

Reporting and classification of
**vaccine-derived
polioviruses**

GPEI guidelines

July 2015

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.

Wild poliovirus type 2 (WPV2) was last isolated in October 1999 in India and is thought to be eradicated. In 2014, persistent cVDPV2 strains circulated only in northern Nigeria and Pakistan and several persistent strains were likely interrupted in both countries during 2014.

The use of type 2 OPV, the source of cVDPV2, should be stopped as soon as possible. As part of the 'polio endgame', the GPEI Strategic Plan 2013-2018 calls for the cessation of OPV2 use as soon as this can be done with no or minimal risk. OPV2 will be stopped through a globally synchronized switch (also called OPV2 withdrawal) to replace trivalent OPV (tOPV) with bivalent OPV (bOPV, not containing OPV2) for routine vaccination in all OPV-using countries; as of mid-2015, this switch is scheduled for April 2016.

The SAGE (WHO's Scientific Advisory Group of Experts on Immunization) has determined that the interruption of all persistent transmission of cVDPV2 strains is a key precondition for the tOPV-bOPV switch. Therefore, global surveillance for VDPVs during 2015 and beyond needs to be as sensitive, timely and complete as the surveillance for wild polioviruses.

Currently, VDPV isolates are being reported from laboratories of the Global Polio Lab Network (GPLN) to WHO Regional Offices and HQ. However, VDPV reporting does not follow the same procedures and pathways as reporting of wild polioviruses. Also, 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 sufficiently standardized.

It is urgent to improve the timeliness and completeness of VDPV reporting and classification.

2 Definitions

The following definitions have been developed, taking into consideration both virologic 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 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 apart¹

or

- *a single VDPV isolate, with genetic features indicating prolonged circulation (i.e. a number of nucleotide changes suggesting > 1.5 yrs of independent circulation).*

c) *Immune-deficiency associated VDPV (iVDPV)*: VDPVs isolated from persons with proven immunodeficiencies.

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

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

A VDPV classified as 'ambiguous' may need to be reclassified as 'c' or 'i', if there is subsequent evidence of circulation or of derivation from an immune-deficient individual.

3 Virus isolation, VDPV detection and VDPV classification

The Global Polio Laboratory Network (GPLN) uses standardized laboratory algorithms to screen poliovirus isolates obtained from any source (AFP cases, contacts of AFP cases, healthy individuals, environmental samples, or any other source, including routine enteroviral diagnosis or enterovirus surveillance) for possible VDPV status. 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 or elsewhere, or 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 programme, and with the polio teams at the WHO Regional Office and at HQ.

New VDPV isolates need to be classified, without delay, as either 'circulating' (c) VDPV, 'immune-deficiency associated' (i) or 'ambiguous' (a) VDPV, based on all available laboratory and epidemiological data, in order to consider their programmatic importance (see Figure 1). The regional polio lab coordinator and the regional adviser for Polio, 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, from mid-2015 onwards, any new VDPV isolate must prompt a rapid immunisation response, without waiting for final classification of the VDPV (see section 6, below). Classification remains urgent, however, because it may lead to the scope of the immunisation response being expanded.

¹ Classification as 'cVDPV' 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

The most urgent programmatic need for VDPV classification is to establish whether the new isolate belongs to a chain of circulating VDPVs. 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 VDPV isolate, for which no genetic linkage with currently circulating or historical VDPVs is found, can be classified. Only if 'c' and 'i' VDPV status cannot be confirmed following further more detailed epidemiological and case investigations (responsibility of regional and country polio teams), should the new isolate be classified as 'ambiguous' (aVDPV).

For all VDPVs, especially those without link to previously isolated strains, as well as for all cVDPVs reported from new areas of a country, the RO team, in close coordination with country teams and if needed with WHO/HQ, should rapidly plan and coordinate a series of additional epidemiological and case investigations in the field to facilitate final classification (see 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 vaccine-derived poliovirus isolates newly reported from GPLN sequencing labs.* A standardized format should be used for the weekly reports (see template, Figure 2).

This weekly reporting of VDPVs will be similar to the weekly reporting of wild poliovirus isolates, and should include all new VDPV isolates from the Region detected in GPLN laboratories, regardless of source (AFP cases, healthy contacts, environmental samples) or current classification status (see below). The 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 AFP case (or contact) resides, including
 - an active search for additional unreported cases and retrospective case search in local health facilities (review of patient registers) and to take measures to enhance AFP reporting
 - to conduct a community immunization coverage survey - i.e. a house-to-house survey of at least 20 houses with a child under five years of age to determine polio immunization status of all children 6 weeks to < 5 yrs in the neighbourhood of the index case;
 - an assessment of administrative (reported) polio vaccination coverage for the district in recent years.
- b) Full clinical follow-up examination of the individual (AFP case and/or contact) from whom VDPV was isolated, to check for a possible immune deficiency. The investigation should include detailed medical and travel history and physical examination to search for evidence of repeated infections, hereditary conditions, or other signs of possible immunodeficiency (using the attached table with 'ten warning signs of primary immunodeficiency - Table 1). Blood should be drawn and sent to a lab for basic laboratory immune screening (i.e. quantification of immunoglobulins).
- c) Collection of one stool specimen from at least 5 immediate contacts of the VDPV-positive person (i.e. siblings, household contacts, playmates) as well as from at least 10 persons of the

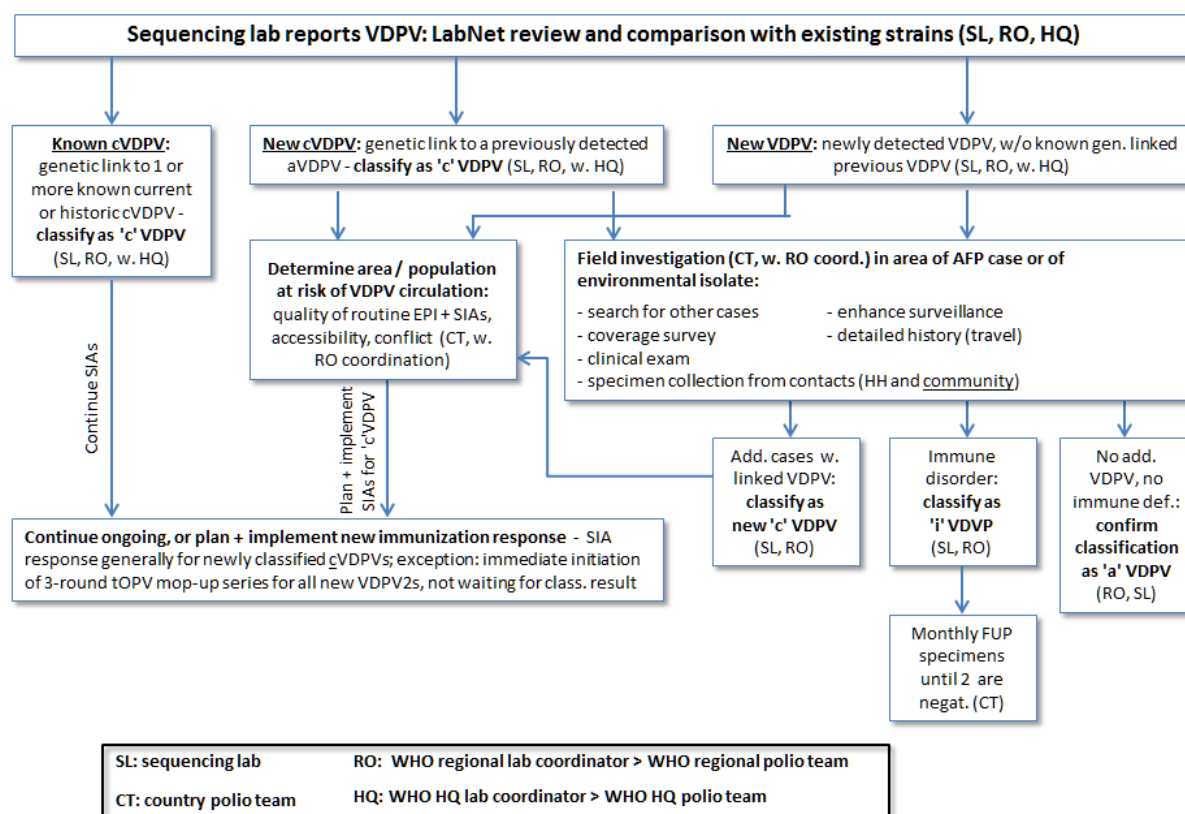
same age group living in the community (i.e. in another part of the village or in a nearby village) of the VDPV-positive person. Under certain circumstances (i.e. if the quality of AFP surveillance in the area is low), and in consultation with WHO Regional Office and possibly HQ teams, a decision should be made whether to sample a larger number of community contacts, from a wider area.

- d) For any i-VDPV-positive person identified, the collection of a stool sample each month should be organized, until results have been negative for two successive months.
- e) Assess the value and opportunities within the wider area to introduce or enhance existing environmental surveillance 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 during the period before withdrawal of type 2 OPV

From mid-2015, rapid response mop-up immunization should be initiated within 14 days of diagnosis for every report of VDPV2, before and regardless of final classification. The size of target population and geographic scope should be determined based on risk of spread and estimated duration of circulation before detection. At least 3 tOPV rounds should be planned and conducted. The required response is described further in a separate WHO operational guidance note.

Figure 1: Classification of and response to reported VDPV isolates



The '10 Warning Signs' of primary immunodeficiency

Children up to age 18

- If a child has two or more of these signs, primary immunodeficiency becomes more likely as the underlying cause.

| | |
|----|---|
| 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 |

Table 1: The ten warning signs of primary immunodeficiency (Jeffrey Modell Foundation, 2014)

Proposed Reporting template for Human VDPV
(ver. 3.23.06.2015)

| Region | Country | Province | District | EPID No. | SpecimenID | Source (WV, Contact, healthy, others) | Patient Name | Gender | Date of Birth (DDMM/YYYY) | Age (in mos.) | Total OPV doses | Date of paralytic onset (DDMM/YYYY) | Stool Collection Date (Last Positive sample) (DDMM/YYYY) | VDPV Category Type | VDPV Category | RT ₂ GH from Subin | % Homology to Subin | Cluster or Emergence Group | EPID No. does match to VDPV | Comments | Date reported to WHO/RO (DDMM/YYYY) | | |
|--------|---------|----------|----------|----------|------------|---|-----------------|--------|------------------------------|------------------|--------------------|---|---|--------------------------|------------------|-------------------------------------|---------------------------|----------------------------------|--------------------------------|----------|--|--|--|
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Proposed Reporting template for ENV VDPV
(ver. 3.27.2015)

| REGION | COUNTRY | Province | District | ES Site ID | ES Collection Site Name | EPID No. | Specimen ID | Date collected | VDPV Type | VDPV category | Rt ₂ GH from Subin | % Homology to Subin | Cluster or Emergence Group | EPID No. of closest match | Comments | Date Reported to RO | |
|--------|---------|----------|----------|------------|-------------------------|----------|-------------|-------------------|-----------|------------------|----------------------------------|------------------------|----------------------------------|------------------------------|----------|------------------------|--|
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Figure 2: templates for the reporting of VDPVs from humans and environmental samples



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