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Use of fractional dose IPV in routine immunization programmes:

Considerations for decision-making

Purpose: **This document provides a brief overview of the scientific basis and key programmatic considerations to guide national decision-making on the use of fractional dose IPV (fIPV), administered intradermally, in routine immunization programmes.** Further details on the available evidence, key studies, and resources for implementation and training that are described in this document are available here.

Background: Based on the progress made towards the global eradication of poliovirus, in April 2016 a switch from trivalent to bivalent oral polio vaccine (OPV) was implemented. In the lead-up to the switch, all OPV-only using countries committed to introducing IPV. In March 2014, long term supply agreements were established with two manufacturers to meet the projected global requirements for IPV, however since 2015 both manufacturers have reported a series of challenges in scaling up bulk production. This has led to a severe global shortage of IPV and only 105/126 of these countries have been able to introduce the vaccine to date. **For more information on the background to the IPV supply constraints, please refer to the Information Note posted on this page.**

A. Evidence base

Efficacy of fractional dose IPV: fIPV has been researched since the 1990s. In recent years, the evidence has grown to conclusively demonstrate that two fractional doses administered via the intradermal (ID) route **offer higher immunogenicity compared to one full intramuscular (IM) dose of IPV** [1,2,3,4]. As a result, a two-dose fIPV schedule has been strongly recommended to countries by the WHO Strategic Advisory Group of Experts on Immunization (SAGE) [5,6], and in the WHO Position Paper on polio vaccines [7].

- A fractional dose is one-fifth (1/5, 0.1 ml) of a full dose of IPV, injected via the intradermal (ID) route
- fIPV is safe, effective and immunogenic
- fIPV can be given alone, or at the same time as any other vaccine
- In children also receiving oral polio vaccine (OPV), two doses of fIPV **given at 6 and 14 weeks** will help to "boost" their mucosal immunity against polioviruses [8]
- fIPV can be used in all types of polio immunization activities: in routine immunization, in supplementary immunization activities (SIAs), and in outbreak response [9]

Immunogenicity: Results from multiple clinical trials (Cuba, Oman and Bangladesh), using IPV from different suppliers, demonstrated **superior immunogenicity** against all poliovirus serotypes, following the administration of two ID fIPV doses compared to one IM full IPV dose, when the ID dose was properly delivered. For the purposes of this guidance note, we focus on protection against poliovirus type 2.

Table 1. Summary comparison of two ID fIPV doses with one full IM IPV dose

Publication (Year)	Country	Schedule		Seroconversion (%)	
		2 fractional doses	1 full dose	2 fractional doses	1 full dose
Resik S, et al. (2010) [1]	Cuba	6, 10 weeks	6 weeks	**55**	36
Mohammed AJ, et al. (2010) [2]	Oman	2, 4 months	2 months	**72**	32
Resik S, et al. (2013) [3]	Cuba	4, 8 months	4 months	**98**	63
Anand A, et al. (2015) [4]	Bangladesh	6, 14 weeks	6 weeks	**81**	39

Regulatory considerations: IPV is not currently licensed by manufacturers for fractional use, and there are no plans at this time for IPV suppliers to pursue a label change for fIPV. Therefore, any move to fractional IPV will involve off-label use of IPV, and should require a decision by the Ministry of Health of the country, following recommendations from National Technical Advisory Groups on Immunization (NITAGs), or equivalent. It is not unusual for countries to make evidence-based decisions for vaccine administration that may differ from the labelled indications (for example, hepatitis A, human papillomavirus, pneumococcal conjugate, Haemophilus influenza type b, rotavirus, and yellow fever vaccine). Given the current supply situation and the high efficacy of a two-dose fIPV schedule, SAGE has encouraged countries to move to fIPV despite the off-label use, citing the studies above. [6]

B. Programmatic considerations

Clinical trials have demonstrated the operational feasibility of administering two doses of fIPV in a health care setting [3,4,10]. In addition, countries such as India and Sri Lanka have already successfully introduced fIPV into their routine programmes in order to maximize their IPV stocks.

For each country to properly evaluate whether use of fractional IPV is operationally feasible in the national context, a range of programmatic factors must be considered, as highlighted in the table below. Further information on key considerations such as Gavi support and the role of adoption of fIPV in prioritization for IPV supply will be shared once available.

Factor	Two doses of intradermal fIPV
Licensing	Decision required by a national regulatory authority, NITAG, or equivalent, to accept off label use of IPV.
Age of administration	Recommended at 6 and 14 weeks, or nearest contact. For most countries, this will not require an additional visit, only an additional injection at these contacts. Countries should carefully assess their dropout rate between the 6 week and 14 week visit. Countries with large dropout rates need to balance the feasibility of a two-dose schedule and ensure that children will receive both of the required doses.
Vaccine administration	Intradermal injection, using 0.1 ml syringes — additional training will be required. Health worker training materials and job aids are available here.
Technologies to facilitate administration	Data from studies (Bangladesh, Cuba, the Gambia, United States, and Pakistan) demonstrated that using ID injection devices (such as needle adaptors or needle-free jet injectors) is equally immunogenic as when using a syringe alone [4,10,11,12,13] and is clearly preferred by health workers for ease of ID administration.[10] Currently three products are registered for use with prequalification expected in early 2017 [14]; additional ID immunization devices are under development and/or registration and may be considered in the future. Further information about devices to facilitate intradermal injection can be found here.
Vaccine vial presentations	The septum of the IPV vials tolerates multiple punctures without leakage. A study by PATH has demonstrated that septums meet the performance targets of the U.S. Pharmacopeial Convention (USP) for fragmentation to beyond 50 punctures.[15] However, use of 1 and 5 standard dose vials are recommended when implementing fIPV in a routine programme (yielding up to 5 and 25 doses, respectively).
Multi-dose Vial Policy	IPV contains the preservative 2-phenoxyethanol, which means that under certain conditions, as described in the WHO Multi Dose Vial Policy, [16] the opened vials can be kept and used for up to 28 days after opening. When using fIPV, a 5 dose vial will yield up to 25 doses. As a consequence, the vaccine presentation for fIPV is an important choice, as the maximum number of doses must be consumed within the 28 day time-frame.
Cold chain	For all vaccine presentations, using fractional dose will require 2/5 (40%) of the cold chain capacity per full course as compared to what is typically required for a 1-dose full IPV schedule.
Data	All forms for data recording should be updated, i.e. registers, records, home-based cards, etc. to note the administration of two doses of fIPV.
Communications	A communication plan will be required to convey the decision to all key local stakeholders, including medical associations, health workers and caregivers, explaining the benefits of IPV and emphasizing the evidence showing the non-inferiority of fractional dose.
Training	Will require training of health workers in a number of areas: proper intradermal injection technique; ability to reassure caregivers, correct timing of administration, and correct data recording of the two doses. Health worker training materials and job aids are available here.
Cost	A recent analysis by PATH shows that the estimated cost of two ID fIPV doses *plus* devices would amount to $1.0 – $3.0 per immunized child. This is comparable to the current IPV administration cost ($1.1 - 2.3 for one full IM dose).[14]
Post-marketing AEFI surveillance	There is no evidence of increased adverse events following immunization (AEFIs) with use of the fractional dose. Standard AEFI monitoring and reporting should be in place, as for all vaccines.

[1] Resik S. et al. Randomized controlled clinical trial of fractional doses of inactivated poliovirus vaccine administered intradermally by needle-free device in Cuba. Journal of Infectious Diseases 2010; 201(9):1344-52
[2] Mohammed AJ. et al. Fractional doses of inactivated poliovirus vaccine in Oman. New England Journal of Medicine 2010; 362(25):2351-9
[3] Resik S. et al. Priming after a Fractional Dose of Inactivated Poliovirus Vaccine. N Engl J med 2013;368:416-424
[4] Anand A. et al. Early Priming with Inactivated Poliovirus Vaccine (IPV) and Intradermal Fractional Dose IPV Administered by a Microneedle Device: A Randomized Controlled Trial. Vaccine 2015;33(48):6816-6822
[5] Meeting of the Strategic Advisory Group of Experts on Immunization, April 2016 – conclusions and recommendations. Accessed at: www.who.int/wer/2016/wer9121/en
[6] Meeting of the Strategic Advisory Group of Experts on Immunization, October 2016 – conclusions and recommendations. Accessed at www.who.int/wer/2016/wer9148/en/
[7] Polio vaccines: WHO position paper, 25 March 2016. Accessed at: www.who.int/wer/2016/wer9112/en/
[8] Jafari H. et al. Efficacy of inactivated poliovirus vaccine in India. Science. 2014 345:6199: 922-925.
[9] Bahl S. et al. Fractional Dose Inactivated Poliovirus Vaccine Immunization Campaign – Telangana State, India, June 2016. MMWR Morb Mortal Wkly Rep 2016:65:859-863
[10] Resik S. et al. Immune Responses after Fractional Doses of Inactivated Poliovirus Vaccine using Newly Developed Intradermal jet injectors: a randomized controlled clinical trial in Cuba. Vaccine 2015;33(2):307-13
[11] Clarke E. et al. Safety and immunogenicity of inactivated poliovirus vaccine when given with measles-rubella combined vaccine and yellow fever vaccine and when given via different administration routes: a phase 4, randomised, non-inferiority trial in The Gambia. Lancet Global Health 2016; 4(8):e534-47
[12] Troy SB. et al. Comparison of the immunogenicity of various booster doses of inactivated polio vaccine delivered intradermally versus intramuscularly to HIV-infected adults. Journal of Infectious Diseases 2015; 211(12):1969-76
[13] Saleem A. Intradermal administration of fractional dose of inactivated poliovirus vaccine using intradermal adapters vs. BCG syringe. 2016 (unpublished)
[14] Okayasu H. et al. Intradermal administration of fractional doses of inactivated poliovirus vaccine: a dose-sparing option for polio immunization. Journal of Infectious Diseases 2017 (in press)
[15] PATH. (Publication pending)
[16] WHO Policy Statement: Multi-dose Vial Policy (MDVP), Revision 2014, Accessed at: http://apps.who.int/iris/bitstream/10665/135972/1/WHO_IVB_14.07_eng.pdf