SAGE evidence to recommendations framework

Question: Should countries continue IPV vaccination in their routine immunization programme after the certification of polio eradication? If so, what is the optimum schedule and for how long should countries continue?

Population: Newborn children (esp. those in currently OPV-using countries)
Intervention: Vaccination (One or two doses of inactivated poliovirus vaccine; IPV)
Comparison(s): No vaccination
Outcome: Prevention of poliomyelitis, possibly caused by vaccine-derived poliovirus (VDPV) or intentional and unintentional release of poliovirus from polio-essential facilities (PEFs)

Background:
The Oral Poliovirus Vaccine (OPV) offers safe and effective lifelong protection for humans against polio paralysis. Over the past ten years, more than 10 billion doses of OPV have been given to nearly three billion children worldwide. However, on rare occasions, giving OPV can result in cases of polio due to vaccine-associated paralytic polio (VAPP) in fully susceptible individuals (approximately 1 in 2.7 million doses of OPV) and OPV use in populations with insufficient coverage can allow ongoing transmission of OPV-related viruses that can lose their attenuating mutations and cause outbreaks of circulating vaccine-derived polioviruses (cVDPVs). For this reason, the global eradication of polio requires the cessation of all OPV in routine and supplementary immunization, as soon as possible after the eradication of wild poliovirus (WPV) transmission. In late-April-early May 2016, all OPV-using countries switched from trivalent OPV to bivalent OPV to minimize the risks associated with type 2 cVDPV, and most countries introduced at least one dose of IPV in their routine immunization prior to the switch.

Anticipating the global certification of serotype 1 and 3 wild poliovirus eradication in near future, SAGE requested the Polio WG to discuss and propose a post-OPV immunization policy.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies by setting* ☐	In May 2014, WHO Director General declared that international spread of poliovirus as Public Health Emergency of International Concern (PHEIC). The public health significance will be even higher, if poliovirus spreads after the global	

			certification of polio eradication	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐ *Uncertain* ☐ *Yes* ☐ *Varies* ☒	**Risk of poliovirus circulation after the global OPV cessation.** The risk of poliovirus re-emergence and circulation continues as long as live polioviruses exist, however, the risks change with time and they can be managed. Mathematical modelling and past epidemiology suggested VDPV/WPV types 1 and 3 could potentially emerge 0-4 years after the OPV withdrawal, with this risk depending in large part on management of population immunity prior to and just before coordinated global cessation of bOPV, outbreak response capacity and actions, and surveillance quality. The current epidemiology indicates that iVDPVs could excrete for up to 5 years in middle income countries and for 10+ years in high income countries. Lastly, containment failure or unintentional release of poliovirus from a polio essential facility (e.g. vaccine production or research facility) could happen anytime, even after 10 years, and	

			bioterrorism represents a potential threat. **Effectiveness of IPV** A significant body of evidence shows that one or two doses of full or fractional IPV can induce individual protection against poliovirus. 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). There is no direct data on the duration of protection (e.g. sufficient antibody) following the receipt of 2 fractional or full IPV doses. However, there is no evidence which suggests that there is waning immunity against polioviruses. Although antibody decline over time, and may fall	

			below detectable levels, in no instance such decreases increased susceptibility to poliomyelitis (paralytic disease) or led to outbreaks of poliovirus. The role of IPV with respect to community protection remains more mixed. Some evidence (e.g. India) suggests lower shedding of an IPV-protected individual upon re-exposure with a live poliovirus, which may reduce transmission if re-infected individuals account for an important part of the population responsible for transmission. In India, individual children who received 3 doses of DTP-IPV have a significantly lower rate of poliovirus shedding than in control children (without IPV) 7 days post challenge. Yogyakarta, Indonesia, which introduced IPV relatively early into its routine immunization, did not detect VDPVs after switching from OPV to IPV in 2007. However, the sustained WPV1 transmission among IPV-only vaccinated children in Israel, despite high coverage with IPV, suggests the limited ability of IPV alone in inducing mucosal immunity and	

			preventing transmission in a population. Dynamic transmission models show limited benefit of routine immunization with IPV in reducing transmission in low-income settings (i.e., in places with conditions conducive to relatively high faecal-oral transmission).	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	Numerous studies suggest that IPV is safe to administer.	
	Balance between benefits and harms	*Favours intervention* ☒ *Favours comparison* ☐ *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 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* ☒	A large body of evidence supports individual effectiveness (see the WHO GRADE Table) and safety of IPV (see the GACVS Report) http://www.who.int/immunization/polio_grad_ipv_effectiveness.pdf?ua=1 http://www.who.int/vaccine_safety/committee/reports/wer8907.pdf?ua=1	

VALUES & PREFERENCES	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	No evidence was retrieved on the values and preferences or the variability of these at the national level. On the individual level, avoidance of poliomyelitis related disease would likely outweigh any adverse effect of vaccination (pain during immunization, AEFIs). Economic modelling related to this topic suggests that countries will face different risks of potential reintroduction of polioviruses over time, with those countries that include polio essential facilities, providing long-term, high-quality supportive care for iVDPVs, and/or expressing greater concern about bioterrorism (i.e., relatively higher income countries) likely to place more value on the insurance provided by long-term IPV immunization than countries that face lower risks and/or remain less concerned about desiring insurance from bioterrorism.	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* ☒ *Uncertain* ☐ *Yes* ☐ *Varies* ☐	The current range of IPV price for UNICEF market is about 1-3 USD per dose. If a country adopts a fractional dose IPV schedule, the expected cost of the vaccine per child per dose is significantly	There is an opportunity cost associated with continued long-term use of IPV given other competing investments in public health, especially if the dedicated external funding for

			lower.	IPV is not available.
	Cost-effectiveness	*No* ☐ *Uncertain* ☐ *Yes* ☐ *Varies* ☒	The only published cost-effectiveness analysis supports the recommendation that all countries should continue at least one dose of IPV immunization in their national program for a minimum of 5 years after coordinated bOPV withdrawal. The analysis reported less favourable economics for a policy recommendation of a minimum of 10 years of IPV use in all countries after coordinated bOPV cessation. The majority of Polio WG members preferred a recommendation of IPV use for a minimum of 10 years to ensure protection against the risks of intentional or unintentional release of poliovirus in the long run.	One Polio WG member stated the recommendation should be consistent with the best strategy identified in the cost-effectiveness analysis (i.e., a minimum of 5 years of including at least one dose of IPV use in all countries) after coordinated bOPV cessation. The member emphasized that any country could choose to include IPV in its national immunization program for longer (and emphasized an expectation that relatively higher income countries would do so given their relative risks and benefits), but emphasize that application of a uniform recommendation does not account for the differences in risks, benefits, or the long-term willingness-to-pay for IPV.

EQUITY	What would be the impact on health inequities?	*Increased* ☒ *Uncertain* ☐ *Reduced* ☐ Varies ☐	It is important to ensure protection in all populations (especially in developing countries) from an equity perspective as most high-income countries have already introduced more than 3 doses of IPV into their routine immunization schedule	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)?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	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. However, at this point, there is not clear commitment from the donor community to support IPV after OPV cessation (since the recommendation would become effective only in 2021 or later). If there is no external funding for IPV, countries would need to prioritize available resources for IPV over other pressing needs.	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?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	It is presumed that the use of one or two doses of IPV would be acceptable to the target group if no additional visit at the health clinic is needed and the costs are covered by the health care provider.	

FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	The intervention is feasible as it does not require additional visits. However, current IPV supply remains highly limited, such that some countries that planned to introduce IPV had to delay their introduction. There is a risk of IPV shortage continuing into the long-term, especially if the market after the global cessation is limited. The recommendation of the use of IPV for 10+ years should encourages vaccine suppliers to continue IPV supply in the pre and post eradication periods.		

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)	• All countries should expect to continue using at least one dose of IPV after the coordinated bOPV withdrawal. If IPV supply and funding allows, the WG recommends that countries should adopt a two dose IPV schedule as a preferred option to ensure adequate individual protection against potential reintroduction of wild or vaccine-derived poliovirus. • If an OPV-using country is to adopt a two dose IPV schedule after bOPV withdrawal, two doses of IPV should be given at or after 14 weeks (e.g. with the 2nd or 3rd dose of DTP-containing vaccine) and at 9-12 months (e.g. with measles). Ideally, two full doses IM should be given, but two fractional doses may provide a similar level of seroconversion based on the available results of clinical trials, although no data provide information on the duration of protection (e.g. sufficient antibody) following the receipt of 2 fractional or full IPV doses. • Countries with Poliovirus Essential Facilities (PEFs) should continue the use of IPV as long as mandated by Global Action Plan (GAP III). However, countries, without PEFs should maintain IPV in their routine immunization schedule for at least 10 years after global OPV withdrawal, to address immediate (VDPVs), intermediate (iVDPV) and longer-term (containment failure and bioterrorism) risks. If there is no external funding for IPV available, countries need to decide how to prioritize available resources given other pressing public health needs. • WHO should review the secondary safeguard requirements in the Global Action Plan (GAP III) to ensure adequate protection in countries with PEFs
Implementation considerations	Recommendations will be made available in the standard WHO format (WHO position paper). As mentioned above, the implementation of recommendation is contingent on availability of sufficient IPV and external funding support.
Monitoring and evaluation	It is important to continue monitoring of immunization coverage and sustain disease surveillance even after the global certification of polio eradication.

Research priorities	Further research is recommended for • More information about immunogenicity and feasibility of two full-dose and fractional doses administered at time of 3rd dose of DTP-containing vaccine and measles or other schedules (ongoing) • Long-term duration of protection induced by fractional dose IPV

Table 1

Seroconversion rates following 1–3 doses of inactivated poliovirus vaccine (IPV) in different routine immunization schedules

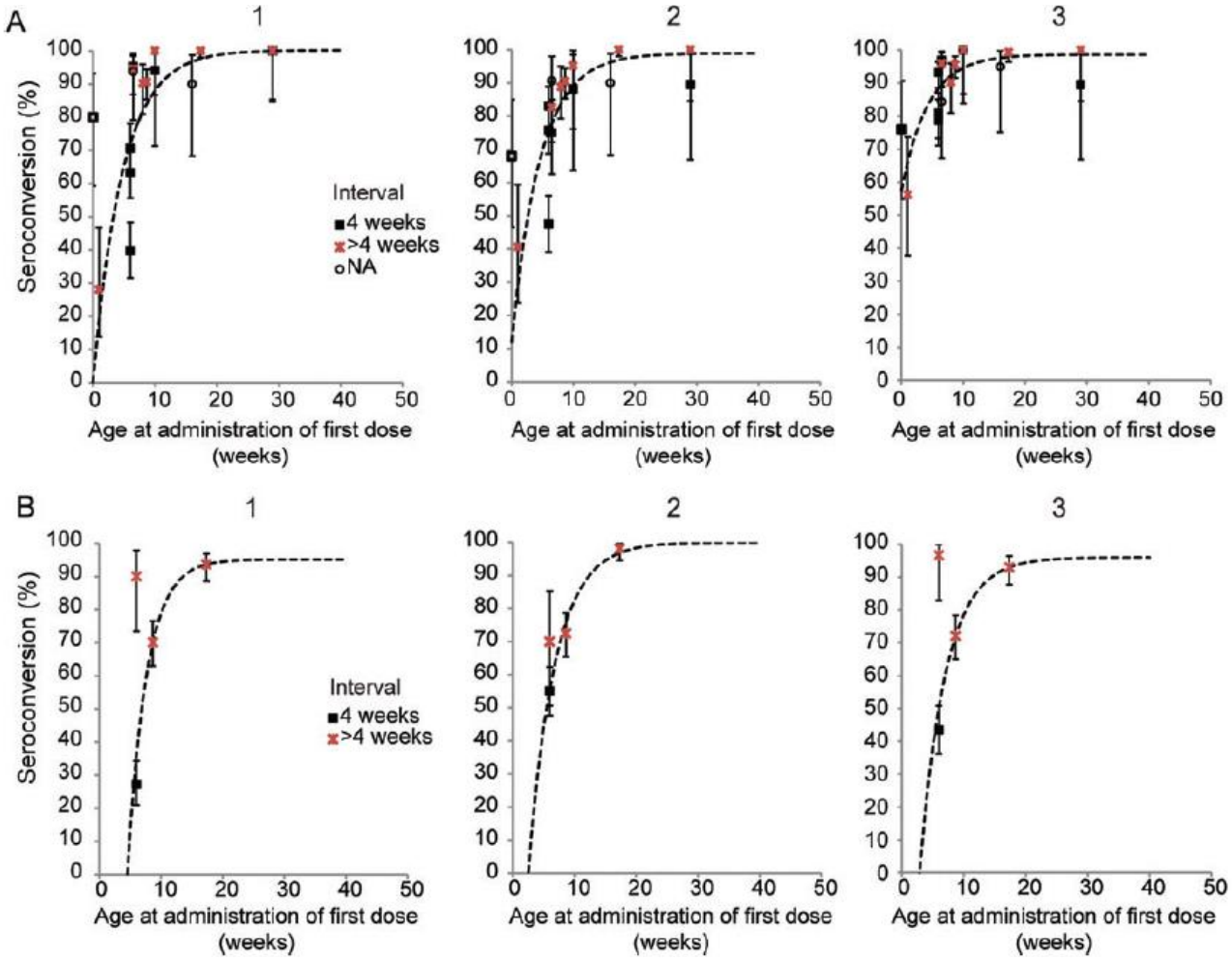
Author year (Ref.)	Country	Schedule	*N*	% seroconversion[a]		
				Type 1	Type 2	Type 3
Intramuscular administration of 1 dose						
McBean 88 [45]	US	2 mo	309	42%	35%	54%
Simasathien 94 [46]	Thailand	2 mo	103	25%	39%	28%
Resik 10 [40•]	Cuba	6 wk	177	19%	36%	42%
Mohammed 10 [47•]	Oman	2 mo	186[b]	22%	32%	45%
Resik 13 [39••]	Cuba	4 mo	153	46%	63%	32%
Intramuscular administration of 2 doses						
WHO 97 [48]	Oman	6, 10 wk	136	71%	83%	81%
WHO 97 [48]	Thailand	6, 10 wk	141	40%	48%	79%
Cuba IPV group 05 [27]	Cuba	8, 16 wk	72	90%	89%	90%
Resik 10 [40•]	Cuba	6, 10 wk	177	63%	76%	93%
Mohammed 10 [47•]	Oman	2, 4 mo	186[b]	91%	91%	96%
Resik 13 [39••]	Cuba	4, 8 mo	153	100%	100%	99%
Intramuscular administration of 3 doses						
McBean 88 [45]	US	2, 4, 18 mo	219	99%	100%	100%
Simasathien 94 [46]	Thailand	2, 4, 6 mo	92	96%	95%	98%
WHO 97 [48]	Oman	6, 10, 14 wk	136	90%	96%	95%
WHO 97 [48]	Thailand	6, 10, 14 wk	141	67%	65%	94%
Dayan 05 [49]	P. Rico	6, 10, 14 wk	225	86%	86%	97%
Dayan 05 [49]	P. Rico	2, 4, 6 mo	230	100%	100%	99%
Cuba IPV Group 05 [27]	Cuba	6, 10, 14 wk	52	94%	83%	100%
Resik 10 [40•]	Cuba	6, 10, 14 wk	177	89%	96%	99%
Mohammed 10 [47•]	Oman	2, 4, 6 mo	186[b]	100%	100%	100%
Cadorna-Carlos 12 [50]	Philippines	6, 10, 14 wk	115	98%	98%	100%
Intradermal administration of 1–3 fractional doses						
Resik 10 [40•]	Cuba	6 wk	187	5%	19%	8%
Resik 10 [40•]	Cuba	6, 10 wk	187	21%	55%	43%
Resik 10 [40•]	Cuba	6, 10, 14 wk	187	53%	85%	69%
Mohammed 10 [47•]	Oman	2 mo	187[b]	10%	17%	9%
Mohammed 10 [47•]	Oman	2, 4 mo	187[b]	70%	72%	72%
Mohammed 10 [47•]	Oman	2, 4, 6 mo	187[b]	97%	96%	98%
Cadorna-Carlos 12 [50]	Philippines	6, 10, 14 wk	115	99%	95%	95%
Resik 13 [39••]	Cuba	4 mo	157	17%	47%	15%
Resik 13 [39••]	Cuba	4, 8 mo	157	94%	98%	93%

[a] Cumulative seroconversion rates defined as children with antibody concentrations ≥4-fold the expected value based upon decline from baseline levels.

[b] Denominators varied for each serotype.Included studies conducted with enhanced IPV, with a sample size ≥50 and that provided information on seroconversion rates.

Source: Estivariz C, et al. Current Opinions in Virology 2013;3:309-315.

Figure 1: Proportion of children seroconverting to each serotype after 2 doses of IPV (A: Full-dose, B: Fractional dose)



Source: Grassly NC. J Infect Dis 2014; 210 Suppl 1: S439-46