Implementation of fractional doses of the inactivated poliovirus vaccine (fIPV)

28 July 2017

Following the recommendation issued by the Technical Advisory Group on Vaccine Preventable Diseases (TAG) of the Pan American Health Organization/ World Health Organization (PAHO/ WHO) in March and July 2017, regarding the implementation of fractional doses of the inactivated poliovirus vaccine (fIPV) in the routine immunization schedule, the PAHO/WHO Immunization Unit has prepared this document to support countries in planning and implementing fIPV into the routine immunization program.

Pan American Health Organization
World Health Organization
REGIONAL OFFICE FOR THE Americas

1. Background

As part of the *Polio Eradication and Endgame Strategic Plan 2013-2018* and as recommended by WHO, 126 countries, that at the beginning of 2013 were only using the oral polio vaccine (OPV), were requested to introduce at least one dose of the inactivated poliovirus vaccine (IPV) in their routine immunization schedules.

Prior to the introduction of IPV, the two WHO prequalified manufacturers of IPV, established long-term agreements to supply this vaccine. However, both manufacturers have encountered technical difficulties to increase bulk production of IPV, which resulted in more than a 40% reduction of the initial offer.

This situation has sparked a global shortage of the vaccine, which has resulted in delaying the introduction of the vaccine or stock-outs of the vaccine after introduction in more than 49 countries. It is expected that the limited supply will extend through 2018-2019, and only begin to improve in 2020 when new producers are available.

In March 2016, the WHO Strategic Advisory Group of Experts (SAGE) on immunization recommended that to face the limited supply of IPV, countries could consider using fractional doses, administered intradermally (1/5 of the complete dose), but should consider the programmatic and logistical implications.

In the Region of the Americas, PAHO's Revolving Fund and Immunization Unit have been closely monitoring IPV stock in countries and adjusting the vaccine delivery schedule to ensure stock for all countries that procure through the Revolving Fund. However, even maintaining these collaborative efforts, it was expected that as of July 2017, some countries in the Region would begin facing stock outs of the vaccine.

Considering this situation, in March 2017, the TAG reviewed evidence on the immunogenicity of intradermal administration (ID) of two fractional doses of IPV and the worldwide availability of the vaccine, and issued the following recommendations:

- Countries that administer more than 100,000 doses of IPV per year and have the technical ability to conduct training and provide adequate supervision should immediately begin to prepare for the use of fIPV.
- A sequential schedule of two fractional doses of vaccine should be administered, followed by two or three doses of bOPV, with the first dose at two months of age, and intervals of eight weeks between vaccines in the primary schedule during the first year of life.

2. Immunogenicity of two doses of fIPV

A recent literature review conducted by the Centers for Disease Control and Prevention (CDC) and WHO[1] concluded that the immunological response after the intradermal administration of 2 doses of fIPV is more robust than the response after only one complete dose administered intramuscularly.

Seroconversion following ID administration of two doses of fIPV has an absolute average increase of 37% (range: 19%-42%), and the antibody titers are 10 times greater (range: 2-32 times) compared with the response after intramuscular administration of one complete dose of IPV.

A study from the Philippines did not find any difference with respect to the reduction of antibody titers 12 months after completion of a schedule with 3 fractional doses of IPV doses administered intradermally compared to 3 complete doses administered intramuscularly[2].

Currently, WHO and CDC are conducting two studies (in Pakistan and Bangladesh) whose results will provide more evidence on the duration of immunity.

3. Planning for the use of fIPV

For the decision making process at the national level, national immunization committees should review and discuss the worldwide limited supply of IPV and the recommendations of the SAGE and TAG.

A national plan and timetable should be developed. To do this, it is necessary to examine the current levels of IPV stock and syringes, and determine the feasible dates of implementing fractional doses, taking into consideration the required time for health care worker training at all levels and the time needed to adapt the vaccine registration forms.

The change in the polio vaccination schedule will require an initial investment to train health care workers, adapt registration forms, and purchase syringes. However, in the long run, the use of fIPV will decrease the yearly investment required to purchase the vaccine by around 60%.

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[1] Anand, A., Molodecky, N. A., Pallansch, M. A., & Sutter, R. W. (2017). Immunogenicity to poliovirus type 2 following two doses of fractional intradermal inactivated poliovirus vaccine: A novel dose sparing immunization schedule. *Vaccine*.

[2] Cadorna-Carlos, J., Vidor, E., & Bonnet, M. C. (2012). Randomized controlled study of fractional doses of inactivated poliovirus vaccine administered intradermally with a needle in the Philippines. International Journal of Infectious Diseases, 16(2), e110-e116.

During the process of adapting this guide, the technical team involved should ensure consistency with procedures provided in other national documents, guidelines, and policies; such as the preparation of micro-planning for the regular vaccination program; National Regulatory Authority (NRA) legislation, safe injection procedures, open-vial policies, sharps waste disposal, adjustments to the vaccine registry information systems, supervision, among others. Ensuring the consistency of the current national guidelines will be key to facilitate a smooth introduction of fIPV.

It is recommended that the national health authorities establish a team to lead the technical and administrative processes, oversee the implementation, track progress, and detect and manage any issues that arise during implementation and supervision. Representatives of the following areas should be included on this team:

- Immunization Advisory Committee
- National Immunization Program
- Department of Epidemiology
- National Regulatory Authority
- Department of Pharmacovigilance
- Department of Communication
- Department of Statistics and information systems
- Intermediate and local health authorities

Coordination with the National Regulatory Authority is importance since the fractional use of IPV is based on scientific evidence, but not included on the vaccine inserts.

All changes to the vaccination schedule should be followed by a training process. In this specific case, the training is particularly relevant since the technical administration of giving a vaccine intradermally requires special training.

4. Target Population

Fractional doses of IPV will be given to infants two months old at the time of the change in schedule, and to those who have not yet received a full dose of IPV.

This new schedule will not apply for children that have already received one full dose of IPV given intramuscularly.

5. fIPV vaccination

fIPV vaccination	
Type of vaccine to be used	Inactivated Poliovirus Vaccine (IPV)
Presentation of the vaccine vial	The vaccine comes in transparent glass vials sealed with a (latex-free) rubber stopper and an aluminum cap. For each complete 0.5 ml dose, there are five 0.1 ml fractional doses.
Storage and transportation conditions	The vaccine should be stored between +2°C and +8°C in refrigerators and transport thermoses, and not be exposed to sunlight or freezing temperatures. The shake test does not effectively determine whether a vial of IPV has been frozen. This means that it is very important to store vials at the recommended temperature. If you suspect that a vial of IPV has been frozen, it should be discarded.
Volume per dose	A fractional dose of IPV (fIPV) = 0.1 ml
Form of administration	Intradermal (ID)

fIPV vaccination

Administration site

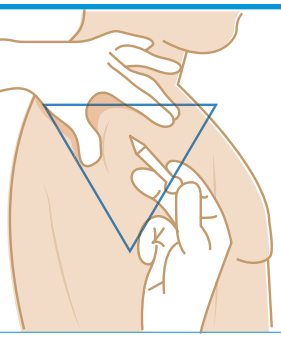

Imagen: MAGC

Upper third of the deltoid region of the right arm

Type of syringe and needle

Auto-disable (AD) Syringe 0.1 cc 27G x 3/8”.

For countries that still use the conventional syringe, the syringe to be used is 1 cc 27G x 3/8”

Number of fractional doses

Two (2)

Minimum interval between 1st and 2nd dose

8 weeks (2 months)

Vaccination schedule

BASIC SCHEDULE				BOOSTERS	
DOSE	**1st dose**	**2nd dose**	**3rd dose**		
Age at administration	2 months	4 months	6 months	18 months	4-5 years
Type of vaccine	fIPV	fIPV	bOPV	bOPV	bOPV

fIPV vaccination

Open vial policy

Multidose vials of IPV can be used until 28 days after opening, if the following four criteria are met:

a) the expiration date has not passed;

b) the vaccine has been stored in appropriate cold chain conditions at the recommended temperature;

c) the stopper of the vaccine vial has not been submerged in water due to the thawing of the ice packs, and the vial remains clean and dry;

d) the vaccine vials are handled with good aseptic practices.

In extramural vaccination activities, the open vials may be returned to the health facility and used until 28 days after opening provided that the four criteria indicated above are met and handling precautions are taken to reduce the risk of contamination.

Order of vaccine administration

The fIPV vaccine should be administered in a given order, with the most painful vaccines at the end. For example:

Age	Order of administration of the vaccines
2 months	• Step 1: Rotavirus • Step 2: fIPV • Step 3: Pentavalent • Step 4: Pneumococcus
4 months	
6 months	• Step 1: bOPV • Step 2: Pentavalent • Step 3: Pneumococcus
18 months and 4-5 years	• Step 1: bOPV • Step 2: DPT

Administration technique

- Check that the child is eligible to receive this dose of the vaccine.
- A wide range of positions and ways of holding the child can be used, such as holding the child on a lap or on the examination table. Prevent the child from moving during vaccination.
- Wash hands before starting the procedure.
- Select a healthy area of skin tissue on the upper third of the deltoid region.
- Check the type of vaccine, expiration date, as well as the date and hour the vial was opened, and ensure it is within the 28 days according to the open vial policy.
- Aspirate 0.1 ml of vaccine with indicated syringe and needle while maintaining aseptic conditions.
- Clean the skin with a cotton pad dampened in water using centrifugal or top-down motions, taking care not to wipe the same place twice. Do not use moist cotton pads kept in multi-use holders.
- Select a zone of healthy skin, stretch the skin between the index finger and thumb so that it is tight and insert the needle with the bevel facing upwards at an angle of 10° to 15°, insert about 9mm of the needle, ensuring that it reaches only the dermis, the needle will be visible under the skin.
- Slowly inject 0.1 ml of IPV vaccine and proceed to withdraw the needle without forcing the skin.
- A small bleb will be formed immediately. Do not massage, press, or place any compress on the bleb.
- It is not recommended to revaccinate if the bleb does not form.

Intradermal injection, needle parallel to the skin with the bevel face up

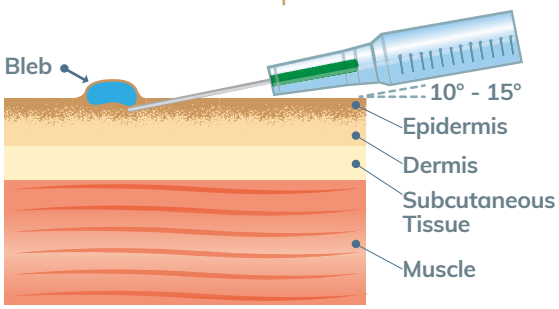

Imagen: MAGC

fIPV vaccination

Administration technique

- Never recap, break, or bend the needles.
- Discard the material used, following the standards for sanitary disposal of biological material.
- Fill out the required registration (vaccination log, card, etc), include the date of administration, and the date for the next dose.
- Explain to parents or caregivers what vaccine was given, and not to massage, or apply medications or compresses at the site of administration. Indicate what the side effects may be and when they should return to complete the vaccination schedule.

Contraindications and side effects

IPV should not be given to people with documented or known allergy to streptomycin, neomycin or polymyxin B, or a history of allergic reaction following a previous injection of IPV.

IPV can be given to preterm infants (born less than 37 weeks gestation) at the recommended chronological age for other routine schedule vaccines.

Polio vaccines (IPV complete, fIPV and bOPV) can be given to asymptomatic infants infected with HIV. HIV testing is not a prerequisite for vaccination.

6. Diameter of the bleb

After the administration of fIPV, in most cases a bleb, whose diameter can vary between 5-8 mm, will be formed. However, recent studies in Cuba[3], Gambia[4] and Pakistan[5] have evaluated the association of immunogenicity with fIPV and the size of the bleb formed after administration. According to these results, the diameter of the bleb has a limited value in determining the immunogenicity of the fIPV vaccine.

It is not recommended to revaccinate if the bleb is not formed or it is of a smaller diameter.

7. Vaccination of special populations, contraindications and precautions

Polio vaccines (IPV complete or fractional dose and bOPV) can be given to asymptomatic infants infected with HIV. HIV testing is not a prerequisite for vaccination.

bOPV is contraindicated in severely immunocompromised patients with known underlying conditions such as primary immunodeficiencies, thymus disorders, symptomatic HIV infection or low CD4 T cell levels, malignant neoplasms treated with chemotherapy, recent haematopoietic stem cell transplantation, drugs with known immunosuppressants or immunomodulators, for example, high dose systemic corticosteroids, alkylating drugs, antimetabolites, TNF-α inhibitors, IL-1 blocking agent or other monoclonal antibodies directed to immune cells, and recent radiotherapies. These populations can receive IPV (fractional or complete doses).

Infants with suspected or confirmed diagnosis of primary immunodeficiency should not receive the bOPV vaccine. Two doses of IPV (fractional or complete) are recommended in these cases, but the immunogenicity of IPV depends to a large extent on the underlying immunodeficiency disorder

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[3] Resik, S., Tejeda, A., Mach, O., Sein, C., Molodecky, N., Jarrahian, C., ... & Alemany, N. (2015). Needle-free jet injector intradermal delivery of fractional dose inactivated poliovirus vaccine: Association between injection quality and immunogenicity. *Vaccine*, 33(43), 5873-5877.

[4] Bibby, J., Saidu, Y., Umesi, A., Moneke-Anyanwoke, N., Bashorun, A. O., Hydara, M. B., ... & Clemens, R. (2017). The immunogenicity of fractional intradermal doses of the inactivated poliovirus vaccine is associated with the size of the intradermal fluid bleb. *Clinical Infectious Diseases*.

[5] Saleem, A. F., Mach, O., Yousafzai, M. T., Khan, A., Weldon, W. C., Oberste, M. S., ... & Zaidi, A. K. (2017). Needle adapters for intradermal administration of fractional dose of inactivated poliovirus vaccine: Evaluation of immunogenicity and programmatic feasibility in Pakistan. *Vaccine*, 35(24), 3209-3214.

8. Inventory control

It is important to maintain strict control of inventory of IPV vials to ensure that all the services have the vaccine in stock, and to identify any services that experience excessive waste so that timely recommendations can be given on how to prevent such waste.

When the switch is made from the use of a full dose of IPV to a fractional dose, vaccine warehouse and vaccination center managers will have to change the different inventory registries (e.g.: vaccine inventory management software, Kardex cards, record books). For example, the labeling of the IPV vial of 5 complete doses should be changed to 25 fractional doses.

Open and closed vials should be identified and marked by writing fIPV directly on the vial. This will serve as a reminder about the change in dosage to be administered.

Each time a vial is opened, the date and time of opening must be recorded on the label, which will allow verification of compliance with WHO's 28 days open vial policy

9. Vaccination schedule in case of stock-out

If no IPV is available for the administration of fIPV, bOPV should be administered. In these cases, two doses of fIPV should be administered as soon as the vaccine becomes available, while always respecting the minimum interval of eight weeks between doses of fIPV.

All vaccinators must be informed of the importance of clearly recording the type and dosage of vaccine administered, both in the vaccine registry and in the child's vaccination card, so that there is clear documentation of whether the child already received the two doses of fIPV.

10. Adaptation of the information system

The vaccination information system should be adjusted to allow for recording of two doses of fIPV, ensuring adjustments in all instruments of vaccination records (daily records, nominal records, weekly / monthly consolidated records, follow-up records, vaccination cards, etc).

This is very important in order to ensure correct follow up and make sure that all children complete their vaccination schedule.

Health care workers should be trained to fill out all of the possible alternatives (example: if the child has received the two doses of fIPV, only one dose, or no doses).

11. Calculating Requirements

The formula for calculating the number of complete doses of IPV to cover a schedule of 2 fractional doses given at 2 and 4 months of age is as follows:

Number of doses required = ((Target population x wastage rate) x 2) ÷ 5

Where:

- **Target population:** children under 1 year
- **25% Wastage factor** = 1.25
  NOTE: Initial programming can be done using a wastage rate of 25%. However, each country may subsequently readjust its estimates based on the monthly analysis of the wastage rate.
- **Multiplied by two doses** (2 doses per child)
- **Divided the previous result by 5**, since a full dose is equivalent to 5 divided doses.

12. Communication and Social Mobilization

A communication and mobilization strategy should be implemented for strategic partners, health workers and parents/caregivers. This is a critical aspect for the vaccine acceptance and obtaining high coverage.

The communication strategy should aim to:

– sensitize health personnel on the reason for switching from IPV to fIPV
– foster confidence in the safety and effectiveness of the vaccination schedule
– stress the importance of completing the vaccination schedule in a timely manner
– avoid rumors and misinformation

The communications strategy should be tailored to the national context. In order to introduce fIPV, the population must receive clear and straightforward information on its characteristics and benefits. Therefore, it is important to decide on the materials to be used and how they will be disseminated at the different levels of the health system.

13. Supervision

Supervision of health workers should be ensured to verify that the guidelines given are being applied.

The following aspects should be checked:

- Compliance with technical administration
- Inventory management
  - Control of existing stock
  - Control of existing syringes
- Compliance with registering information

14. Monitoring and evaluation

The monthly monitoring and evaluation plan of the regular vaccination program should be modified to include the following aspects:

- Compliance with the date of the change in the vaccination schedule with fIPV
- Inventory management
  - Report of stock-outs
  - Control of vaccine stock
  - Control of syringe stock
  - Change in the information records from 5 full doses to 25 fractional doses
  - Estimation of wastage rate
- Adaptation of information systems for administered doses
- Surveillance of events supposedly attributed to immunization or vaccination
- Strategies implemented to reduce vaccine wastage
- Implementation of communication, informational and educational strategies for parents or family caregivers

To the extent possible, the information collected should be documented through minutes, questionnaires, checklists, reports, and photographs.

It will be helpful to implement a formal or informal mechanism (eg WhatsApp Group) to expeditiously share best practices, lessons learned or issues that need to be reviewed and considered during the supervision.

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