POLIO GLOBAL ERADICATION INITIATIVE

Classification and reporting of vaccine-derived polioviruses (VDPV)

GPEI guidelines

August 2016

1- Importance of sensitive and timely surveillance for VDPVs

With continued progress towards global interruption of wild poliovirus transmission, it is increasingly important to manage the risks associated with circulating vaccine-derived poliovirus (cVDPV) that can cause paralysis. Almost 500 children were paralyzed by cVDPV, largely type 2, in outbreaks reported during the last 10 years.

Indigenous wild poliovirus type 2 (WPV2) was last isolated in October 1999 in India and the Global Commission for the Certification of Poliomyelitis Eradication (GCC) concluded in September 2015 that indigenous WPV2 had been eradicated worldwide.

Sporadic vaccine-derived poliovirus type 2 (VDPV2) isolates continue to be detected. To eliminate the risk associated with type 2 oral polio vaccine (OPV2), the use of OPV2 was stopped in May, 2016 through a globally synchronized 'switch' to replace trivalent (types 1, 2 and 3) with bivalent (type 1 and 3) OPV in all OPV-using countries.

At their April 2016 meeting, SAGE, the WHO Strategic Advisory Group of Experts on immunization, noted that a small number of cVDPV2 outbreaks are expected within 12 months after the tOPV-bOPV switch. SAGE recommended that the GPEI should enhance surveillance for polioviruses, particularly in countries with high risk of VDPV emergence, and respond to any emergence of VDPV2 post-switch as an emergency.

Currently, VDPV isolates are being reported from laboratories of the Global Polio Lab Network (GPLN) to WHO Regional Offices and HQ. However, the criteria and processes used to classify VDPV isolates according to their programmatic importance, including the additional investigations needed in the field to support such classification (see below), are not yet sufficiently standardized.

It is urgent for the polio eradication endgame to improve the timeliness and completeness of VDPV reporting and classification.

2- Definitions

The following definitions have been developed, taking into account both virological and epidemiological considerations; they should be used when referring to vaccine-derived polioviruses:

a) ***Vaccine-derived poliovirus (VDPV):*** OPV virus strains that are > 1% divergent (or >= 10 nt changes, for types 1 and 3) or > 0.6% divergent (>= 6 NT changes, for type 2) from the corresponding OPV strain in the complete VP1 genomic region.

b) ***Circulating VDPV (cVDPV)*****:** VDPV isolates for which there is evidence of person-to-person transmission in the community. The following definition was used previously to classify a VDPV as 'circulating':

- '*genetically linked VDPVs isolated from at least two AFP cases*'.

To improve the sensitivity of surveillance in detecting circulating VDPVs, the following new 'cVDPV' definition should now be used:

- *genetically linked VDPVs, isolated:*
  - *i) from at least two individuals (not necessarily AFP cases), who are not direct (i.e. household) contacts,*
  - *ii) from one individual and one or more environmental surveillance (ES) samples, or*
  - *iii) from two or more ES samples if they were collected at more than one distinct ES collection site (no overlapping of catchment areas), or from one site if collection was more than two months apart*[1].

c) Immune-deficiency associated VDPV (iVDPV): VDPVs isolated from persons with evidence of primary immunodeficiency (PID).

d) ***Ambiguous VDPV (aVDPV)*****:** a VDPV isolate from individuals or from environmental samples, without evidence of circulation and from individuals with no known immunodeficiency.

A VDPV isolate should only be classified as 'ambiguous' once additional investigations have excluded that it is part of an ongoing chain of transmission, i.e. a cVDPV, or derived from an iVDPV.

Such investigations should include enhanced surveillance for AFP cases in the area and collection of stool specimens from healthy persons in the community (see section 5 below). Efforts to rule out local circulation should be particularly intense if sequencing of the index VDPV isolate is consistent with prolonged independent replication.

A VDPV classified as 'ambiguous' may need to be reclassified as 'circulating' if genetically linked isolates are found subsequently.

[1] Classification as 'c'VDPV' for this scenario only after detailed joint review of complete epidemiological and virological evidence by regional and global polio lab coordinators and other GPLN experts

3- Virus isolation, VDPV detection and VDPV classification

The GPLN uses standardized laboratory algorithms to screen **poliovirus (PV) isolates** obtained from any source for possible VDPV status, including AFP cases, contacts of AFP cases, healthy individuals, environmental samples, or any other source, such as routine enterovirus diagnosis or enterovirus surveillance. All isolates that are non-vaccine-like or discordant in intratypic differentiation (ITD) tests are referred to a WHO-accredited polio sequencing laboratory for genetic sequencing. On average, only a small percentage (i.e. 5% or less) of PV isolates screened out as 'ITD-discordant' are confirmed as VDPV.

The only way to confirm **VDPV status** is through sequencing of the VP1 region of the poliovirus genome. As soon as the final sequencing result is available, the sequencing laboratory determines whether the VDPV is genetically linked to other current or historical VDPVs found in the country of origin or elsewhere, or if the isolate is a newly emerged, not previously detected strain of VDPV. The sequencing lab shares this result with the laboratory that referred the isolate, with the respective country immunization programme, and with the polio teams at the WHO Regional Office and at WHO HQ.

New VDPV isolates, regardless of source, need to be **classified** without delay as either cVDPV, iVDPV or aVDPV, based on all available laboratory and epidemiological data, in order to consider their programmatic importance (see Figure 1). The WHO regional polio laboratory coordinator and the regional adviser for polio eradication, in consultation with the sequencing laboratory, the global polio lab coordinator, and designated experts from the WHO/HQ polio team, have the main responsibility for the timely final classification of the VDPV isolate.

It is important to note that, following the tOPV-bOPV switch in May 2016, **any newly detected VDPV2 isolate** must prompt an immediate response (investigation and preparation for a rapid immunisation response) without waiting for final classification of the VDPV (see section 6, below). Final classification remains urgent, however, because it may lead to expanding the scope of the immunisation response.

The most urgent programmatic need for VDPV classification is to establish whether the new isolate belongs to a chain of cVDPVs. If the new isolate is genetically linked to one or more previously found isolates, classification as 'cVDPV' is straightforward. Further investigations in the field are needed before a new VPDV isolate, for which no genetic linkage with currently circulating or historical VDPVs is found, can be classified. A new isolate can only be classified as aVDPV, once 'c' and 'i' VDPV status have been reliably excluded following further more detailed investigations.

For all reported VDPVs, the WHO RO team, in close coordination with WHO country teams and if required with WHO/HQ, should rapidly plan and coordinate a series of additional epidemiological, contact and case investigations in the field to facilitate final classification (see section 5 and Figure 1).

4- Routine weekly reporting of new VDPV isolates

To improve global surveillance for VDPVs, **WHO Regional Office polio teams** should submit to WHO HQ a weekly line listing of all VDPV isolates reported from GPLN sequencing labs. A standardized format/template should be used for the weekly reports (see Figure 2). Completeness of information including follow-up/update on any VDPV pending classification should be included before submission of the template.

This weekly reporting of VDPVs will be similar to the weekly reporting of WPV isolates, and should include **all VDPV isolates** from the Region detected in GPLN laboratories, regardless of source (AFP cases, healthy individuals, and environmental samples) or current classification status.

The **WHO HQ polio team** will include detailed and timely VDPV data in reports and weekly updates provided to the GPEI and to the public.

5- Main field activities following the report of a new VDPV

Coordinated by the WHO Country Office team, and with guidance from WHO Regional and HQ level, the respective MoH/WHO polio country team should conduct the following key activities to facilitate final VDPV classification and response:

a) Detailed epidemiological investigation in the area where the VDPV-positive AFP case resides, or in the community surrounding the VDPV-positive environmental sampling site, including:

i) an active search for unreported AFP cases and a retrospective AFP case search in local health facilities (review of patient registers covering at least the last 6 months) and measures to enhance AFP reporting;

ii) a community immunization coverage survey - i.e. a house-to-house survey of at least 20 households with one or more child under five years of age to determine the polio immunization status of all children 6 weeks to < 5 Years old in the neighbourhood of the index case;

III) an assessment of administrative (reported) polio vaccination coverage for the district in recent years.

b) Full clinical examination of the AFP case from whom VDPV was isolated, to check for possible immunodeficiency. The investigation should include detailed medical and travel histories and physical examination to search for evidence of repeated infections, hereditary conditions, or other signs of possible PID, using the attached table with 'ten warning signs of primary immunodeficiency' (Figure 2). If history and clinical examination suggest possible immunodeficiency, a blood sample should be drawn and sent to a lab for basic laboratory immune screening (i.e. quantification of immunoglobulins - QIG).

c) *For VDPV isolates from AFP cases*: collection of one stool specimen from at least 5 direct contacts of the AFP case (i.e. siblings, household contacts, playmates) as well as from at least 20 healthy persons of the same age group living in the community of the VDPV-positive AFP case (i.e., in another part of the village or in a nearby village). Under certain circumstances (e.g., if the quality of AFP surveillance in the area is low), and in consultation with WHO Regional Office and possibly HQ teams, a decision should be made whether to sample a larger number of healthy persons in the community, and/or from a wider area.

For VDPV isolates detected in environmental samples: stool surveys of healthy persons in the community will not be done routinely, except under special circumstances, following consultation between virologists and epidemiologists.

d) For any iVDPV-positive person identified (i.e. patient diagnosed with primary immune deficiency - PID who excretes VDPV), the collection of a stool sample each month should be organized, until results have been negative for two successive months.

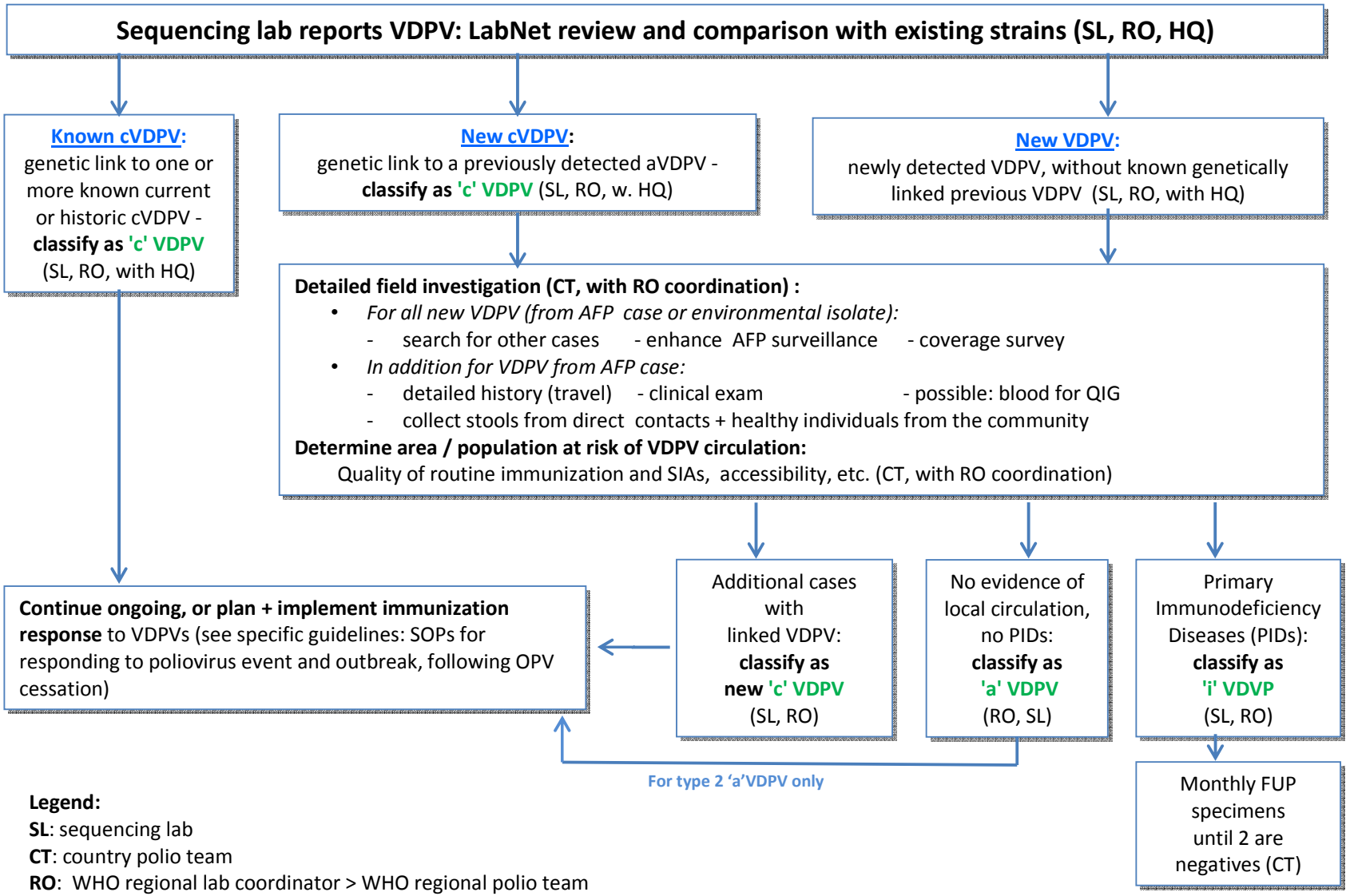
e) Assessment of the value and opportunities to introduce or enhance existing environmental surveillance within the wider area by expanding the number of sampling sites and/or increasing sampling frequency.

f) To help in planning response immunization to cVDPV or newly emerged aVDPV, the area at risk for VDPV transmission should be defined, based on results of community coverage survey as well as routine and SIA coverage results at district and sub-district level.

6- Immunization response to VDPV2

Standard Operating Procedures (SOPs) have been drafted (here are links to part 1 and part 2) which describe the response to all types and type 2 poliovirus event and outbreaks post-switch in detail.

Figure 1: Classification of and response to reported VDPV isolates



Legend:
SL: sequencing lab
CT: country polio team
RO: WHO regional lab coordinator > WHO regional polio team
HQ: WHO HQ lab coordinator > WHO HQ polio team

Table 1: 10 Warning Signs of primary immunodeficiency diseases (PIDs). (©2009 Jeffrey Modell Foundation)

Children up to age 18: If your child has two or more of these signs, Primary Immunodeficiency becomes more likely as the underlying case.

1	**Four or more new ear infections within 1 year**
2	**Two or more serious sinus infections within 1 year**
3	**Two or more months on antibiotics with little effect**
4	**Two or more pneumonias within 1 year**
5	**Failure of an infant to gain weight or grow normally**
6	**Recurrent, deep skin or organ abscesses**
7	**Persistent thrush in mouth or fungal infection on skin**
8	**Need for intravenous antibiotics to clear infections**
9	**Two or more deep-seated infections including septicemia**
10	**A family history of Primary Immunodeficiency**

Figure 2: Templates for the reporting of VDPVs from human and environnemental samples (rev 11Nov.2015)

Data Intructions for completing the VDPV Reporting Template

(rev 11Nov.2015)

Table Variables	Description
Region	4 character region code (SEARO = 5)
Lab Name	Name of Laboratory. Use same Code as in Lab Database
Country	Country name
Province	Province / State name
District	District name
ES Site Code	Country (3 digit code) /Admin1/Admin2/Unique Code assigned by Lab
ES Collection Site Name	Name/Location of env. sample collection site
EPID No.	EPID number of AFP, contact, community sample, healthy child, or Environmental Sample. Same EPID. No. in Lab. database.
Specimen ID	Unique Specimen ID/code assigned by laboratory
Source	Human Source of specimen (AFP, Contact, healthy, iVDPV research study, others);
EPID No. of Index case	EPID No. number of negative AFP case (or case without specimen) reported as VDPV from other source, e.g. Contact)
Patient Name	Patient Name
Gender	Male, Female, Unknown
Date of birth (DD/MM/YYYY)	Date of birth (DD/MM/YYYY)
Age (in months)	Age in months (integer)
Total OPV doses	Total OPV doses received through routine and SIA (Integer)
Date of paralysis onset	Date of paralysis onset of AFP case (DD/MM/YYYY)
Sample collection date	Date 1st sample positive for VDPV was collected (DD/MM/YYYY)
VDPV Type	Serotype VDPV1, VDPV2, VDPV3
VDPV Category	Indicate if aVDPV, cVDPV, iVDPV, pending
Date of classification	Date classified as aVDPV, cVDPV or iVDPV following field investigation, Blank (pending)
NT_Diff From homogous Sabin	Number of nucleotide difference from parental Sabin strain (Integer)
% Homology to Sabin	Percentage homology to parental Sabin strain (Number/Decimal)
EPID No. of closest match to cVDPV	EPID No. (Case / Contact / Healthy / ENV/Others) that has the closest sequence match to cVDPV being reported:
Cluster	Transmission link/Emergence Group/Cluster
Comments	Any other information such as: another closest match EPID No.; Orphan virus; Lab. result of "Index Case" if classified from other sources, "Nth follow-up specimen" of an iVDPV case, etc.
Date reported to WHO RO	Date sample/case reported to Regional Office (DD/MM/YYYY)
Date reported to WHO HQ	Date sample/case officially reported to HQ (DD/MM/YYYY)

Reporting template for VDPV from Human Sources

(rev 11Nov.2015)

Region	Lab Name	Country	Province	District	EPID No.	Specimen ID	Source (AFP, Contact, healthy, others)	EPID No. of Index case (if classified from other source)	Patient Name	Gender	Date of birth (DD/MM/YYYY)	Age (in mos.)	Total OPV doses	Date of paralysis onset (DD/MM/YYYY)	Stool Collection date (1st Positive sample) (DD/MM/YYYY)	VDPV Type	VDPV Category	Date of classification (DD/MM/YYYY)	nt_Diff from homologous Sabin	% Homology to Sabin	Cluster or Emergence Group	EPID No. closest match to cVDPV	Comments	Date reported to WHO RO (DD/MM/YYYY)	Date official reporting to WHO/HQ (DD/MM/YYYY)

Reporting template for VDPV from Environmental Sources

(rev 11Nov.2015)

REGION	Lab Name	Country	Province	District	ES Site Code	ES Collection Site Name	EPID No.	Specimen ID	Date collected (DD/MM/YYYY)	VDPV Type	VDPV category	Date of classification (DD/MM/YYYY)	nt_diff from homologous Sabin	% Homology to Sabin	Cluster or Emergence Group	EPID. No. of cVDPV closest match	Comments	Date Reported to RO (DD/MM/YYYY)	Date official reporting to WHO/HQ (DD/MM/YYYY)