衞生防護中心
Centre for Health Protection

Scientific Committee on Vaccine Preventable Diseases

Updated Recommendations on the Use of 13-valent Pneumococcal Conjugate Vaccine in Childhood Immunisation Programme

Use of pneumococcal conjugate vaccines in Hong Kong

Upon the recommendation of the Scientific Committee on Vaccine Preventable Diseases (SCVPD), 7-valent pneumococcal conjugate vaccine (PCV7) was incorporated into the Hong Kong Childhood Immunisation Programme (HKCIP) in September 2009 for all eligible infants born on or after 1 September 2007. Eligible children receive a primary series of three doses at 2, 4 and 6 months, followed by a booster dose at 12 months (3p+1 schedule), according to the schedule recommended by the manufacturer. PCV7 covers serotypes 4, 6B, 9V, 14, 18C, 19F and 23F.

2. In October 2010, PCV7 was replaced by 10-valent pneumococcal conjugate vaccine (PCV10) covering three additional serotypes 1, 5 and 7F. In December 2011, PCV10 was subsequently replaced by PCV13 covering three more serotypes 3, 6A and 19A.

3. The overall coverage of PCV has been maintained at a very high level in Hong Kong children all along. Preliminary results of the immunisation coverage survey conducted by the Department of Health in 2018 among preschool children born in 2012-2014 showed that the overall proportion of surveyed children aged three to five years who had

completed 4 doses of PCV was >95%. However, lower PCV uptake was noted for non-local children[a]. The proportion of surveyed non-local children who had completed 4 doses of PCV was only 60.4%, compared to 99.4% among local children.

Local epidemiology of invasive pneumococcal disease

4. Since the introduction of pneumococcal vaccination for children in Hong Kong, the incidence of invasive pneumococcal diseases (IPD) has reduced significantly in very young children aged below 2 years and a reduction of IPD caused by PCV7 serotypes was observed for all age groups. These showed that the PCVs used in Hong Kong were effective in reducing the incidence of IPD caused by PCV7 serotypes.

5. On the other hand, the disease burden of IPD has shifted to children aged 2 years and above in recent years. The incidences of IPD caused by "PCV13, non-PCV7" serotypes have increased among children aged 2-4 years and to a lesser extent among children and teenagers aged 5-17 years. An increase in non-PCV13 serotypes was also observed among children aged 2-4 years. In 2018, the incidence of IPD caused by "PCV13, non-PCV7" serotypes was 14.5 per 100,000 population among children aged 2-4 years as compared with 3.8 among children aged less than 2 years. Among the 175 paediatric IPD cases recorded from 2015 to June 2018, 112 (64%) and 21 (12%) cases were caused by serotypes 3 and 19A which were only included in PCV13 but not PCV7 and PCV10.

6. Although serotype 3 is included in PCV13, studies have shown that PCV13 is less effective against serotype 3 than other serotypes[1]. Moreover, local genomic studies on pneumococcal isolates showed that a novel sequence cluster of serotype 3 ST6011 has emerged in Hong Kong in recent years[2]. This sequence cluster is highly resistant to macrolides and its invasive odds ratio[b] is

[a] Non-local children refer to those who were either not born in Hong Kong, or did not reside in Hong Kong before 2 years of age or during preschool.

[b] Invasive odds ratio of a sequence cluster was determined by the equation a·d / b·c, where a and b are

higher than other lineages isolated in Hong Kong[3],which may also partially explain the relatively high burden of serotype 3 IPD in young children.

World Health Organization's recommendations on use of PCV

7. For PCV10 and PCV13, the manufacturers recommend 3 primary doses with an interval of at least 4 weeks plus a booster dose at least 6 months after the third primary dose (3p+1 schedule). However a variety of off-label schedules have been used in many countries. Many countries chose to use 3 primary doses (3p+0 schedule) or 2 primary doses plus a booster (2p+1 schedule) in their routine immunisation programmes.

8. In its position paper on pneumococcal vaccines published in 2012, following a comprehensive review of the relevant evidence and cost-effectiveness, the World Health Organization (WHO) recommended a 3-dose PCV schedule for infants, either 3p+0 or 2p+1 as alternatives to the manufacturers' labelled 3p+1 schedule[4].

9. In October 2017, the WHO Strategic Advisory Group of Experts Working Group on PCVs (SAGE PCV WG) met and reviewed the evidence to inform PCV vaccination policy, including an extensive systematic review on PCV impact data that assessed evidence on potential differences on various clinical endpoints by schedule, product and catch-up vaccination [PCV Review of Impact Evidence (PRIME)][5].

10. Regarding the 3p+0 and 2p+1 schedules, PRIME showed that both were effective in reducing vaccine-type carriage and diseases. As for immunogenicity, 3 primary doses were more immunogenic than 2 primary doses after the primary series, but 2p+1 was more immunogenic than 3p+0 after the booster/third dose. The SAEG PCV WG continued to recommend either a 3p+0 or 2p+1 schedule.

number of IPD and carriage isolates in the sequence cluster respectively, and c and d are the total number of IPD and carriage isolates not in the sequence cluster, respectively.

11. Regarding the choice of PCV, PRIME assessed the impact of PCV10 and PCV13 on immunogenicity, nasopharyngeal carriage and IPD. It showed that both PCV10 and PCV13 had impact on the disease and carriage caused by the 10 common vaccine serotypes. There were differences in the impact of PCV10 and PCV13 on the 3 additional serotypes (i.e. 3, 6A and 19A) included only in PCV13. Overall, impact on serotype 3 was not demonstrated for **BOTH** products, although PCV13 could elicit a higher immune response. In spite of limited data, the overall impact on serotype 19A was better for PCV13 and the impact on nasopharyngeal carriage of serotype 19A was not demonstrated by PCV10. Both products showed impact on serotype 6A.

12. The SAGE PCV WG regarded that both PCV10 and PCV13 are safe and effective, and demonstrated both direct and indirect effects against pneumococcal diseases. It also noted that there was limited evidence on the superiority in impact between PCV10 and PCV13 against IPD and pneumonia, but PCV13 might have advantage in settings where serotypes 19A and 6C are common. The country level choice will depend on factors such as local or regional programmatic considerations, disease epidemiology, serotype prevalence, cost-effectiveness, or other issues.

13. The SAEG PCV WG also looked into additional values of catch-up vaccination with 1 or 2 doses of PCV in vaccine-naïve healthy children as compared with vaccination of only age eligible children. It found that catch-up vaccination programmes conferred additional direct and indirect benefits compared with routine immunisation alone. For catch-up vaccination, 1 dose of PCV should be offered for those initiating PCV vaccination at 24 months and older.

Use of PCV in overseas countries

14. For the about 140 countries that have introduced PCV in their childhood immunisation programme (as of December 2018), the majority

(about 84%) have adopted a 3-dose schedule recommended by the WHO, with about half adopting the 2p+1 schedule and another half the 3p+0 schedule. Only about 16% adopted the 3p+1 schedule[6].

15. After replacing PCV7 with PCV13, both countries adopting a 3p+1 schedule (such as the United States[7] and Japan[8]) and a 2p+1 schedule (such as the United Kingdom (UK)[9] and Denmark[10]) experienced significant reductions in IPD in children, in particular PCV7 serotypes. Reductions of IPD caused by "PCV13, non-PCV7" serotypes (including serotype 19A) were also observed in these countries. The UK introduced a 2p+1 PCV7 programme in 2006 and IPD caused by serotype 19A increased in young children afterwards[11]. However, the incidence of IPD caused by serotype 19A rapidly decreased after replacing PCV7 with PCV13 in 2010 while maintaining a 2p+1 schedule[11].

Recommendations

16. After reviewing local epidemiology of IPD from 2007 to 2018, overseas studies, as well as recommendations from the WHO and overseas health authorities, the SCVPD and its Working Group on Pneumococcal Vaccination (WGPV) have made the following recommendations on the schedule of PCV13 and catch-up vaccination under HKCIP.

17. First, the SCVPD and WGPV recommend a change of the schedule of PCV13 under HKCIP from a 3p+1 to a 2p+1 schedule. Under the updated 2p+1 schedule, children should receive 2 primary doses of PCV13 at 2 and 4 months, followed by a booster dose of PCV13 at 12 months. Based on the available evidence and overseas experience, the SCVPD and WGPV regarded that the 2p+1 schedule is non-inferior to the current 3p+1 schedule and should provide comparable protection against IPD to children in Hong Kong.

18. In view of the much higher disease burden of IPD among children aged 2-4 years in Hong Kong and studies showing that the immune response after the booster dose at 1 year in a 2p+1 schedule was better when compared

to that after the third dose in a 3p+0 schedule, the SCVPD and WGPV recommend a 2p+1 schedule to be adopted under HKCIP. This change will simplify the vaccination schedules of HKCIP with one less vaccine given at 6 months.

19. Second, in view of the relatively low PCV13 uptake among non-local preschool children, the SCVPD and WGPV also update its previous recommendation on catch-up vaccination (**Annex**). Under the updated recommendation, a single dose of PCV13 catch-up vaccination should be provided to children who have not received any booster dose of PCV13 between the age of one year to <6 years.

20. Given the more favourable impact on serotype 19A, the SCVPD and WGPV also continue to recommend the use of PCV13 in HKCIP.

March 2019

Annex

Updated vaccination schedule of PCV13 in HKCIP

Standard regimen*	
A standard 2-dose primary series at 2 and 4 months of age with a booster dose at 12 months (2p+1)	
Catch up schedule for missed or delayed doses	
Age at presentation	Schedule
6 months or below*	A 2-dose primary series at any time with 4-8 weeks' interval between doses; then a booster dose at 12 months (i.e. 2p+1)
7 months to less than 1 year	A 2-dose primary series with an interval of 4-8 weeks but not later than the age of 1 year; then a booster dose at 12 months or 2 months after the last dose whichever is later (i.e. 2p+1) If the second dose of the primary series is not administered by the age of 1 year, only give a booster dose at 12 months or 2 months after the last dose whichever is later (i.e. 1p+1)
1 year to less than 6 years^	One single dose (irrespective of the number of doses received before 1 year of age)

*The primary series is changed from 3 doses to 2 doses.

^The upper age limit is changed from less than 2 years to less than 6 years.

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