THE EVOLUTION OF PNEUMOCOCCAL VACCINES:
PAST FINDINGS, PRESENT WORK, AND FUTURE STRATEGIES
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Unit No. 2 & 3

PNEUMOCOCCAL VACCINE EFFICACY AND REAL-WORLD EVIDENCE

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ABSTRACT

***Streptococcus pneumoniae* is the most common cause of bacterial pneumonia, meningitis, otitis media, and sinusitis in many parts of the world. Risk factors for pneumococcal disease in adults include age ≥65 years, an underlying immunocompromised state, the presence of cochlear implants, and cerebrospinal fluid leak. The introduction of pneumococcal conjugate vaccines in routine immunisation programmes has resulted in the decreased incidence of invasive pneumococcal disease and nasopharyngeal carriage. However, poor vaccination uptake, advent of antimicrobial resistance, and serotype replacement remain significant challenges.**

Keywords: pneumococcal vaccination, pneumococcal disease

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INTRODUCTION

Pneumococcal disease (PD) is caused by *Streptococcus pneumoniae*, a gram-positive microorganism that frequently colonises the upper respiratory tract. Invasive pneumococcal disease (IPD) is a subset of PD, defined as an infection confirmed by isolation of *Streptococcus pneumoniae* from a sterile site (e.g., blood, pleural fluid, pericardial fluid, peritoneal fluid, joint fluid; but not from respiratory secretions such as sputum). PD is commonly seen in both immunocompetent and immunocompromised hosts and is the most common cause of bacterial pneumonia and bacterial meningitis in many parts of the world. More than 90 serotypes have been identified to date.[1] A retrospective study of mortality from PD between 1997 and 2013 in Singapore showed a mortality rate of up to 19 percent in adults and 3 percent in children.[2]

PATHOPHYSIOLOGY

Asymptomatic *Streptococcus pneumoniae* nasopharyngeal colonisation is thought to precede respiratory and/or systemic infection in humans and is believed to be an important source of horizontal transmission of this pathogen within the community.[3] Colonisation is more common in children (20-50 percent) than in adults (5-20 percent).[1]

Opsonin-dependent phagocytosis is thought to be the primary mediator of the human body's defence against *Streptococcus pneumoniae*. The surface of *Streptococcus pneumoniae* is covered by a polysaccharide capsule that constitutes one of the most important virulence factors of the pathogen and is also the basis for capsular serotyping.[1,3,4] To date, over 90 serologically distinct pneumococcal capsular serotypes have been identified. Fortunately, only a subset of the known serotypes commonly results in asymptomatic carriage and disease.[4] The active components of currently available pneumococcal vaccines contain capsular polysaccharides from serotypes that more commonly cause PD.

RISK FACTORS

The burden of PD is high in young children and older adults. Specific underlying medical conditions and behavioural risk factors that may predispose to the development of PD include cigarette smoking, chronic pulmonary disease, chronic cardiovascular disease, chronic liver disease, chronic kidney disease, diabetes mellitus, underlying cochlear implant, cerebrospinal fluid leak, chronic alcoholism, and immunocompromising states (e.g., anatomical/functional asplenia, sickle cell disease or other haemoglobinopathies, lymphomas, leukaemia, multiple myeloma, congenital or acquired immunodeficiencies including human immunodeficiency virus infection, organ transplant recipients, iatrogenic immunosuppression) where current guidelines have recommended the benefit of pneumococcal vaccination.[5,6]

CLINICAL PRESENTATION

Common infective syndromes caused by pneumococcus include pneumonia, meningitis, bacteraemia, otitis media, and sinusitis. A study of 561 adult (≥16 years) and 328 paediatric cases of PD diagnosed between 1997 and 2013 in Singapore revealed that the most common syndromes in both groups were bacteraemic pneumonia (69.3 percent vs 44.2 percent), followed by primary bacteraemia (14.3 percent vs 13.4 percent), meningitis (6.4 percent vs 7.6 percent) and non-bacteraemic pneumonia (5.2 percent vs 21 percent).[2] In addition, 49.2 percent of the patients in this study had at least one significant comorbidity, with the few most common comorbidities being diabetes mellitus (13.5 percent), followed by immunocompromised state (12.8 percent), chronic heart disease (12.0 percent), smoking (10.7 percent), and asthma (8.2 percent). Mortality risk factors for the adults in this study include age ≥65, dementia, acute cardiac events, critical illness,

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and multilobar pulmonary involvement. Mortality risk factors for children include meningitis, critical illnesses, and bilateral pulmonary infiltrates.

Unusual and rarer manifestations of PD include bone and joint infections (e.g., septic arthritis, osteomyelitis), cardiovascular infections (e.g., endocarditis, pericarditis, mycotic aneurysms), extrameningeal neurologic infections (brain abscesses), gastrointestinal infections (primary peritonitis), renal and urinary tract involvement (e.g., pneumococcosuria, haemolytic uremic syndrome, glomerulonephritis, glomerular/arterial thrombosis), genital tract infections (e.g., tubo-ovarian abscess/salpingitis, vulvar abscess/bartholinitis, endometritis), head and neck infections (e.g., parotitis, epiglottitis, buccal/facial cellulitis, mastoiditis, gingival lesions), ophthalmologic infections (e.g., endophthalmitis, corneal ulceration/perforation, keratitis, orbital cellulitis), and skin and soft tissue infections (e.g., cellulitis, pyomyositis).[7] A classical triad of pneumonia, meningitis, and endocarditis, known as Austrian syndrome, and florid presentations with quadruple valve endocarditis are also well-described.[8]

ANTIMICROBIAL RESISTANCE

Treatment with beta-lactam antibiotics is the preferred therapeutic option for PD, but antimicrobial resistance has been an enormous concern. Locally, a study by Martinez-Vega et al reported penicillin resistance of 79 percent among children and 35.4 percent among adults.[2] Pneumococcal isolates from children were also more likely to be non-susceptible to multiple antibiotics than isolates from adults (51.4 percent vs 10.2 percent). Indeed, increasing antibiotic resistance in pneumococcus-colonising children has been well-described through a study by Vasoo et al.[9] Comparing two cross-sectional prevalence surveys (1997 vs 2007-2008), multidrug resistance (defined as non-susceptibility to three or more classes of antibiotics) amongst children attending daycare centres in Singapore increased from 33.3 percent to 74.6 percent. A cross-national database study in Europe showed that European countries with higher outpatient penicillin use had higher rates of penicillin-resistant *Streptococcus pneumoniae*, indicating the importance of appropriate antibiotic prescribing in curbing the rising tide of antimicrobial resistance.[10] Apart from protecting at-risk groups from PD, pneumococcal vaccination is a potential strategy to help curtail the spread of pneumococcal resistance in the community.

VACCINATION

PD is a vaccine-preventable disease. Currently available vaccine types include the pneumococcal polysaccharide vaccines (PPSV) and pneumococcal conjugate vaccines (PCV), targeting multiple serotypes more commonly associated with invasive disease potential.[11] Further, there are also studies demonstrating the effectiveness of PCV in reducing the prevalence of drug-resistant pneumococcal infections.

Unfortunately, results from the National Health Surveillance Survey in 2013 suggest a very low local pneumococcal vaccination uptake amongst adults, with vaccination rates of only 7.8 percent among adults aged 50 years and above and 1.7 percent among adults aged 65 years and above.[12] In the study by Martinez-Vega et al of PD in the local setting, only 3.9 percent of the adults with PD had prior pneumococcal vaccination.[2]

1. Pneumococcal Vaccine Efficacy and Real-World Evidence

PPSVs have been developed since the 1970s, with the current 23-valent PPSV (PPSV-23) being widely available worldwide for the prevention of IPD in older adults and those with risk factors. PPSVs are often used in combination with lower valency PCV, such as the 13-valent or 15-valent PCVs. While its usefulness in the prevention of IPD in adults is well-established, its role in preventing non-bacteraemic pneumonias is contradictory.[13] A 2013 Cochrane review of 18 randomised controlled trials and seven non-randomised controlled trials involving 64,852 participants showed a 74 percent protective vaccine efficacy against IPD.[14] In this review, PPSV was effective in preventing pneumococcal pneumonia caused by vaccine-type strains, with an odds ratio of 0.13, based on data obtained from four studies. However, this result came with a caveat: only one of four studies reviewed used PPSV-23, and the study did not show the benefit of PPSV-23s. In another study, Schiffner-Rohe et al performed a meta-analysis of four studies, which failed to prove PPSV-23's role in preventing pneumococcal pneumonia in the elderly (≥60 years).[15] PPSV-23 is less immunogenic than its conjugate counterparts as it elicits a T cell-independent response.

Following the introduction of the 7-valent PCV (PCV-7) in routine childhood vaccination programmes, substantial reductions in its covered serotypes were also noted amongst adults.[5,16] This is attributed to the benefits of PCV-7 in reducing nasopharyngeal colonisation in children, with resultant herd immunity in the general population. The CAPITA trial, which is a randomised, double-blind, placebo-controlled trial involving 84,496 adults, showed conclusively that the 13-valent PCV (PCV-13) was effective in preventing vaccine-type pneumococcal, bacteraemic and non-bacteraemic community gained pneumonia, and vaccine-type IPD.[17] Based on the per-protocol analysis, vaccine efficacy was found to be 45.6 percent for the prevention of vaccine-type pneumonia and 75 percent for the prevention of vaccine-type IPD.

McLaughlin et al evaluated the real-world effectiveness of PCV-13 in preventing hospitalisation for vaccine-type community-acquired pneumonia in elderly adults ≥65 years following universal recommendation for the use of PCV-13 and found an unadjusted vaccine efficacy of 72.8 percent.[18] In another prospective multicentre study of elderly aged ≥65 years hospitalised with community-acquired pneumonia, adjusted rates of vaccine efficacy for prevention of vaccine-type community-acquired pneumonia were

41.1 percent, 6.3 percent, and 44.6 percent for PCV-13, PPSV-23, and sequential PCV-13/PPSV-23 vaccination, respectively.[19] Of note, in the subgroup of adults aged 65-74, the adjusted vaccine efficacy for PCV-13, PPSV-23, and sequential PCV-13/PPSV-23 vaccination was 58.1 percent, 15.7 percent, and 63.6 percent, respectively. This suggests immunosenescence is an important contributing factor to poorer vaccine efficacy in the elderly.

2. Higher Valency Pneumococcal Vaccines

In October 2021, the Advisory Committee on Immunization Practices (ACIP) within the United States Centers for Disease Control and Prevention (CDC) updated its recommendations to include the use of the 15-valent PCV (PCV-15) in series with PPSV-23 (with PCV-15 replacing PCV-13) in adults and 20-valent PCV (PCV-20) alone, in their pneumococcal vaccination guidelines.[5] In June 2022, the ACIP recommended PCV-15 as an option for pneumococcal conjugate vaccination in persons aged <19 years, allowing it to be used interchangeably with PCV-13.[20]

The results of the first phase 1 and phase 2 trials of a 20-valent pneumococcal conjugate vaccine (PCV-20) were published in 2019 and 2021, respectively, showing PCV-20 to be well-tolerated in healthy adults with good immunogenicity based on opsonophagocytic activity (OPA) geometric mean titers (GMT).[21,22] A subsequent pivotal phase 3 clinical trial of PCV-20 in adults aged 18 years and above randomised patients to receive either PCV-13 or PCV-20. If the participants were aged 60 years and above, they went on to receive either (for those randomised to the PCV-13 arm), or saline (for those randomised to the PCV-20 arm) a month later. A comparison of the OPA GMT of all 13 matched serotypes showed PCV-20 is non-inferior to PCV-13 in eliciting the immune responses. Additionally, non-inferiority criteria were also met for the six of the seven additional serotypes covered by PCV-20 (but not PCV-13). A comparison of local reactions and systemic events following vaccinations showed they were similar in both groups and were mostly mild-to-moderate in severity.[23]

Table I shows the serotype coverage by PPSV-23, PCV-13, PCV-15, and PCV-20.

In the United States, both PCV-15 and PCV-20 have been updated as preferred pneumococcal vaccines of choice for individuals with risk factors.[24] Based on ACIP's latest recommendations, adults aged 65 years and above who have not previously received PCV or whose previous vaccination history is unknown should receive either PCV-20 or PCV-15. When PCV-15 is used, it should be followed by a dose of PPSV-23. Similarly, for adults aged 19-64 years with underlying medical conditions that put them at increased risk of PD, they should also receive PCV-20 or PCV-15 if they have not previously received PCV or if their previous vaccination history is unknown. Where PCV-15 is used, it should be followed by a dose of PPSV-23. When PCV-20 is used, no further doses are recommended at this point in time.

In November 2022, the Health Sciences Authority (HSA) of Singapore approved the use of PCV-20 for the prevention of IPD and pneumococcal pneumonia in individuals aged 18 years or older. Of note, at the time of writing this review, PCV-20 has not been officially recommended as a vaccine under the National Adult Immunisation Schedule in Singapore, and PCV-15 has not been approved for use by the HSA.

Table II shows a pneumococcal vaccination algorithm based on ACIP guidelines and PCV-20 availability.

3. Co-administration with Other Vaccines

In a phase 3, randomised, double-blind, multicentre study of adults aged 65 years and above to evaluate the co-administration of PCV-20 with quadrivalent influenza vaccine (QIV), immune responses after co-administration of the two vaccines were non-inferior to separate administrations of either vaccine.[25] Local and systemic side effects were also similar between the two groups. Considering the findings from this study, current ACIP guidelines support co-administration of PCV-15, PCV-20, and PPSV-23 with the QIV in adults.[24] However, no data are currently available on the co-administration of higher-valency pneumococcal vaccines with other vaccines.

4. Improving Pneumococcal Vaccination Uptake Amongst Adults in Singapore

A local epidemiological study by Äng et al suggested that factors associated with pneumococcal vaccine uptake include a higher level of education, higher monthly household income, better self-rated health, and having a regular family physician.[12] This emphasises the role of primary care providers in this aspect of clinical care.

A quality improvement initiative to improve uptake of pneumococcal and influenza vaccines in peritoneal dialysis patients at a local nephrology unit found that the most common patient factors for not having received either vaccine in the prior 12 months were a lack of physician recommendation and a lack of awareness of vaccine indications and benefits.[26] The most common physician-cited factors include a lack of reminders and competing demands in clinics. Through a series of interventions, including offering vaccination opportunities at peritoneal dialysis training visits, physician audits and feedback, and improving reminder systems, PCV-13 uptake improved from the baseline of 54 percent to 85 percent by the end of the study. Improving physician recommendations with reminders and improvement of awareness for both physicians and patients alike, are important strategies for us to consider in our fight to prevent PD. This is further highlighted in a local primary care study.[27] In this study, a cluster-randomised crossover trial was undertaken in 22 private general practitioner clinics. One of the key interventions included distribution of posters and flyers educating key benefits of pneumococcal and influenza vaccinations to patients, who were instructed to show

Table I. Comparison of serotype coverage between available pneumococcal vaccines

Serotypes	1	2	3	4	5	6A	6B	7F	8	9N	9V	10A	11A	12F	14	15B	17F	18C	19A	19F	20	22F	23F	33F
PPSV23	√	√	√	√	√		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
PCV13	√		√	√	√	√	√	√			√				√			√	√	√			√	
PCV15	√		√	√	√	√	√	√			√				√			√	√	√		√	√	√
PCV20	√		√	√	√	√	√	√	√		√	√	√	√	√	√		√	√	√		√	√	√

Table II. Advisory Committee on Immunization Practices Guidance for 20-Valent Pneumococcal Conjugate Vaccine

At-Risk Group	Prior Pneumococcal Vaccine	When to give PCV-20
Adults age ≥65 years	None	Now
	PPSV-23	At least 1 year after last pneumococcal vaccine
	PCV-13	At least 1 year after last pneumococcal vaccine
	PCV-13 + PPSV-23 at age **<65** years	At least 5 years after last pneumococcal vaccine
	PCV-13 + PPSV 23 at age **≥65** years	At least 5 years after last pneumococcal vaccine *(shared decision)*
Immunocompromised* adults age 19 – 64 years	None	Now
	PPSV-23	At least 1 year after last pneumococcal vaccine
	PCV-13	At least 1 year after last pneumococcal vaccine
	PCV-13 + x1 dose PPSV-23	At least 5 years after last pneumococcal vaccine
	PCV-13 + x2 doses PPSV-23	At least 5 years after last pneumococcal vaccine
Adults age 19 – 64 with cochlear implant or cerebrospinal fluid leak	None	Now
	PPSV-23	At least 1 year later
	PCV-13	At least 1 year after last pneumococcal vaccine
	PCV-13 + x1 dose PPSV-23	At least 5 years after last pneumococcal vaccine
*Chronic renal failure, nephrotic syndrome, asplenia, immunodeficiency, generalised malignancy, HIV, Hodgkin's disease, iatrogenic immunosuppression, sickle cell disease/hemoglobinopathies, solid organ transplant		

them to their attending doctor during their consultation. A statistically significant post-intervention vaccination uptake was observed for both vaccinations, with pneumococcal vaccination uptake improving from 3.7 percent to 5.7 percent.

5. Limitations of Current Available Pneumococcal Vaccines

While current data shows that the introduction of PCVs has significantly decreased the incidence of IPD worldwide, the phenomenon of serotype replacement (replacement of vaccine serotypes by non-vaccine serotypes) has reduced the protective effect of PCVs over time.[28] More research into higher-valency PCVs would help in ameliorating this phenomenon.

CONCLUSION

PD is a disease in which significantly more can be done to reduce its incidence by improving vaccination uptake within our community, amongst the elderly, and those with risk factors for infection. Increasing awareness amongst our population of vaccine availability is important and our primary care providers play a crucial role in this.

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CONFLICT OF INTEREST

The author declares that he has no conflict of interest in relation to this article.

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LEARNING POINTS

- **Pneumococcal disease is a vaccine-preventable illness with significant disease burden in the young and the elderly. Despite the availability of pneumococcal vaccines for primary prevention, vaccination uptake remains generally low in the local adult at-risk population based on current available data.**
- **Current adult vaccination guidelines strongly recommend the use of the pneumococcal vaccine in elderly adults ≥65 years of age or in younger adults with risk factors for IPD.**
- **The availability of higher-valency pneumococcal vaccines such as PCV-20 has the potential to allow for simplification of the vaccination schedule. The availability of safety data pertaining to co-administration with the quadrivalent influenza vaccine may also enhance vaccination uptake of both vaccines.**
- **Primary care physicians have an important role to play in protecting our vulnerable patients from PD through pneumococcal vaccinations.**