POLIO GLOBAL ERADICATION INITIATIVE

Photo: Gavi

GUIDELINES

for Implementing Poliovirus Surveillance among Patients with **Primary Immunodeficiency Disorders (PIDs)**

Revised May 2022

Contents

Acronyms and abbreviations

AFP	Acute flaccid paralysis
cVDPV	Circulating vaccine-derived poliovirus
CVID	Common variable immunodeficiency
EPI	Expanded Programme on Immunization
ES	Environmental surveillance
EU	Emergency use
FUP	Follow-up
GPEI	Global Polio Eradication Initiative
GPLN	Global Polio Laboratory Network
HIV	Human immunodeficiency virus
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgM	Immunoglobulin M
IHR	International Health Regulations
IPV	Inactivated poliovirus vaccine
iVDPV	Immunodeficiency-associated vaccine-derived poliovirus
L20B	Mouse transgenic cell line
MoH	Ministry of Health
NPEV	Non-polio enterovirus
OPV	Oral poliovirus vaccine
PID	Primary immunodeficiency disorder
RD	Rhabdomyosarcoma continuous cell line
RT-PCR	Reverse transcriptase polymerase chain reaction
SIA	Supplementary immunization activity
SL	Sabin-like
SL1	Sabin-like type 1
SL2	Sabin-like type 2
SL3	Sabin-like type 3
VAPP	Vaccine-associated paralytic poliomyelitis
VDPV	Vaccine-derived poliovirus
VDPV1	Vaccine-derived poliovirus type 1
VDPV2	Vaccine-derived poliovirus type 2
VDPV3	Vaccine-derived poliovirus type 3
VP1	Viral protein 1
WHO	World Health Organization
WPV	Wild poliovirus
WPV1	Wild poliovirus type 1
WPV2	Wild poliovirus type 2
WPV3	Wild poliovirus type 3

1 Introduction

The Global Polio Eradication Initiative (GPEI) owes its success to the effective use of the oral poliovirus vaccine (OPV) in routine immunization and supplemental immunization activities (SIAs).[1] Unfortunately, in rare circumstances, the attenuated Sabin strains in OPV cause vaccine-associated paralytic poliomyelitis (VAPP) in the vaccine recipient or a close contact.[2,3] In addition, through prolonged replication in a single immunodeficient host or serial transmission in an under-vaccinated community, these attenuated polioviruses can regain the neurovirulence and transmission characteristics of wild poliovirus.[4,5] When this occurs, these polioviruses are referred to as vaccine-derived polioviruses (VDPVs).

VDPVs that have been established through community circulation in under-vaccinated populations are referred to as circulating vaccine-derived polioviruses (cVDPVs). cVDPVs have become a fundamental concern for the polio eradication programme as they have been responsible for thousands of poliomyelitis cases since their first description in 2001.4,6,7 Strengthening routine immunization systems is necessary to avoid an emergence of cVDPV. After community transmission has become established, interrupting cVDPV requires an implementation of outbreak response, including high-quality SIAs that reach every child in affected communities.[7]

A far smaller but potentially serious problem is represented by VDPVs that evolve in patients with inherited primary immunodeficiency disorders (PIDs) following exposure to OPV viruses, referred to as immunodeficiency-related vaccine-derived polioviruses (iVDPVs).[4,8] To mitigate the individual and community risks posed by iVDPVs during the polio endgame and the post-eradication era, it is important to identify those PID patients excreting polioviruses and provide the strategies and treatments available to rid both the individual and the community of the risk posed by iVDPVs.[9,10] However, the current poliovirus surveillance systems are not well designed to identify non-paralyzed iVDPV-infected PID patients who may shed iVDPV for months or years before they become paralyzed or initiate community circulation. Acute flaccid paralysis (AFP) surveillance can only detect transmission through cases of paralysis, and although environmental surveillance can detect iVDPV shed by asymptomatic carriers, it is unable to identify the individual shedder.

The surveillance system proposed in these guidelines is designed to supplement the current AFP and environmental surveillance systems to help identify all poliovirus excretors and thus achieve and maintain eradication of all polioviruses. They are provided for country teams, mid-level managers, and surveillance staff at all levels.

2 Background and current epidemiology of iVDPVs

Primary immunodeficiency disorders (PIDs) represent a spectrum of genetically acquired disorders of the immune system.[8] Individuals with PIDs affecting the B-cell system are at higher risk for developing VAPP upon receiving OPV or being in close contact with someone recently vaccinated.[1,11,12] In addition, because of their inability to mount an adequate humoral immune response, poliovirus intestinal replication and shedding may persist longer than the usual four to six weeks observed in healthy individuals. This prolonged intestinal replication can lead to the development of iVDPVs. Although most individuals with PID clear poliovirus infection within six months, some excrete polioviruses for six months to five years (defined as prolonged infections), and a few may excrete vaccine strains for more than five years (chronic infections).[4,13]

Between 1961 (the year OPV was introduced) and 2000, only 19 PID patients with prolonged or chronic excretion of poliovirus were reported and recorded in the World Health Organization (WHO) registry, most of whom lived in high-income countries.[1,13] Between 2001 and 2018, 122 additional cases were reported, with a shift in prevalence to middle-income countries in the Middle East and Asia.[13] The shift from high- to middle-income countries may be partly explained by the adoption of IPV in high-income countries, as well as an improvement in the survival of PID patients in OPV-using middle-income countries. In low-income countries, the possibility of increased survival of PIDs may be due to the availability of private health facilities in some areas. Higher incidence of PID patients in countries with high prevalence of consanguineous marriages may also explain higher reports in certain Middle Eastern countries. Among the 141 PID patients excreting poliovirus identified between 1961 and 2018, 62.4% excreted type 2 poliovirus – and the most common PID associated with poliovirus excretion was severe combined immune deficiency. Only 22.2% of PID patients shedding poliovirus were prolonged excretors, and 1.6% were chronic excretors.[13]

Multi-country studies searching for asymptomatic poliovirus excretors among ≈1200 individuals with PIDs found poliovirus excretion in ≈3%, with ≈1% excreting iVDPV.[14] These and other studies also confirmed that prolonged poliovirus excretion is associated with severe B-cell or combined PIDs, such as common variable immunodeficiency (CVID) or severe combined immune deficiency. Individuals with partial immunoglobulin deficiencies or individuals with primary or secondary T-cell deficiencies, such as chronic HIV infection, clear poliovirus as efficiently as healthy individuals.[15]

In addition to the risk of developing paralytic poliomyelitis, individuals infected with iVDPV present the potential risk of initiating VDPV outbreaks. Community and household contact spread of iVDPV or Sabin strains shed by a PID patient has been rare to date with only two documented reports in 2005 among an Amish community with low immunization coverage in the U.S. and in Spain.[16,17] However, the risk of community spread of iVDPVs may change with the reduction of population immunity expected after wild poliovirus (WPV) eradication and the improvement in healthcare enabling PID patients to survive longer in lower resource settings. Modeling analysis suggests that five to ten years following cessation of OPV use, asymptomatic long-term iVDPV excretors living in countries with poor sanitation (which raises the potential for intense fecal-oral transmission of poliovirus) pose a significant risk for the re-emergence of poliovirus circulation.[9]

3 Implementing polio surveillance among PID patients

3.1 - Objectives and types of surveillance

Objectives: To detect excretors of poliovirus among PID patients, to outline effective case management protocols, and to propose a public health response to reduce both the individual's risk of developing poliomyelitis and the community's risk of poliovirus transmission.

Type of surveillance: Both passive and active surveillance will need to be implemented due to the expected low incidence and prevalence of PID cases in each facility.

- *Passive surveillance*: Data and reports will be sent by designated health facilities. Such reporting will include immediate notification of confirmed PID cases at risk of poliovirus excretion, as well as ongoing periodic follow-up. A monthly report of zero cases will be submitted by the facility focal person.
- *Active surveillance*: A designated surveillance official, usually external to the health facility, will conduct visits at least quarterly. These visits will include interviews with physicians and support staff and reviews of registers, log books, or medical records to ensure that no reports/data are incomplete or missing. These visits to sentinel facilities are also used for sensitization and refresher training of facility staff.

3.2 - Steps to set up poliovirus surveillance among PID patients

The following steps are recommended for the initial implementation of polio surveillance for PIDs.

Initial steps for establishing poliovirus surveillance among PID patients	
• Sensitize public health officials on the importance of poliovirus surveillance among PID patients, using results of the global risk assessment model and data from national registries from PID centers and referral systems for PID patients.	
• Identify sentinel reporting sites using the criteria of being a referral health facility for diagnosis and treatment of patients with immunodeficiency disorders. Identify a focal point in each sentinel site, preferably a specialized physician.	

• Adapt the general surveillance guidelines to country requirements.
  ○ Integrate PID surveillance with the other polio surveillance systems in the country: AFP, environmental, enterovirus, etc. To facilitate operations, define clear leadership for poliovirus surveillance among PIDs within the polio surveillance structure by designating a dedicated national focal person/team and facility focal points.
  ○ Develop country-specific guides for the management of PID patients with poliovirus excretion including access to immunoglobulin therapy and use of antiviral drugs.	

Assigning roles and responsibilities for poliovirus surveillance among PID patients	
At the sentinel reporting site	• Focal point (physician) at the sentinel site is the liaison with the surveillance staff and is responsible for case detection and immediate notification, coordination of investigation and follow-up at facility level, treatment of cases, and preparation and submission of monthly/zero reports. • Physician(s) at the sentinel facilities to detect confirmed PID patients and initiate testing for poliovirus in coordination with the focal point. • Administrative and health staff to support the submission of monthly zero reports, collection and shipment of specimens in coordination with

	surveillance officer and recording information into facility electronic database.
Surveillance officers (could be AFP surveillance officers at district and provincial levels)	• Conduct active surveillance visits to sentinel sites (at least every quarter) and sensitization of facility staff. • Conduct notifications, investigations, collection and transport of stool samples (when required) and follow-ups of PIDs with specimens positive for Sabin or VDPV or the very unlikely possibility of WPV.
National PID surveillance focal point/coordinator	• Coordinate surveillance activities, technical support, training, and supportive supervision. • Maintain the national database, submitting case-based and aggregated reports to country surveillance authorities and the WHO. • Be the liaison with AFP surveillance, laboratory, and environmental surveillance. • Coordinate response activities. • With support of the regional level, adapt the generic training material. • Conduct training of surveillance staff and focal points of reporting sites, as well as provide orientation to physicians and support staff in identified sentinel sites. • Facilitate access to antiviral therapy.
WHO surveillance focal point/polio team at the regional level	• Conduct risk assessment and country prioritization for implementing poliovirus surveillance among PID patients. • Provide technical support to country programmers regarding guidelines, planning, training, and evaluation activities. • Provide data management support and maintain regional database. • Coordinate laboratory services, response activities and facilitate access to therapy. • Conduct fundraising activities to address financial gaps, where required.
WHO polio team at the global level	• Overall technical guidance and support. • Conduct research and evaluation activities. • Coordinate global laboratory activities. • Maintain the global database. • Liaise with Jeffrey Modell Foundation and immunologists network. • Facilitate process of continued antiviral research and availability of and access to therapy.
Staff in the Global Polio Laboratory Network (GPLN)	• Test the specimens according to GPLN protocols. • Report results to the facility focal person and surveillance officer. • Enter results in the polio laboratory database (Polio Information System). • Report and send isolates that need further analysis to referral laboratories.

3.3 - Role of the laboratory

The role of the laboratory is critical to the polio endgame generally and to poliovirus PID surveillance specifically, as it is the laboratory that confirms the presence or absence of the virus in humans and the environment.

Patients who meet the case definition of PIDs at risk of excreting poliovirus will have their stool samples tested in one of the 164 WHO-accredited poliovirus laboratories in the Global Polio Laboratory Network (GPLN). Similar to AFP surveillance:

- Laboratory confirmation is based on isolation of poliovirus on monolayers of tissue culture cells (RD and L20B). Isolation of non-polio enterovirus (NPEV) is also possible and should be reported as a separate result.

- Intratypic differentiation is conducted by reverse transcriptase polymerase chain reaction (RT-PCR) to identify the virus as WPV, VDPV, or Sabin, as well as the virus serotype (1, 2, 3).
- Genetic sequencing helps monitor the evolution of strains within the same patient (i.e., Sabin to VDPV, development of resistance to antivirals) and detects potential spread in the community by comparing the nucleotide sequence of the VP1-coding region of poliovirus isolates with poliovirus isolated in samples from other sources. This information will guide the type and intensity of the public health response required.

4 Case detection

4.1 - PID patients at risk of poliovirus excretion

The purpose of surveillance is to identify PID patients with poliovirus excretion before the virus paralyzes them and before they may initiate community transmission. The focal person and other physicians at the sentinel site will be responsible for identifying patients with a PID that is eligible for testing because of the associated risk for poliovirus excretion (as per case definition in Section 5).

The programme will identify two types of cases:

- Individuals previously diagnosed with a PID that meet the case definition, who will be identified through retroactive search of national and facility registries.
- Individuals newly diagnosed with a PID known to be associated with prolonged poliovirus excretion, who will be screened for poliovirus excretion shortly after confirming the PID diagnosis.

The physician will notify the surveillance officer and complete and submit a notification form for "PID patient at risk of poliovirus excretion."

The information reported in the notification form should include:

- Basic demographics (age, sex, area of residence, detailed contact information including address and phone number).
- PID diagnosis, if available (including results of quantitative immunoglobulin measurement).
- Presence or absence of symptoms that could be related to poliovirus infection (paresis, paralysis, meningitis, other).
- Type and dates of polio vaccination (OPV, IPV) and history of recent (<3 months) exposure to OPV from close contact (family member) or community (OPV campaign in the area).

What to do with identified PID patients?

1. Fill in a notification form and send to the surveillance officer.
2. Collect at least one stool sample, fill out appropriate form, and ship to WHO-accredited laboratory.
3. Upon receipt of laboratory result, inform patients and any interested parties.
4. If results are positive, follow the protocol for detailed investigation and case management (section 6).
5. If results are negative, plan follow-up stool testing on an annual basis (or following exposure to OPV polioviruses).

The opportunity will be used to emphasize to the family that PID patients and their close contacts should never receive OPV.

4.2 - Specimen collection from PID patients at risk of poliovirus excretion

The physician in coordination with the surveillance officer will initiate collection of stool specimens, preferably two stool specimens at least 24 hours apart; however, in some circumstances, it may not be feasible to collect more than one specimen. Support staff at the sentinel facility will ensure that collection of stool specimens and shipment to the poliovirus laboratory adhere to the established country requirements.

Specimen collection guidelines	
Volume of stool	8–10 g, about the size of two adult thumbnails. This amount permits duplicate testing, if required.
Storage and handling	Specimens should be placed in appropriate containers with a tight seal to ensure there is no leakage or possibility of desiccation. Specimen containers must be placed immediately in a designated cold box at 4–8°C and between frozen ice packs. Specimens should arrive at a WHO-accredited laboratory within 72 hours of collection. If this is not possible, the specimens must be frozen at -20°C and then shipped frozen, preferably with dry ice or with cold packs that have also been frozen at -20°C.
Documentation	All specimens should reach the laboratory accompanied by a specimen collection form completed accurately and legibly. Laboratory forms must include variables pertinent for the laboratory staff to identify the patient; apprehend the reason for testing and type of testing required (i.e., first test in a PID patient or a follow-up of a poliovirus shedder or previously tested PID patient with negative results); and communicate results to the required parties (focal point/physician in sentinel facility, surveillance officer, referral laboratory, and the WHO).

5 Case definitions and case classification

5.1 - Case definition for PID patient at risk of poliovirus excretion

The PID case at risk of poliovirus infection is an individual of any age who has a primary antibody disorder, humoral (B-cell) or combined humoral (B-cell) and cellular (T-cell) immunodeficiency disorder, confirmed for levels of immunoglobulin below standards for age.

Specific PIDs with known risk of prolonged poliovirus excretion are highlighted (see panel at right).

Because of the very low likelihood of prolonged poliovirus excretion,[15,18] individuals with the following immunodeficiency disorders are not to be included and are not eligible for poliovirus testing in the absence of paralysis:

1. Isolated deficiencies of IgA or IgM, or IgE abnormality.
2. Transitory or secondary immunodeficiency (i.e. related to infections including HIV, chronic illness, treatment with immunosuppressive therapy, etc.).

If paralysis is present at the time of PID diagnosis, the case should be reported as an AFP case to the polio surveillance officer and investigated according to AFP surveillance guidelines.[19] At the same time, the case will also be included in the PID surveillance database for coordinated treatment, contact sampling, and follow-up.

PIDs with risk of prolonged poliovirus excretion

- Predominant antibody disorders:
  - Common variable immunodeficiency disorder (CVID) and other primary hypogammaglobulinemias
  - Agammaglobulinemia including X-linked agammaglobulinemia,
- Immunodeficiencies affecting cellular and humoral immunity including:
  - Severe combined immunodeficiency disorder
  - Combined immunodeficiencies, including major histocompatibility complex deficiencies, immunodeficiency centromeric facial anomalies syndrome (ICF)
- Other immunodeficiencies with hypogammaglobulinemia or increased susceptibility to viral infections

5.2 - Case definition for PID patient with confirmed poliovirus excretion

For poliovirus surveillance among PID patients, a ‘confirmed’ case is a PID case at risk of prolonged poliovirus shedding – as per the definition above – whose stool specimen tested positive for poliovirus, including VDPV, WPV, or Sabin viruses.

5.3 - Classification based on laboratory results

Based upon the laboratory results, the final classification will be:

Classification *	
PID with VDPV (i.e. iVDPV)	Refers to a PID patient with isolation of VDPV in stool specimen(s). Depending on the serotype, it will be iVDPV1, iVDPV2, or iVDPV3.
PID with WPV	Refers to PID patient with isolation of WPV in the stool specimen. Depending on the serotype, it will be WPV1, WPV2, or WPV3. (Note: Although this situation is possible, it is extremely unlikely).
PID with Sabin virus	Refers to a PID patient with isolation of Sabin-like poliovirus in stool specimen(s). Depending on the serotype, it will be SL1, SL2, or SL3.

PID negative for poliovirus	No poliovirus detected in the stool. It refers to a PID patient with no laboratory evidence of Sabin, VDPV, or WPV in an adequate stool specimen (see Section 4 for adequate specimen guidelines).

*Note: Specimens of PID cases may be positive for non-polio enterovirus (NPEV).

It should be noted that PID patients with poliovirus infection may progress from one classification to another. 'PID with Sabin' may progress to 'PID with VDPV,' and paralysis may also appear in any individual with asymptomatic infection by Sabin or VDPV strains.

A classification and decision-making chart is provided in Annex 1.

PID patients with AFP

PID patients who develop paralysis during follow-up will have stools tested for poliovirus as soon as possible after paralysis onset, with their case classification determined per AFP guidelines.[19] The PID surveillance system will record those patients for follow-up and treatment.

- **Vaccine-associated paralytic poliomyelitis (VAPP) case** – PID patient with AFP and isolation of Sabin-like poliovirus in a stool specimen with residual paralysis at 60 days and beyond, for whom the Expert Review Committee excluded other causes of AFP based on additional clinical information.
- **iVDPV 'paralytic' case** - PID patient with AFP and isolation of VDPV in a stool specimen.
- **Compatible case** - PID patient with AFP but inadequate specimens and no poliovirus isolation, who is classified by the Expert Review Committee as polio-compatible. These individuals should undergo a thorough evaluation to rule out other causes of AFP (including NPEV infection).[19]

6 Case investigation & management

6.1 - Follow-up and repeat sampling of PID patients at risk of poliovirus excretion

The following schedule of specimen collection for poliovirus testing is recommended:

- Initial poliovirus testing is recommended for every individual diagnosed with a PID associated with a risk of prolonged poliovirus excretion. This includes previously diagnosed and known (registered) PID patients, as well as newly diagnosed PID patients.
- Repeat testing for follow-up -
    - Monthly: For PID patients with a specimen positive for SL, VDPV, or WPV as explained next under case investigation.
    - Annually: For PID patients with negative specimens.

6.2 - Detailed investigation for PID patients with confirmed poliovirus excretion

The surveillance officer, in coordination with staff from the sentinel facility, will conduct a case investigation for those PID patients with specimens positive for poliovirus, within 48 hours of receiving the laboratory results. The objectives of the investigation will be to assess the risk of poliovirus circulation in the surrounding community and to initiate case management and public health response.

The investigation should involve the collection of additional information from the patient, close family contacts, and surrounding community.

Investigation guidelines	
Patient	○ Source of exposure of the PID patient to OPV, such as travel, visitors, routine immunization and immunization campaigns, based upon the estimated time of viral intestinal replication inferred from molecular analysis. ○ Assess potential for patient initiating transmission into the community, such as attendance to daycare or school, admission into health facility or institution, and availability of sanitation infrastructure.
Close contacts	○ Determine polio vaccination status. ○ Assess medical history suggestive of immunodeficiency. ○ Stool samples may be collected among close (family) contacts or community contacts of a PID patient with shedding of WPV, Sabin, or VDPV. The surveillance officer(s) conducting the case investigation will oversee organizing stool collection. The number of contacts and the type of contacts to be sampled will follow the guidelines for response to poliovirus event/outbreak.[20,] Procedures for collection and transport of specimens are as explained above.
Community	○ Assess polio vaccination status (IPV, OPV) especially among children younger than five years through community surveys and desk review of coverage data. ○ Assess risk factors for fecal-oral transmission (high population density, inadequate sanitation and sewage infrastructure, etc.). ○ Active search for AFP cases in health facilities and community.

6.3 - Case management and public health response

The case management and scope of public health response will depend on the type of poliovirus isolated, the sequencing data, and the presence of risk factors for community transmission.

Public health response guidelines	
PID patient positive for Sabin-like poliovirus	
If Sabin types 1 or 3 are isolated	Repeat specimen testing monthly to monitor clearance of infection or progression to iVDPV. Confirm clearance of poliovirus infection by obtaining two negative specimens separated at least by one month. In addition, initiate discussions with surveillance and public health officials to consider treatment with antivirals.
If Sabin type 2 is isolated	Notify country public health authorities and WHO according to the International Health Regulations (IHR) Annex 2 (2005), initiate event investigation within **48 hours** of laboratory confirmation of the results, and plan specific public health response as explained in the guidelines.[20] In addition, repeat specimen testing monthly to monitor clearance of infection or progression to iVDPV. initiate discussions with surveillance and public health officials to consider treatment with antivirals.
PID patient positive for WPV, VDPV, or Sabin strains progressing to VDPV in serial samples	
• Once the laboratory identifies WPV or VDPV in any stool sample, the Ministry of Health (MoH) should notify country public health authorities and the WHO according to the IHR Annex 2 (2005). • Local surveillance staff should initiate event investigation that includes enhanced polio surveillance activities and assessment of population immunity as explained above.	
The public health response will depend on the detection of community circulation.	
Any WPV isolation	Conduct outbreak response.
VDPV	If there is evidence of circulation of this polio strain in the community (healthy community contacts or environmental samples), it will be considered an outbreak (cVDPV) and will require vaccination campaigns appropriately scaled depending on the community risk.[20] In addition, repeat specimen testing monthly to monitor clearance of infection or progression; initiate discussions with surveillance and public health officials to consider treatment with antivirals.
	If there is no evidence of circulation of this poliovirus strain in the community, the response may consist of administration of IPV to household members and close community contacts.[20] In addition, repeat specimen testing monthly to monitor clearance of infection or progression; initiate discussions with surveillance and public health officials to consider treatment with antivirals.

6.4 - Treatment with antiviral drug therapy

Antiviral drug therapy should be considered for PID patients in the following circumstances:

- an individual who has VDPV isolated in any stool specimen;
- an individual who is excreting Sabin strains for more than two months; or
- an individual who is excreting WPV.

Antivirals are not indicated for contacts potentially exposed to polio infection.

Because polio antivirals are still currently in development, access to antiviral therapy is restricted for 'compassionate use.' Each sentinel facility conducting surveillance for PID patients with poliovirus excretion should coordinate with central regulatory and public health authorities (MoH) to prepare the necessary documentation to support antiviral drug review, importation and use upon diagnosis of a new patient candidate to the treatment. Health facility staff will also follow a guidance document regarding drug dosage, schedule for administration, and follow-up poliovirus testing to both ensure the safety of

the patient and assess the effectiveness of the treatment. Country-specific regulatory agencies, the antiviral drug manufacturer (ViroDefense, Inc.), and public health officials should endorse the drug procurement plan and the administration procedures. See Annex 2 for details on the available antiviral drug(s) and steps for treatment under compassionate use.

6.5 - Other management measures

All PID patients shedding poliovirus are expected to receive the following case management measures:

- Treatment for the PID and its complications, such as administration of intravenous immune globulin or bone marrow transplant, according to the type of PID and the country standard level of care.
- Counseling and education of the patient and family to avoid future receipt of live vaccines and ensure appropriate hand and toilet hygiene to prevent transmission of poliovirus to contacts.
- Polio vaccination of health staff using IPV and adherence to standard precautions for infection control in healthcare facilities or institutions where the PID patient may receive clinical care.
- Vaccinations of close contacts with IPV, if required. (Similar to the PID patient, close contacts should never receive OPV).

7 Data analysis and monitoring and evaluation

An important aspect of a successful polio eradication programme is a well-developed information system that provides programme managers and health workers with the necessary information to take appropriate actions.

Analysis of PID surveillance data is required for measuring the sensitivity and consistency of the surveillance system to ensure it is functioning at the desired level. Surveillance data is useful in the decision-making process in the following ways:

- Detecting and monitoring PID patients with prolonged excretion of poliovirus.
- Treating infection and preventing the future development of patient paralysis and other adverse neurological outcomes.
- Preventing the introduction and circulation of poliovirus excreted by the patient into the community.
- Including the number and geographical location of excretors of Sabin/iVDPV in periodic country risk assessments of polio outbreaks.

PID surveillance data should be reviewed quarterly at the national level to detect and quantify occurrence, assess changing patterns over time, determine risks for excretion, monitor progress, and evaluate the performance of the surveillance system itself.

7.1 - Information management

- The PID information system will be a case-based data system included in the overall polio information system (POLIS). It will function as a registry with a unique identifier assigned to the patient upon diagnosis of PID (PID patient at risk of excreting poliovirus) and allow for repeated specimen collection and changes in case status over time.
- The PID information system will link with other polio data management systems, such as:
    - *AFP case-based data:* A link between the AFP and PID databases is essential. A PID case with confirmed poliovirus excretion and paralysis will need to be reported through the AFP surveillance system as well. Conversely, an AFP with PID detected through the AFP system will be included in the PID database for follow-up.
    - *Environmental surveillance (ES) data system:* This system compares genetic sequences of VDPV from human and environmental sources to confirm or rule out community circulation of iVDPVs.
    - *Laboratory and polio nuclutide sequencing (PONS) databases:* All laboratory results are entered regardless of the source of the virus. Laboratory results from PID patients and sequencing data from isolated poliovirus will be recorded.

Recommended data elements have been provided in Annex 3.

Main sources of the data:

- Case Investigation Form of “PID patients at risk of excreting poliovirus”
- Detailed Case Investigation Form of “PID patients with confirmed poliovirus excretion”
- Follow-up forms
- PID patient registry/line list
- Completeness and timeliness of reporting units
- Active surveillance visit forms

7.2 - Suggested epidemiologic analysis

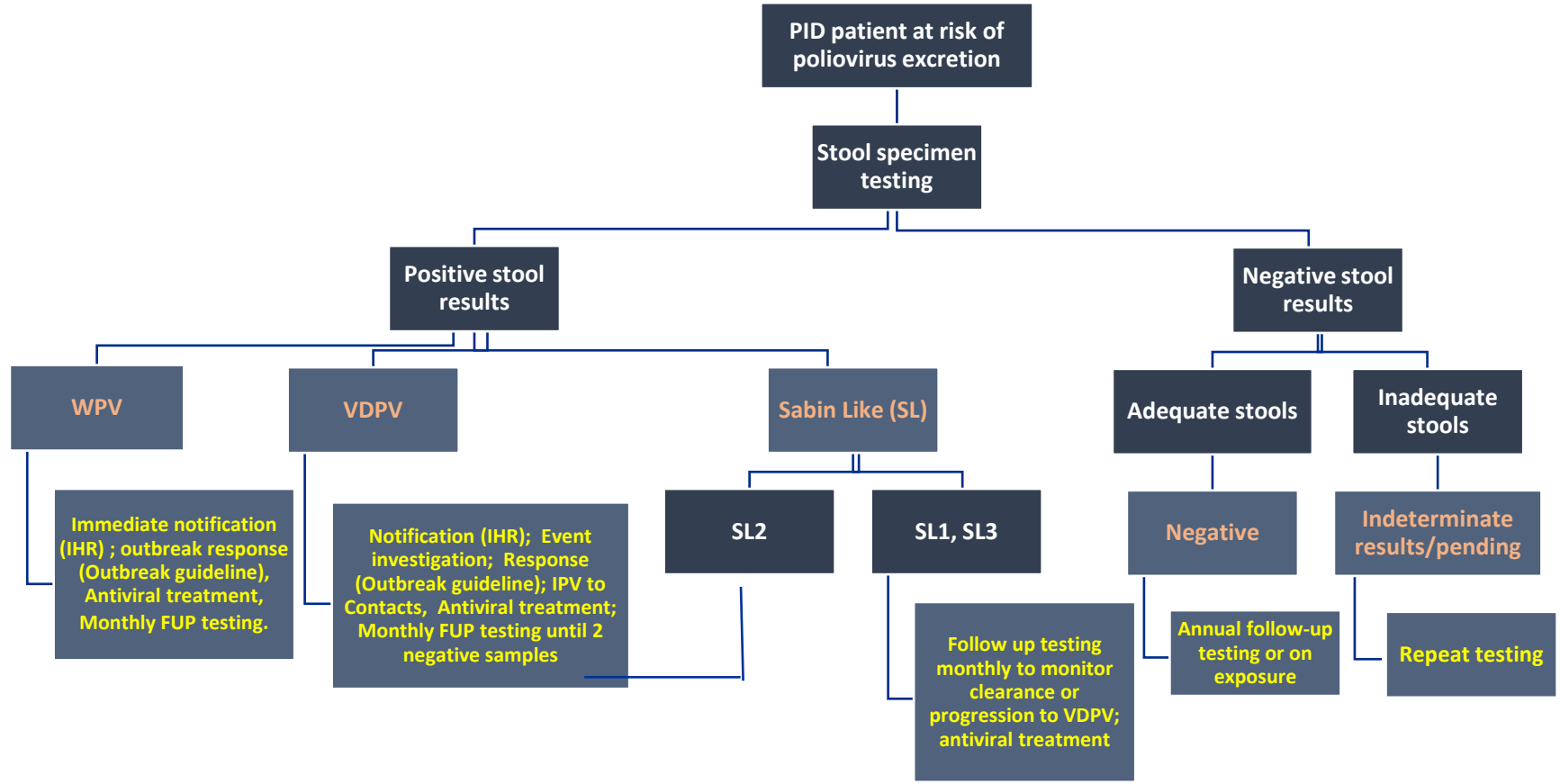
- Number of PID patients at risk of poliovirus excretion reported (and tested) by year, by sentinel facility, and by country
- Number of PID patients with negative poliovirus excretion, prolonged Sabin excretion (more than six months), asymptomatic iVDPV excretion, VAPP or iVDPV by sentinel facility, country, and year
- Spot maps of PID patients with poliovirus excretion by geographic area, country, and year
- Age and sex distribution of PID patients with prolonged Sabin excretion or iVDPV excretion
- Distribution of PID patients diagnosed with prolonged Sabin excretion or iVDPV excretion according to duration of shedding (prolonged versus chronic)
- Distribution of PID patients diagnosed with prolonged Sabin excretion or iVDPV excretion by PID diagnosis
- Percentage of PID individuals diagnosed with prolonged Sabin excretion or iVDPV excretion for whom a detailed investigation (contacts and community) was conducted
- Results of contact and/or environmental sampling conducted to investigate a PID patient with iVDPV excretion
- Percentage of PID patients with prolonged Sabin excretion or iVDPV excretion who received antiviral treatment
- Percentage of PID patients who cleared poliovirus excretion after antiviral treatment
- Percentage of PID patients with NPEV infection
- Outcome of cases (shedding, stop shedding, death, lost to follow-up)

7.3 - Performance indicators

Surveillance for poliovirus excretion among PID patients should be reviewed quarterly at polio eradication data review meetings, together with data from other polio surveillance systems (AFP, ES). The indicators in the table below should be reviewed at all levels at least every six months. Data should also be analyzed in conjunction with information provided by AFP and ES in Annual Country Risk Assessments and reports of the National Committee for the Certification of Poliomyelitis Eradication.

Indicator	Target
Percentage of registered (previously diagnosed) PID patients who are tested for poliovirus excretion per sentinel facility/country. (Denominator should be national registry or facility registry of PID patients that meet the case definition).	≥ 90%
Percentage of PID patients newly diagnosed (in the same year) tested for poliovirus excretion per sentinel facility/country. (Denominator should be national registry or facility registry of PID patients that meet the case definition).	≥ 90%
Percentage of PID patients with poliovirus excretion for whom a detailed case investigation (with contact tracing and community assessment) is conducted within 48 hrs of laboratory results.	≥ 80%
Percentage of specimens arriving at a WHO-accredited laboratory in good condition	≥ 80%
Percentage of specimens arriving at a WHO-accredited laboratory within 3 days of collection	≥ 80%
Percentage of stool specimens for which laboratory results are sent to sentinel facility/submitting agencies within a defined period: - within 14 days of specimen receipt for poliovirus isolation - within 7 days of isolate receipt for intratypic differentiation - within 7 days of intratypic differentiation for sequencing results	≥ 80%
Percentage of follow-up specimens collected out of expected	≥ 80%
Number of active surveillance visits implemented out of planned	≥ 90%

Annex 1 - Classification and decision-making chart



Annex 2 - Antiviral drug therapies

Only two of 250 compounds have met the required antiviral activity and pharmacokinetic and safety profiles to qualify for further development.

- **Pocapavir (V-073)** is a capsid inhibitor that has completed emergency use (EU) Phase 1 single and multiple ascending dose studies and an EU multi-arm placebo-controlled mOPV1 challenge study. It is currently available for compassionate use in and outside the U.S. with open label treatment of 56 NPEV-infected patients and 10 iVDPV-infected patients. An investigational new drug (IND) application was filed for pocapavir in early 2021.
- **V-7404** is a 3c protease inhibitor that is being studied in a Phase 1 clinical study. Unlike pocapavir which is being developed as a single-agent treatment, V-7404 is being developed for combination treatment with pocapavir for PID patients excreting poliovirus and NPEV infections to increase efficacy of the drug and reduce the potential for drug resistance.[1]

Phase 1 clinical study Combo 401 is ongoing and expected to be completed in Q4 2022. Until combined pocapavir and V-7404 treatment becomes available, pocapavir use post-IND approval will be available only under a compassionate use programme. This programme is offered through the antiviral manufacturer ViroDefense, Inc., for PID patients excreting poliovirus or NPEV infections in life-threatening situations (e.g., iVDPVs). For PID patients without life-threatening conditions, ViroDefense recommends maintaining a registry for possible future treatment when the combination treatment becomes available.

WHO can facilitate the importation of available antiviral treatment under compassionate use free of cost and guide the receiving country and institution on regulatory pathway, requirements for use and patient management.

[1] Collett, M. S., J. R. Hincks, K. Benschop, E. Duizer, H. van der Avoort, E. Rhoden, H. Liu, *et al.* "Antiviral Activity of Pocapavir in a Randomized, Blinded, Placebo-Controlled Human Oral Poliovirus Vaccine Challenge Model." *J Infect Dis* 215, no. 3 (Feb 1 2017): 335-43. https://doi.org/10.1093/infdis/jiw542. http://www.ncbi.nlm.nih.gov/pubmed/27932608.

Annex 3 - Recommended data elements

PID Case Investigation Form (Variables)

NOTIFICATION

- Case identification
  - Unique Case Identifier PPD - Country Code - Province Code - District Code – Year – Case Number (PPD-XXX-XX-XX-XX-XXX)
  - First name (Patient)
  - Last name (Patient)
  - Parent or legal guardian's name
  - Physician name
  - Physician's phone number (Number)
  - Country
  - Province
  - District
  - Health facility name
  - Health facility address
  - *Name of reporting person and date*
  - *Health facility record number*
- Demographics
  - Date of birth* (DD/MM/YYYY)
  - Sex (1=male; 2=female; 9=unknown)
  - Residence address (province, district, town/village, street, etc.)
  - Phone number
- Medical History
  - Date of confirmation of PID diagnosis (DD/MM/YYYY)
  - PID diagnosis (1 – Severe Combined Immunodeficiency; 2 – Common Variable Immunodeficiency; 3 – Hypogammaglobulinemia; 4 – Agammaglobulinemia; 5 – Other; 6 – Pending)
    - If 5 – Other, please specify

INVESTIGATION

- (Polio Surveillance Team) Notification date (of confirmed PID to Polio Surveillance Team; DD/MM/YYYY)
- Investigation Date (by polio surveillance; DD/MM/YYYY)
- Paralysis present at the time of first notification (1=Yes, 2=No). If 1-Yes, please notify through the AFP surveillance system – insert AFP EPID number
- Initial Stool Collection Stool 1 Collection Date (DD/MM/YYYY) Stool 2 Collection Date (DD/MM/YYYY)
- Stool date sent to lab (DD/MM/YYYY)
- Date stool specimen arrived at the laboratory* (DD/MM/YYYY)
- Condition of stool on arrival to the laboratory (1=Good, 2=poor, 99=unknown) *
- Laboratory results
  - Date final culture results sent from laboratory to PID physician/EPI*
  - Date intratypic differentiation (ITD) results sent from laboratory to PID physician/EPI*
  - Date genomic sequencing results sent from laboratory to PID physician/EPI*
  - Polio type 1 isolated? (1=yes, 2=no, 3=specimen not processed) *
    - If yes, specify the type (WPV, VDPV, Sabin-like, mixture)
    - If VDPV, number of nucleotide change

- Polio type 2 isolated? (1=yes, 2=no, 3=specimen not processed) **
  - If yes, specify the type (WPV, VDPV, Sabin-like, mixture)
  - If VDPV, number of nucleotide change
- Polio type 3 isolated? (1=yes, 2=no, 3=specimen not processed) **
  - If yes, specify the type (WPV, VDPV, Sabin-like, mixture)
  - If VDPV, number of nucleotide change
- Non-polio enterovirus (NPEV) isolated? (1=yes, 2=no, 3=specimen not processed) * *typing results*

- Classification
  - Current Diagnosis & Classification (1-PID with WPV; 2-PID with VDPV; 3-PID with Sabin; 4-PID negative for polio; 5-PID pending polio lab result)
  - Is the child registered for follow-up stool testing? (1-Yes; 2-No; 99-Not applicable/unknown)
    - If 1-Yes, when is the date for follow-up? (DD/MM/YYYY)

DETAILED INVESTIGATION

- Has the patient received any other treatment for PID
  - IVIG (1 – yes; 2 – no)
  - Bone marrow transplant (1 – yes; 2 – no)
- Other (please explain) immunoglobulin level (mg/dl)

- Polio Vaccination
  - Number of IPV doses received (Number; 99 if unknown
  - Number and type of OPV doses received (Number; 99 if unknown)
  - Date and type of last OPV dose received*
  - Close family members have received OPV doses in last 6 months? (1=Yes, 2=No)
  - Date when family member received OPV *if yes date*
  - Date of last OPV campaign in community

- Classification
  - Is the child eligible for antiviral polio treatment? (1-Yes; 2-No)
  - Is the antiviral polio treatment requested? (1-Yes; 2-No)
  - Date start of treatment (DD/MM/YYYY)
  - Date end of treatment (DD/MM/YYYY)
  - Comments (e.g. type of antiviral, compliance, etc.)
  - Are contact specimen collected (1-Yes; 2-No; 99-Not applicable/unknown)
    - If 1-Yes, fill in PID contact form

References

1. Sutter RW, Kew OM, Cochi SL, Aylward RB. Poliovirus vaccine – live [Chapter 26]. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. 6th ed. Philadelphia: Saunders Elsevier, 2012:598-645.
2. Polio vaccines: WHO position paper – March 2016. *Weekly Epidemiol Record*. Geneva, WHO; 25 Mar 2016; 12:145-167. (https://apps.who.int/iris/bitstream/handle/10665/254399/WER9112_145-168.pdf?sequence=1&isAllowed=y)
3. Platt LR, Estívariz CF, Sutter, RW. Vaccine-associated paralytic poliomyelitis: a review of the epidemiology and estimation of the global burden. *J Infect Dis* 2014 Nov 1;210(S1):S380–9.
4. Burns CC, Diop OM, Sutter RW, Kew OM. Vaccine-derived polioviruses. *J Infect Dis* 2014 Nov 1;210(S1):S283-93.
5. Global Polio Eradication Initiative. Polio Endgame Strategy 2019–2023: Eradication, integration, certification and containment. WHO/POLIO/19.04. Geneva, WHO; 2019. (http://polioeradication.org/wp-content/uploads/2019/06/english-polio-endgame-strategy.pdf)
6. Global Polio Eradication Initiative. Polio today. Circulating Vaccine-Derived Poliovirus. (http://www.polioeradication.org/polio-today/polio-now/this-week/circulating-vaccine-derived-poliovirus)
7. Global Polio Eradication Initiative. Reporting and classification of vaccine-derived polioviruses. (http://polioeradication.org/wp-content/uploads/2016/07/VDPV_ReportingClassification.pdf)
8. Aghamohammadi A, Abolhassani H, Kutukculer N, Wassilak SG, Pallansch MA, Kluglein S et al. Patients with primary immunodeficiencies are a reservoir for neurovirulent vaccine-derived poliovirus strains and represent a risk to the polio eradication. *Front Immunol* 2017;8(685):1-10.
9. Duintjer Tebbens RJ, Thompson KM. Comprehensive screening for immunodeficiency-associated vaccine-derived poliovirus: an essential oral poliovirus vaccine cessation risk management strategy. *Epidemiol Infect.* 2017 Jan;145(2):217-26.
10. McKinlay MA, Collett MS, Hincks JR, Oberste MS, Pallansch MA, Okayasu H, Sutter RW, Modlin JF, Dowdle WR. Progress in the development of poliovirus antiviral agents and their essential role in reducing risks that threaten eradication. *J Infect Dis* 2014 Nov 1;210(S1):S447–53.
11. Kew OM, Sutter RW, de Gourville EM, Dowdle WR, Pallansch MA. Vaccine-derived polioviruses and the endgame strategy for global polio eradication. Annu Rev Microbiol 2005;59:587-635.
12. Alexander LN, Seward JF, Santibanez TA, Pallansch MA, Kew OM, Prevots DR, Strebel PM, Cono J, Wharton M, Orenstein WA, Sutter RW. Vaccine policy changes and epidemiology of poliomyelitis in the United States. JAMA 2014 October 13;292(14):1696-701.
13. Meeting of the Strategic Advisory Group of Experts on immunization, April 2019 – conclusions and recommendations; Weekly Epidemiological Record, Nos 22/23, 31 May 2019. https://apps.who.int/iris/bitstream/handle/10665/325018/WER9422-23-261-279-en-fr.pdf?sequence=1&isAllowed=y

14. Li L, Ivanova O, Driss N, Tiongco-Recto M, da Silva R, Shahmahmoodi S, et al. Poliovirus excretion among persons with primary immune deficiency disorders: summary of a seven-country study series. *J Infect Dis* 2014 Nov 1;210(S1):S368-72.

15. Hennessey KA, Lago H, Diomande F, Akoua-Koffi C, Caceres VM, Pallansch M, et al. Poliovirus vaccine shedding among persons with HIV in Abidjan, Cote d'Ivoire. *J Infect Dis* 2005 Dec 15;192(12):2124-8.

16. Alexander JP, Ehresmann K, Seward J, Wax G, Harriman K, Fuller S, et al. Transmission of imported vaccine-derived poliovirus in an undervaccinated community in Minnesota. *J Infect Dis* 2009 Feb 1;199(3):391-7.

17. Avellon A, Cabrerizo M, de Miguel T, et al. Paralysis case and contact spread of recombinant vaccine-derived poliovirus, Spain. *Emerg Infect Dis* 2008;14(11):1807-9.

18. Ryder RW, Oxtoby MJ, Mvula M, Batter V, Baende E, Nsa W, et al. Safety and immunogenicity of Bacille Calmette-Guerin, diphtheria-tetanus-pertussis, and oral polio vaccines in newborn children in Zaire infected with human immunodeficiency virus type 1. *J Pediatr* 1993 May;122(5 Pt 1):697-702.

19. Global Polio Eradication Initiative. Surveillance for Acute Flaccid Paralysis (in preparation).

20. Global Polio Eradication Initiative. Standard operating procedures for responding to a poliovirus event or outbreak. 4th version. Geneva: World Health Organization, 2022. *(https://polioeradication.org/wp-content/uploads/2022/04/Standard-Operating-Procedures-For-Responding-to-a-Poliovirus-Event-Or-Outbreak-20220417_OBR_SOP_final_pre_pub_website.pdf)*