SAGE Evidence to Recommendation Framework: Reduced-dose (1p+1) schedules

Policy question: **Do the cost and programmatic benefits of a 1p+1 schedule outweigh the potential risk of reduced disease impact related to dropping a dose?**

Population: Children aged < 5 years of age
Intervention: **Comparison(s)**: Reduced dose (1p+1) schedules: 3-dose (2p+1 or 3p+0) schedules
Outcome: Invasive pneumococcal disease, pneumonia and nasopharyngeal carriage

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.

In countries with mature childhood PCV programmes, the incidence of IPD decreased and plateaued. It is likely that a 2-dose schedule consisting of 1 primary and 1 booster dose (1p+1) could sustain the low levels of IPD incidence achieved using schedules containing 3 or more doses of PCV. The use of reduced-dose schedules could free up resources to support other immunization activities, including the introduction of other life-saving vaccines.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	No ☐	Uncertain ☐	Yes ☒	Varies by setting ☐	Pneumococcal disease is an important cause of severe childhood diseases including bacteraemia, pneumonia and meningitis. In low- and low-middle-income countries, it is also a leading cause of deaths in children aged < 5years.	

BENEFITS & HARMS	**Benefits**: are the desired anticipated effects large?	No ☐	Uncertain ☐	Yes ☐	Varies ☒	The primary benefit of a reduced-dose schedule is the lower associated costs compared to the WHO-recommended 3-dose schedules. The 2-dose schedule would result in a 1/3 reduction in vaccine costs; the total amount saved will depend on the price per dose of PCV.	
	Harms: are the undesirable anticipated effects small?	No ☐	Uncertain ☐	Yes ☐	Varies ☒	There is a likelihood of a loss in impact following a switch from a 3-dose to a 2-dose PCV schedule. Evidence from mathematical modelling predicts that the loss of impact would vary depending on the prevalence of residual VT carriage following the use of a 3-dose schedule. The loss of impact could be further exacerbated if the coverage with the 2nd (booster) dose is not sustained at a high level.	
	Balance of benefits and harms	Favours intervention ☐	Favours comparison ☐	Favours both ☐	Favours neither ☐	Unclear ☒	
		Effectiveness of the intervention					

	What is the overall quality of this evidence for the critical outcomes?	No included studies ☐	Very low ☐	Low ☐	Moderate ☒	High ☐	The certainty of evidence varies by outcome and the vaccine product. The certainty of evidence on the effectiveness of PCV13 on IPD was low. The certainty of evidence on the effectiveness of PCV 13 against radiological pneumonia was moderate. The certainty of evidence on the effect on VT carriage was low to high, depending on the vaccine and the time of evaluation. The certainty of evidence on immunogenicity ranges from low to moderate.	
		Safety of the intervention						
		No included studies ☐	Very low ☐	Low ☐	Moderate ☐	High ☒	Evidence from observational studies and several RCTs did not show any adverse events of using a 1+1 schedule in comparison to the 3-dose schedules.	Predictions from mathematic models indicated the possibility of a loss of effectiveness against IPD and VT carriage in certain settings.
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 ☐	There is a possibility of reduced effectiveness of a reduced dose (1p+1) schedule against pneumococcal disease and vaccine-type carriage compared to a 3-dose schedule. This reduction in effect may vary by settings.	The possible reduction in effectiveness of the reduced dose schedule has to be weighed against the cost-savings from using one dose less of the vaccine.

	Values and preferences of the target population: are the desirable effects large relative to undesirable effects?	No ☐	Probably no ☐	Uncertain ☐	Probably yes ☒	Yes ☐	Varies ☐	A single study in The Gambia showed that 87% of caregivers of children preferred a 2-dose schedule because of the reduced pain and discomfort to the child because of fewer injections and because of fewer immunization visits.	
RESOURCE USE	Are resource required small?	No ☐		Uncertain ☐	Yes ☒		Varies ☐	A switch in schedule would require health worker training and a change in immunization monitoring tools. These costs are likely to be lower than the cost-savings from the reduced dose schedule.	
	Is the intervention cost-effective?	No ☐		Uncertain ☐	Yes ☐		Varies ☒	The cost-effectiveness would vary depending on the cost-savings from the reduced-dose schedule and the healthcare costs resulting from the loss of impact on disease outcomes.	
EQUITY	What would be the impact on health inequities?	Increased ☐		Uncertain ☐	Reduced ☐		Varies ☐	In countries that are unable to sustain a 3-dose PCV schedule, if a 2-dose schedule enables the programme to be sustained, there would be an impact on health inequities. In settings where the coverage with a 9-12-month vaccination dose is low in certain communities, the switch could increase health inequities by increasing the pneumococcal disease burden.	

ACCEPTABILITY	Which option is acceptable to key stakeholders (MOH, Immunization Managers)?	Intervention ☐	Comparison ☐	Both ☐	Neither ☐	Uncertain ☒	In a study in The Gambia, 67% of vaccinators preferred the alternate schedule since it would cause less pain and discomfort to the child, and it would be more cost-effective and free up funds for other purposes. The preference for the standard schedule was related to perceived incremental immunity benefits.	These data are from a single study. Opinions may vary between countries. Additional research is recommended to assess the acceptability of the off-label use of reduced dose schedules in other settings.
	Which option is acceptable to target groups?	Intervention ☒	Comparison ☐	Both ☐	Neither ☐	Uncertain ☐	A single study in The Gambia showed that 87% of caregivers of children preferred a 2-dose schedule because of the reduced pain and discomfort to the child because of fewer injections and because of fewer immunization visits.	The preferences may vary between countries. Additional research is recommended to assess the acceptability of the off-label use of reduced dose schedules in other settings.
FEASIBILITY	Is the intervention feasible to implement?	No ☐	Probably no ☐	Uncertain ☐	Probably Yes ☐	Yes ☒	Varies ☐	A switch to a 1p+1 schedule would be feasible to accommodate within the national immunization schedule in all countries without increasing the number of immunization visits.	Countries would need to ensure high coverage with the second dose of PCV in the reduced-dose schedule to sustain the reduction in pneumococcal disease.

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 wishing to reduce the cost of their PCV programme or reduce the number of injections in the infant immunization schedule may switch to a 1p+1 schedule as an off-label alternative to a 3-dose schedule, provided that both of the following criteria are met:

1. There is well-established population immunity among children aged <5 years. This can be indicated by one of the following:
   - having a mature 3-dose PCV programme with average routine third-dose PCV coverage of ≥80% during the 5 preceding years;
   - a recent multi-age cohort PCV campaign, with ≥80% coverage among children aged <5 years;
   - having low levels of vaccine-type carriage or disease, as indicated by high-quality surveillance or carriage surveys.
2. Evidence of capacity to administer vaccination between the ages of 6 and 18 months (e.g. PCV booster, measles-containing vaccine, yellow fever, meningococcal conjugate vaccine) with average coverage of ≥80% during the 5 preceding years.

In addition to the above, the following criteria would be desirable before implementing a 1p+1 schedule:

- an evaluation to weigh the costs, risks and benefits, including potentially reduced protection that would be considered acceptable for the given cost-savings;
- adequate surveillance for vaccine-type IPD or carriage to detect pneumococcal disease and/or transmission above that predicted at the point of schedule change.
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The first dose of the 1p+1 schedule can be given at ≥6 weeks of age, and the booster dose can be given at ≥9 months of age. For programmatic simplicity, both doses can be given at time points in the current immunization schedule. Evidence supporting the use of the 1p+1 schedule is based on studies with PCV10-GSK or PCV13-PFZ. There is currently no evidence supporting a 1p+1 schedule using PCV10-SII, although immunogenicity data show non-inferiority with PCV10-GSK and PCV13-PFZ in 3-dose schedules, indicating that PCV10-SII would also be likely to be effective in a 1p+1 schedule. Countries wishing to use PCV10-SII in a 1p+1 schedule should evaluate its effectiveness against carriage and/or disease. The use of extended-valency PCVs needs further evaluation before being recommended for use in a 1p+1 schedule because of the “immunogenicity creep” phenomenon.

Trade-offs of alternative PCV strategies

Countries considering either of the alternative dosing strategies should balance the trade-offs between the savings in programme costs with the potential reduction of pneumococcal disease control, as well as the increased need for surveillance. Uncertainties should be considered, including the potential reduced impact on disease outcomes and potential reduced duration of protection. Subnational areas with lower routine immunization coverage and higher baseline VT carriage prevalence need to be considered when making programme decisions. In early adopter countries of an alternate strategy, serotype-specific surveillance of pneumococcal disease or nasopharyngeal carriage should be implemented to monitor the impact. If monitoring reveals an unacceptable increase in VT carriage, increased VT IPD, or last-dose coverage

	substantially below 80% for more than one year, population immunity should be re-established through a single-dose PCV multi-age cohort campaign and/or reversion to a 3-dose schedule. Implementing multiple adjustments to the PCV programme at the same time (e.g. reducing the number of doses and introducing a new PCV product) may have unpredictable results and is not recommended.