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Adult pneumococcal vaccination - advances, impact and unmet needs

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Abstract:

Purpose of the review: Preventing pneumonia in the elderly and subjects with comorbidities is an unmet clinical need. *Streptococcus pneumoniae* is the commonest bacterial cause of pneumonia, and we summarise recent findings regarding current *S. pneumoniae* vaccines, and debate their efficacy and cost effectiveness in risk groups. We also discuss potential future vaccine strategies such as protein antigen vaccines.

Recent findings: Current vaccination with PPV does not prevent *S. pneumoniae* pneumonia. Vaccination with PCV prevents nasopharyngeal colonisation, but although PCV13 has recently been shown to prevent *S. pneumoniae* pneumonia in adults its overall efficacy was relatively low. The results of cost-effectiveness studies of PCV vaccination in adults are variable with some showing this is a cost effective strategy, whereas others have not. The lack of cost-effectiveness is predominantly due to the current cost of the PCV vaccine and the existing herd immunity effect from childhood PCV vaccination on vaccine serotypes.

Summary: S. pneumoniae pneumonia is a vaccine preventable disease but remains a common cause of morbidity and mortality. Advances in vaccination using approaches that induce serotypes-independent immunity and are immunogenic in high risk groups are required to reduce the burden of disease due to *S. pneumoniae*.

Key phrases: *Streptococcus pneumoniae*, unconjugated vaccine, conjugated vaccine, pneumonia, immunosenescence

Introduction

Despite routine vaccination of children in many children with the pneumococcal conjugated vaccine (PCV) and adults with the pneumococcal polysaccharide vaccine (PPV) S*treptococcus pneumoniae* infection is still responsible for the greatest proportion of respiratory infection deaths globally amongst all age groups[1,2]. It is of particular concern in the elderly, with for example in the UK the incidence of pneumonia (with 40 – 50% of cases caused by *S. pneumoniae*) increasing from 2.8/1000/year in 65-69 years age group to 22/1000/year in 85-89 years[3,4]. Even though most cases are due to strains that are highly susceptible to antibiotics (at least in the UK), severe *S. pneumoniae* pneumonia has a greater than 20% mortality[3,5]. Strategies to attenuate excessive inflammation seen in *S. pneumoniae* pneumonia[6,7] or enhance the immune response[8] may improve clinical outcomes. However, ultimately reducing the direct (via pneumonia) and indirect (via exacerbations of underlying lung disease) mortality caused by *S. pneumoniae* will need improved vaccines that protect against the majority of strains even in the elderly and in subjects with comorbidities.

Existing *S. pneumoniae* vaccines

The *S. pneumoniae* polysaccharide capsule consists of chains of repeating units of oligosaccharides that surround the bacterium and protect it against host-mediated immunity. Due to variations in their chemical structure there are over 97 serotypes of *S. pneumoniae* capsule. Current *S. pneumoniae* vaccines use polysaccharide capsular antigen either alone (PPV) or conjugated to a carrier protein (PCV). The current PPV (Pneumovax®23 (Merck & Co., Inc, New Jersey, USA)) consists of pneumococcal polysaccharide antigens covering 23 serotypes. There are several types of PCV produced by different companies, and with different carrier proteins. Prevenar® (Pfizer limited, Kent, UK) which covers against 7 (PCV7: 4, 6B, 9V, 14, 18C, 19F and 23F) or 13 (PCV13: 1, 3,

4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) serotypes uses modified tetanus toxoid as the carrier protein, and Synflorix® GlaxoSmithKline Incp. Ontario, Canada), which covers against 10 (PCV10: 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) serotypes uses *Haemophilus influenzae* Protein D, tetanus toxoid or diptheria toxoid as the carrier proteins depending on the capsular antigen. Both PPV and PCV will only induce antibody-mediated protection against the capsular serotypes included in the vaccine preparation.

Efficacy of PPV

Pneumovax®23 covers the 23 most frequent serotypes associated with pneumococcal disease. There is some suggestion that there could be some additional cross-serotype protection as a recent study suggest that 6B in PPV23 induced cross-functional immune responses against serotypes 6A and 6C[9]. In developed countries PPV is given routinely to adults at high-risk of *S. pneumoniae* infection, which includes all subjects aged 65 years of age and older, or those 19 – 64 years with long term health conditions, including chronic lung, liver, renal, cardiac and neurological disease, or who are immunocompromised. Although recent assessments suggest that this strategy is cost-effective[10,11], the effectiveness of PPV in >65 years declines significantly within 5 years of vaccination[12] and the introduction of routine PCV vaccination of children has reduced the cost-effectiveness of adult vaccination with PPV due to reductions in disease caused by the serotypes common to both PPV and PCV.

According to the most recent Cochrane meta-analysis PPV only prevents septicaemia caused by vaccine serotypes (OR 0.26, 95% CI 0.14 - 0.45)[13] and it has much weaker, if any, efficacy against lung infections (OR 0.72, 95% CI 0.56 - 0.93); the effect on pneumonia seems to be only significant in low-income countries[13]. Additionally, PPV trials are underpowered for detection of significant efficacy in the highest risk groups (chronic comorbidities or the very elderly) [13]. Hence PPV does not prevent pneumonia

and instead is largely used in adults to prevent septicaemia associated with *S. pneumoniae* pneumonia. Despite this, vaccination with PPV has no overall effect on adult mortality (OR 0.87 95% CI 0.69-1.1), probably due to the relative low frequency of severe invasive *S. pneumoniae* infections even in the elderly compared to other causes of mortality. These drawbacks of PPV highlight that an alternative vaccine to the PPV will be necessary to reduce the burden of *S. pneumoniae* lung infections in adults.

Efficacy of PCV in children

As PCVs contain capsular antigen conjugated to a carrier protein they stimulate a T cell dependent antibody response to the capsular antigen even in infants whereas PPV does not, and in many developed countries all infants are routinely vaccinated with PCV. PCV is very effective at preventing disease in children caused by *S. pneumoniae* serotypes included in the vaccine formulations, for example causing an 80% reduction in septicaemia caused by vaccine serotypes[14]. The overall effect of PCV is also impressive, reducing the incidence of all cause (that is including cases caused by other pathogens as well as *S. pneumoniae*) radiographic proven pneumonia by 27%, and overall infant mortality in a developing world setting by 11%[14]. In developed countries introduction of routine vaccination with PCV has essentially eliminated the vaccine serotypes as causes of invasive *S. pneumoniae* infection (septicaemia and meningitis) in children. Additionally, vaccine failure is rare with only 2% of childhood IPD caused by PCV13 serotypes in the UK[15].

Herd immunity generated by PCV

A perhaps unexpected effect of routine use of PCV in infants has been the rapid and dramatic reduction in nasopharyngeal colonisation with vaccine serotypes of *S. pneumoniae*. As colonisation of the nasopharynx precedes disease, prevention of

colonisation rather than septicaemia or lung infection is probably the main mechanism by which PCV prevents disease caused by *S. pneumoniae*. Recent data obtained using mouse and a human model of experimental *S. pneumoniae* colonisation have demonstrated the mechanism by which PCV prevents colonisation. Anti-capsular antibody can leak into the airway lining fluid of the nasopharynx, where it agglutinates vaccine serotypes and this enhances their clearance from the nasopharynx before they can establish colonisation[16,17]. As children are the main reservoir and transmitters for *S. pneumoniae* causing disease in adults, an important consequence of eradication of vaccine serotypes as colonisers of infants is a significant degree of herd immunity. For example, routine vaccination of infants with PCV was associated with a subsequent 56% fall in incidence of adult pneumonia caused by vaccine serotypes[18]. However, it is unclear if the effect of PCV on nasopharyngeal carriage will be sustained. Results from a recent meta-analysis show that although protection post-PCV is sustained for some time the vaccine efficacy at 5 years was only 42% (95% CI 19-54%), with significant variation between serotypes[19]. Another recent study, although likely to be underpowered, did not show an association between vaccination status and serotype carriage in children with asthma[20]. Additionally, approximately 20% of all IPD cases are still caused by PCV13 serotypes[18] and the herd effect alone is not sufficient to completely protect adults from non-bacteraemic pneumococcal pneumonia caused by vaccine serotypes [21]. An important consequence observed in multiple countries of the large reductions in the nasopharyngeal carriage of *S. pneumoniae* vaccine serotypes in response to PCV is a compensatory major expansion in the prevalence of non-vaccine serotypes as nasopharyngeal commensals, and inevitably as a cause of disease[18,22–24]. The expansion of disease caused by non-vaccine serotypes particularly affects herd immunity benefits for adults[18].

Adult vaccination with PCV

Given the efficacy of PCV at preventing pneumonia in children, an obvious strategy to overcome the limitations of PPV vaccination at preventing lung infection is to vaccinate adults with PCV. The efficacy of PCV at preventing pneumonia and IPD in adults was assessed by the CAPITA study. In this 5 year study 84,496 adults aged 65 years or over were either vaccinated with PCV13 or placebo[25]. The mean age of the subjects was 73 years, 55% were male, and 42% had at least one comorbidity. PCV had an efficacy of 46% (95% CI 22-63%) and 75% (95% CI 41-91%) at preventing pneumonia and IPD due to vaccine serotypes, respectively. However, only 36% of *S. pneumoniae* pneumonia cases were due to vaccine serotypes, hence the overall efficacy of PCV protecting against *S. pneumoniae* pneumonia was 31% (95% CI 10-47%). Efficacy against all cause pneumonia was only 5% (95% CI -5.1-4.2%)[25] and since the microbiological diagnosis is not made for many cases of pneumonia[26] the vaccine efficacy in protecting against *S. pneumoniae* pneumonia may be overestimated. Additionally, there was no effect on overall mortality[25]. Hence, the absolute effect of PCV13 was relatively weak. Importantly, the CAPITA study highlights that only extremely large clinical trials will be able to demonstrate the efficacy of preventative measures against pneumonia and death.

There are only limited additional data on PCV efficacy in adults to the CAPITA study. An Italian observational cohort of adults > 65 years hospitalised with CAP suggested those who had received PCV had increased survival compared to vaccination with PPV[27]. In the elderly antibody responses to PPV are impaired[28] and vaccine efficacy is reduced with time[12]. A prime boost approach of administration of one dose PCV13 to aged individuals previously given PPV23 may overcome this, as this strategy induces higher opsonophagocytosis titres for 11 of 13 serotypes [29]. A second dose of PCV13 did not result in any additional benefit.

Vaccination with PCV is expensive, and PCV efficacy in adults will be undermined by the reduction in prevalence of vaccine serotypes due to PCV vaccination of infants. Therefore, national bodies considering introducing PCV into routine use in adults need to carefully consider the cost effectiveness of this vaccine strategy. However, cost effectiveness assessments have given variable results. Dutch and Japanese studies suggested that using PCV in adults >65 years would be cost effective[30,31], yet the UK Joint Committee on Vaccination and Immunisation came to the opposite conclusion and suggest PCV should only be given to adults who are immunocompromised[32]. Other more recent assessments have also concluded that PCV in adults would not be cost-effective when taking into account the anticipated herd protection seen with infant immunisation[33–35]. However, in adults with co-morbidities such as COPD PCV13 maybe more likely to be cost-effective than PPV23 [36,37].

Two potential considerations could improve the cost effectiveness of PCV in adults. Firstly if PCV could prevent the 25% of infective exacerbations of COPD (one of the commonest causes for emergency admission to hospital) that are associated with *S. pneumoniae* that would markedly improve the cost effectiveness of using PCV in adults. However the anatomical and immunological effects of chronic lung disease could readily impair PCV protective efficacy; furthermore non-serotypable strains are a significant cause of infections in patients with COPD [38]. Further data are needed on the efficacy of PCV against infective exacerbations of COPD. Secondly, the PCV preparation used in the CAPITA study was designed for preventing serotypes associated with invasive disease in children; an adult specific PCV formulated to include serotypes that cause lung infection in populations in which children are already routinely vaccinated with PCV could be more cost effectiveness. However, altering PCV serotype coverage is at present a prohibitively expensive process.

Future directions

Natural adaptive immunity to S. pneumoniae: As discussed above existing vaccines are unlikely to be adequate at preventing adult *S. pneumoniae* lung infections, and there remains a strong need for alternative cost-effective approaches that are not limited to preventing infection by only a small subset of *S. pneumoniae* serotypes. Repetitive colonisation of the human nasopharynx with *S. pneumoniae* is ubiquitous in children and is now known to stimulate a strong protective adaptive immune response, and this is thought to contribute to the large fall in pneumococcal carriage rate at the end of infancy. A combination of longitudinal studies of natural human colonisation and mouse and human models have shown that colonisation induces both humoral and cellular immune responses to multiple protein antigens as well as antibody against capsular polysaccharide[39,40]. In mouse models lung immunity to *S. pneumoniae* seems to require both an antibody and a CD4 Th17 response to protein antigens[39]. As the protein antigen targets are often highly conserved between *S. pneumoniae* strains, these data provide a potential starting point for novel vaccines that provide universal protection against all *S. pneumoniae* strains and can protect against lung infection.

Effect of immunosenescence on adaptive immunity to S. pneumoniae: The high incidence of *S. pneumoniae* infections in the elderly is at least partly due to waning of naturally-acquired adaptive immune responses due to immunosenescence – the changes in immune function associated with natural ageing. Ageing is associated with several defects in immune responses and metabolic activity that can result in impaired innate and adaptive immunity, as well as vaccine immunogenicity. These are not only associated with loss of immune function; some aspects of the aged immune system can also be preserved while others are in fact enhanced, such as the chronic low level inflammation seen in the elderly (known as “inflammaging”). The interactions between these different effects of age on

immune responses are complex and their downstream consequences on host susceptibility to *S. pneumoniae* or response to vaccination are poorly understood. Likely to be important are the decrease in number and function of antigen presentation cells, loss of naïve B- and T-cells with a corresponding increase in memory cells, with responses becoming more homogenous and less antigen specific with increasing age[41,42]. Aged T-cells also have a less diverse repertoire which reduces the ability to mount responses to novel antigens[42]. Importantly, the elderly have reduced frequency of Th17 memory T-cells[41], which might be particularly relevant for the development of pneumonia. A detailed analysis of the natural adaptive immune responses that protect adults against *S. pneumoniae* lung infection and how they are affected by age may identify novel strategies for preventing adult *S. pneumoniae* pneumonia. For example, the immunogenicity of vaccines in the elderly could be optimised by either simple measures such as increasing antigen dose or altering dose scheduling, or by more complex strategies designed to overcome specific aspects of immunosenescence using novel adjuvants, immunomodulators to reverse the effects of inflammaging, or developing vector based vaccines that target CD8 T-cell responses that are preserved in the elderly[42–44].

Novel vaccine approaches: S. pneumoniae protein antigens are conserved amongst a large majority of strains and vaccine approaches using these antigens may therefore offer cross-serotype protection. Several protein antigens have been shown to be highly immunogenic and can elicit antibody or Th17 CD4 responses[45] that protect against colonisation or infection in murine models (**Error! Reference source not found.**). The vaccine antigens PhtD, StkP, PcsB and PsaA have been used in phase I/II clinical trials and although they all demonstrate immunogenicity and are considered safe as yet no protein vaccine has progressed to a phase III trial[45]. Other novel approaches include the identification and development of a semi-synthetic oligosaccharide conjugate vaccine

(tetrasaccharide-CRM197 carrier protein conjugate), the use of whole-cell killed pneumococci, and novel heat shock protein multivalent *S. pneumoniae* protein antigen vaccines that are protective against murine pneumonia[46–49].

Conclusion

Current *S. pneumoniae* vaccination strategies are only partially effective at preventing pneumonia in the elderly, and good quality studies investigation the effects of vaccination on clinical outcomes in this age group are lacking. Novel approaches vaccines such as protein antigen, killed whole bacteria, or vector based vaccines need to be identified to cover the majority of *S. pneumoniae* serotypes and improve vaccine efficacy in high-risk groups. Furthermore, the development of novel strategies to counter the effects of immunosenescence on natural and vaccine acquired immunity may also improve prevention of *S. pneumoniae* pneumonia in risk groups. Novel models such as the experimental human pneumococcal colonisation model[50] may be the ideal biological system in which to the study the effects of vaccines or immunomodulators on mucosal immunity to *S. pneumoniae* in humans whilst avoiding the expense of a large clinical trial of efficacy against disease.

Key points:

1. Current *S. pneumoniae* vaccination strategies are only partially effective at preventing adult *S. pneumoniae* pneumonia.

2. Novel vaccine approaches will be required to prevent the high morbidity and mortality caused by *S. pneumoniae* pneumonia in the elderly and subjects with chronic lung disease

3. An understanding of the effects of age on immunity to *S. pneumoniae* will be important for the development of effective novel preventative strategies.

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Highlighted references

9 * Interesting study that demonstrates that the polysaccharide of one serotype present in the pneumococcal vaccine can potentially protect adults from serotypes in the same serogroup

16 * Important study which highlights the importance of agglutination antibodies for mucosal host defence

17 ** Important study that demonstrates how agglutination antibodies to pneumococcal polysaccharide capsule limits nasopharyngeal carriage in a novel experimental human pneumococcal carriage model

18 ** Important epidemiological study looking at the effect of 8 years of PCV use in England and Wales

22 * Important study highlighting the emergence of macrolide resistance genes in non-PCV serotypes.

25 ** Outstanding study demonstrating the efficacy of PCV13 in reducing vaccine serotype pneumonia and IPD in adults

35 * Important study which demonstrates that PCV in adults is efficacious but will not be cost-effective in the immunocompetent elderly due to the benefits seen with PCV13 immunisation in children.

41 * Extensive review of the potential effects of age on innate immunity to *S. pneumoniae*

50 ** Important study demonstrating the usefulness of the experimental human pneumococcal carriage model to investigate the effects of novel vaccines on *S. pneumoniae* nasal colonisation.