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Unit No. 3

UPDATES ON PNEUMOCOCCAL VACCINATION FOR ADULTS IN SINGAPORE (PCV20)

Adj A/Prof See Kay Choong

ABSTRACT

Pneumococcal infection, caused by the gram-positive diplococcus *Streptococcus pneumoniae*, is the leading bacterial cause of adult community-acquired pneumonia requiring hospitalisation, accounting for about one-third of cases. Occasionally, it invades normally sterile areas, resulting in invasive pneumococcal disease with complications such as empyema, bacteraemia, or meningitis. Mortality among adults hospitalised for pneumococcal disease in Singapore ranges from 18.5-26.1 percent. Individuals at the extremes of age, with multiple chronic conditions, or who are immunocompromised are at higher risk of developing severe disease. The 20-valent pneumococcal conjugate vaccine (PCV20) is safe and effective against most circulating *Streptococcus pneumoniae* serotypes and is approved for adults aged 19 and older in Singapore. It covers most serotypes included in the older 13-valent pneumococcal conjugate vaccine (PCV13) and 23-valent pneumococcal polysaccharide vaccine (PPSV23). A single dose of PCV20 is recommended for adults aged 65 and older without comorbid conditions and adults aged 19 and older with underlying medical conditions, replacing the need for sequential PCV13 and PPSV23 vaccinations. Patients with prior PPSV23 or PCV13 should be given PCV20 at least one year after PPSV23/PCV13. PCV20 can be co-administered with inactivated influenza or COVID-19 (BNT162b2) vaccines.

Keywords: Immunisation Programmes; Immunocompromised Host; Pneumococcal Vaccines; Streptococcus pneumoniae; Vaccines, Conjugate

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INTRODUCTION

Pneumococcal infection, caused by the gram-positive diplococcus *Streptococcus pneumoniae* is the most common bacterial cause of adult community-acquired pneumonia requiring hospitalisation, accounting for about one-third of cases.[1] Epidemiology in Singapore mirrors global trends, which is unsurprising given our relatively open economy and travel patterns. Occasionally, *Streptococcus pneumoniae* invades into normally sterile regions like the pleura, blood, and brain. Severe community-acquired pneumococcal pneumonia, and invasive pneumococcal disease with empyema, bacteraemia, or meningitis, then exerts a high burden of human disease. In one Singapore study, 18.5 percent of adults hospitalised for pneumococcal disease died. In another Singapore study, 20.7 percent of patients with invasive pneumococcal disease required intensive care unit (ICU) admission and 26.1 percent died.[2] As with other diseases, patients at the extremes of age, those who have multiple chronic co-morbid conditions, and those who are immunocompromised are at risk of severe and complicated disease.

To mitigate the burden of pneumococcal disease, antibiotics should be given promptly and appropriately, with most isolates being susceptible to beta-lactams, though antimicrobial drug resistance to the commonly given macrolides is prevalent in Asia.[3] However, elevated mortality and morbidity may occur even with appropriately administered antibiotics. Another way of reducing the human impact of pneumococcal disease is through prevention of disease via reducing the spread of disease and via vaccination.

Reducing the spread of disease is not easy as pneumococcal infection is spread via droplets, unless strict masking, physical distancing, and isolation procedures are being followed.[4] To allow usual human activities and interactions to occur, vaccination would then be required for protection against pneumococcal disease. The incidence of pneumococcal disease, including invasive pneumococcal disease, has been reducing over time, in part due to prior vaccination with current and older forms of pneumococcal vaccines.[5]

Vaccination uptake not only depends on improved access; it also requires clinicians to be aware of relevant theory and practices concerning vaccination, to identify, counsel, and manage patients appropriately. This article will therefore discuss key concepts and practical considerations for frontline clinicians, with a focus on the relatively new 20-valent pneumococcal conjugate vaccine (PCV20) for adults ≥19 years old in the Singapore context.

KEY CONCEPTS FOR PNEUMOCOCCAL VACCINATION

The level of protection afforded by pneumococcal vaccination would depend on several factors:

1. Number of serotypes covered
2. Immunogenicity against the covered serotypes
3. Generation of mucosal immunity

ADJ A/PROF SEE KAY CHOONG
Senior Consultant Respiratory Physician & Intensivist, National University Hospital, Singapore
Adjunct Associate Professor, Yong Loo Lin School of Medicine, National University of Singapore

Number of Serotypes Covered

Effective immunity against pneumococcus needs to be as broad as possible, targeting specific serotypes. Variations in the composition of *Streptococcus pneumoniae* capsular polysaccharide have given rise to at least 100 serotypes.[6] However, not all serotypes are common, and vaccines should cover the predominantly circulating ones. In Singapore, the major serotypes responsible for adult pneumococcal disease requiring hospitalisation are 3, 4, 6B, 14, 19F, and 23F.[7] PCV13 and PPSV23 cover >70 percent of serotypes giving rise to invasive pneumococcal disease[8] and prevent ~80 percent of invasive pneumococcal disease cases.[2] Given that vaccines cannot cover all pathogenic serotypes, the natural consequence of covering some serotypes would favour a gradual shift towards non-vaccine replacement strains emerging as the main contributors to pneumococcal disease. As such, vaccine development is a constant struggle against breadth of coverage and serotype shift.

Serotype coverage of selected pneumococcal vaccines in Singapore are as follows:

- 13-valent pneumococcal conjugate vaccine (PCV13): 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F
- 20-valent pneumococcal conjugate vaccine (PCV20): 8, 10A, 11A, 12F, 15B, 22F, and 33F, in addition to PCV13 serotypes
- 23-valent pneumococcal polysaccharide vaccine (PPSV23): 2, 9N, 17F, 20, in addition to PCV20 serotypes, less 6A

Note that the combination of PCV13 and PPSV23 would only cover four additional serotypes (2, 9N, 17F, 20) compared to PCV20, and could be replaced by the latter for most patients.

Immunogenicity Against the Covered Serotypes

Apart from the number of serotypes covered, immunogenicity against the vaccine-covered serotypes would determine the level of antibody production against infection. Such immunogenicity cannot be empirically guessed and requires the use of controlled trials to uncover important efficacy endpoints such as levels of immunogenicity, clinical benefits of such immunogenicity, and the duration of protection. Using a randomised trial design to obtain clinical outcomes like morbidity and mortality is time-consuming and expensive. Therefore, after the publication of the landmark PCV13 CAP Immunisation Trial in Adults (CAPiTA) demonstrated correlation between immunogenicity and clinical benefit (near halving of vaccine-type pneumococcal pneumonia cases),[9] subsequent trials of higher valency pneumococcal conjugate vaccines used immunogenicity compared to PCV13 as their surrogate endpoint and are known as bridging studies. Based on bridging trials, PCV20 was safe and well tolerated, with immunogenicity of PCV20 comparable to that of PCV13.[10,11]

Generation of Mucosal Immunity

Nasal carriage of pneumococcus is regarded as the reservoir for human-to-human disease transmission. Nasal carriage can be reduced by mucosal antibodies. Conjugate vaccines (e.g., PCV20), but not polysaccharide vaccines (e.g., PPSV23), elicit mucosal immunity and are therefore valuable for preventing nasal colonisation. Provided a high level of vaccination has been achieved, the reduced levels of colonisation among the vaccinated would avoid onward transmission of infection, indirectly protecting the unvaccinated via the herd effect.[12] However, if vaccination coverage is low or if adults travel to areas with poor vaccination rates, herd protection cannot be relied upon,[13] and individual vaccination would be required.

PNEUMOCOCCAL VACCINATION EFFICACY AND REAL-WORLD EVIDENCE

Controlled clinical trials for efficacy of PCV20 are all bridging studies and demonstrate safety and efficacy in adults of varying immunisation history. Among >4,400 pneumococcal vaccine-naïve adults ≥60 years of age in Japan, South Korea, Sweden, Taiwan, and the United States, it was demonstrated by Essink et al and Haranaka et al that PCV20 was safe and well tolerated, with immunogenicity of PCV20 comparable to that of PCV13.[10,11] Among 875 adults ≥65 years of age with prior pneumococcal vaccination in Sweden and the United States, Cannon et al demonstrated that PCV20 was immunogenic one month after PCV20 administration, regardless of prior PCV13 or PPSV23 vaccination.[14]

In contrast to efficacy endpoints under controlled trial conditions, real-world effectiveness endpoints are needed to determine vaccination benefits in situations where participants have a wider range of comorbid conditions, environmental exposures, and risk of severe disease. If these real-world studies are done using observational study designs, then one would expect a trade-off between reduced validity owing to residual confounding by unknown risk factors for severe disease, and increased generalisability of clinical outcomes.

Real-world evidence supports the clinical effectiveness of PCV13, which prevented >70 percent of vaccine-type community-acquired pneumonia.[15] Globally, PCV13 is likely to be cost-effective for disease prevention on a population basis.[16] Similarly, PCV20 has been shown to be cost-effective in Japan,[17] a high-income Asian country with an ageing population just like Singapore. On the same note, an abstract presented at the Professional Society for Health Economics and Outcomes Research (ISPOR) Europe conference in 2023 demonstrated that using PCV20 is more cost-effective than the current adult pneumococcal vaccination recommendations by the Singapore Ministry of Health (MOH), which rely on PCV13 and PPSV23.[18]

PNEUMOCOCCAL VACCINATION STRATEGIES AND GUIDELINES

Pneumococcal vaccination strategies involve vaccinating persons at risk for severe disease (see **Table I** for PCV20) and individualising methods that enhance the efficacy and adherence to vaccination.[19-22] Persons at risk are those at the extremes of age, those with comorbid conditions including an immunocompromised state,[23] and those with anatomical risk for pneumococcal meningitis. These persons at risk include those who are scheduled for elective splenectomy, cochlear implantation, or immunosuppressive therapy. For the immune response to vaccination to fully develop, it is recommended, if feasible based on clinical circumstances, to administer the vaccination at least two weeks prior to the planned elective procedure.[24]

How PCV20 is given depends on prior pneumococcal vaccination history, which is described in **Table II** with some simplification of the US Centers for Disease Control Pneumococcal Vaccine Recommendations.[20-22] PCV20 vaccination strategies in Canada[25] and some European countries[26] align with those from the US Centers for Disease Control. In Singapore, while PCV13 and PPSV23 are listed in the National Adult Immunisation Schedule, PCV20 is not, due to being a new vaccine. As PPSV23 and PCV13 are commonly used locally in Singapore, pneumococcal vaccination history would be discussed in relation to these. Generally, a single dose of PCV20 can replace the need for sequential vaccination of PCV13 and PPSV23, reducing the number of visits required for pneumococcal vaccination.

In terms of vaccination timing, for persons who are pneumococcal vaccination-naïve, PCV20 is given as a single intramuscular dose. In persons who have received PCV13 and have separately received PPSV23 at ≥65 years old, the decision to get PCV20 is based on shared clinical decision-making between patient and physician due to potentially lower benefit. Should these individuals receive PCV20, they should wait five years after the last pneumococcal vaccine dose.

Female adults eligible for pneumococcal vaccination due to underlying medical conditions should receive PCV20 before becoming pregnant. This precaution is necessary as maternal antibodies generated by PCV, as seen with PCV10, can reduce infant antibody production for similar childhood vaccines, a phenomenon known as negative maternal antibody interference.[27]

Separately, it is anticipated that the immune response to vaccination will be significantly attenuated in patients undergoing hematopoietic stem cell transplantation (HSCT).[23] In these patients, four doses of PCV are required for optimal immune response. If no PCV had been given, administer three doses of PCV20, four weeks apart starting 3-6 months after HSCT. Then, administer a fourth PCV20 dose ≥6 months after the third dose of PCV20, or ≥12 months after HSCT, whichever is later. If PCV13 had been given, then complete the PCV20 series less the number of PCV13 doses administered.[22]

To facilitate vaccination and minimise healthcare visits, PCV20 may be co-administered with inactivated influenza[28] or COVID-19 (BNT162b2) vaccines,[29] as safety and immunogenicity were comparable to those observed when the vaccines were administered individually. Safe and effective co-administration of PCV20 with other vaccines are not yet supported by currently available evidence.

AREAS OF UNCERTAINTY

Three areas of uncertainty exist:

1. Whether PCV20 vaccination should be administered after severe or invasive pneumococcal disease in an otherwise healthy patient younger than 65 years old, given that lack of pneumococcal vaccination predisposes to recurrent pneumonia independent of age.[30] Shared decision-making weighing the possible benefit of reducing pneumonia recurrence versus the relatively minor risks of PCV20 vaccination should be done.

2. Whether additional PPSV23 after PCV20 vaccination may help the highest-risk patients (e.g., those who are severely immunocompromised) by covering four additional serotypes (2, 9N, 17F, 20). Shared decision-making weighing the possible benefit of reducing pneumonia occurrence versus the relatively minor risks of PPSV23 vaccination should be done. For extended coverage, people at highest risk of pneumococcal disease who have not gotten PPSV23 may get PPSV23 at least 12 months after PCV20.

3. Waning immunity after vaccination is expected, though what remains unknown are when such waning renders immunity insufficient and when repeated PCV20 vaccination is needed. Since efficacy of PCV13 persisted over the four-year follow-up duration of the CAPiTA trial,[9] longer-term studies would then be required.

CONCLUSION

In summary, *Streptococcus pneumoniae* is a common cause of community-acquired pneumonia, and occasionally causes invasive pneumococcal disease with empyema, bacteraemia, or meningitis. PCV20, which covers most serotypes included in both PCV13 and PPSV23, is safe and immunogenic compared to PCV13, and elicits mucosal immunity. Given the proven efficacy and safety of PCV20 for individuals who are pneumococcal-naïve or who have received prior pneumococcal vaccination, it can serve as a single-dose method to complete pneumococcal vaccination for a broad range of at-risk individuals, regardless of vaccination history. It can also be co-administered with seasonal influenza and COVID-19 vaccines. This ease of pneumococcal vaccination with PCV20 might help improve vaccine acceptance and adherence.

Table I. Persons recommended for PCV20 vaccination

Comorbid condition	Age group
None	≥65 years
Underlying medical conditions: Alcoholism, asplenia (congenital or acquired), chronic heart disease (including heart failure, cardiomyopathies), chronic liver disease, chronic lung disease (including chronic obstructive pulmonary disease, emphysema, asthma), cigarette smoking, diabetes mellitus, immunocompromising conditions (e.g., chronic renal failure, congenital or acquired immunodeficiency, human immunodeficiency virus infection, malignancy, nephrotic syndrome, solid organ or hematopoietic stem cell transplant), sickle cell disease or other hemoglobinopathies	≥19 years
Anatomical risk: Cerebrospinal fluid leak, cochlear implant	≥19 years

PCV: Pneumococcal conjugate vaccine

Table II. PCV20 administration based on prior pneumococcal vaccination history*

Pneumococcal vaccination history	Time of administration
None or unknown	Administer PCV20 once
PCV13	Administer PCV20 at least 12 months after the last PCV13 dose
PPSV23	Administer PCV20 at least 12 months after the last PPSV23 dose
Both PCV13 and PPSV23, with PPSV23 given before 65 years old	Administer PCV20 at least 5 years after the last pneumococcal vaccine dose. PCV20 administration may be delayed till ≥65 years old if no comorbid condition exists, or if the individual only has less immunocompromising comorbid conditions**
Both PCV13 and PPSV23, with PPSV23 given 65 years old or later	PCV20 is optional (shared decision-making). If given, administer PCV20 at least 5 years after the last pneumococcal vaccine dose
PCV20	Additional PCV20 dosing not needed

*See main text for adults aged ≥19 years who received hematopoietic stem cell transplant. These patients require 4 doses of PCV to complete their pneumococcal vaccination series

**Alcoholism, chronic heart disease (including congestive heart failure, cardiomyopathies), chronic liver disease, chronic lung disease (including chronic obstructive pulmonary disease, emphysema, asthma), cigarette smoking, diabetes mellitus

PCV: Pneumococcal conjugate vaccine
PPSV: Pneumococcal polysaccharide vaccine

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LEARNING POINTS

- ***Streptococcus pneumoniae* is a common cause of community-acquired pneumonia, and occasionally causes invasive pneumococcal disease with empyema, bacteraemia, or meningitis.**
- **PCV20, which covers most serotypes included in both PCV13 and PPSV23, is safe and immunogenic compared to PCV13, and elicits mucosal immunity.**
- **Prevention of pneumococcal disease with a single dose of intramuscular PCV20 is recommended for use in all adults ≥65 years without comorbid conditions, and for all adults ≥19 years with underlying medical conditions.**
- **A single dose of PCV20 can replace the need for sequential vaccination of PCV13 and PPSV23, reducing the number of visits required for pneumococcal vaccination.**
- **Patients with prior PPSV23 or PCV13 should be given PCV20 at least one year after PPSV23/PCV13.**
- **PCV20 can be co-administered with inactivated influenza or COVID-19 (BNT162b2) vaccines.**