SAGE evidence to recommendations table[i]:
Pneumococcal Conjugate Vaccine (PCV)
PICO 1: Dosing Schedule Impact

When available, please refer to background papers on the underlying evidence. *The evidence made available to SAGE to support their recommendations on the use of pneumococcal conjugate vaccine can be found in the PRIME Report on the WHO SAGE website.*

Question:

How does PCV administered to healthy children in a 2p+1 schedule compare with the vaccine administered in a 3p+0 schedule, with respect to immune response in vaccinated children and impact on clinical outcomes (IPD, pneumonia, and mortality), and nasopharyngeal carriage in the vaccinated children as well as unvaccinated age groups through indirect protection?

Population: Vaccinated children; unvaccinated older children and adults.
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
VS.
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:
IgG response – mean GMC and percent responders in immunized infants for vaccine- serotypes (VT)
Mortality – vaccine effectiveness and/or change in mortality rates, pre/post vaccination, for all-cause mortality, pneumonia mortality, and IPD mortality for directly immunized and unimmunized populations through indirect effects; 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 among directly immunized and unimmunized populations through indirect effects.
Pneumonia – vaccine effectiveness and/or change in incidence, pre/post vaccination, of either clinical pneumonia or chest x-ray (CXR) confirmed pneumonia among directly immunized and unimmunized populations through indirect effects
Carriage – vaccine effectiveness and/or change in incidence, pre/post vaccination, of vaccine type or serotype specific pneumococcal carriage among directly immunized and unimmunized populations through indirect effects

Background:

S. pneumoniae causes a variety of diseases, ranging from deadly invasive disease and pneumonia to less severe non-invasive diseases such as sinusitis and otitis media; pneumococcus is carried in the nasopharynx, usually without causing any overt disease. Though pneumococcal infections can be treated with antibiotics if care is adequate and sought in a timely fashion, infant vaccination is the most effective way to prevent infections and reduce the burden, mortality and sequelae both within the child and adult populations.

Pneumococcal conjugate vaccines (PCVs) have been used since 2000, with the introduction of PCV7. PCV10 and PCV13 products have since been licensed and introduced; both are prequalified by WHO. PCV7 is no longer produced. PCV introduction and coverage in lower income countries began in 2009 and has continued to increase since then as a result of Gavi support. WHO has recommended that PCV10 and PCV13 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.

The 2012 WHO position paper expressed no preference for product or schedule, though individual countries were encouraged to make these decisions based on local epidemiological and programmatic considerations. 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.

Current data reporting PCV immunogenicity, and impact on carriage and disease from settings using either schedule and either PCV10 or PCV13 were assessed to determine whether there was differential impact by schedule 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* ☐ *Uncertain* ☐ *Yes* ☒ *Varies by setting* ☐	The global burden of pneumococcal disease remains high though it has been substantially reduced, in part as a result of	Global PCV introductions have dramatically increased in the past 7

			PCV introduction. In 2015, there were an estimated 335,000 deaths among children under five (294,000 deaths among HIV negative children) attributed to pneumococcal disease[1]. Pneumonia remains a predominant cause of death among children, particularly in low and middle-income countries (16% of total deaths from these countries)[2]. Pneumococcus is a leading etiology of pneumonia deaths. Of pneumococcal attributable deaths, approximately 80% are due to pneumonia, and 12.8% are due to meningitis. The pneumococcal mortality rates vary significantly by global region, with the highest mortality rates (>200 deaths per 100,00 children) occurring predominantly in central and sub-Saharan Africa. Though 141 out of 194 countries have introduced PCV, coverage levels are disparate across regions and approximately 14 countries have PCV coverage of <60%, predominantly in countries in sub-Saharan Africa and Southeast Asia. Information and guidance that would support decisions on vaccine introduction and optimize their impact will lead to significant public health benefits[3].	years, particularly since Gavi began supporting PCV rollout in low income countries. India has recently begun subnational introduction of PCV13 in 2017. PCV impact on pneumococcal disease in India is expected to have substantial impact on the global burden of pneumococcal disease because of the country's large birth cohort and substantial rate of pneumococcal disease. 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.

BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the interventions</u> Are the desirable anticipated effects large?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	PCV has demonstrated direct efficacy against vaccine serotype invasive pneumococcal disease that exceeds 80% in most settings. Substantial evidence in the routine use settings has demonstrated very high indirect protection of unimmunized age groups to the point of near elimination of vaccine serotypes in some epidemiologic settings. At the global level, approximately 190,000 pneumococcal deaths among children under 5 years of age are estimated to have been averted from 2000 to 2015 as a result of PCV. Dosing optimization could enhance the desirable effects especially in settings with high pneumococcal disease burden and transmission intensity. 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. ***<u>Immunogenicity</u>*** 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.	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. serotype 1).

			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 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 serotype 1, there is strong evidence of 2p+1 impact on disease. There is much less evidence on the impact of a 3p+0 schedule on serotype 1 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.	
	<u>Harms of the interventions</u> Are the undesirable anticipated effects small?	*No* ☐ *Uncertain* ☐ *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	There is no evidence to suggest that there should be separate recommendations for subgroups based on harms. The review did not assess subgroups in whom immunogenicity of PCV may be compromised such as children with untreated HIV infection

			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 what which ever 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.	or children who are malnourished.
	Balance between benefits and harms	*Favours intervention* ☐ *Favours comparison* ☐ *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 serotype 1, there is strong evidence of 2p+1 impact on disease. There is much less evidence on the impact of a 3p+0 schedule on serotype 1 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 interventions *No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☐ *High* ☒	The overall quality of evidence to distinguish the relative merits of one or another schedule was considered GRADE 1 (IPD) to 3 (NP carriage and Immunogenicity), depending on the outcome. The GRADE tables are available on the SAGE website as background material. GRADE tables assessing safety were reported in 2012 for the SAGE meeting	

		Safety of the interventions *No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☐ *High* ☒	leading to the development of the 2012 WHO position paper on PCV immunization. The evidence indicating safety of PCV was determined to be strong (GRADE 4). Additional review of safety data in relation to the choice of schedule was not considered necessary and therefore not assessed.	

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 target populations consider the prevention of pneumococcal diseases, which constitute an important public health burden in most countries, as a very desirable outcome. Therefore, the selection of a schedule with the highest impact is an important desirable outcome. Finding that there is no compelling evidence to recommend one schedule over another addresses the desirability of the outcome.	The majority of caregivers likely view avoiding pneumococcal disease with high importance because they would want to avoid their child from becoming severely ill or costs associated with severe infection

	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 It is possible in settings of vaccine hesitancy in target populations, additional advocacy may be needed.

RESOURCE USE	Are the resources required small?	*No* ☐ *Uncertain* ☐ *Yes* ☐ *Varies* ☒	There are no 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. The current assessment was only to determine whether the choice of schedule would provide any further benefits in terms of maximizing the impact.	It is important to maintain and sustain PCV immunization efforts globally. The data on the impact and effectiveness of the available PCV products used in one or the other schedule would be important when countries consider sustaining the vaccines in their national immunization schedule.
	Cost-effectiveness	*No* ☐ *Uncertain* ☐ *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* ☐ *Uncertain* ☐ *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)?	*Intervention* ☐ *Comparison* ☐ *Both* ☒ *Neither* ☐ *Unclear* ☐	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 group?	*Intervention* ☐ *Comparison* ☐ *Both* ☒ *Neither* ☐ *Unclear* ☐	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	Are the interventions feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	Feasibility: 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 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.	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.

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 *clearly outweigh* undesirable consequences in most settings ☒
Type of recommendation	We recommend the interventions* ☒ *note: SAGE PCV WG recommends either the 2p+1 and 3p+0 schedules	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)	**Schedule Choice Recommendations:** 1. For PCV administration to infants, at least 3 doses of vaccine, administered **either** as 2 primary doses plus booster (2p+1) or 3 primary doses without a booster (3p+0), are recommended. • For countries that have yet to introduce PCV, decisions regarding the choice of schedule should take into consideration operational and programmatic issues, including 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. • Once a program has been initiated, schedule switching is not necessary unless one or more factors that led to the original choice of schedule changes substantially. 2. A dosing interval of 8 weeks between the first two doses of a 2p+1 schedule and a dosing interval of at least 4 weeks for a 3p+0 schedule is recommended. However, the 8-week interval recommended for the 2p+1 schedules may be shortened if there is compelling reason to do so, such as timeliness in receipt of the second dose and/or higher coverage that may be achieved with the schedule. The dosing interval between primary doses within each schedule should not be shorter than 4 weeks. 3. The timing of the booster dose should be selected to maximize coverage. The selected age for administration of the booster dose in most programs is at 9, 12, 15 or 18 months, depending on operational and programmatic factors, including the timing of vaccination contacts in the national

	immunization schedule for other vaccines. There is insufficient evidence to inform optimal timing of 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	Based on current evidence and remaining evidence gaps, the WG proposes several recommendations to guide future surveillance and research efforts. *3.5.1 Surveillance Recommendations* 1. High quality, long-term, post-introduction, serotype-specific pneumococcal surveillance is needed in a representative number of settings.

	2. ***Methodology of disease surveillance:*** Pneumococcal surveillance can be conducted as population-based or only in sentinel health facilities (which is not population-based). While population-based surveillance is required to document disease impact and serotype replacement, non-denominator based IPD surveillance in sentinel sites provides additional information on the distribution of serotypes in the PCV routine use era and a qualitative measure of PCV impact. Population-based surveillance may not currently be feasible in a sufficient number of representative countries and sites, so high quality sentinel site surveillance can provide useful complementary data. In addition to disease surveillance, periodic carriage surveillance could offer insight on the case-carrier ratio and ongoing circulation of vaccine serotypes. Pneumococcal surveillance does not need to be conducted in every country, but SAGE encourages countries to conduct high-quality surveillance with the ambition for surveillance and laboratory capacity to be strengthened everywhere. 3. ***NP colonization surveillance:*** Since pneumococcal colonization is a critical driver of population level disease and PCV impact, periodic monitoring of carriage is an important adjunct to disease surveillance. It offers a means to interpret pneumococcal disease and syndromic surveillance findings, and provides important insights into case-carrier ratios, ongoing circulation of vaccine serotypes, and a means to monitor the PCV program implementation. 4. ***Diseases under surveillance:*** Pneumococcal surveillance can monitor not only IPD, but also other syndromes caused by pneumococcus, such as meningitis, pneumonia, and sepsis. At a minimum, we recommend that meningitis be monitored due to the severe nature of the disease, the need for

	identification of etiology for clinical management, and the higher yield of pathogens from cerebrospinal fluid, compared with the yield from blood cultures which are usually obtained from children with pneumonia and sepsis. 5. ***Duration of surveillance:*** Surveillance should be sustained indefinitely during the post-introduction period. The minimum duration is 5 years following PCV introduction, as evidenced by the time required for a plateau in IPD serotype replacement and PCV impact on overall IPD as concluded by a previously published global analysis. However, changes in distribution and pneumococcal disease impact are still being seen in many settings up to 17+ years following PCV introduction and use. 6. ***Location of surveillance:*** Surveillance should be conducted in a representative number of settings to monitor changes in disease following the use of different PCV products, in different dosing schedules, and in different geographic and epidemiologic settings with different pneumococcal burden and transmission. 7. WHO should periodically review global pneumococcal surveillance data to identify specific evidence gaps that need to be addressed through additional surveillance or special studies, including periodic cross-sectional studies on NP carriage prevalence.
Research priorities	1. Additional data from head-to-head studies of schedules are needed to address differences in biological outcomes such as NP carriage, immunogenicity, duration of protection, and transmission dynamics, including herd immunity.

	2. Coverage achieved by different PCV schedules, including the timeliness of vaccination, and the age of vaccination should be evaluated. 3. Serotype specific quantitative immune correlates of protection against invasive pneumococcal disease should be investigated from different epidemiologic settings. These can be carried out by using data from serotype specific vaccine effectiveness studies, with nested immunogenicity data. 4. Studies to evaluate the serotype specific duration of protection from different schedules are needed, especially to inform modeling efforts on schedule optimization. 5. Modeling studies should be undertaken to systematically evaluate key drivers of the relative benefits of 2p+1 vs 3p+0 schedules. Such drivers may include local epidemiology of carriage and disease, demographic structure, vaccine efficacy, timeliness and booster dose coverage. These models should further help quantifying scenarios under which one schedule can achieve a discernably higher impact than the other.

[i] This Evidence to Recommendation table is based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel). http://www.decide-collaboration.eu/WP5/Strategies/Framework

[1] Wahl B, O'Brien K, Greenbaum A, Liu L, Chu Y, Majumder A, et al. Global, regional, and national burden of Streptococcus pneumoniae and Haemophilus influenzae tybe b in children in he era of conjugate vaccines: updated estimates from 2000-2015. Submitt Publ 2017.

[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).

SAGE evidence to recommendations table[i]
Pneumococcal Conjugate Vaccine
PICO 2: Product Choice Impact

The evidence that was made available to SAGE to support their recommendations on the use of pneumococcal conjugate vaccine can be found in the PRIME Summary Report on the WHO website.

Question: *Is the impact or effectiveness of PCV10 and PCV13 (using either WHO recommended dosing schedules) different, based on data reporting immune response following vaccination, and impact on NP Carriage and clinical outcomes (IPD, pneumonia and mortality) in vaccinated children as well as unvaccinated age groups through indirect protection?*

Population: Vaccinated children; unvaccinated older children and adults.

Intervention:
PCV10 administration in infants <2 years of age using either WHO recommended dosing schedules (2p+1 or 3p+0)
VS.
PCV13 administration in infants <2 years of age using either WHO recommended dosing schedules (2p+1 or 3p+0)

Outcomes:
IgG response – mean GMC and percent responders in immunized infants for vaccine- serotypes (VT)
Mortality – vaccine effectiveness and/or change in mortality rates, , for all-cause mortality, pneumonia mortality, and IPD mortality for directly immunized and unimmunized populations; change in case fatality ratios, pre/post vaccination, for pneumonia and IPD.
Invasive Pneumococcal Disease (IPD) – vaccine effectiveness and/or change in incidence, pre/post vaccination, of VT or serotype specific IPD among directly immunized and unimmunized populations through indirect effects.
Pneumonia – vaccine effectiveness and/or change in incidence, pre/post vaccination, of either clinical pneumonia or chest x-ray (CXR) confirmed pneumonia among directly immunized and unimmunized populations through indirect effects
Carriage – vaccine effectiveness and/or change in incidence, pre/post vaccination, of vaccine-type or serotype specific pneumococcal carriage among directly immunized and unimmunized populations through indirect effects

Background:

S. pneumoniae causes a variety of diseases, ranging from deadly invasive disease and pneumonia to less severe non-invasive diseases such as sinusitis and otitis media; pneumococcus is carried in the nasopharynx, usually without causing any overt disease. Though pneumococcal infections can be treated with antibiotics if care is adequate and sought in a timely fashion, infant vaccination is the most effective way to prevent infections and reduce the burden, mortality and sequelae both within the child and adult populations.

Pneumococcal conjugate vaccines (PCVs) have been used since 2000, with the introduction of PCV7. PCV10 and PCV13 products have since been licensed and introduced; both are prequalified by WHO. PCV7 is no longer produced. PCV introduction and coverage in lower income countries, began in 2009 and has continued to increase since then as a result of Gavi support. WHO has recommended that PCV10 and PCV13 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. The 2012 WHO position paper did not state any preference for a specific product or schedule, though individual countries were encouraged to make these decisions based on local epidemiological and programmatic considerations.

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
		No	*Uncertain*	*Yes*	*Varies by setting*		
PROBLEM	Is the problem a public	☐	☐	☒	☐	The global burden of pneumococcal disease remains high though it has been	Global PCV introductions have dramatically increased in the past 7 years, particularly since

	health priority?		substantially reduced, in part as a result of PCV introduction. In 2015, there were an estimated 335,000 deaths among children under five (294,000 deaths among HIV negative children) attributed to pneumococcal disease[1]. Pneumonia remains a predominant cause of death among children, particularly in low and middle-income countries (16% of total deaths from these countries)[2]. Pneumococcus is a leading etiology of pneumonia deaths. Of pneumococcal attributable deaths, approximately 80% are due to pneumonia, and 12.8% are due to meningitis. The pneumococcal mortality rates vary significantly by global region, with the highest mortality rates (>200 deaths per 100,00 children) occurring predominantly in central and sub-Saharan Africa. Though 141 out of 194 countries have introduced PCV, coverage levels are disparate across regions and approximately 14 countries have PCV coverage of <60%, predominantly in countries in sub-Saharan Africa and Southeast Asia.	Gavi began supporting PCV rollout in low income countries. India has recently begun subnational introduction of PCV13 in 2017. PCV impact on pneumococcal disease in India is expected to have substantial impact on the global burden of pneumococcal disease because of the country's large birth cohort and substantial rate of pneumococcal disease. 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.

			Information and guidance that would support decisions on vaccine introduction and optimize their impact will lead to significant public health benefits[3]. sub-Saharan Africa and Southeast Asia. Information and guidance that would support decisions on vaccine introduction and optimize their impact will lead to significant public health benefits.	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the interventions</u> Are the desirable anticipated effects large?	*No* ☐ *Uncertain* ☐ *Yes* ☐ *Varies* ☒	The two products, PCV10 and PCV13, each contain antigens from 10 common serotypes. PCV13 contains 3 additional antigens (type 3, 6A and 19A). The review of serotype specific data on immunogenicity, and impact on IPD, and NP carriage, demonstrated that both products 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 6A and there is mixed evidence, for and against, PCV10 impact on 19A among immunized children. In epidemiologic settings where	Impact of PCV10 is similar to that of PCV13 across different subgroups of age, gender, race, and socioeconomic status; however, in settings of high ST19A burden, PCV13 may offer added benefits compared to PCV10. Both vaccines exhibit comparable impact and effectiveness overall on clinical outcomes; however, in settings of high ST19A or 6C burden, PCV13 may lead to greater reductions than PCV10, as these serotypes are contained in PCV13 and cross protection

			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 clinical implications, if any, of these relatively small differences in immunogenicity for the common serotypes have not been established. *Serotype 3* PCV13 induced an immune response to ST3 (documented by serotype specific IgG GMCs and	from serotypes in PCV10 did not appear to offer the same magnitude of benefit as those observed from using PCV13

			the proportion of vaccine recipients with a concentration above the correlate of efficacy). 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. *Serotype 6A* 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. *Serotype 6C* ST6C immunogenicity data are rarely reported and thus could not be systematically assessed. *Serotype 19A* 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. ***IPD*** *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.* *VT Serotypes* Available evidence indicates both products are effective in reducing overall vaccine type IPD caused by serotypes within each vaccine as a whole among both vaccinated individuals and those who remain unvaccinated in the population. 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. *Serotype 3 IPD* 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 type 3 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. Data assessing PCV13 impact on ST6A IPD were predominantly in settings of prior PCV7 use, with very low levels of residual 6A IPD. 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 Syndrome Evidence of PCV impact by product on syndromic pneumonia was available but was not used by the WG to develop the proposed recommendations because of confounding in the pneumonia data and the WG's decision to prioritize review 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* *<u>VT Serotypes</u>* 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 (Miller et al, personal communication), in line with observed herd effects in unvaccinated age groups. NP carriage with vaccine serotypes is reduced by both PCV products but non-vaccine type 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. *Serotype 3* 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. *Serotype 6A* Direct effects on ST 6A 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. *Serotype 19A* 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. *Serotype 6C* 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.	
	Harms of the interventions Are the undesirable anticipated effects small?	*No* ☐ *Uncertain* ☐ *Yes* ☐ *Varies* ☒	Both PCV10 and PCV13 have strong safety profiles. There is no preference for one or another product on the basis of safety. 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	In settings where ST6C or ST19A constitute significant public health problems, PCV13 may have added benefit. The pneumococcal epidemiology associated with the region of interest should be considered when determining which product to use.

			assessment of any differential magnitude of replacement disease by serotype was not part of this systematic review.	
	Balance between benefits and harms	*Favours intervention* ☐ *Favours comparison* ☐ *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 high safety profile, with no serious deleterious 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 differential 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 interventions *No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☐ *High* ☒ Safety of the interventions *No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☐ *High* ☒	GRADE tables assessing the strength of evidence comparing the relative impact of PCV10 and PCV13 on immunogenicity, colonization and disease are available on the SAGE website as background material. The strength of evidence was considered to be GRADES 1(IPD), 2(NP Carriage), and 3(Immunogenicity) GRADE tables assessing safety were reported for the SAGE meeting leading to the development of the 2012 WHO position paper on PCV immunization. The evidence indicating safety of PCV was determined to be strong (GRADE 4). Additional review of safety data in relation to the choice of product was not considered necessary.	

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 the organisms. 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 19A or 6C disease, the potential limitations of PCV10 use are unlikely to be substantial.	

	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 preferences of individuals within the target populations was not assessed.	Vaccination with either PCV will be beneficial for both privileged and disadvantaged populations. All critical or relevant outcomes were measured. 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. 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* ☐ *Uncertain* ☐ *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.	Each country will need to make a decision regarding optimal product choice. The evidence provided will help inform such decisions at the national level.
	Cost-effectiveness	*No* ☐ *Uncertain* ☐ *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. 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. The comparative cost-effectiveness between the two products may vary depending on the country context, but each product is cost-effective in of itself.	
EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *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. 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. There is no specific equity issue regarding product choice, except if there is differential disease burden from serotype 19A or 6C for which the evidence suggests PCV13 is more impactful than PCV10.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Intervention* ☐ *Comparison* ☐ *Both* ☒ *Neither* ☐ *Unclear* ☐ *Both PCV10 and PCV13 interventions are considered acceptable to stakeholders	Both PCV products are considered highly effective options. While there may be a perception 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. Countries should assess which product could better facilitate disease protection given programmatic considerations, supply, cost, and the baseline serotype specific burden in their country in order to make a decision about which product to use.	

	Which option is acceptable to target group?	*Intervention* ☐ *Comparison* ☐ *Both* ☒ *Neither* ☐ *Unclear* ☐	Both products are currently in extensive use globally and have been well accepted by the target populations	
FEASIBILITY	Are the interventions 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 does not entail additional health care visits.	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 if they do not receive additional financial support.

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 *clearly outweigh* undesirable consequences in most settings ☒ Both PCV10 and PCV13 are of substantial benefit; evidence does not result in a product preference
Type of recommendation	We recommend the interventions ☒ *SAGE WG recommends either PCV10 or PCV13	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	*Product Choice Recommendations* 1. Both vaccines have impact against overall vaccine-type disease and carriage. PCV13 may have additional benefit in settings where disease attributable to ST19A or ST6C constitutes a significant public health problem; however, there is at present no supportive evidence of different net impact on overall disease burden between the two products.				

	2. The country-level product choice should consider programmatic characteristics, vaccine supply, vaccine price, local/regional vaccine serotype prevalence, antimicrobial resistance patterns among vaccine serotypes. 3. Given the relative comparability of existing PCV products and programmatic challenges that may be associated with product switching, once a program has been initiated product switching is not recommended unless one or more factors that led to the original choice of product changes substantially (see Recommendations 1 and 2). 4. Interchangeability between PCV10 and PCV13 has not been studied in the 2 or 3-dose *primary* series; however, limited evidence suggests that products confer comparable immunogenicity for the *booster* dose regardless of which product was used in the primary series. Therefore, when a 2- or 3-dose primary immunization series is initiated with one of these vaccines, ideally the remaining doses needed to complete the primary series should be administered with the same product. If it is not possible to complete the primary series with the same product, the other vaccine should be used, rather than miss a primary or booster dose. There is no evidence to suggest that restarting the vaccination series is necessary if a product switch occurs, therefore restarting the series is not recommended even for the primary series.
Implementation considerations	Local or regional pneumococcal epidemiology, programmatic characteristics, vaccine supply, and vaccine price should all be considered when implementing a PCV immunization programme
Monitoring and evaluation	*Surveillance Recommendations* 1. High quality, long-term, post-introduction, serotype-specific pneumococcal surveillance is needed in a representative number of settings. 2. ***Methodology of disease surveillance:*** Pneumococcal surveillance can be conducted as population-based or only in sentinel health facilities (which is not population-based). While population-based surveillance is required to document disease impact and serotype replacement, non-denominator based IPD surveillance in

	sentinel sites provides additional information on the distribution of serotypes in the PCV routine use era and a qualitative measure of PCV impact. Population-based surveillance may not currently be feasible in a sufficient number of representative countries and sites, so high quality sentinel site surveillance can provide useful complementary data. In addition to disease surveillance, periodic carriage surveillance could offer insight on the case-carrier ratio and ongoing circulation of vaccine serotypes. Pneumococcal surveillance does not need to be conducted in every country, but SAGE encourages countries to conduct high-quality surveillance with the ambition for surveillance and laboratory capacity to be strengthened everywhere. 3. ***NP colonization surveillance:*** Since pneumococcal colonization is a critical driver of population level disease and PCV impact, periodic monitoring of carriage is an important adjunct to disease surveillance. It offers a means to interpret pneumococcal disease and syndromic surveillance findings, and provides important insights into case-carrier ratios, ongoing circulation of vaccine serotypes, and a means to monitor the PCV program implementation. 4. ***Diseases under surveillance:*** Pneumococcal surveillance can monitor not only IPD, but also other syndromes caused by pneumococcus, such as meningitis, pneumonia, and sepsis. At a minimum, we recommend that meningitis be monitored due to the severe nature of the disease, the need for identification of etiology for clinical management, and the higher yield of pathogens from cerebrospinal fluid, compared with the yield from blood cultures which are usually obtained from children with pneumonia and sepsis. 5. ***Duration of surveillance:*** Surveillance should be sustained indefinitely during the post-introduction period. The minimum duration is 5 years following PCV introduction, as evidenced by the time required for a plateau in IPD serotype replacement and PCV impact on overall IPD as concluded by a previously published global analysis. However, changes in distribution and pneumococcal disease impact are still being seen in many settings up to 17+ years following PCV introduction and use. 6. ***Location of surveillance:*** Surveillance should be conducted in a representative number of settings to monitor changes in disease following the use of different PCV products, in different dosing schedules, and in different geographic and epidemiologic settings with different pneumococcal burden and transmission. 7. WHO should periodically review global pneumococcal surveillance data to identify specific evidence gaps that need to be addressed through additional surveillance or special studies, including periodic cross-sectional studies on NP carriage prevalence. Please outline monitoring and evaluation considerations

Research priorities	1. Field data and modeling are needed to better understand the drivers of, and predictors of pneumococcal serotype replacement in disease. Specifically, potential differences in product-specific serotype replacement need to be characterized to better understand their differential impact on pneumococcal disease. 2. Head to head studies comparing immunological and carriage impact of future and existing PCV products are needed to adequately inform product and schedule choices for maximum control of pneumococcal disease. Assessment of PCV impact on carriage has additional value in predicting herd effects of vaccination and pneumococcal circulation, whereas measuring immunogenicity is important for establishing correlates of protection against IPD and carriage. 3. Studies are needed to understand the effects of maternal antibodies and maternal immunization with vaccines containing diphtheria and/or tetanus toxoid proteins on infant vaccination with PCVs containing pneumococcal polysaccharides conjugated to CRM, diphtheria, or tetanus toxoid proteins. These assessments should also include the effect of maternal vaccination on early infant PCV and diphtheria, tetanus, and pertussis (DTP) immunization in terms of optimizing timing of the first infant dose. 4. Data are needed on PCV product interchangeability to inform the effects of product switching during the primary immunization series (i.e. when programs switch PCV products) and on the use of schedules intentionally using different products to optimize impact.

[i] This Evidence to Recommendation table is based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel). http://www.decide-collaboration.eu/WP5/Strategies/Framework

[1] Wahl B, O'Brien K, Greenbaum A, Liu L, Chu Y, Majumder A, et al. Global, regional, and national burden of Streptococcus pneumoniae and Haemophilus influenzae tybe b in children in he era of conjugate vaccines: updated estimates from 2000-2015. Submitt Publ 2017.
[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).

SAGE evidence to recommendations table[i]
Pneumococcal Conjugate Vaccine (PCV)
PICO 3: Catch Up Vaccination Impact

The evidence that was made available to SAGE to support their recommendations on the use of pneumococcal conjugate vaccine can be found in the PRIME Summary Report on the WHO website.

Question:
What additional value does catch-up vaccination with 1 or 2 doses of PCV in vaccine-naïve healthy children offer as compared with vaccination of only age eligible children (as per the vaccination schedule in the country) in relation to the overall impact on pneumococcal disease?

Population: General population
Intervention: Catch-up vaccination with 1 or 2 doses of PCV in vaccine-naïve children older than the routine immunization age group defined by the national immunization program (i.e. usually the birth cohort).
Comparison(s): No catch-up vaccination (only vaccination of age-eligible children at the time of national PCV introduction)
Outcome:
Review of modelled data on the impact of PCV catch-up among different age groups under age 5 on IPD and pneumococcal NP carriage

Background:

S. pneumoniae causes a variety of diseases, ranging from deadly invasive disease and pneumonia to less severe non-invasive diseases such as sinusitis and otitis media; pneumococcus is carried in the nasopharynx, usually without causing any overt disease. Though pneumococcal infections can be treated with antibiotics if care is adequate and sought in a timely fashion, infant vaccination is the most effective way to prevent infections and reduce the burden, mortality and sequelae both within the child and adult populations.

Pneumococcal conjugate vaccines (PCVs) have been used since 2000, with the introduction of PCV7. PCV10 and PCV13 products have since been licensed and introduced; both are prequalified by WHO. PCV7 is no longer produced. PCV introduction and coverage in lower income countries began in 2009 and has continued to increase since then as a result of Gavi support. WHO has recommended that PCV10 and PCV13 be administered using either a 2p+1 or 3p+0 schedule in infants. In a 2012 position paper, WHO also recommended 2-dose catch up vaccination during the time of introduction at dosing intervals at least 2 months apart to unvaccinated children ages 12-24 months old and children ages 2-5 years old who are at high risk of infection[1]. The SAGE WG is reviewing evidence to continue optimizing catch up immunization recommendations.

Evidence regarding the impact of catch up immunization is limited across different age groups; however, the available evidence suggests PCV immunization, at the time of national introduction, for children outside the birth cohort accelerates both direct and indirect protection and thereby hastens the impact of PCV.				
	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies by setting* ☐	The global burden of pneumococcal disease remains high though it has been substantially reduced, in part as a result of PCV introduction. In 2015, there were an estimated 335,000 deaths among children under five (294,000 deaths among HIV negative children) attributed to pneumococcal disease[2]. Pneumonia remains a predominant cause of death among children, particularly in low and middle-income countries (16% of total deaths from these countries)[3]. Pneumococcus is a leading etiology of pneumonia deaths. Of pneumococcal attributable deaths, approximately 80% are due to pneumonia, and 12.8% are due to meningitis. The pneumococcal mortality rates vary significantly by global region, with the highest mortality rates (>200 deaths per 100,00	Global PCV introductions have dramatically increased in the past 7 years, particularly since Gavi began supporting PCV rollout in low income countries. India has recently begun subnational introduction of PCV13 in 2017. PCV impact on pneumococcal disease in India is expected to have substantial impact on the global burden of pneumococcal disease because of the country's large birth cohort and substantial rate of pneumococcal disease. 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.

			children) occurring predominantly in central and sub-Saharan Africa. Though 141 out of 194 countries have introduced PCV, coverage levels are disparate across regions and approximately 14 countries have PCV coverage of <60%, predominantly in countries in sub-Saharan Africa and Southeast Asia. Information and guidance that would support decisions on vaccine introduction and optimize their impact will lead to significant public health benefits[4].	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	Evidence regarding the impact of catch up immunization is limited; however, the available evidence suggests PCV immunization, for children beyond those age-eligible (i.e. the birth cohort) at the time of introduction accelerates both direct and indirect protection and, thereby, the impact of PCV. Modeling of NP carriage and IPD in Kilifi, Kenya demonstrated that at the time of PCV introduction a catch-up campaign in those under	The benefits of catch up vaccination, and the number of doses needed to optimize the effects of such vaccination, can depend on age, programmatic setting, and the epidemiology of pneumococcal disease in the population of interest. Based on the available evidence, 1 to 3 doses should be administered depending on the age of the child. 1 dose of vaccine is sufficient for those 24 months or older,

			5 years of age can accrue a greater benefit per dose administered if compared to smaller campaigns in more narrow age strata, or compared to routine infant vaccination alone[5] . No evidence was available for review on the effectiveness of PCV as a means of response to pneumococcal disease outbreaks or to supplement ineffective routine vaccination in humanitarian crises. Based on available evidence, any catch up vaccination program confers additional benefits. If logistically feasible, catch-up campaigns at the time of PCV introduction can enhance the benefit accrued per dose of PCV administered, especially in settings with high VT carriage and disease beyond infancy. PCV catch up campaigns among children may also be desirable in the post-introduction settings with a weak routine vaccination programme or when rapid disease control is sought. Example situations include settings of vaccine serotype	whereas 1 or 2 doses have been used for toddlers between 12 and 23 months. For infants under 6 months of age, 3 doses should be administered, while those between 7 and 11 months of age can have either 2 to 3 doses. Younger children should be prioritized for catch up immunization because they are at highest risk of pneumococcal disease.

			disease outbreaks or humanitarian emergency settings with high risk of pneumococcal disease. Limited evidence is available to determine whether a single dose is sufficient or whether 2 doses are required for catch up vaccination beyond infancy. The relative benefit of including various age groups in catch up programs depends on the epidemiology of disease and nasopharyngeal colonization rates in the community, in addition to cost, expected benefit, potential delays in PCV introduction as a result of the logistical challenges of a catch-up campaign, and vaccine supply.	
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐ *Uncertain* ☒ *Yes* ☐ *Varies* ☐	Serious adverse events associated with PCV immunization are rare and not expected. There are no data currently available to suggest any resulting shifts in serotype-specific pneumococcal epidemiology, or other	Evidence of potential harms or adverse events associated with catch up immunization were not available; however it is not expected that the extent of potential undesirable effects would differ significantly by subpopulations or subgroups. The effects of catch up vaccination may, however, vary

			unintended harms resulting from catch up PCV immunization..	depending on baseline disease burden and epidemiology.
	Balance between benefits and harms	*Favours intervention* ☒ *Favours comparison* ☐ *Favours both* ☐ *Favours neither* ☐ *Unclear* ☐	Though evidence is limited, data indicate clear benefits to 1 or 2 PCV doses for catch up immunization compared to no catch up immunization at time of introduction. The individual and population-level benefits of overall herd immunity and impact on pneumococcal disease in the population outweigh possible risks or harms of vaccinating in children beyond the birth cohort.	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☐ *High* ☒ Safety of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☐ *High* ☒	The SAGE WG reviewed modeled data to update catch up vaccination recommendations. Modelled data do not fit into the GRADE framework and thus there is no GRADE available for these data at this time[5]. GRADE tables assessing safety were reported for the SAGE meeting leading to the development of the 2012 WHO position paper on PCV immunization. Safety evidence	

			was not reviewed in this iteration because there are no particular safety issues that need to be addressed related to PCV. The evidence indicating safety of PCV was determined to be strong (GRADE 4).	

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 relative importance of added benefit and potential cost or rare adverse event from a PCV catch up vaccination program among the target population was not assessed; however, reports from post-introduction evaluations conducted in countries that have introduced vaccines indicate a high community demand for vaccination of children who were not age-eligible at the time of vaccine introduction.	.

	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	The evidence for population value and preferences for catch up vaccination were not systematically reviewed. However, reports from post-introduction evaluations indicate that demand for vaccination for children who were not age-eligible at the time of vaccine introduction was high.	A systematic assessment of the values and preferences among children under 5 and their caretakers regarding PCV catch up immunization was not conducted but the vaccine is used widely among advantaged and disadvantaged population and there are no reports of any difference in how the vaccines are valued by each group.

RESOURCE USE	Are the resources required small?	*No* ☐ *Uncertain* ☐ *Yes* ☐ *Varies* ☒	Data on the costs for catch up are limited and not systematically reviewed by the SAGE WG; the modeling indicates that catch up in any of the age strata under 5 years of age confers substantial efficiency of PCV dosing. Countries should assess the relative merits of the resources required for a catch up program relative to the use of those resources for other purposes.	The overall benefit of catch up vaccination and the public health need for this intervention can vary based on pneumococcal epidemiology in the population and baseline carriage. These factors should be considered when determining prioritization of interventions.
	Cost-effectiveness	*No* ☐ *Uncertain* ☒ *Yes* ☐ *Varies* ☐	Cost effectiveness data on PCV catch up immunization are not available to be systematically reviewed, but current assessments on the cost effectiveness are ongoing and should be completed within the next 2 years. Based on emerging evidence from Viet Nam, the cost effectiveness is most appropriate in settings of high vaccine type carriage and disease in the age strata between 1-5 years of age.	

EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☒ *Reduced* ☐ Varies ☐	Catch up vaccination at the time of vaccine introduction and in areas with low routine vaccination coverage, especially when conducted through a campaign approach, is meant to reduce inequities in coverage and maximize impact. This is expected to have greatest benefit for those with lowest coverage and with highest burden of disease.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Key stakeholders should consider the programmatic and financial feasibility of implementing PCV catch up immunization in the target population, as catch up vaccination programs can be highly effective and highly cost efficient, but only if such programs do not interfere with the delivery of other health services or delay the rollout of the PCV introduction program. .	
	Which option is acceptable to target group?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Information available through post-introduction evaluation reports indicate a high population demand for PCV catch up vaccination.	

FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ *Varies* ☒	Higher income countries and countries with well established health systems would be more easily able to conduct PCV catch up immunization programs. Countries with low PCV coverage or with events that acutely inhibit coverage with routine PCV would likely benefit the most from this intervention; however, the programmatic feasibility, cost, and possible additional strain on the health care providers and workers to sustain catch up vaccination should be considered. Additionally, PCV catch up vaccination efforts should be structured in such a way that the vaccine is convenient to access to maximize feasibility and acceptability from the target population.	Resource requirements to engage in and sustain catch up immunization can vary across settings and would depend on the strategy adopted to administer catch up doses. Settings where routine PCV immunizations are difficult to access may be priority areas, to maximize PCV impact and promote health equity

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 *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)	*Catch Up Recommendations* 1. Catch-up vaccination as part of PCV introduction will accelerate both direct and indirect protection and therefore accelerate PCV impact on disease, particularly in case of high VT carriage prevalence and disease burden in children aged 1 to 5 years old. 2. Catch-up vaccination with PCV can be done with 1 dose of vaccine for those initiating vaccine at age 24 months and older. For those who are 12-23 months at the time of first vaccination some programs have used 2 PCV doses separated by at least 8 weeks, and others have used 1 dose. For those initiating vaccination at age 6 months or under, a 3 dose regimen should be offered. For infants aged 7-11 months, some programmes have used 2 doses, and others have used 3 doses. If there is				

	limited availability or capacity for catch-up immunization, the youngest children should be prioritized to receive catch-up doses of PCV because of the higher pneumococcal disease risk. 3. Unvaccinated children up to 5 years of age who are at high risk for pneumococcal infection based on a medical condition (e.g. HIV infection, sickle cell disease) should receive at least 2 PCV doses separated by at least 8 weeks to assure immunogenicity. 4. In areas/communities where low vaccination coverage has permitted sustained vaccine serotype pneumococcal transmission (or disease),especially those with coverage below 50%, catch up campaigns (also termed periodic intensification of routine immunization) can be used to reduce the disease burden. 5. Catch-up vaccination to replace missed doses among individual children should be encouraged with particular focus on children at highest risk of pneumococcal disease. 6. In humanitarian or emergency situations, age-appropriate schedules of PCV vaccination should be implemented, certainly for children under 1 year of age, and usually for children up to 5 years of age as indicated by the situation, through the use of the framework for vaccination in humanitarian emergencies. Immunization of children over age 5 may be indicated in certain situations. 7. Vaccination may be considered in response to outbreaks of confirmed VT pneumococcal disease, based on the characteristics of the outbreak, including the outbreak size, duration and age group affected.

Implementation considerations	Recommendations will be made available in the standard WHO format (WHO position paper).
Monitoring and evaluation	*Surveillance Recommendations* 1. High quality, long-term, post-introduction, serotype-specific pneumococcal surveillance is needed in a representative number of settings. 2. ***Methodology of disease surveillance:*** Pneumococcal surveillance can be conducted as population-based or only in sentinel health facilities (which is not population-based). While population-based surveillance is required to document disease impact and serotype replacement, non-denominator based IPD surveillance in sentinel sites provides additional information on the distribution of serotypes in the PCV routine use era and a qualitative measure of PCV impact. Population-based surveillance may not currently be feasible in a sufficient number of representative countries and sites, so high quality sentinel site surveillance can provide useful complementary data. In addition to disease surveillance, periodic carriage surveillance could offer insight on the case-carrier ratio and ongoing circulation of vaccine serotypes. Pneumococcal surveillance does not need to be conducted in every country, but SAGE encourages countries to conduct high-quality surveillance with the ambition for surveillance and laboratory capacity to be strengthened everywhere. 3. ***NP colonization surveillance:*** Since pneumococcal colonization is a critical driver of population level disease and PCV impact, periodic monitoring of carriage is an important adjunct to disease surveillance. It offers a means to interpret pneumococcal disease and syndromic surveillance

	findings, and provides important insights into case-carrier ratios, ongoing circulation of vaccine serotypes, and a means to monitor the PCV program implementation. 4. ***Diseases under surveillance:*** Pneumococcal surveillance can monitor not only IPD, but also other syndromes caused by pneumococcus, such as meningitis, pneumonia, and sepsis. At a minimum, we recommend that meningitis be monitored due to the severe nature of the disease, the need for identification of etiology for clinical management, and the higher yield of pathogens from cerebrospinal fluid, compared with the yield from blood cultures which are usually obtained from children with pneumonia and sepsis. 5. ***Duration of surveillance:*** Surveillance should be sustained indefinitely during the post-introduction period. The minimum duration is 5 years following PCV introduction, as evidenced by the time required for a plateau in IPD serotype replacement and PCV impact on overall IPD as concluded by a previously published global analysis. However, changes in distribution and pneumococcal disease impact are still being seen in many settings up to 17+ years following PCV introduction and use. 6. ***Location of surveillance:*** Surveillance should be conducted in a representative number of settings to monitor changes in disease following the use of different PCV products, in different dosing schedules, and in different geographic and epidemiologic settings with different pneumococcal burden and transmission. 7. WHO should periodically review global pneumococcal surveillance data to identify specific evidence gaps that need to be addressed through additional surveillance or special studies, including periodic cross-sectional studies on NP carriage prevalence.

Research priorities	1. Further assessment is needed of pneumococcal epidemiology in outbreaks, and outbreak response opportunities with PCV. a. A better understanding of ST1 epidemiology is needed for directing immunization efforts to prevent or control outbreaks of this serotype. Also review of historical data on pneumococcal outbreaks, particularly of ST 1, may be useful to define outbreak thresholds and age groups for vaccination 2. Further assessment is needed of the benefits or limitations of developing and using PCV products containing single or a limited number of outbreak-associated serotypes as a tool for controlling pneumococcal outbreaks. 3. Studies should be conducted in settings where outbreaks or humanitarian emergencies have recently occurred to evaluate risk of pneumococcal disease, including pneumonia, and assess impact of PCV use in these settings. 4. A systematic analysis of evidence comparing 1-dose versus 2-dose catch-up vaccination at the time of vaccine introduction should be conducted. Data to compare 1-dose vs 2-dose catch-up vaccination at the time of vaccine introduction should be collected for systematic analysis.

	5. Additional data are needed, through modeling or impact studies, on the relative benefit and cost of catch-up vaccination at the time of PCV introduction or switch to PCVs containing different serotypes or valencies.

[i] This Evidence to Recommendation table is based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel). http://www.decide-collaboration.eu/WP5/Strategies/Framework

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