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Narrative Review

Community-acquired pneumonia in adults: Highlighting missed opportunities for vaccination

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ABSTRACT

Pneumococcal pneumonia remains a clear unmet medical need for adults worldwide. Despite advances in vaccine technology, vaccination coverage remains low, putting many people at risk of significant morbidity and mortality. The herd effect seen with paediatric vaccination is not enough to protect all older and vulnerable people in the community, and more needs to be done to increase the uptake of pneumococcal vaccination in adults. Several key groups are at increased risk of contracting pneumococcal pneumonia, and eligible patients are being missed in clinical practice. At present, community-acquired pneumonia costs over €10 billion annually in Europe alone. Pneumococcal conjugate vaccination could translate into preventing 200,000 cases of community-acquired pneumonia every year in Europe alone.

This group calls on governments and decision makers to implement consistent age-based vaccination strategies, and for healthcare professionals in daily clinical practice to identify eligible patients who would benefit from vaccination strategies.

1. Introduction

Despite technological advances in pneumococcal vaccination in recent years, pneumococcal pneumonia still represents a considerable disease burden in adults worldwide. Pneumonia is the most common pneumococcal disease in adults, and has a short incubation period of 1–3 days, with fast onset of fever and chills accompanied by chest pain, cough, dyspnea, tachypnea, hypoxia, tachycardia and general malaise and weakness [1]. *Streptococcus pneumoniae*, a bacterial pathogen commonly carried in the nasopharynx, is the leading cause of a range of diseases including community-acquired pneumonia (CAP) and invasive pneumococcal disease (IPD). *S. pneumoniae* is found in almost half of all pneumonia cases [2–4], and results in a more severe episode of pneumonia than any other causative pathogen [4]. Lower respiratory tract infections are reported to be the fourth-leading cause of death worldwide [5], and up to one-third of these infections are caused by pneumococcal pneumonia [6,7]. Additionally, pneumonia can be associated with serious cardiac and respiratory complications and in 2010 across the globe almost 1.5 million deaths were attributed to the disease [7]. IPD predominantly presents as pneumococcal meningitis, bacteraemic pneumococcal pneumonia and pneumococcal bacteraemia with incidence rates of 11 to 27 per 100, 000 in Europe [8]. IPD is particularly prevalent in people aged >65 years [9].

Despite these dramatic figures pneumococcal disease is a vaccine-preventable disease, and pneumococcal conjugate vaccines (PCV7, PCV10 and PCV13) and pneumococcal polysaccharide vaccines (PPV23) have been available for routine use for many years. Data collected after the introduction of the 7-valent PCV into paediatric national immunisation programmes suggest that there is a herd effect achieved from high vaccine coverage in children that also works to protect adults through a reduction in carriage and a decline in disease-causing vaccine serotypes [10,11]. However, the herd effect alone is not enough to adequately protect entire adult populations against all pneumococcal diseases [11] – particularly patients with comorbidities or older people. Therefore, despite a protective herd effect from paediatric vaccination, unvaccinated adults are likely to have a residual burden of pneumococcal disease [11]. There has been a lack of consistent results demonstrating the ability of pneumococcal polysaccharide vaccines to prevent in particular non-bacteremic pneumococcal pneumonia [12]. Vaccination rates also show that only 75% of adults aged over 65 years are receiving

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their vaccination, contributing further to the increase in pneumococcal disease in adults [13]. Due to the difficulty in distinguishing between *S. pneumoniae* that simply colonises the upper respiratory tract and that which causes pneumonia, accurate diagnosis of CAP remains a challenge along with assessing the efficacy of the vaccinations available [14]. The medical community and regulatory agencies worldwide have identified this as a clear and important unmet medical need [12,15–17].

Age-based vaccination strategies for pneumococcal vaccines are being introduced in an effort to combat pneumococcal pneumonia in adults, but currently these strategies show wide variation between different continents, countries and regions and the uptake in terms of vaccination coverage is generally low [18–22]. For example, coverage with the 23-valent pneumococcal polysaccharide vaccine (PPV23) in adults aged between 65 and 79 is less than one-third of the population in Germany [19], and even in Australia where the vaccine has been provided free of charge under government-funded initiatives or by employers still only just over half of target adults have received it [20]. These statistics are further reflected in the UK where it is advised that the PPV23 immunisation programme should continue for those aged 65 and over and for adults in a clinical risk group [23], however the proportion of adults aged 65 and over vaccinated up to and including March 2015 stands at only 35.1% [24]. The most common barriers cited for the non-acceptance of adult pneumococcal vaccination at a healthcare professional and patient level are a perception of non-efficacy, a lack of resources (unfunded vaccination), patient refusal, organisational problems or simple lack of time [25,26].

The content of this paper is based on a series of presentations given by the authors at a meeting held in October 2015 in Vienna, Austria. At the meeting, three-quarters of attending healthcare professionals reported that it is difficult to implement adult vaccination in everyday clinical practice, and that current awareness of the burden of pneumococcal disease is low among vaccinators. This report aims to improve awareness and understanding of pneumococcal pneumonia in adults, and to raise the profile of adult vaccination.

2. Burden of cap in adults

In adults, pneumococcal disease most frequently manifests as pneumonia, with 25% of cases classified as IPD [27]. CAP incidence estimates in Europe range from 1.6–11.6 per 1000 population [8]. Cases of CAP are two-fold higher in winter than summer [28], and frequently follow outbreaks of influenza. Observational studies have assessed the epidemiological burden and found up to 74% of the serotypes causing CAP are included in PCV13 and 83% in PPV23 [29]. Further studies of IPD have reported 67% of cases attributed to a PPV23 serotype and 33% attributed to a PCV13 serotype [30].

It is widely accepted that paediatric vaccination with PCVs has resulted in reduced nasopharyngeal carriage of vaccine serotypes and lower rates of pneumococcal disease, including CAP, in both vaccinated and unvaccinated children [10,31–35], with hospitalisation rates for pneumonia in children under the age of 2 years decreasing by over 20% since the introduction of 13-valent pneumococcal conjugate vaccine (PCV13) [36]. The herd effect associated with high levels of paediatric vaccine coverage has brought about a decrease in cases of invasive pneumococcal disease in adults over the time period since PCV7 was introduced [10,36]. However, despite these impressive reductions, the herd effect alone is not enough to protect all older adults in the community [11,37], which is a concern given that the incidence and severity of CAP typically increases with age [28,38]. A study in Spain found that the CAP incidence rate in people over the age of 85 is almost three-times that of the 65–74-year age bracket [28]. Additionally, serotypes traditionally classified as less invasive are increasingly able to cause disease in older people and those with comorbidities [38]. For people with chronic medical conditions and complications – or those with previous episodes of pneumonia who contract CAP – *S. pneumoniae* is the most frequently isolated pathogen [39–41].

This has serious implications for our global ageing population, as well as for healthcare funding: as many as three-quarters of pneumococcal CAP cases require hospitalisation, with an average stay of 10–12 days [28,42–45]. Full recovery takes close to a month on average, but can be up to seven weeks in some patients [39]. Clearly, CAP places a significant burden on resources – both medical and financial [46]. It also has many indirect socioeconomic costs [3]. Typically, pneumonia patients over the age of 65 accrue the majority of direct medical costs associated with all pneumococcal diseases in all groups, whilst the indirect costs arising from lost productivity and work absences are significant in those aged 18–50 [47].

CAP is a severe disease. Of those patients who require hospitalisation 2–14% will die as an in-patient [38,48,49], and 12% will require readmission within 30 days of discharge [50]. Even those who recover and are discharged with no readmission will have reduced odds for both short- and long-term survival [44,51], with a case-fatality rate of 39% reported at 5 years [44] and an overall difference in survival seen as far out as 10 years between pneumonia survivors and age- and sex-matched peers. This may be due to underlying inflammation or predisposing host or environmental factors, although to date the precise mechanism is unclear [51].

In addition to a reduction in long-term survival and an increased risk of repeat episodes, CAP may cause worsening of pre-existing comorbidities [52], and patients may be at an increased risk of suffering from major cardiac adverse events such as myocardial infarction, serious arrhythmia or chronic heart failure [53]. There may also be an impact on patients with chronic obstructive pulmonary disease (COPD), with an increase in exacerbations and a decrease in quality of life [54,55]. In patients with COPD, return to baseline health is not achieved until at least 2 months after the CAP episode [56].

Alongside the clinical burden of CAP, the economic burden also has implications with pneumonia costs in Europe standing at approximately €10.1 billion per annum. Of these costs, inpatient care, outpatient care and drugs account for 64% with indirect costs of lost work days amounting to 36% [57]. Treatment of patients with CAP places a high burden on hospital resources, with patients with pre-existing comorbidities and of an older age shown to further increase costs [58]. Antibiotic resistance seen in pathogens associated with CAP and the rise in antibiotic-resistant strains has led to further increasing the cost of treatment through use of more expensive classes of antibiotics or longer hospitalisation required [57].

It is therefore clear that the burden of CAP is much broader and has more far-reaching effects than the isolated pneumonia episode itself.

3. Benefits of vaccines for the prevention of pneumonia

Pneumococcal vaccination can reduce the burden of disease. There are currently two types of vaccines available: PCV13 and PPV23. These vary not only in the serotype antigens they carry, but also in their structural composition and mechanism of action. Vaccines work very differently in adults and children. Conjugated vaccines offer benefits in children over traditional polysaccharide formulations as the conjugates elicit higher antibody responses and can generate an immune memory. They can also work at the mucosal surfaces to prevent nasopharyngeal colonisation and carriage, which PPV23 is unable to do [59,60]. PCVs work in all adult age groups, and PCV13 has been shown to be effective in preventing episodes of vaccine-type pneumococcal CAP, with a recorded vaccine efficacy of 45%, and IPD in older adults, with a recorded vaccine efficacy of 75% [61,62]. Based on current figures, we have calculated that this rate of prevention of pneumonia could translate into preventing 200,000 cases of community-acquired pneumonia every year in Europe alone [62,63]. In contrast, the efficacy of PPV23 is uncertain [17,64,65].

Pneumococcal vaccines may be administered sequentially, but it is recommended that PCV13 be given before PPV23 as prior doses of PPV23 may diminish the response to PCV13, although the same is not seen in reverse [66,67]. Studies have shown that PCV13 can be co-

administered with the trivalent influenza vaccine (TIV) with no significant impact on immunogenicity or safety [61,68,69]. This concomitant administration of PCV13 and TIV may help to reduce the disease burden on vaccinators in everyday clinical practice by allowing multiple vaccines to be given at the same clinic appointment [69].

4. Identifying eligible patients to improve vaccination uptake

Being able to identify eligible patients who would benefit from vaccination is critical for reducing the disease burden of CAP and IPD in adult populations. In the past, isolating *S. pneumoniae* cultures from normally sterile body fluids was the gold standard used to identify and diagnose pneumococcal disease; however, this was not always practical in the clinic – not least because the results can take several days. Clinicians now have access to urinary antigen detection (UAD) tests, which represent a major advance. UAD has a specificity of up to 99.7% in adults and a sensitivity of 79–97% for both bacteremic and non-bacteremic pneumococcal pneumonia [14,70]. As well as allowing tailoring of antibiotic treatment, a positive diagnosis of pneumococcal pneumonia can identify those patients who should receive vaccination on disease resolution or discharge from hospital. It is important to understand that an episode of CAP does not prime the immune system against future infection; in fact, individuals previously diagnosed with pneumococcal pneumonia are at a clear increased risk of a subsequent episode for at least 2 years, independent of comorbidities or other risk factors [40,71]. With this in mind, routine vaccination with PCV13 on discharge from hospital following an episode of pneumococcal pneumonia should be advocated in all healthcare systems.

In addition to positively diagnosing and identifying current cases of CAP, there is a need to identify those people in the community who may be at increased risk of infection. For example, some people may be at increased risk of contracting pneumococcal pneumonia due to inherent environmental factors in their living or working arrangements. Typically only 5–10% of healthy adults without children carry pneumococci in their nasopharynx. These figures increase dramatically for adults in families with pre-school age children or grandchildren, as well as for adults living or working in communal institutions such as schools, hospitals, military bases and nursing homes – and asymptomatic carriage may be found in as many as 70% of adults in these groups [1]. Vaccination rates for other pathogens such as influenza are high in some areas – 68% of older adults in the US and 45% in the EU have routinely received a 'flu vaccination', while only 60% in the US and 10% in the EU have been vaccinated against pneumococcus [72–76].

The risk of pneumococcal infection is influenced by host as well as environmental factors. This extends beyond age, and many conditions may increase susceptibility – particularly those that lower a person's innate immunity or require immunosuppressive treatment [22,77–79]. As such, CAP represents a heavy disease burden in particular groups, with higher infection and case fatality rates seen in high-risk and immunocompromised patients [78]. There are also significantly higher incidence rates seen in men and those aged over 65 years. Being underweight can be a factor, possibly due to nutritional deficiencies limiting the efficiency of the immune system [40]. Lifestyle choices such as being a current or past smoker or frequent alcohol user also confer a significantly increased risk in all adult age groups [80]. Even a passive exposure to tobacco smoke can increase a person's risk of developing CAP [40]. Encouragingly, these elevated risks do decrease for ex-smokers after 4 years [40] – even in those with HIV [81]. As such, patients should be counselled on the risks and offered smoking cessation programmes.

Common underlying medical conditions increase the risk of pneumococcal pneumonia in adults [80]. At-risk definitions include people with chronic or immunocompromising conditions such as asthma, diabetes and COPD. These conditions have been found to increase the risk of CAP many times over – particularly in patients with COPD with fold increases of between 1.3 and 13.5 for CAP and 1.3 and 16.8 for IPD for those patients with COPD [8,40,65,81–85]. High-risk patients include those with sickle-cell anaemia, an immunodeficiency or people taking immunosuppressive drugs [22,79] (Table 1).

Table 1
Traditional risk definitions for CAP [22,86–89].

At risk	High risk
Metabolic diseases (diabetes mellitus)	Immunodeficiency (B or T cell deficiency)
Chronic respiratory disease (asthma, COPD, interstitial lung diseases)	Cerebrospinal fluid leakage, skull fracture, cochlear implant
Chronic heart, liver, renal diseases	Functional asplenia or splenectomy
Chronic alcoholism	Sickle-cell anaemia
Smoking	Nephrotic syndrome
Patients living within an institution	Transplantation (organ or bone marrow)
People with a history of (pneumococcal) pulmonary infection	Immunosuppressive therapy
	Leukaemia, lymphoma, multiple myeloma
	Neoplastic disease
	HIV infection
	Autoimmune diseases

A study in Germany found that 22% of patients with CAP also had pulmonary diseases (including COPD), 19% had cardiac comorbidities, 14% had disorders of the central nervous system and 9% had diabetes [48]. In a large cohort looking at COPD patients, 8% experienced an episode of CAP over the 10-year observation period; this was strongly associated with age, COPD severity and a history of previous pneumonia [84]. A critical consideration in assessing the factors for an individual patient is that multiple underlying conditions have a cumulative effect, with the risk for a person with two conditions being similar to someone officially classified as 'high risk', and those with three or more conditions being much greater [80]. A study of a German database for quality in healthcare found increased case fatality rates for hospitalised CAP in patients with at least one comorbidity (17.4%) compared to overall hospital deaths in CAP patients of 13.7 and 14.4% across 2 years [48].

The ability to identify eligible patients in clinical practice therefore has a huge impact on prevention strategies. Currently, recommendations vary widely in whether they are based on age or risk, and how schemes are funded and implemented [22]. Overall, pneumococcal vaccination rates in adults are low, especially compared to other routine preventative vaccines; for example, vaccine rates for influenza in adults in France are four-times higher than those achieved for pneumococcal vaccination [25].

To ensure that the most is made of the available vaccines the value of adult pneumococcal vaccination must be promoted for eligible patients through both cost-effectiveness analysis and working to overcome vaccine hesitancy. PCV13 has been shown to be cost-saving in high-risk adults aged 65–74 years of age and cost-effective for those deemed at medium-risk in the same age group [92]. With these cost-savings possible, encouraging vaccination uptake through education and improved infrastructure to overcome vaccine hesitancy is imperative [93].

Eligible patients are easy to recognise (Box 1), and should be targeted for long-term monitoring and management [84]. People with increased age, or those with environmental or host risk factors should be proactively offered pneumococcal vaccination in order to reduce the burden of

Box 1
Eligible patients: identifying key risks for adults in the general population [84,90,91].

- Age over 65
- Current or past smoker
- High alcohol intake
- Under- or overweight
- Living or working in institutions such as schools, hospitals, prisons or care homes
- Comorbidities such as diabetes, asthma or COPD
- Previous pneumococcal infection
- Chronic immunosuppressive disease

pneumococcal disease and prevent unnecessary morbidity and mortality, as well as to reduce healthcare spend. Incidence and case fatality rate are increased in people over the age of 65, and this should influence the development of age-based recommendations for vaccination.

5. Learning points

- Pneumonia is a vaccine-preventable disease and PCV13 has been shown to be effective in preventing vaccine-type pneumococcal non IPD CAP and IPD in older adults [62].
- PCV13 should be considered for co-administration alongside the influenza vaccine in adults [61,62].
- Lifestyle changes could help to lower the risk of CAP [80].
- PCV13 should be given to all people diagnosed with CAP on discharge from hospital or resolution of infection in order to prevent further episodes [40,71].
- Age-based recommendations are needed for PCV13 vaccination.

6. Summary

Pneumococcal pneumonia is a major health problem in adults. General awareness of the disease burden and severity of pneumococcal disease remains low, despite significant advances in vaccination technology in recent years and many local and national recommendations and society guidelines [18]. Regulatory agencies have suggested that there is a clear unmet medical need in this area [15]. Given that data do exist to support the use of PCV13 in adult populations, it is critical that consistent age-based strategies are put in place to increase the uptake of preventative vaccination and reduce the significant disease burden of pneumococcal pneumonia on medical resources and funding.

Currently, many opportunities for vaccination are being missed. The most common barriers to acceptance of adult vaccination are a perception of non-efficacy, a lack of resources, organisation or time, or simply patient refusal [25,26], but these are not insurmountable issues, and can be overcome with education and improved awareness. Vaccination against other pathogens is well-recognised, and has a significantly higher uptake. Pneumococcal vaccination should be seen as an important part of promoting a healthy lifestyle for children and adults alike.

Contributors

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Conflicts of interest

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