incidence of IPD was strongly age-related with 38% of cases occurring in children under 2 years of age and another 54% in adults above 50 years of age. IPD was more common in blacks than in whites (incidence rates 16.6 vs 11.0/100 000) [30]. Incidence rates of IPD in Europe ranged from 11 to 27 per 100 000, whereas estimates from North America in the same period ranged from 15 to 49 per 100 000 [31–33]. Even higher incidence rates of IPD are reported in particular regions of Asia, i.e. up to 216 cases per 100 000 annually in Taiwan [34]. Furthermore, numbers of IPD in the developing world are probably underestimated because of low diagnostic sensitivity and limited access to care.

Obviously, the incidence of IPD is influenced by preventive measures such as vaccinations. PCVs have been developed since the 1990s, and the use of PCV7 vaccination in children was approved in 2000 by the US Food and Drug Administration and in 2001 by the European Union. Currently, 70% of high-income countries are using PCV7 in their national immunization programmes [35].

A large amount of data are available describing the impact of PCV7 on IPD worldwide. A recent review, including ten studies, showed a reduction in the post-vaccination incidence rate of all serotype-IPD of 26.8% in comparison with the pre-vaccination period. Highest reductions were seen in the USA (44.7%) [36].

Of note, unvaccinated persons seem to be indirectly protected from IPD, probably because of a reduction in circulating infectious pathogens in the whole population, an effect that is called 'herd protection' [37].

It is important that, in the above-mentioned review, two European studies showed non-significant increases in incidence of IPD [36]. An additional European study also showed an increase in overall IPD incidence from 14.2 to 17.9 cases per 100 000. Several mechanisms explaining these (geographical) differences were proposed, including different vaccine coverage in the USA, fluctuations in serotypes or outbreaks of infections in specific areas [38].

Although overall IPD incidence after the introduction of PCV7 decreased in the USA, the proportion of cases among a specific population of high-risk adults (those with Pneumococcal Polysaccharide Vaccine 23 indications) rose. In 1998, 51% of nearly 6000 IPD cases were among these adults, whereas in 2009, this proportion rose to 61% of over 3000 cases, suggesting that despite the 'herd protection' these, often elderly patients with comorbidities, remain a very susceptible group for IPD [39].

Serotypes in IPD

Currently, at least 93 serotypes of pneumococci are known. Serotypes are distinguished by their unique polysaccharide capsule [40]. Before the introduction of PCV7, most pneumococcal infections were caused by the seven serotypes in the vaccine (4, 6B, 9V, 14, 18C, 19F and 23F). In adult and paediatric studies from the USA in the late 1990s these serotypes accounted for 59% and 87% of IPD, respectively [41].

After the introduction of PCV7, the serotype distribution changed dramatically. A recent study from the USA showed that PCV7-type IPD in all age groups decreased from 64% to around 4% [42]. Similar observations were seen in Europe, with, for example, one study from the UK showing a 98% decrease in PCV7-type IPD in children younger than 2 years and an 81% decrease in adults above 65 years [37].

In the post-vaccine era, serotype 19A became the most prevalent serotype (20% of isolates). However, after introduction of PCV13 (PCV7 plus 1, 3, 5, 6A, 7F and 19A), no further increase in prevalence was observed [42]. As expected, even a reduction of 58% of serotype 19A isolates in young children was observed after PCV13 introduction [43].

Outcome of IPD

Risk factors for short-term mortality in IPD are shown in Table 1 [19–21]. Case mortality rates for IPD range from 11 to 30% in adults in the western world [31,44–46]. Recent reports from Asia show case fatality rates of 26–30% [47,48]. The reported impact of PCV7 introduction on mortality rates is variable. Studies from the USA generally show reductions in mortality across all age groups, ranging from 38% to 78% [49–51]. Another report from the USA found a decline of 18% specifically in adults older than 50 years [52]. A recent study in Europe on the other hand, presented unchanged case fatality rates between periods from 1996 to 2001 and from 2005 to 2009 (15.2% vs 17.1%). IPD in the post-vaccine period was even associated with higher rates of septic shock (19.1% vs 31.1%) and a trend towards higher case fatality in adults aged between 50 and 65 years (11.6% vs 23.5%) [38].

Although paediatric vaccination programmes seem to positively influence (especially vaccine-type) IPD incidence, morbidity and mortality remain high.

Pneumococcal Disease in the Elderly

The human population is ageing, posing major challenges for future health care [53]. Rates of PD have always been highest among the very young and the very old [54]. In the elderly, PP mainly determines the burden of PD. The presence of underlying comorbid diseases, impaired mucociliary clearance and a waning immune system all contribute to an increased risk of (pneumococcal) pneumonia in the elderly [55].

As only a few studies have examined PP *per se*, most conclusions can be drawn from reports about CAP in elderly populations. Also in this elderly group, *S. pneumoniae* is the most frequently isolated pathogen (40–50%) [56, 57].

The overall incidence of CAP rises dramatically with age, with estimated rates ranging from 18.2 per 1000 person-years in people aged 65–69 years, to as high as 52.3 per 1000 person-years in those aged over 85 years [58]. In a study from Germany, overall incidence of CAP was 2.9 per 1000, rising up to 7.7 in adults over 60 years and to 35.8 in adults over 90 years of age [23]. Furthermore, hospitalization rates for elderly patients with pneumonia tend to increase, illustrated by a 20% increase between 1988–1990 and 2000–2002 in the USA [59]. Among US adults aged 50 years or older, nearly 30 000 cases of IPD and over 500 000 cases of non-bacteraemic PP were estimated to occur yearly, resulting in more than 25 000 pneumococcus-related deaths [60].

Mortality rates in the elderly with CAP are significantly higher than in CAP patients under 65 years, being 10.3% versus 2.2% in a large Spanish cohort [61]. In elderly patients with severe CAP requiring mechanical ventilation, mortality rates rose as high as 55% [62].

Overall, it seems important to focus on preventive measures against PD, especially in this group of vulnerable elderly patients. Unfortunately, the changing immune system in the elderly makes antibody responses weaker and protective effects of vaccination are likely to be insufficient precisely in this group, which needs protection the most [63].

Economic Burden of Pneumococcal Disease

Pneumococcal disease carries a high economic burden. Direct healthcare costs of PD totalled $3.5 billion in the USA in 2004. PP accounted for 72% of these costs [64]. Therefore, it is interesting to look into the more detailed data available about costs for CAP. In Europe, total healthcare costs related to CAP were estimated to be as high as €10.1 billion annually. One-third is related to indirect costs, i.e. loss of working days [65]. Furthermore, several studies measured hospitalization costs for CAP in Europe. They were estimated to be between €1201 and €2330 per episode [66–68]. One of these studies specifically compared the costs of PP with non-PP, and found that PP had significantly higher overall costs (€2865 vs €2260, respectively) [68]. Hospital costs in the USA are much higher than in Europe. One review determined hospitalization costs resulting from CAP to be $7000 to $8000 per episode [69].

Future costs for PD will probably rise, because the elderly population will increase worldwide. One study used an analytical model to calculate future economic costs of PP in the USA. These costs will increase annually by $2.5 billion [70]. On the other hand, possible future reductions in hospital stay could substantially reduce CAP costs, with an approximate $2300 per reduced day in the USA [71]. Furthermore, better preventive measures will probably help to counteract the rise in costs for PD.

Impact of Novel Vaccines

Pneumococcal vaccination has seen important technical developments within the last decade. Other articles in this supplement cover pneumococcal vaccines in more detail. A limitation of the polysaccharide vaccine is the limited

protection against PP [72]. Because of the limited effectiveness of polysaccharide vaccines in high-risk adults, at present new conjugate vaccines (particularly PCV13) are being evaluated for preventing PD in adults [73]. Previous experience in children and from immunological studies suggest improved efficacy [74,75]. Most is expected from a large randomized trial in the Netherlands, establishing the preventive effect on PP of PCV13 in 85 000 adults over 65 years of age [76]. Inclusion and follow up into this trial have been completed and the first results are expected early in 2014. Many countries already changed their recommendations to include conjugate vaccines [77].

Conclusion

Both non-invasive PD and IPD elicit a high medical and economic burden. Elderly patients with comorbidities carry the highest risk of developing PD.

In non-invasive PD, CAP carries the highest risk for morbidity and mortality. *Streptococcus pneumoniae* remains the most frequent pathogen in CAP and this is true for all treatment settings. Pneumonia is also the most common infectious source in adult IPD. The epidemiology of IPD changed as the result of the introduction of paediatric PCV7 vaccination with a shift occurring towards serotypes not included in the vaccine. Incidence rates of IPD generally decreased, although a few studies showed (small) increases, primarily in the elderly. Likewise, varying evidence is reported about changes in IPD mortality after PCV7. Nevertheless, again the vulnerable elderly remain exposed to a high risk of dying because of IPD.

Hence, it is important to further develop and evaluate new preventive measures.

Transparency Declaration

GGUR has received speaker's fees from Pfizer, Boehringer Ingelheim, Solvay, GSK, Essex Pharma, MSD and Novartis, and travel expenses from GSK. JJCD has no conflicts of interest.

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