SAGE Evidence to Recommendation Framework: Extended-valency PCVs

Policy question: What is the incremental benefit of using higher valency (14-valent or higher) PCVs in children < 5 years of age?

Population: Children aged < 5 years
Intervention: **Comparison(s)**: PCVs containing > 13 serotypes: PCV13 or PCV10
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.

Although the overall incidence of IPD in the pre-PCV period is lower than in the pre-PCV period, many countries report a high proportion of severe pneumococcal disease caused by serotypes not included in PCV products currently used in childhood immunization programmes. The proportion of severe disease caused by non-vaccine serotypes varies between countries. Evidence suggests that the proportion of IPD due to non-vaccine serotypes is lower in Gavi-eligible low- and low-middle-income countries compared to non-Gavi-eligible middle- and high-income countries. However, the paucity of high-quality surveillance data may contribute to the difference.

Several extended-valency PCV products containing >13 serotypes of pneumococcus have recently been licensed and several more are in the pipeline. Evidence suggests that, if effective, these PCV products could further reduce the burden of pneumococcal diseases.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION

PROBLEM	Is the problem a public health priority?	No ☐	Uncertain ☐	Yes ☒	Varies by setting ☐	Available evidence suggests that a sizeable proportion of the residual burden of pneumococcal disease in children aged < 5 years is caused by pneumococcal serotypes present in the recently licensed and pipeline PCV products.	
BENEFITS & HARMS	**Benefits**: are the desired anticipated effects large?	No ☐	Uncertain ☒	Yes ☐	Varies ☐	There are currently no data on the efficacy, effectiveness or impact of higher valency vaccines on clinical outcomes. PCV14-BE is non-inferior to PCV13 for all the shared serotypes following the 3 primary series when administered in a 3p+0 schedule. The immunogenicity of the recently licensed PCV15 and PCV20 is non-inferior to that of PCV13. However, the antibody levels for most of the shared serotypes are lower than the levels elicited by PCV13. PCV15 demonstrated non-inferiority to PCV13 for all the shared serotypes in both a 2p+1 and 3p+1 schedule. For PCV20, the non-inferiority criteria were not met after a 3-dose primary schedule, though non-inferiority was established after the booster dose using 3p+1 and 2p+1 schedules.	A modelling study in the UK predicted that PCV15 when used in a 1p+1 schedule would result in an overall increase in IPD since the reduction in IPD due to the two additional serotypes would be counterbalanced by an increase in disease by other serotypes because of their higher invasive potential.

	Harms: are the undesirable anticipated effects small?	No ☐	Uncertain ☐	Yes ☒	Varies ☐		The safety profiles of PCV15 and PCV20 are similar to those of PCV13.	
	Balance of benefits and harms	Favours intervention ☐	Favours comparison ☐	Favours both ☐	Favours neither ☐	Unclear ☒	The incremental benefits in terms of preventing overall pneumococcal disease are still unknown. The proportion of serotypes causing pneumococcal disease varies between countries and, hence, the impact of the newer products may also vary between countries.	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention						
		No included studies ☐	Very low ☐	Low ☒	Moderate ☐	High ☐	Our confidence in the effect estimate is limited, as the true effect may differ substantially due to indirectness. Vaccine impact is based on the antibody levels elicited by the vaccination, and immunogenicity data come exclusively from high- and upper-middle income countries. No data are available from low- and low-middle income countries.	
		Safety of the intervention						

		No included studies ☐	Very low ☐	Low ☐	Moderate ☒	High ☐	Limited data from clinical trials indicate that the safety profiles of PCV15 and PCV20 are similar to PCV13. Given the lower antibody levels elicited by these vaccines following the primary series, the possibility of increased disease cannot be ruled out.	
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 uncertainty mainly relates to the desirable outcomes due to limited data on vaccine efficacy or effectiveness in preventing clinical disease and the variability in the proportion of disease caused by additional serotypes across countries.	
	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 is inadequate evidence on the values and preferences of the target populations on the relative merits of the newer PCV products compared to the existing products.
RESOURCE USE	Are resource required small?	No ☐	Uncertain ☐	Yes ☐	Varies ☒			The prices of PCV15 and PCV20 may vary between countries and depend on the procurement mechanisms. They are likely to be higher than the currently used vaccines in many countries.
	Is the intervention cost-effective?	No ☐	Uncertain ☐	Yes ☐	Varies ☒			The cost-effectiveness of PCV15 and PCV20 will vary between countries depending on the price and incremental benefit of the vaccines compared to the existing PCV products.

EQUITY	What would be the impact on health inequities?	Increased ☐	Uncertain ☒	Reduced ☐	Varies ☐					There is no evidence to assess the impact on health inequities.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (MOH, Immunization Managers)?	Intervention ☐	Comparison ☐	Both ☐	Neither ☐	Uncertain ☒				There is no evidence on the acceptability of PCV15 and PCV20 in most countries and it is likely to depend on the incremental benefits and prices of these vaccines compared to the PCV products currently in use.	
	Which option is acceptable to target groups?	Intervention ☐	Comparison ☐	Both ☐	Neither ☐	Uncertain ☒				There is no evidence on the acceptability of PCV15 and PCV20 in target groups in most countries.	
FEASIBILITY	Is the intervention feasible to implement?	No ☐	Probably no ☐	Uncertain ☐	Probably Yes ☒	Yes ☐	Varies ☐			Based on affordability, the use of PCV15 and PCV20 is feasible, though health worker training will be required on the use of these products.	

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	Countries should consider extended-valency PCVs if they offer a better match to the range of serotypes causing disease in their setting. In doing so, the trade-offs that may exist should be considered carefully including in terms of: (i) potential higher price; (ii) potential partial loss of some direct or indirect protection against serotypes included in PCV10-GSK and PCV13-PFZ due to reduced immunogenicity leading to higher disease and/or higher acquisition of carriage; and (iii) potential need for an increased number of doses used to compensate for the loss in immunogenicity (e.g. moving from a 2p+1 to a 3p+1 schedule). If a switch to an extended-valency PCV is planned, serotype-specific surveillance is recommended to monitor the direct and indirect impact on the pneumococcal disease burden.