SAGE Evidence to recommendation framework

Pneumococcal Conjugate Vaccine (PCV) PICO 1: Dosing Schedule Impact

More information can be found in the Working Group report[1] and in the summary of the Strategic Advisory Group of Experts (SAGE) on Immunization meeting in October 2017.[2]

Question: How does PCV administered to healthy children in a 2p+1 schedule compare with the vaccine administered in a 3p+0 schedule?

Population: (a) Vaccinated children (direct effects); (b) unvaccinated older children and adults (indirect effects).
Intervention: 2 primary doses before 6 months of age and 1 booster dose at 9 months of age or later (2p+1) in infants <2 years of age with WHO prequalified PCV products
Comparison(s): 3 primary doses before 9 months of age without a booster dose (3p+0) in infants <2 years of age with WHO prequalified PCV products
Outcome:
Direct effects and indirect effects using the following measures:
IgG response – mean GMC and percent responders in immunized infants for vaccine- serotypes (VT) (direct effect only)
Mortality – vaccine effectiveness and/or change in mortality rates, pre/post vaccination, for all-cause mortality, pneumonia mortality, and IPD mortality change in case fatality ratios, pre/post vaccination, for pneumonia and IPD.
Invasive Pneumococcal Disease (IPD) – vaccine effectiveness and/or change in incidence of VT or serotype specific IPD pre/post vaccination
Pneumonia – vaccine effectiveness and/or change in incidence, pre/post vaccination, of either clinical pneumonia or chest x-ray (CXR) confirmed pneumonia
Carriage – vaccine effectiveness and/or change in incidence, pre/post vaccination, of vaccine type or serotype specific pneumococcal carriage

[1] Working Group report, available at http://www.who.int/immunization/sage/meetings/2017/october/en/ , accessed February 2019.
[2] Meeting of the Strategic Advisory Group of Experts on immunization, October 2017 – conclusions and Recommendations. https://apps.who.int/iris/bitstream/handle/10665/259533/WER9248.pdf;jsessionid=0650CFB4034DE9A4FD3FDAB46FF35346?sequence=1, accessed February 2019

Background:
S. pneumoniae causes a variety of diseases, ranging from serious invasive disease and pneumonia to less severe non-invasive diseases. Infant vaccination is the most effective way to prevent infections and reduce the burden, mortality and sequelae both within the child (direct effect) and adult populations (by indirect effects).
Pneumococcal conjugate vaccines (PCVs) have been used since 2000, with the licensure of PCV7. Currently, only PCV10 and PCV 13 are available. PCV introduction in lower income countries began in 2009 and has continued to increase over time. WHO has recommended that PCVs be administered using either a 2p+1 or 3p+0 schedule in infants, with the primary doses of each schedule administered by six months of age and the booster dose of the 2p+1 administered at 9 months of age or later. Intervals between doses can vary, but are generally at least 8 weeks apart for the two primary doses in the 2p+1 schedule and at least 4 weeks apart for the
3p+0 schedule.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Un-certain*	*Yes*	*Varies by setting*	Prior reviews of evidence suggested that the booster dose in a 2p+1 schedule may confer a disease control advantage; however, the timing of doses in the 3p+0 schedule could be more programmatically and epidemiologically suitable for lower income countries with earlier ages of infection and lower coverage levels of vaccine doses given late in the first year of life. As a result, lower income countries have been more likely to adopt the 3p+0 schedule and higher income countries have been more likely to adopt the 2p+1 schedule.	Global PCV introductions have dramatically increased in the past 7 year.CV is one of the most expensive vaccines in the EPI schedule, and thus provision of evidence to support vaccine introduction, impact optimization, and sustained investment in the program is considered to be of great public health value.
		☐	☐	☒	☒		

BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No*	*Un-certain*	*Yes*	*Varies*	PCV has demonstrated direct effectiveness against vaccine serotype invasive pneumococcal disease that exceeds 80% in most settings. Overall, the evidence did not support a compelling preference for 2p+1 or a 3p+0 schedule. Available evidence informing potential benefits of these two schedules is listed below by outcome assessed. **Immunogenicity** Head to head studies suggest that a two dose primary schedule elicits lower post primary series antibody concentrations than a three dose primary schedule for most serotypes; however, antibody concentrations after the booster dose in 2p+1 schedule exceed those after the third dose of the 3p+0 schedule. Head to head studies demonstrate that, after the primary series, a two-dose primary schedule has lower GMCs but a similar percentage of responders compared with a three-dose primary schedule for most serotypes. For ST6A and ST6B, a three-dose primary schedule had both higher GMCs and higher percentage of responders compared to a two-dose primary schedule. When assessing immunogenicity after the third dose of each schedule (post-booster for 2p+1 and post primary for 3p+0), a 2p+1 schedule elicited higher GMCs but a similar	The relative benefits of a 2p+1 schedule, compared to a 3p+0 schedule, may vary across and within countries based on the epidemiology of disease including the peak age of infection and disease, and programmatic considerations such as the coverage that can be achieved by either schedule. For settings with substantial disease early in life or for those settings with low coverage of a booster dose, a 3p+0 schedule may be preferred. For settings with substantial likelihood of administering a dose at 9 months or older, a 2p+1 schedule may confer some additional benefit on colonization or on specific serotypes (e.g. ST1).
		☐	☐	☒	☐		

				percentage of responders compared with a 3p+0 schedule for most serotypes, including ST6A. For ST6B, both the GMCs and percent responders indicated an advantage from a 2p+1 schedule compared to a 3p+0 schedule, post third dose. Immunogenicity data are confounded by factors such as serotype specific carriage prevalence; disease rates; age at vaccination; the adjuvant effect of concomitant whole cell pertussis vaccine; maternal antibodies; and maternal vaccination with diphtheria or tetanus toxoid containing vaccines. Furthermore, the clinical significance of differences in immunogenicity remains unknown. For other outcomes, including IPD and NP carriage, no available evidence indicated overall differential impact by a 2p+1 vs 3p+0 schedule at the population level, though data were confounded by prior PCV7 use, country income levels, and baseline carriage rates, age at vaccination among other factors. For ST1, there is strong evidence of 2p+1 impact on disease. There is much less evidence on the impact of a 3p+0 schedule on ST1 disease. The limited evidence that exists is mixed in terms of demonstrated impact and some of it comes from only a limited number of years of product implementation.	

	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	There is no evidence for a differential risk of adverse events associated with one or the other PCV schedule (ie. 2p+1 or 3p+0). There is no evidence that one or another of the two schedules results in a shift in the age of residual disease. On the population level, a 2p+1 schedule may demonstrate higher immunogenicity after the third dose compared to a 3p+0 schedule; however, the timing of the booster dose may pose an epidemiologic or programmatic challenge in settings where either coverage of the booster dose could be lower, or the most common age of pneumococcal disease is younger. Therefore, a possible undesirable effect of the 2p+1 schedule could be the mitigated protection or impact in higher burden settings where the age distribution of disease centers around younger infants. Country-specific considerations should be taken to ensure whichever schedule is most appropriate for the needs of the target population. Replacement non-vaccine serotype disease in children exists but the magnitude is small relative to the reduction in vaccine serotype disease. The review did not assess the relative difference in serotype replacement according to schedule. The magnitude of indirect effect was not distinguishable by schedule.	

	Balance between benefits and harms	*Favours inter-vention* ☐ | *Favours com-parison* ☐ | *Favours both* ☒ | *Favours neither* ☐ | Unclear ☐	There is no clear advantage or demonstration of differential impact for either the 2p+1 or 3p+0 schedules. While some data indicate that 2p+1 schedule may have an added advantage because the booster dose is more immunogenic than the third primary dose in the 3p+0 schedule, the clinical significance of this difference has yet to be established. Additionally, there may be programmatic or epidemiologic factors (such as timeliness, coverage, and age distribution of disease burden) that may warrant certain settings using a 3p+0 schedule and others to use a 2p+1 schedule. For ST1, there is strong evidence of 2p+1 impact on disease. There is much less evidence on the impact of a 3p+0 schedule on ST1 disease. The limited evidence that exists is mixed in terms of demonstrated impact and some of it comes from only a limited number of years of product implementation. The benefits of either schedule outweigh any associated potential harms.	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Mod-erate* ☐ | *High* ☒ Safety of the intervention *No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Mod-erate* ☐ | *High* ☒	The overall quality of evidence to distinguish the relative merits of one or another schedule were similar, depending on the outcome. The evidence indicating safety of PCV was determined to be strong from previous reviews using different schedules.	

VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	***Important uncertainty or variability*** ☐ ***Possibly important uncertainty or variability*** ☐ ***Probably no important uncertainty or variability*** ☐ ***No important uncertainty or variability*** ☒ ***No known undesirable outcomes*** ☐	The prevention of pneumococcal disease, constitutes an important public health burden in most countries. Therefore, the selection of a schedule with the highest impact is an important desirable outcome. No evidence is available, though it is assumed, that in general there is no important uncertainty or variability between schedules.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	Panel discussions with national programme managers were used to assess the factors that influenced or were likely to influence the choice of schedule. Evidence of the preferences of individuals within the target populations was not assessed. Both schedules include the same number of doses and therefore injections. Some schedules may result in more or less injections at a visit, which is known to vary in preference across individual caregivers and providers.	Evidence of the values and preferences of individuals within the target population for PCV immunization schedules were not reviewed, and thus a systematic qualitative assessment of these values or preferences should be conducted in the future. In settings of vaccine hesitancy in target populations, additional advocacy may be needed.
RESOURCE USE	Are the resources required small?	*No* ☐ *Un-certain* ☐ *Yes* ☐ *Varies* ☒	There are variable differences in resources required to deliver a 2p+1 vs. a 3p+0 schedule. The costs and cost-effectiveness of a 3-dose PCV program were already assessed and considered when recommendations on the inclusion of PCV in national immunization programmes were made in 2007 and revised in 2012. For countries with strong health infrastructure to deliver immunization service delivery	

					beyond one year of life the resources for either schedule are likely the same. For countries with weak health infrastructure where immunization delivery beyond one year of life is difficult, there may be additional costs.	
	Cost-effectiveness	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Earlier analysis has shown that the introduction of PCV was cost-effective in all settings. Earlier analyses were based on the use of a 3p+0 schedule for low and middle income countries. Cost-effectiveness of PCV 2p+1 vs 3p+0 dosing schedules was not systematically assessed in this review; however, it is assumed that both 2p+1 and 3p+0 schedules are cost effective since the 2p+1 was shown to have a similar level of effectiveness as the 3p+0 schedule with no added vaccine or delivery costs.	
EQUITY	What would be the impact on health inequities?	*Increased* ☐	*Un-certain* ☐	*Reduced* ☒	*Varies* ☐	Pneumococcal disease is more common among the socially and economically disadvantaged groups. These groups also carry a disproportionate mortality burden and stand to gain the most from vaccination.	Evidence regarding the impact of the 2p+1 and 3p+0 dosing schedules on equity was not assessed; however, recommendations do note that achieving high and equitable coverage with 3 doses of PCV would be an important consideration when choosing the vaccination schedule.

ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-vention* ☐	*Com-parison* ☐	*Both* ☒	*Neither* ☐	*Un-clear* ☐	Both PCV immunization schedules (2p+1 and 3p+0) are considered viable options for key stakeholders; however, countries should assess which schedule could better facilitate disease protection while maintaining appropriate levels of PCV coverage in order to make a decision about which schedule to use. Alignment of the PCV schedule with the other vaccines administered in the national program is a priority consideration.	
	Which option is acceptable to target groups?	*Inter-vention* ☐	*Com-parison* ☐	*Both* ☒	*Neither* ☐	*Un-clear* ☐	It is presumed that either schedule will be acceptable to the target group since both schedules require an equal number of health care visits and injections.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐	*Probably No* ☐	*Un-certain* ☐	*Probably Yes* ☐	*Yes* ☒	*Varies* ☐	Both schedules are considered generally feasible to implement and have been successfully implemented in countries across all income levels. The question under consideration is whether a 2+1 schedule offers additional benefits in terms of impact. However, national programs are cautioned that they should take programmatic issues into consideration, especially the ability to achieve high and equitable coverage with the third dose, irrespective of the schedule they choose. Providers: It is predicted that both schedules have relatively similar costs	Decisions about which schedule to use should take into consideration the programmatic suitability of such an intervention, and the ability for the target population of that region to access health clinics at the given times for vaccine administration, especially for subpopulations with least coverage, least access to care, and least timely vaccination.

				associated with health care worker training and logistical considerations. Target population: Both schedules require the same number of visits to complete, thus it is predicted the target population would not strongly prefer a particular schedule. However, it may be possible that completing the schedule in early infancy rather than a booster in late infancy may be preferred for some caregivers.		
Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences of both intervention and comparison *clearly outweigh* undesirable consequences in most settings ☒	
Type of recommendation	We recommend the intervention ☒	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations		We recommend the comparison ☒	We recommend against the intervention and the comparison ☐	

Recommendation (text)	For administration of PCV to infants, WHO recommends a 3-dose schedule administered either as 2p+1 or as 3p+0, starting as early as 6 weeks of age. In choosing between the 2p+1 and 3p+0 schedules, countries should consider programmatic factors, including timeliness of vaccination and expected coverage. The 2p+1 schedule has potential benefits over the 3p+0 schedule, when programmatically feasible, as higher antibody levels are induced in the second year of life, which may be important in maintaining herd immunity, although no high-quality evidence is available. If the 3p+0 schedule is used, a minimum interval of 4 weeks should be maintained between doses. If the 2p+1 schedule is selected, an interval of ≥8 weeks is recommended between the 2 primary doses, but the interval may be shortened if there is a compelling reason to do so, such as timeliness of receipt of the second dose and/or achieving higher coverage when a 4-week interval is used. For the 2p+1 schedule, the booster dose should be given at 9–18 months of age, according to programmatic considerations; there is no defined minimum or maximum interval between the primary series and the booster dose.
Implementation considerations	For countries that have yet to introduce PCV, decisions regarding the choice of schedule should take into consideration operational and programmatic issues, such as timeliness of vaccination, the coverage expected to be achieved at the third dose, and pneumococcal disease age distribution patterns, if known. Low population vaccine coverage at visits occurring between 9-12 months of age or later may warrant the use of a 3p+0 schedule.
Monitoring and evaluation	WHO recommends that the epidemiological impact of PCV be carefully monitored in sustained, high-quality sentinel and population-based surveillance for pneumococcal disease and in periodic NP carriage surveys. Such surveillance and surveys should be conducted to monitor changes in disease and the circulation of pneumococcal serotypes in the community after use of different PCV products at different dosing schedules and in different geographical and epidemiological settings with different pneumococcal disease burdens and transmission. Ideally, surveillance should be started at least 1–2 years before introduction of PCV and be continued indefinitely but at least for 5 years after introduction.
Research priorities	Additional research should be conducted on: (1) further assessment of vaccine impact, duration of protection and indirect effects of different dosing schedules; (2) serotype replacement; (3) further establishment of serotype-specific immune correlates of protection against IPD in different transmission settings; (4) the epidemiology of pneumococcal outbreaks, particularly epidemics of serotype 1 disease, including use of PCV to prevent or respond to outbreaks; (5) the impact of PCV on antimicrobial use and resistance; and (6) comparison of a 1-dose versus a 2-dose catch-up schedule for children >12 months of age.

[1] Wahl B, O'Brien K, Greenbaum A, Liu L, Chu Y, Majumder A, et al. Burden of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000–15. Volume 6, ISSUE 7, Pe744-e757, July 01, 2018
[2] Black RE, Levin C, Walker N, Chou D, Liu L, Temmerman M. Reproductive, maternal, newborn, and child health: key messages from Disease Control Priorities 3rd Edition. Lancet 2016;388:2811–24. doi:10.1016/S0140-6736(16)00738-8.
[3] VIEW-hub n.d. http://view-hub.org/viz/ (accessed February 19, 2017).