SAGE Evidence to recommendation framework

Pneumococcal Conjugate Vaccine PICO 2: Product Choice 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: Is the impact or effectiveness of PCV10 and PCV13 (using either WHO recommended dosing schedules) different?

Population: (a) Vaccinated children (direct effects); (b) unvaccinated older children and adults (indirect effects).
Intervention: PCV10 administration in infants <2 years of age using either WHO recommended dosing schedules (2p+1 or 3p+0)
Comparison(s): PCV13 administration in infants <2 years of age using either WHO recommended dosing schedules (2p+1 or 3p+0)
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.

Current data reporting immunogenicity, and impact on carriage and disease from settings using either PCV10 or PCV13 with either 2p+1 or 3p+0 schedules were assessed to determine whether differential impact between the products existed that would warrant a revision to the 2012 WHO recommendations

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Un-certain*	*Yes*	*Varies by setting*	The two products, PCV10 and PCV13, each contain antigens from 10 common serotypes. PCV13 contains 3 additional antigens (type 3, 6A and 19A). Currently there is no WHO position on a preference for a specific PCV-product. Countries make these decisions for a product based on local epidemiological and programmatic considerations. With this review, countries should receive further guidance in their	PCV 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.
		☐	☐	☒	☐		

					choice of product for their immunization schedule.	
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☐	*Varies* ☒	The review of serotype specific data on immunogenicity, and impact on IPD, and NP carriage, demonstrated that both products PCV 10 and PCV 13 exhibited overall impact on the outcomes. The evidence does not conclude that PCV13 has a consistent or substantial impact on serotype 3. The evidence demonstrates that PCV10 has some impact on serotype ST6A and there is mixed evidence, for and against, PCV10 impact on ST19A among immunized children. In epidemiologic settings where there is substantial burden attributable to ST19A and ST6C, it is possible that PCV13 may have added benefit. The following is a more detailed description of conclusions by outcome and serotype group **Immunogenicity** Evidence is from both single product and head-to-head studies of the two products. *VT Serotypes* Both PCV10 and PCV13 induce antibodies against the serotypes common across the two vaccines. Although there are small differences in antibody response between the two products for these serotypes, in general, PCV10 and PCV13 have comparable, albeit not identical, immunogenicity. The	Impact of PCV10 is similar to that of PCV13 across different subgroups of age, gender, race, and socioeconomic status. Both vaccines exhibit comparable impact and effectiveness overall on clinical outcomes; however, in settings of high ST19A or ST6C burden, PCV13 may lead to greater reductions than PCV10, as these serotypes are contained in PCV13 and cross protection from serotypes in PCV10 did not appear to offer the same magnitude of benefit as those observed from using PCV13.

				clinical implications, if any, for the common serotypes have not been established. <u>Serotype 3</u> PCV13 induced an immune response to ST3 (documented by serotype specific IgG GMCs and the proportion of vaccine recipients with a concentration above the correlate of protection). PCV10 contains neither ST3 nor any cross-reactive serotypes, and therefore is not expected to induce an immune response to this serotype. Consequently, PCV10 studies, in general, do not measure immunogenicity against this serotype. <u>Serotype 6A</u> Both PCV10 and PCV13 induce an antibody response to ST6A, a serotype included in PCV13 but not in PCV10. Evidence indicates, however, that PCV13 induces higher ST6A GMCs and percentage of responders than PCV10. The clinical significance of these immunogenicity differences cannot be inferred based on the antibody levels alone. <u>Serotype 6C</u> ST6C immunogenicity data are rarely reported and thus could not be systematically assessed. <u>Serotype 19A</u> Both PCV10 and PCV13 induce an antibody response against ST19A; however, evidence indicates that PCV13 induces higher ST19A GMCs and percentage of responders than	

				PCV10. The clinical significance of these differences in immunogenicity cannot be inferred based on the antibody levels alone. **<u>IPD</u>** There were no head to head studies comparing the impact or effectiveness of the two products on IPD outcomes. Only single product studies were assessed. <u>*VT Serotypes*</u> Available evidence indicates both products are effective in reducing overall vaccine type IPD as a whole among both vaccinated individuals and those who remain unvaccinated in the population (indirect effects). Although PCV13 contains three additional serotypes, there is currently insufficient evidence to determine whether there is any differential impact on overall IPD burden (vaccine and non-vaccine type disease combined) between the two products. <u>Serotype 3 IPD</u> As expected, PCV10 use did not result in a reduction in ST3 IPD in vaccine-eligible or non-eligible age groups, because the vaccine does not contain ST3. Evidence for direct or indirect reduction in ST3 IPD following PCV13 was inconclusive with the majority of studies showing impact on ST3 IPD in neither vaccine eligible cohorts nor in unvaccinated age groups.	

				Serotype 6A IPD Data on PCV10 impact on ST6A IPD are limited but generally supportive of a direct effect. PCV13 showed a reduction in the residual low burden of ST 6A IPD that remained after the implementation of PCV7 in both vaccine eligible and non-eligible cohorts. Serotype 19A IPD Case-control effectiveness studies of PCV10 against ST19A IPD indicate some protective effect in vaccine eligible age groups, but not all reached statistical significance; however, studies evaluating population-level impact were less conclusive. Among vaccine non-eligible cohorts, evidence from PCV10- using populations shows an increase or no change in ST19A IPD rates. Effectiveness and impact against ST19A IPD in vaccinated and unvaccinated cohort were both demonstrated for PCV13. Serotype 6C IPD There are very few data on PCV10 effects against ST6C IPD. Some studies, though not all, showed a significant impact of PCV13 on ST6C IPD. **Pneumonia:** Evidence of PCV impact by product on syndromic pneumonia was available but was not considered for the development of the proposed recommendations because of confounding in the pneumonia data and	

				prioritization of serotype-specific data. The PRIME systematic review of pneumonia evidence reviewed PCV impact data by product on syndromic pneumonia (including chest x-ray confirmed pneumonia, empyema, pneumococcal pneumonia). PRIME found these data were subject to confounding, however, evidence demonstrate impact from both products, both on directly vaccinated populations and unvaccinated age groups. There are currently no data supporting differential impact on overall pneumonia between the two products. **NP Carriage** Limited head to head evidence was available to compare differential impact or effectiveness between PCV10 and PCV13 VT Serotypes. Both products were found to be effective and have impact on carriage of serotypes included in the respective vaccines as a whole; however, quantitative comparisons across studies of individual products were difficult because of substantial confounding by schedule, local epidemiology and prior PCV7 use. PCV10 was found to decrease overall VT carriage among unimmunized populations. Data reporting on indirect effects in populations that have been using PCV13 for at least three years are limited; however, recent data from the UK indicate PCV13 also	

				demonstrates indirect effects against overall VT carriage, in line with observed herd effects in unvaccinated age groups. NP carriage with vaccine serotypes is reduced by both PCV products but NVT replacement is well described such that overall pneumococcal carriage can remain unchanged. It is currently unknown whether the net effect of VT reductions and replacement with NVTs in carriage and disease would direct choice of one product over another and further investigation is needed. <u>Serotype 3</u> No significant direct or indirect effects were found for PCV10 on ST3 carriage, as expected. No conclusive direct effect of PCV13 on ST3 NP carriage was found, as results were mixed. No data were available assessing indirect effects of PCV13 on ST3 NP carriage. <u>Serotype 6A</u> Direct effects on ST6A carriage, for both products, were observed but there was insufficient evidence to conclude whether the magnitude of impact differed between products. Possible indirect effects against ST6A carriage have been demonstrated for PCV10 in studies where there was no prior use of PCV7. No evidence on indirect effects is available for PCV13 because carriage had	

				already been substantially reduced due to prior PCV7 use where this was studied. <u>Serotype 19A</u> PCV10 use was associated with statistically significant increases in ST19A carriage in some studies and non-significant increases or reductions in ST19A carriage in other studies with low pre-study carriage; statistically significant reductions in 19A carriage were observed from PCV10 in settings of high baseline carriage, though non-vaccine related reduction in 19A carriage, i.e. natural temporal variation, cannot be excluded. Evidence on indirect effects of PCV10 suggests a non-significant increase in ST19A carriage in settings where the vaccine is used. PCV13 studies demonstrated more consistent reductions in ST19A carriage in children age-eligible for vaccination in routine use settings. Analyses of PCV13 indirect effects are not available. <u>Serotype 6C</u> No clear conclusion can be drawn as availability of results for impact of vaccination on ST6C colonization were limited for both products and generally underpowered. Only one PCV13 study had sufficient power and it showed substantial reduction. Development of pneumococcal resistance to commonly used antimicrobials such as	

				penicillins, macrolides, cephalosporins and co-trimoxazole is a serious problem in some parts of the world. Since largescale introduction of pneumococcal vaccination, however, a reduction in the circulation of antimicrobialresistant strains has been observed.	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Both PCV10 and PCV13 have strong safety profiles. Evidence has indicated that while PCV10 and PCV13 confer comparable impact in pneumococcal disease overall, settings with high ST19A or ST6C burden may prioritize the use of PCV13. At the population level, replacement disease with serotypes not included in the vaccine likely occurs. An assessment of any differential magnitude of replacement disease by serotype was not part of this systematic review.	The pneumococcal epidemiology associated with the region of interest should be considered when determining which product to use.
	Balance between benefits and harms	***Favours inter-vention*** ☐	***Favours com-parison*** ☐	***Favours both*** ☒	***Favours neither*** ☐	**Unclear** ☐	Both products exhibit effectiveness and impact on overall disease and carriage and therefore there is no clear preference or advantage to using one product over the other in most settings. PCV13 may have additional benefit over PCV10 in settings with high burden attributable to particular serotypes. Both vaccines have a very good safety profile, with no serious side effects on the individuals vaccinated. At the	

			population level, some of the benefits of vaccination may be offset by increased rates of disease caused by serotypes not in the vaccine. The review did not analyze any difference between the two products. The potential incremental benefit of one product over the other was assessed to be small in most settings.	
	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* ☒	GRADE tables assessing the strength of evidence comparing the relative impact of PCV10 and PCV13 on immunogenicity, carriage and disease are published with this position paper. The evidence indicating safety of PCV was determined to be strong.	
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* ☐	Both vaccines would be most beneficial in infants and young children who have the highest rates of disease from the serotypes contained in the vaccines. Older children and adults, especially the elderly will benefit indirectly through reduced transmission of Streptococcus pneumoniae. There is substantial certainty that either product will confer high public health benefit. Although some incremental benefit might be achieved with PCV13, especially in settings with substantial ST19A or ST6C disease, the potential limitations of PCV10 use are unlikely to be substantial.	

				No evidence is available though it is assumed that in general there may be possibly important uncertainty or variability with preference to the vaccine covering a larger number of serotypes.	
	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 product. Evidence of the values and preferences of individuals within the target population for PCV immunization were not reviewed, and thus a systematic qualitative assessment of these values and preferences of the target group should be conducted in the future.	Vaccination with either PCV will be beneficial for both privileged and disadvantaged populations. All critical or relevant outcomes were measured. It is possible in settings of vaccine hesitancy in target populations, additional advocacy may be needed for either product.
RESOURCE USE	Are the resources required small?	*No* ☐ *Un-certain* ☐ *Yes* ☐	*Varies* ☒	Costing data of PCV products were not systematically reviewed, but the costs associated with PCV immunization vary by country and the product used, and on the economic strata to which the country belongs. The programmatic costs may also vary depending on the product packaging and presentation selected for use in the national programme. However, they are not expected to vary substantially between the two products, provided a similar product presentation is used. Both products have, or	

						are likely to have very similar product presentations.	
	Cost-effectiveness	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Cost-effectiveness of PCV10 and PCV13 was not systematically assessed. Such an assessment would need to be carried out at the national level. The comparative cost- effectiveness between the two products may vary depending on the country context, but each product is cost-effective in of itself.	Available data from several countries across different economic strata have shown PCVs to be highly cost-effective and in most settings, cost saving. Global analysis of cost- effectiveness in low and middle income countries that was used in support of the existing position papers on PCV indicated that both vaccines would be highly cost-effective.
EQUITY	What would be the impact on health inequities?	*Increased* ☐	*Un-certain* ☐	*Reduced* ☒	*Varies* ☐	Pneumococcal disease is more common among socially and economically disadvantaged groups. These groups also carry a disproportionate mortality burden and stand to gain the most from vaccination. Available data show that PCV is likely to provide the highest benefits to the disadvantaged populations belonging to the lower socio-economic strata since they carry a disproportionate burden of disease.	Impact of PCV vaccination on equity and discrimination were not systematically assessed, although the high price of both PCV products can potentially inhibit the ability for lower or middle income countries to sustain PCV immunization.

				There is no specific equity issue regarding product choice, except if there is differential disease burden from serotype ST19A or ST6C for which the evidence suggests PCV13 has more impact than PCV10.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-vention* ☐ | *Comparison* ☐ | *Both* ☒ | *Neither* ☐	*Un-clear* ☐	Both PCV products are considered highly effective options. While there may be a perception, which could influence the acceptability of stakeholders, that products containing a greater number of serotypes will demonstrate higher impact on pneumococcal clinical outcomes, those trends may not be observed in all settings due to the serotype distribution of a particular setting.	
	Which option is acceptable to target groups?	*Inter-vention* ☐ | *Comparison* ☐ | *Both* ☒ | *Neither* ☐	*Un-clear* ☐	Both products are currently in extensive use globally and have been well accepted by the target populations.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒	*Varies* ☐	Both products are currently being extensively used, including in low income countries. Both vaccines are likely programmatically feasible as PCV10 and PCV13 can each be delivered at the same visit as other infant vaccinations; thus PCV immunization with	.

			one or the other product does not entail additional health care visits.		
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)	Both PCV10 and PCV13 have substantial impact against pneumonia, vaccine-type IPD and NP carriage. There is at present insufficient evidence of a difference in the net impact of the 2 products on overall disease burden. PCV13 may have an additional benefit in settings where disease attributable to ST19A or ST6C is significant. The choice of product to be used in a country should be based on programmatic characteristics, vaccine supply, vaccine price, the local and regional prevalence of vaccine serotypes and antimicrobial resistance patterns .				

Implementation considerations	Local or regional pneumococcal epidemiology including antimicrobial resistance patterns, programmatic characteristics, vaccine supply, and vaccine price should all be considered when implementing a PCV immunization programme.
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).