Strategic Advisory Group of Experts (SAGE) on Immunization Evidence to recommendations framework[i]

Question: Should a second dose of IPV be implemented alongside bOPV + 1 dose IPV in RI?
Population: Immunocompetent individuals, Children
Intervention: bOPV + 2 IPV
Comparison(s): bOPV + 1 IPV
Outcome: Serological levels of type 1, 2 and 3 poliovirus antibodies/Prevention of spread and infection of poliomyeltis

Background:
OPV withdrawal remains one of the goals necessary to complete eradication of all polioviruses as outlined during the current Polio Endgame Strategy 2019-2023. To prepare towards complete OPV withdrawal, WHO recommended in 2013 that all countries should introduce at least 1 dose of IPV in their routine immunization schedule to provide an immunity base against paralysis caused by circulating vaccine-derived poliovirus type 2 (cVDPV2) and boost immunity against poliovirus types 1 and 3. By April 2019, this milestone was achieved by all 194 Member States. A second IPV dose is the next step towards complete OPV withdrawal and provides a higher protection against cVDPV2 which represents a risk in many regions of the world. One IPV dose provides immunity base against paralysis caused by cVDPV2 and boosts immunity against poliovirus types 1 and 3 (it was a necessity due to IPV shortage). Two IPV doses provide protection against cVDPV2 and further boost overall immunity against polioviruses. IPV supply is now mostly sufficient for IPV2 introduction and Gavi pledged support. In April 2020, SAGE re-prioritized IPV stock usage and made IPV2 higher priority for 2021.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	The international spread of poliovirus was first declares as a Public Health Emergency of International Concern (PHEIC) in May 2014. Most recently, this status was	

					extended in November 2021[1] because of the increase in cVDPV2 cases, despite the progress in the two remaining WPV1 endemic countries.	
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	A systematic review and meta-analysis presented in the September 2020 SAGE WG meeting demonstrated that two doses of IPV provide much higher immunogenicity against type 2 than one dose; the later the age at first dose and the longer the interval between doses, the higher the immunogenicity; two fractional doses provide similar immunogenicity as two full doses of IPV when age of first dose is late and interval is longer. In the context of the eradication of type 2 wild poliovirus and the subsequent withdrawal of type 2 oral polio vaccine, that immunity base produced by the first IPV dose could be rapidly boosted by a second dose of IPV, manifested by high antibody titers that would be expected to mitigate the consequences of cVDPV2 outbreak.	

[1] World Health Organization. Statement of the Thirtieth Polio IHR Emergency Committee. 23 November 2021. Available at https://www.who.int/news/item/23-11-2021-statement-of-the-thirtieth-polio-ihr-emergency-committee, accessed Jan 25, 2022.

				Studies indicate at least two fractional or two full IPV doses (for prime and boost) are required to achieve 90% or more seroconversion (individual protection). Available evidence suggests the seroconversion is optimized if the first IPV dose should be given at 14 weeks or later and the interval between this and the second dose should be greater than 4 months (See separate table and figure on immunogenicity).	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Numerous studies suggest that IPV is safe to administer. The risks are associated to procedural harms of injection.	
	Balance between benefits and harms	***Favours inter-vention*** ☒	***Favours com-parison*** ☐	***Favours both*** ☐	***Favours neither*** ☐	**Unclear** ☐	On the individual level, benefit of protection from poliomyelitis related disease outweighs any adverse effect of vaccination (e.g. pain during immunization, AEFIs).	
	What is the overall quality of this evidence for	Effectiveness of the intervention ***No included studies*** ☐	***Very low*** ☐	***Low*** ☐	***Mod-erate*** ☒	***High*** ☐	A large body of evidence supports individual effectiveness (see the WHO	

	the critical outcomes?	Safety of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Mod-erate* ☐ *High* ☒	GRADE Table) and safety of IPV (see the GACVS Report)[2].	
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* ☒	Preventing paralysis from poliomyelitis; there are no known undesirable outcomes.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	On the individual level, avoidance of poliomyelitis related disease would likely outweigh any adverse effect of vaccination (pain during immunization, AEFIs).	At the same time, it is important to advocate for the value of continued immunization against poliovirus after the global certification, in order to ensure community acceptance and population immunity.
RESOURCE USE	Are the resources required small?	*No* ☒ *Un-certain* ☐ *Yes* ☐ *Varies* ☐	In the past, IPV supply suffered constraints upon the introduction of one dose. Large supply of IPV is required for the introduction of a second dose worldwide. There is the option of administering	

[2] World Health Organization. Weekly Epidemiological Record. Global Advisory Committee on Vaccine Safety, 11-12 December 2013. Available at http://www.who.int/vaccine_safety/committee/reports/wer8907.pdf?ua=1, Accessed on Feb 2, 2022.

					fractional doses of IPV as a method to optimize resources. Considerable financial resources are also required (see below).	
	Cost-effectiveness	*No* ☐	*Un-certain* ☐	*Yes* ☐	*Varies* ☒	IPV manufacture is costly, so naturally introducing an additional dose of IPV into RI schedules has significant cost considerations. The current range of IPV price for UNICEF market is about 1-3 USD per dose. Gavi supports IPV2 introduction with a (product use) switch grant of $0.25/child. If a country adopts a fractional dose IPV schedule, the expected cost of the vaccine per child per dose is significantly lower.	
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☐	*Re-duced* ☒	*Varies* ☐	It is important to ensure protection in all populations (especially in developing countries) from an equity perspective. The majority of middle- and high-income countries have already at least 2 doses of IPV in their RI schedules yet have the lowest risk of cVDPV2.	One Polio WG member noted that requiring countries to pay for IPV could lead to opportunity costs that would shift resources away from more cost-effective non-polio interventions, and thus, while recommending IPV increases equity related to protection from poliomyelitis, it could at least theoretically reduce overall equity with respect to protection from infectious diseases or overall health.

ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-vention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Un-clear* ☐	The previous SAGE recommendation to introduce one IPV dose into the routine immunization was adopted by all countries, so the recommendation of an additional dose of IPV should be acceptable as a policy, given the sufficient funding is available.	One Polio WG member suggested that costs of IPV remain an issue for countries and that further work on the cost-effectiveness of the 2-dose IPV schedule appear warranted, although going from a 1 full IPV dose schedule to a 2 fractional IPV dose schedule could provide significant cost savings. This WG member indicated an expectation that some countries would probably not prioritize scarce resources for IPV in the context of competing priorities.
	Which option is acceptable to target group?	*Inter-vention* ☐ *Comparison* ☐ *Both* ☒ *Neither* ☐ *Un-clear* ☐	A second dose of IPV can be administered at the same time as other programmed vaccinations (either DTP3 for the early schedule or alongside the measles-containing vaccine for the later schedule), therefore an additional visit to a healthcare facility is not required. IPV coverage of one dose has increased from 47% in 2016 to 82% in 2019.	71% of countries that applied to Gavi for funding for a second dose of IPV are opting for it to be administered at 9 months over 14 weeks. This is beneficial since current dropout rates globally are higher in the 6-14 weeks schedule than the 14 weeks-9 months schedule. Moreover, this provides the best levels of immunogenicity (however lower early-in-life protection).
FEASIBILITY	Is the intervention feasible to implement?	*No* *Probably No* *Uncertain* *Probably Yes* *Yes* *Varies*	As of 2021, the supply of IPV is sufficient for all countries to introduce the second dose of IPV (IPV2) and complete catch-up immunization; and it is likely that 2021 will	DTP3 remains high at ~85% in the past years (even in high-risk countries at 83%). Moreover, drop out-rates are lowest in the

		☐ ☐ ☐ ☐ ☐ ☒		end with significant supply available with manufacturers. Globally, 94 countries have to introduce IPV2. Out of the 63 Gavi eligible countries that are yet to introduce IPV2, 35 have been approved, of which 6 have already rolled out IPV2. The timelines for the 28 remaining applications are not known and, except for the high-risk countries, GAVI is not actively encouraging submissions due to the pandemic. If the demand were to increase supply, a revised risk assessment strategy developed by Imperial College London (15 to 0 risk score) to be used as a guiding tool for IPV2 allocation.	preferred IPV2 schedule (14 weeks-9 months). However, the COVID-19 pandemic has had a significant negative impact on vaccination efforts. An immunization pulse poll developed by WHO, UNICEF and Gavi in collaboration with various partners (i.e., CDC and Johns Hopkins) demonstrated reductions in routine immunization coverage in numerous countries of Southeast Asia including large disparities in Indonesia, Myanmar and India. As the world accommodates to COVID-19 handling, immunization coverage is expected to rise once again.
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)	Please see Polio vaccines: WHO position paper – June 2022 (www.who.int/publications/i/item/WHO-WER9725-277-300)				
Implementation considerations	Please see Polio vaccines: WHO position paper – June 2022 (www.who.int/publications/i/item/WHO-WER9725-277-300)				
Monitoring and evaluation	Please see Polio vaccines: WHO position paper – June 2022 (www.who.int/publications/i/item/WHO-WER9725-277-300)				

Research priorities	Please see Polio vaccines: WHO position paper – June 2022 (www.who.int/publications/i/item/WHO-WER9725-277-300)

[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

	IPV	n	SC % (95% CI)	P1 value	fIPV	n	SC % (95% CI)	P1 value	P2 value
4 weeks interval	6, 10 weeks	5	72.0 (58.0-84.2)	<0.001					
	8, 12 weeks	2	91.6 (87.7-94.9)	<0.001					
	14, 18 weeks	4	92.9 (84.8-98.2)	0.001					

8 weeks interval	6, 14 weeks	2	89.3 (84.4-93.4)	<0.001	6, 14 weeks	6	79.6 (70.8-87.2)	<0.001	0.037
	8, 16 weeks	5	92.4 (89.7-94.8)	<0.001	8, 16 weeks	1	72.4 (65.4-78.7)	<0.001	0.001
	14, 22 weeks	1	98.5 (96.2-99.6)	0.021					
16 or 22 weeks interval	16, 32 weeks	4	99.8 (99.1-100.0)	0.185	16, 32 weeks	4	98.8 (96.4-100.0)	0.896	0.180
	14, 36 weeks	3	100.0 (99.6-100.0)	R	14, 36 weeks	1	98.2 (93.8-99.8)	R	0.053

P1 value: comparison between schedules (Ref=14 and 36 weeks); P2 value: comparison between IPV and fIPV (Ref=IPV)
n – Number of study arms; SC – seroconversion; IPV – inactivated poliovirus vaccine: fIPV – fractional IPV

Table 1. Type 2 seroconversion (%) with two doses of IPV or fIPV at different time intervals. Two doses of IPV provide much higher immunogenicity against type 2 than one dose. The later the age at first dose and the longer the interval between doses, the higher the immunogenicity. Two fractional doses provide similar immunogenicity as two full doses of IPV when age of first dose is late and interval is longer

Option	6 weeks	10 weeks	14 weeks	>=8 months	1-dose SC	2-dose SC	Comment

1	bOPV	bOPV	bOPV+IPV1	IPV2	46.5 (41.8, 51.2)	99.8 (99.1-100.0)	Best immunogenicity
2	bOPV+IPV1	bOPV	bOPV+IPV2		19.2 (13.5, 25.6)	89.3 (84.4-93.4)	Early in-life protection

Table 2. Proposed schedules for IPV2 introduction into bOPV+IPD RI schedules. The implementation of either schedule depends on region-specific priorities.

Include- Pros and cons of IPV schedules in SAGE report