SAGE Evidence to Recommendation Framework: Multi-age cohort PCV campaigns

Policy question: Is there a role for multi-age cohort campaigns with PCV to enhance the direct and indirect effects of the vaccine in special settings***?***

Population: Children < 15 years of age
Intervention: **Comparison(s)**: Multi-age cohort campaigns targeting children aged 1 to 15 years of age in special settings: routine childhood vaccination without multi-age cohort campaigns
Outcome: Invasive pneumococcal disease

Background: *Streptococcus pneumoniae* (pneumococcus) is the leading cause of bacterial pneumonia and a major cause of bacterial meningitis in children aged < 5 years worldwide. Countries in Africa, South Asia, and Southeast Asia bear a disproportionate share of pneumococcus-related deaths. In 2015, an estimated 3.7 million cases and 294,000 deaths attributed to pneumococcus occurred globally among children aged < 5 years, corresponding to a mortality rate of 45 deaths per 100,000 children in this age group. Widespread use of PCVs could prevent an estimated 1.6 million deaths in children aged < 5 years by 2030.

The introduction of 10 and 13-valent pneumococcal conjugate vaccines (PCV10 and PCV13) in childhood immunization programmes has resulted in a significant decline in invasive pneumococcal diseases (IPD) and pneumonia. These vaccines provide direct protection to vaccine recipients and indirect protection to unvaccinated individuals within vaccinated communities.

Outbreaks of pneumococcal disease have been reported even after the introduction of PCVs in childhood immunization programmes. In the African meningitis belt, pneumococcal meningitis outbreaks of have been reported occurred, predominantly caused by serotype 1. Outbreaks involving various serotypes have also been reported in certain settings, including among people experiencing homelessness, prison inmates, shipyard workers and hospitalized patients.

Several countries face challenges in achieving optimal coverage in certain settings, particularly in: (i) settings experiencing pneumococcal disease outbreaks; (ii) areas with low coverage of routine childhood immunization; and (iii) regions affected by humanitarian emergencies, where the risk of pneumococcal disease is high and access to health services, including immunization, is limited and/or intermittent.

In these special settings, multi-age cohort campaigns (MAC) with a single dose of PCV could rapidly boost population immunity, reduce transmission of vaccine-type pneumococci, and lower the risk of pneumococcal disease.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION

PROBLEM	Is the problem a public health priority?	No ☐	Uncertain ☐	Yes ☒	Varies by setting ☐	There is evidence of outbreaks of pneumococcal disease in certain settings. This includes countries in the African meningitis belt and other special settings such as shipyards, prisons, hospital wards, etc. Marginalized populations with poor access to health services, including immunization, are at high risk for pneumococcal disease and stand to benefit from vaccination. These include: (i) settings affected by conflict and other crises that cause interruption in health services resulting in low routine immunization coverage; and (ii) internally displaced people (IDP) camps.	

BENEFITS & HARMS	**Benefits**: are the desired anticipated effects large?	No ☐	Uncertain ☐	Yes ☐	Varies ☒	Evidence from a mathematical model predicts that reactive vaccination campaigns are effective and efficient only when they are implemented early in large and prolonged pneumococcal outbreaks. Since the size and duration of outbreaks are difficult to predict at the outset, reactive campaigns are unlikely to be efficient in most instances. A cluster-randomized trial showed that the use of full or fractional doses of PCV in MAC significantly reduces the prevalence of carriage in settings with moderate routine vaccination coverage and are likely to enhance direct and indirect protection against pneumococcal disease. Mathematical modelling predicts a reduction in IPD with campaigns targeting children in internally displaced populations. The effect is largest with campaigns targeting children up to 15 years of age, but most efficient (lowest number needed to vaccinate to prevent I case) when targeting those aged < 5 years.	Evidence from the model indicates that the impact of the MAC on community VT carriage would decline in 3 to 5 years if interventions to sustain or boost population immunity are not implemented.

	Harms: are the undesirable anticipated effects small?	No ☒	Uncertain ☐	Yes ☐	Varies ☐		No safety signals have been observed during MAC.	
	Balance of benefits and harms	Favours intervention ☒	Favours comparison ☐	Favours both ☐	Favours neither ☐	Unclear ☐		
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention						
		No included studies ☐	Very low ☐	Low ☒	Moderate ☐	High ☐	The quality of evidence for MAC in settings with moderate routine vaccination coverage and among internally displaced populations is low. For other settings, the evidence is from mathematical models and the validity of the model predictions have limitations based on the assumptions used.	
		Safety of the intervention						
		No included studies ☐	Very low ☐	Low ☐	Moderate ☐	High ☒	No safety signals have been observed during MACs.	

VALUES AND PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	Important uncertainty/ variability ☐	Possible important uncertainty/ variability ☒	Probably no important uncertainty/ variability ☐	No important uncertainty/ variability ☐	No known undesirable outcomes ☐	The evidence does not support the use of reactive MAC in response to pneumococcal outbreaks. The use of MAC is only from one study in a setting with moderate routine immunization coverage and the assessment of impact is based on the reduction in VT carriage of pneumococci. The evidence for use of MAC in IDP camps is based on mathematical modelling.	
	Values and preferences of the target population: are the desirable effects large relative to undesirable effects?	No ☐	Probably no ☐	Uncertain ☒	Probably yes ☐	Yes ☐	Varies ☐	There are no data on the values and preferences of the target population for PCV MAC	MAC campaigns with other vaccines have been conducted in these settings and have been well-accepted by the target population.
RESOURCE USE	Are resource required small?	No ☐	Uncertain ☐	Yes ☐	Varies ☒			The resources required will depend on the size of the target population for the MAC and the price of PCV.	The operational costs could be reduced if the campaign was conducted as part of the multi-antigen campaign.
	Is the intervention cost-effective?	No ☐	Uncertain ☐	Yes ☐	Varies ☒			The cost-effectiveness of the MAC would be context-specific, based on the degree of risk, the size of the target population, and vaccine and operational costs.	

EQUITY	What would be the impact on health inequities?	Increased ☐	Uncertain ☐	Reduced ☒	Varies ☐							Since MACs will target high-risk populations who have reduced access to health services, health inequities will be reduced.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (MOH, Immunization Managers)?	Intervention ☐	Comparison ☐	Both ☐	Neither ☐	Uncertain ☒						Evidence on the acceptability of key stakeholders to conduct a PCV MAC was not reviewed. However, agencies involved in the response to humanitarian emergencies have included PCV among the priority vaccines because of the high risk of pneumococcal diseases in these settings.	Given the settings in which MACs are conducted and the fact that an MAC would stretch the limited local resources, it is likely that key stakeholders would seek external resources to conduct an MAC.
	Which option is acceptable to target groups?	Intervention ☒	Comparison ☐	Both ☐	Neither ☐	Uncertain ☐						Based on the acceptance of other vaccines delivered through MACs, it is likely that PCV MACs would be acceptable to target groups.	
FEASIBILITY	Is the intervention feasible to implement?	No ☐	Probably no ☐	Uncertain ☐	Probably Yes ☒	Yes ☐	Varies ☐					If additional external resources are available the intervention would be feasible to implement, especially if it is part of a multi-antigen campaign.	

BALANCE OF CONSEQUENCES	Undesirable consequences clearly outweigh the desirable consequences in most settings ☐	Undesirable consequences probably outweigh the desirable consequences in most settings ☐	The desirable and undesirable consequences are closely balanced or uncertain ☐	The desirable consequences probably outweigh the undesirable consequences in most settings ☒	The desirable consequences clearly outweigh the undesirable consequences in most settings ☐
TYPE OF RECOMMENDATION	We recommend the intervention ☐	We suggest considering the recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☒ Only in specific contexts or specific subpopulations.		We recommend the comparator ☐	We recommend against the intervention and the comparator ☐

RECOMMENDATION	WHO continues to recommend catch-up campaigns for children aged 1–5 years at the time of introduction of PCVs in the infant immunization schedule to accelerate their impact. Additionally, in some settings, multi-age cohort (MAC) campaigns with a single dose of PCV could be used (e.g. in subnational regions with lower 3-dose coverage), without diverting resources from maintaining and/or strengthening routine immunization with PCVs. **MAC campaigns in settings with reduced population immunity** Reduced population immunity may be indicated by: (i) evidence or suspicion of high or increasing incidence of vaccine-type pneumococcal disease; (ii) recurrent outbreaks of vaccine-type pneumococcal disease; or (iii) evidence or suspicion of persistent low coverage (<50% coverage of the final dose of PCV).[1] In these circumstances, population immunity can be rapidly restored with a MAC campaign using a full or fractional single-dose of PCV10-SII in an off-label use. In most settings, these campaigns should include children aged 6 weeks to 5 years; a broader age range may be appropriate in some settings, such as those with a high prevalence of vaccine-type disease or carriage, vaccine-type outbreaks among older children or adults, or humanitarian settings with high migration rates. If a fractional PCV dose is being considered, in order to maintain uniformity with the use of fractional doses in routine immunization, >40% fractional doses of PCV10-SII may be used in campaigns in settings with at least moderate routine PCV coverage, where a sizeable proportion of the target population for a MAC is likely to be immunologically primed. Evidence indicates that a fractional 20% dose administered in a MAC temporarily reduces VT carriage in such settings: therefore, a 20% fractional dose may be considered in exceptional situations, to increase the number of doses available for a MAC and possibly extend the age range covered. Since PCV13-PFZ has similar polysaccharide amounts and immunogenicity, data suggest that PCV13-PFZ could also be used despite the lack of empirical evidence of effectiveness against carriage and/or disease. PCV campaigns should be coordinated with vaccination campaigns against other diseases and/or other relevant health interventions. **MAC campaigns in humanitarian emergencies** In humanitarian emergencies, a full childhood series of PCV is recommended if the population is sufficiently stable. If the population is not likely to be stable, single-dose MAC campaigns may be considered. Repeated preventive PCV campaigns could be considered when there is a high rate of in-migration and low routine immunization coverage. Routine immunization of infants with a 3-dose PCV schedule should be re-established as soon as logistically possible. **MAC campaigns for pneumococcal meningitis outbreaks** Available evidence does not support recommending reactive campaigns against pneumococcal meningitis outbreaks since it is challenging to predict whether outbreaks are likely to be of sufficient magnitude and duration to make a responsive vaccination campaign efficient. In exceptional situations, where an outbreak is detected early and a rapid response (e.g. within 2 weeks of outbreak confirmation) is possible, a reactive

campaign could be considered. In settings with recurrent outbreaks of vaccine-type disease, a preventive MAC campaign is recommended in preference to a reactive campaign.

[1] MAC campaign is unlikely to be cost-efficient in a humanitarian setting with documented evidence of high existing coverage with 3 doses of PCV.