Standard
Operating
Procedures

Responding to a poliovirus event and outbreak

Part 2: Protocol for poliovirus type 2

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List of acronyms

AFP	Acute flaccid paralysis
aVDPV	Ambiguous vaccine-derived poliovirus
bOPV	Bivalent OPV (contains Sabin 1 and 3)
cVDPV	Circulating vaccine-derived poliovirus
EOMG	Eradication and Outbreak Management Group
EOC	Emergency Operations Center
ES	Environmental surveillance
GAPIII	Third edition of the Global Action Plan to minimize post-eradication poliovirus facility-associated risk
GCC	Global Commission for Certification of the Eradication of Poliomyelitis
GPEI	Global Polio Eradication Initiative
GPLN	Global Polio Laboratory Network
ICG	Interagency Coordinating Group
IHR	International Health Regulations (2005)
IPV	Inactivated polio vaccine
ITD	Intratypic differentiation
iVDPV	Immunodeficiency-associated vaccine-derived poliovirus
mOPV2	monovalent oral polio vaccine type 2
NRA	National Regulatory Authority
OPV	Oral polio vaccine
OPV2	Oral polio vaccine type 2
OBRA	Outbreak Response Assessment
OPRTT	Outbreak Preparedness and Response Task Team
PHEIC	Public health emergency of international concern
RO	Regional Office
RRT	Rapid Response Team
SIA	Supplementary immunization activity
SL	Sabin like poliovirus
tOPV	Trivalent oral polio vaccine (contains Sabin 1, 2 and 3)
VAPP	Vaccine-associated paralytic poliomyelitis
VDPV	Vaccine-derived poliovirus
VDPV2	Vaccine-derived poliovirus type 2
WHA	World Health Assembly
WHO	World Health Organization
WPV	Wild poliovirus
WPV2	Wild poliovirus type 2

1- Introduction

The last detected case of wild poliovirus (WPV) type 2 (WPV2) anywhere in the world occurred in 1999. On 20 September 2015, the Global Commission for the Certification of Poliomyelitis Eradication (GCC) formally declared that WPV2 has been eradicated.[1] However, the continued use of oral polio vaccine (OPV) type 2 component (OPV2) remains responsible for the vast majority of circulating vaccine-derived poliovirus (cVDPV) cases and a substantial portion of vaccine associated paralytic poliomyelitis (VAPP) cases. In order to address this situation and the wider implications of OPV use after global wild poliovirus eradication, Objective 2 of the *Polio Eradication and Endgame Strategic Plan 2013-2018*[2] proposes an endgame strategy of three sequential steps: 1. Introduce at least one dose of inactivated polio vaccine (IPV) into routine immunization in all countries; 2. Cease using type 2-containing oral polio vaccine (OPV2) by a globally-coordinated switch from trivalent OPV (tOPV) to bivalent OPV (bOPV); and 3. Eventually globally-coordinate withdrawal of all OPV.[3]

As of April 2016, all 156 countries and territories using tOPV have either already introduced or made formal commitments to introduce at least one dose of IPV into their routine immunization programs. Consequently, step 2, the globally coordinated switch from tOPV to bOPV (e.g. OPV2 cessation), is on track to proceed between 17 April and 1 May 2016.

Following OPV2 cessation, population immunity and especially intestinal immunity and secondary spread of type 2 OPV-related viruses will decline, which will increase the risk of an outbreak if exposure to a type 2 poliovirus occurs.[4] Three main outbreak threats following OPV2 cessation are: a relatively higher, but primarily short-term risk of the emergence of a cVDPV; a lower, long term risk of poliovirus re-introduction from a manufacturing site or laboratory; and a small, but potentially larger threat in the future posed by prolonged or chronic poliovirus infection in individuals with B-cell related primary immunodeficiencies (e.g. immunodeficiency-related vaccine-derived poliovirus [iVDPV]).[5] Since WPV2 has been declared eradicated and OPV2 should no longer be in use after the tOPV to bOPV switch, the detection of any poliovirus type 2 (wild, vaccine derived, or Sabin) in any sample of any source after the switch will be considered a global public health emergency that requires a concrete strategy with rapid and high-quality coordinated action from the Global Polio Eradication Initiative (GPEI) and national and sub-national health agencies.

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[1] http://www.polioeradication.org/mediaroom/newsstories/Global-eradication-of-wild-poliovirus-type-2-declared/tabid/526/news/1289/Default.aspx

[2] http://www.polioeradication.org/resourcelibrary/strategyandwork.aspx

[3] For a detailed analysis for the rationale to withdraw OPV post WPV eradication see: Duintjer Tebbens RJ, et al. Risks of paralytic disease due to wild or vaccine-derived poliovirus after eradication. Risk Analysis 2006; 26(6):1471-1505 and Thompson KM et al. The risks, costs, and benefits of future global policies for managing polioviruses. American Journal of Public Health 2008; 98(7):1322-1330.

[4] For modeling of the risks associated with withdrawal of OPV see: Thompson KM, Duintjer Tebbens RJ. Modeling the dynamics of oral poliovirus vaccine cessation. J Infect Dis. (2014) 210 (suppl 1): S475-S484.

[5] For modeling of the risks associated with iVDPVs see: Duintjer Tebbens RJ, Pallansch MA, Thompson KM. Modeling the prevalence of immunodeficiency-associated long-term vaccine-derived poliovirus excretors and the potential benefits of antiviral drugs. BMC Infectious Diseases 2015; 15:379, doi: 10.1186/s12879-015-1115-5.

There is a high probability that at least one cVDPV2 and possibly multiple other VDPV2s will emerge within 12 months of the global switch from the use of tOPV to bOPV. The strategic actions following detection of a type 2 poliovirus isolate after OPV2 cessation have the same basic approaches and principles to those currently required for investigating and responding to any polio outbreak as outlined in the Standard Operating Procedures. However, the post-OPV2 era will require a heightened urgency, vigilant surveillance, a carefully planned risk assessment, and usually a specific vaccine response due to the world entering truly new territory with associated uncertainties surrounding the consequences of re-introducing an eradicated pathogen. **(See Table 4, page 24 for a summary of features specific to a type 2 outbreak response.)**

2- Protocol objectives and scope

The objectives of this document are:

1. Outline the main elements of the strategy to detect and respond appropriately to any type 2 polioviruses from environmental sources or circulating in the population post OPV2 cessation.
2. Provide guidance to global, regional and national public health officials and policy makers for the necessary steps required to rapidly notify the proper authorities, conduct an initial risk assessment, and develop an effective response to promptly curtail any type 2 poliovirus outbreaks.

This proposed strategy is based on evidence from past and current program experience dealing with polioviruses as well as existing models projecting possible scenarios.[6] Development of these guidelines is an iterative process that will evolve as further evidence and experience are generated. **While this version of the protocol lays out overall strategic imperatives for dealing with all future type 2 outbreaks, the recommendations focus only on the response required within in the first 12 months following OPV2 cessation (e.g. May 2016 to April 2017).** Further recommendations will be developed in 2017.

These guidelines are intended to provide concrete parameters for decision making, yet they cannot address every possible scenario. Decision makers should flexibly interpret the protocol and actively consider their specific epidemiologic circumstances. In particular, the protocol's recommendations for vaccine use in an outbreak response are targeted specifically to countries which have used OPV within 1 year of the switch. However, any WPV2 or VDPV2 detected in the post-switch era in any country (even in those with exclusive IPV use) must be considered a potential global risk. Given the potential for Sabin type 2 polioviruses to evolve into cVDPV2s, detection of Sabin type 2 polioviruses more than 4 months after the switch and/or use of mOPV2 in responding to a type 2 event or outbreak in any country must also be considered a potential global risk. While detection of a type 2 poliovirus in one location may not

[6] Modeling studies include Duintjer Tebbens RJ, Pallansch MA, Cochi SL, Wassalik SGF, Thompson KM. An economic analysis of poliovirus risk management policy options for 2013-2052. BMC Infectious Diseases 2015; 15:389, doi: 10.1186/s12879-015-1112-8; and Duintjer Tebbens RJ, Pallansch MA, Cochi SL, Wassalik SGF, Thompson KM. Characterization of outbreak response strategies and potential vaccine stockpile needs for the polio endgame. BMC Infectious Diseases 2016; 16:137, doi: 10.1186/s12879-016-1465-7.

generate sufficient concern of further transmission to necessitate an immediate local vaccination campaign, an urgent and aggressive investigation may still be required to trace the origin of the virus in order to rapidly determine an appropriate response at the initial source of the outbreak.

2- Background -preparation for type 2 OPV withdrawal

In May 2014, the World Health Assembly (WHA) adopted criteria which the Strategic Advisory Group of Experts on Immunization (SAGE) recommended to gauge global readiness for OPV2 cessation.[7] OPV2 withdrawal is dependent on satisfying these readiness criteria and the global interruption of persistent cVDPV2 transmission.

Primary actions required at the global level by GPEI:

- Establish a global stockpile of monovalent oral polio vaccine (mOPV) type 2 (mOPV2) for outbreak use (See **Annex A** for details on stockpile operations)
- Provide global guidelines and technical assistance as required to implement Objective 2[8]
- Verify global eradication of wild poliovirus type 2 (completed in September 2015)

Primary actions required at the national level by public health authorities:

- Introduce at least one dose of IPV into routine immunization in OPV-only using countries[9]
- Conduct one or more tOPV campaigns just prior to OPV2 cessation (if OPV coverage levels indicate population could be at risk for type 2 outbreak)
- Strengthen outbreak response capacity and ensure that all relevant public health officials are aware of the recommendations outlined in this protocol in the case of a type 2 outbreak.
- Institute appropriate containment measures as required under the Global Action Plan III (GAPIII)[10]
- Ensure that bOPV is licensed for routine immunization

[7] See World Health Assembly. Poliomyelitis: intensification of the global eradication initiative. Report by the Secretariat. Geneva: World Health Organization, 2014 http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_38-en.pdf; and Meeting of the Strategic Advisory Group of Experts on immunization, November 2013 – conclusions and recommendations. Weekly Epidemiological Record, 2014; 89(1):1–16. http://www.who.int/wer/2014/wer8901.pdf

[8] For overview see: http://www.who.int/immunization/diseases/poliomyelitis/endgame_objective2/en/

[9] For detailed guidelines on IPV introduction see: http://www.who.int/immunization/diseases/poliomyelitis/endgame_objective2/inactivated_polio_vaccine/en/

[10] WHO. GAPIII: WHO Global Action Plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of oral polio vaccine use. http://www.polioeradication.org/Portals/0/Document/Resources/PostEradication/GAPIII_2014.pdf

3- Poliovirus type 2 outbreak response strategy

The overall principles of the strategy to deal with detection of any type 2 poliovirus include:

- Prompt detection and notification of all type 2 poliovirus strains;
- Prompt response in a sufficiently large population to lead to rapid cessation of type 2 poliovirus circulation;
- Utilization of vaccines from a global stockpile for the outbreak response for all countries whether or not they have previously received vaccines through UNICEF;
- Limit exposure to Sabin 2 poliovirus (e.g. from mOPV2) among populations not directly affected by the outbreak to prevent emergence of a new cVDPV2;
- Validate the absence of poliovirus type 2 in the population and the environment following the outbreak response.

In addition to incorporating the several preparatory steps which are required for initiating Sabin type 2 withdrawal, the strategy for addressing the risks associated with withdrawal of OPV2 includes six components: detection, notification, investigation/risk assessment, response, traveler considerations (internal, and international), and follow-up. The proposed guidelines for each component are based on risk factors and epidemiological contexts. Although presented separately, some components should proceed simultaneously.

3.1 Detection

Poliovirus surveillance includes multiple components.[11] Acute Flaccid Paralysis (AFP) surveillance has been the gold standard for global polio eradication and will remain the primary method for detecting any type 2 virus in the post cessation era.[12] AFP surveillance is linked to global, regional, and national laboratories which are part of the Global Polio Laboratory Network (GPLN) with comprehensive, standardized guidelines to distinguish poliovirus as a cause of AFP from diseases other than poliovirus.[13]

Environmental surveillance (ES) will provide an increasingly important adjunct to AFP surveillance. While environmental sampling is already being utilized in key countries to supplement polio eradication efforts, the GPEI is working jointly with specific countries on a strategic expansion plan to markedly increase the number of sites and role of ES between now and 2018.[14] To address surveillance needs in the post OPV2 era ES will be targeted especially in areas of high risk for cVDPV emergence (e.g. low routine coverage and historical cVDPV cases), areas where there is a risk of silent transmission and circulation of poliovirus (e.g. high force-of-poliovirus-infection), and areas at risk due to vaccine production. ES can also be instrumental in tracking the disappearance of Sabin 2 strain polioviruses, detecting any Sabin 2 strain polioviruses that subsequently might surface, and identifying any continued use of tOPV. Establishing ES as a fundamental part of the surveillance strategy for OPV2 withdrawal

[11] Kalkowska DA, Duintjer Tebbens RJ, Pallansch MA, Cochi SL, Thompson KM. Thompson KM. Modeling undetected live poliovirus circulation after apparent interruption of transmission: Implications for surveillance and vaccination. BMC Infectious Diseases 2015; 15:66, doi: 10.1186/s12879-015-0791-5.
[12] http://www.polioeradication.org/Dataandmonitoring/Surveillance.aspx.
[13] http://www.polioeradication.org/Dataandmonitoring/Surveillance/GlobalPolioLaboratoryNetwork.aspx
[14] GPEI. Environmental surveillance expansion plan: Global expansion plan under the endgame strategy 2013-2018. April 2015. http://www.polioeradication.org/resourcelibrary/strategyandwork.aspx

requires sufficient laboratory and staff resources as well as operational procedures following current WHO guidelines[15] and should be instituted through a collaborative strategic global effort to enhance detection capacity for type 2 polioviruses.

Polioviruses may also be detected as an incidental finding in a non-AFP clinical specimen or through a stool survey. Currently, this detection method is not an important surveillance source. Nevertheless, any incidental findings of type 2 poliovirus should be reported through the standard notification system (See ***Notification***).

Primary actions required at the global/regional level by the GPEI/GPLN:

- Assist countries with implementation of the ES global expansion plan
- Adequately support national polio laboratories to ensure rapid and sensitive poliovirus isolation and characterization of polioviruses through intratypic differentiation (ITD). As a global priority, all essential laboratories should expedite processing and sequencing of any type 2 isolates.

Primary actions required at the national level by public health authorities:

- Regularly monitor and evaluate AFP surveillance and laboratory networks to ensure global quality standards are maintained even as wild poliovirus cases disappear.[16]
- Collaborate with GPLN and GPEI to implement the global ES Expansion Plan. At this time countries not already engaged in ES for polioviruses do not need to independently start performing environmental sampling for polioviruses solely for the purpose of detecting Sabin type 2 polioviruses as markers for post-switch use of tOPV.

3.2 Notification

Treaty obligations under the International Health Regulations (2005) [IHR (2005)] specifically designate detection of a WPV from a suspected case or from a close contact to be a notifiable event. Additionally, the isolation of any WPV or cVDPV from other human or non-human sources must also be notified to WHO under the separate notification requirement for 'events which may constitute a public health emergency of international concern'.[17] Post cessation of OPV2 and confirmation of the elimination of cVDPV2 the interpretation of this criterion is expanded to include detection of any poliovirus type 2 (wild, vaccine derived, or Sabin[18]) in any sample (from clinical case or environment) of any provenance as a notifiable event under IHR (2005). The *IHR Emergency Committee* regarding the international spread of poliovirus will advise the WHO Director-General as to the appropriate risk category of the affected country.[19]

[15] GPEI. Guidelines on environmental surveillance for detection of polioviruses. Draft March 2015. http://www.polioeradication.org/Portals/0/Document/Resources/GPLN_publications/GPLN_GuidelinesES_April2015.pdf

[16] See expected surveillance standards: http://www.polioeradication.org/Dataandmonitoring/Surveillance.aspx

[17] WHO. International Health Regulations (2005). http://www.who.int/ihr/publications/9789241596664/en/

[18] Sabin 2 should be reported under IHR starting 1 August 2016 based on GAPIII containment criteria (See pp. 11 and 20).

[19] See http://www.who.int/mediacentre/news/statements/2015/ihr-ec-poliovirus/en/

Primary actions required by national and/or regional laboratories:

- Promptly provide notification to national health authorities and WHO (and to other GPEI partners) within 24 hours of obtaining results.

***Primary actions required by national health authorities*:**

- The National IHR Focal Point should notify WHO of any type 2 poliovirus detection within 24 hours as specified in the IHR (2005). The Ministry of Health should likewise inform relevant national officials.
- Non-laboratory confirmed cases, contradictory laboratory results, an unexpected cluster of AFP cases, or clusters of clinically compatible AFP cases would not trigger global actions or notification under IHR (2005). However, these situations, as well as concerns about suboptimal surveillance should be thoroughly investigated at the appropriate national/sub-national level.

3.3 Investigation and risk assessment

a- Initial investigation

Discovery of <u>any</u> type 2 poliovirus isolate from either AFP or environmental surveillance should initiate an immediate field investigation to: 1) confirm the outbreak/event; 2) determine number and characteristics of the case(s); 3) identify the origin/causes for the outbreak/event; and 4) assess the risk for occurrence and geographic extent of transmission.

Several steps may take place simultaneously. **Figure 1** (see page26) provides an overall timeline of required activities, the agency or persons with primary responsibility, and the expected time frame for completing the action. (For further details see general *Standard Operating Procedures* for responding to any poliovirus outbreak.[20])

Primary actions required by all relevant GPLN laboratories:

- <u>Enhance virologic investigation</u>: Further sequencing analysis beyond initial testing can aid in estimating the duration of poliovirus circulation. Laboratories responsible for covering the area where the poliovirus was detected should also carefully review relevant laboratory indicators (cell-sensitivity testing results, proficiency testing for viral isolation and ITD, accuracy of detection and testing, etc.) to ensure that the laboratory met recommended standards before and at the time of type 2 detection.

***Primary actions required by national public health authorities*:**

- <u>Enhance surveillance</u>: In order to maximize quality and sensitivity of the surveillance system, ensure strict attention to completeness and timeliness of all AFP reporting. Note that minimum standards for the affected country and first administrative level should be increased to three non-polio AFP cases per 100,000 children under 15 years of age for 12 months following outbreak confirmation. Also, for the immediate assessment period, increase frequency of environmental surveillance if available. For the longer term, if any WPV2 or

[20] See GPEI. Responding to a poliovirus outbreak or event: Standard Operating Procedures for non-endemic countries. Geneva. April 2016. http://www.polioeradication.org/Portals/0/Document/Resources/PolioEradicators/1a.PolioOutbreakGuideline20150220.pdf

VDPV2 is detected, investigate with the GPEI about establishing or expanding local environmental sampling sites.

- Conduct an epidemiologic investigation: A prompt field investigation of any AFP case should include specific case characteristics as well as active case finding in the community and local reporting sites. A positive environmental sample should also trigger active case finding in the suspected community and/or catchment area of the ES site.
- Conduct a risk assessment: Based on the findings of the epidemiologic and virologic investigations and the strength of evidence, characterize the virus transmission and the implications for further spread. Assess the critical factors which will influence the type and scale of response and make recommendations for appropriate actions (see ***Key Questions and Determinations*** below). Identify sub-populations outside the primarily affected area which are at-risk for possible transmission.

b- Key questions and determinations for the risk assessment

While laboratory and epidemiologic investigative steps correspond in general to standardized guidelines for following-up any poliovirus detection, the risk assessment following discovery of a type 2 isolate should focus specifically on addressing three core questions:

1. *What is the nature of the virus (e.g. WPV, Sabin, or VDPV)?*
2. *Is there evidence of circulation?*
3. *What is the risk of further spread?*

Following Initial detection, ITD, and sequencing, a poliovirus isolate may be grouped into one of three categories: 1) WPVs, 2) Sabin [e.g. OPV strain], and 3) VDPVs (>1% divergent [PV1 and PV3] or >0.6% divergent [PV2] from the corresponding OPV strain). A thorough risk assessment is required regardless of isolate category.

WPV2. Given the extended period since a circulating WPV2 has been detected, the possibility of further emergence of this virus is very remote. However, if an individual WPV2 infection is detected, rapid case investigation is mandatory since transmission could rapidly take place depending on local population immunity. A WPV2 infected individual without a known exposure to a poliovirus in a laboratory or vaccine production facility should be treated as evidence of *confirmed transmission*. A WPV2 infected individual with a known exposure to a breach in containment is most likely an isolated event but is a risk for *possible future transmission*. Likewise, a WPV2 isolate from an environmental sample is, in all probability, due to a containment breach in a laboratory or research facility. Nevertheless, a thorough investigation is warranted in the community catchment area surrounding the ES site as well as in any nearby laboratory or research facility in order to identify an AFP case or rule out an individual with ongoing sub-clinical infection who is excreting poliovirus. A cautionary approach dictates that discovery of a WPV2 in an ES sample should initially be considered evidence of *probable transmission*.

Sabin 2. While there will be considerable variability depending on the local environment, empirical evidence as well as modeling indicate that Sabin type 2 polioviruses can be expected to remain detectable for approximately 3 months in stool and 4 months in sewage samples after the last use of

tOPV (and/or use of mOPV2).[21] While this detection should prompt increased vigilance through AFP and environmental surveillance, the risk for this occurrence should rapidly diminish with time.[22] Detection of Sabin type 2 polioviruses after this 4-month period following the switch (i.e. from September 2016 onwards) or last use of mOPV2 in a type 2 outbreak/event response could be evidence of continued use of OPV2-containing vaccine, and as such would represent a risk for *possible future transmission*. A single individual AFP case with a Sabin type 2 poliovirus could also indicate a rare isolated exposure in a vaccine production facility or research laboratory.[23] This situation warrants a thorough case investigation, including checks for any remaining local stocks of tOPV and review of containment procedures and good manufacturing practices at nearby facilities.

VDPV2. Aside from Sabin 2 isolates in the immediate post-switch era, the most common poliovirus to be detected following withdrawal of tOPV will likely be a VDPV.[24] Genetic sequencing of the detected poliovirus through a combination of molecular and antigenic methods or real-time reverse transcription–polymerase chain reaction (rRT-PCR) targeting sequences within the VP1 capsid region that are selected for during replication of OPV in the human intestine will provide more specific categorization. VDPVs are further classified as: 1) cVDPVs when there is evidence of person-to-person transmission in the community; 2) iVDPVs, which are isolated from persons with primary, B-cell immunodeficiencies; and 3) ambiguous VDPVs (aVDPVs), which do not fit into the other two categories.

As an isolate linked either to known cVPDVs or a previously detected aVDPV demonstrates ongoing circulation and *confirmed transmission* in the community it represents the same public health threat as a WPV.[25] Given the critical importance of detecting and stopping cVDPV transmission during the endgame, in July 2015 WHO increased the sensitivity of surveillance to include the following expanded definition:

[21] For an example of empirical evidence see Wahjuhono G, et al. Switch from oral to inactivated poliovirus vaccine in Yogyakarta Province, Indonesia: summary of coverage, immunity, and environmental surveillance. J Infect Dis. (2014) 210 (suppl 1): S347-352. Modeling indicates that the mean time until OPV-related viruses die out is approximately 4 months (range 2-12 months). See Thompson KM and Duintjer Tebbens RJ. Modeling the dynamics of oral poliovirus vaccine cessation. J Infect Dis. (2014) 210 (suppl 1): S475-484.

[22] Tebbens, R. J. D et al. Risks of Paralytic Disease Due to Wild or Vaccine-Derived Poliovirus After Eradication. Risk Analysis, 2006. 26: 1471–1505.

[23] GAPIII requires that all research laboratories or production facilities must have adequate containment procedures in place for Sabin 2 polioviruses no later than 1 August 2016.

[24] For a comprehensive review of VDPVs, see Burns C, Diop OM, Sutter RW, and Kew OM. Vaccine-derived polioviruses. J Infect Dis 2014:210 (Supl 1):S283-293.

[25] See Kew O et al. Vaccine-derived polioviruses and the endgame strategy for global polio eradication. Annu Rev Microbiol. 2005; 59:587-635.

cVDPV

- 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 apart *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).[26]

A sample that does not initially meet the above definition should be considered a "New VDPV," which requires more intensive investigation to determine if additional infections are occurring in the community (See **Figure 2,** page 27). A single VDPV2 without evidence of prolonged circulation or a single VDPV2 case not linked to a previously detected aVDPV may only represent an isolated event without any other consequences. However, given the large risks inherent in failing to promptly respond to even low level type 2 spread, initial discovery of these scenarios should be treated as evidence of *probable transmission*.

Further active surveillance in the catchment area of an environmental sample or community search and contact tracing of a human case may find additional case(s) linked to the new VDPV, which would lead to classification of the cases as cVPDVs.

The case investigation should also determine whether an individual VDPV case represents a long-term, immunodeficient carrier for poliovirus (i.e. an iVDPV). Classification of iVPDV should be made only after a thorough investigation including: a) detailed history, b) competently performed physical examination, and c) results of quantitative immunoglobulin (IG) testing.[27] Acute or chronic malnutrition, which may cause a form of secondary depression of the immune system, should not be confused with serious primary immune deficiency (such as a- or hypo-gammaglobulinemia, common variable immunodeficiency, x-linked agammaglobulinemia, other antibody deficiency; or some form combined immunodeficiencies - most commonly severe combined immunodeficiency (SCID)).

Detection of iVDPVs is rare (e.g. ~100 known cases worldwide since 1961) and these cases have predominantly been found in developed countries.[28] Recent studies in developing and middle income countries have demonstrated that such cases may occur more frequently than previously thought; however, the survival rates for persons with primary immune deficiencies are probably very low in areas

[26] GPEI. Reporting and classification of vaccine-derived polioviruses. July 2015. http://www.polioeradication.org/Portals/0/Document/Resources/VDPV_ReportingClassification.pdf

[27] Note: if necessary, countries should contact WHO for assistance to conduct sophisticated molecular level testing of individuals suspected of being immunodeficient.

[28] Diop OM, Burns CC, Wassilak SG, Kew OM. Update on vaccine-derived polioviruses - worldwide, July 2012-December 2013. MMWR Morb Mortal Wkly Rep. 2014 Mar 21;63(11):242-8 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6311a5.htm

with the highest risk for polio transmission.[29] With one possible exception,[30] there is no evidence that iVDPV excretors have triggered substantial cVDPV transmission or outbreaks to date. However, all known iVDPV excretors have lived in settings of very high population immunity to poliovirus transmission and/or high hygiene and sanitation settings with reduced transmission potential of polioviruses. Therefore, especially in the first year following OPV2 cessation while type 2 immunity remains relatively high, the potential of further transmission from an iVDPV is deemed low in most countries but still *possible*. Modelling indicates that the future risk of live poliovirus reintroduction into the population from iVDPVs may rise considerably after global wild poliovirus eradication and subsequent OPV cessation.[31]

3.4 Response

a- Classification of poliovirus events/outbreaks, type 2 transmission, and further risk of post-switch transmission

Based on the nature of the virus and strength of evidence of circulation (e.g. confirmed, probable, or possible), three scenarios emerge reflecting the potential risk of further poliovirus type 2 transmission: high, medium, and low (see **Table 1**). Note that unlike type 1 or 3 isolates, for type 2 isolates post switch, the transmission classification (not typology) determines response. The level of concern should increase with the higher likelihood of further transmission.

[29] Li L, Ivanova O, Triki H, et al. Poliovirus excretion among persons with primary immune deficiency disorders: summary of a seven-country study series. J Infect Dis. 2014:210 (Supl 1):S368-72.
[30] Alexander JP, et al. Transmission of imported vaccine-derived poliovirus in an under vaccinated community in Minnesota. J Infect Dis 2009; 199:391-7.
[31] Duintjer Tebbens R, Pallansch M, and Thompson K. Modeling the prevalence of immunodeficiency-associated long-term vaccine-derived poliovirus excretors and the potential benefits of antiviral drugs. BMC Infectious Diseases (2015) 15:379; and Duintjer Tebbens RJ, Pallansch MA, Cochi SL, Wassalik SGF, Thompson KM. Characterization of outbreak response strategies and potential vaccine stockpile needs for the polio endgame. BMC Infectious Diseases 2016; 16:137, doi: 10.1186/s12879-016-1465-7.

Table 1: Definitions of poliovirus events/outbreaks and classification of type 2 transmission during Phase 1

Typology	Sample source	Classification	Type 2 transmission	Potential risk for further transmission[a]
Event	*Human/AFP*[b]	"new VDPV2" awaiting classification	Probable	Medium
		aVDPV2	Probable	Medium
		iVPDV2	Possible	Low
		Sabin2	Possible	Low
		WPV2 with documented exposure in a laboratory or vaccine production facility	Possible	Low
	Environmental	VDPV2 single sample without evidence of prolonged circulation of >1.5 years	Probable	Medium
		WPV2 single sample without follow-up evidence of virus excretion[c]	Probable	Medium
		Sabin2	Possible	Low
Outbreak	*Human/AFP*[b]	cVDPV2	Confirmed	High
		WPV2 without documented exposure in a laboratory or vaccine production facility	Confirmed	High
	Environmental	cVDPV2	Confirmed	High
		≥2 separate WPV with genetic sequencing indicating sustained local transmission[d]	Confirmed	High
		WPV2 single sample with follow-up evidence of virus excretion[c] & no documented exposure	Confirmed	High

[a] Additional factors (e.g. force-of-infection, population density, season of the outbreak, indigenous vs. imported virus, etc.) will ultimately determine the risk of further transmission and directly influence the required type and scale of response.
[b] Infected individual can be an AFP case or an asymptomatic/healthy person
[c] Evidence of virus excretion = identification of polio compatible AFP case or WFP infected individual
[d] 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

b- Factors influencing type and scale of response

If the initial investigation and risk assessment indicate that either confirmed or probable type 2 poliovirus transmission has been detected, an immunization response will mostly likely be required even before waiting for final classification. Further assessment to determine an appropriate type and scale of response is critical given the potential risks associated with mOPV2 use following OPV2 withdrawal and the need to balance this risk with the necessity to stop the type 2 transmission.

The risk for emergence of any type 2 poliovirus following withdrawal of OPV2 is not homogenous across countries or even within large countries. A significant factor will be the predominant polio vaccine in use within a country.

Countries exclusively using IPV

For countries that exclusively use IPV, the risk for cVDPVs (detected in either an ES sample or an individual case) depends on their relatively limited risk of exposure to imported OPV through travelers or migrants. Even the definitions of confirmed or probable transmission for their situation may depend on whether the type 2 poliovirus isolates demonstrates genetic features consistent with local transmission vs. importation. These countries may still be at risk, albeit at a low level, for discovery of WPV2 or Sabin2 virus traced to a breach in containment from a laboratory or vaccine production facility. Given the generally high vaccination coverage and levels of sanitation found in these countries, the risk of type 2 transmission is relatively low in all these circumstances but poliovirus may still spread to under-vaccinated sub-populations.[32] The level of concern (and associated degree of response) in these countries will thus depend on a thorough virologic and epidemiologic investigation and tailored to the individual situation.

However, from a global perspective, detection of any type 2 poliovirus should be a cause of concern. An attempt to identify the origin of any outbreak, including those due to importations, will be important in order to determine an appropriate response at the source. Nevertheless, the recommendations below regarding a vaccination response following detection of a type 2 poliovirus are focused on countries with use of tOPV within the 12 months prior to the switch.

Countries using tOPV in the last 12 months prior to type 2 OPV withdrawal

For countries with prior recent use of OPV, two dynamically inter-related trends determine post-cessation risk of cVDPV emergence: decreasing population immunity to transmission and decreasing OPV-related virus presence. These same factors that predispose for the emergence of a new poliovirus type 2 will also be critical in determining the potential risk for further transmission and the extent of any transmission which might occur.

NOTE: Risk factors and response strategies presented below apply to countries using tOPV within the last 12 months prior to the switch.

Critical factors for countries to consider in reaching response decisions include time, place, and characteristics of the affected population.

i) Time

How many months/years have elapsed between OPV2 cessation and detection of poliovirus type2?

Multiple high quality SIAs (i.e. ≥3 SIAs with ≥ 80% coverage) in the 4-6 months before the switch will significantly reduce the risk of emergence.[33] However, modelling suggests a high probability that at least one cVDPV will emerge within 12 months of the switch.[34] While specific cutoff dates cannot be determined, three broad phases –based on the time elapsed since tOPV cessation shown in Table 2--

[32] Oostvogel PM, et al. Poliomyelitis outbreak in an unvaccinated community in The Netherlands, 1992-93. Lancet. 1994 Sep 3;344(8923):665-70

[33] See Thompson KM and Duintjer Tebbens RJ. Modeling the dynamics of oral poliovirus vaccine cessation. J Infect Dis. (2014) 210 (suppl 1): S475-484

[34] Institute for Disease Modeling. Unpublished data, January 2016.

can be identified, which reflect the exposure to type 2 poliovirus and the risk for initial VDPV occurrence and further transmission.[35] Phase 1 (within 1 year of cessation of tOPV) has the highest risk of initial occurrence of a type 2 virus detection; however, assuming pre-cessation mitigation activities (i.e., tOPV SIAs) have taken place prior to withdrawal of tOPV, this phase should have the lowest risk of further transmission. Phase 2 (2-3 years post-cessation) reflects medium risks of occurrence and further circulation. Similarly, Phase 3 (4+ years since cessation of OPV2) will have the lowest exposure risk to type 2 virus, but will have an accelerating risk of further transmission due to waning mucosal immunity in the population.

Table 2. Phases of risk for type 2 poliovirus emergence and circulation

Phase	Time after cessation of OPV2	Comment	Relative Risk for initial type 2 occurrence	Risk for further circulation
1	≤1 year	General population immunity remains high if mucosal immunity is boosted in <5 population by pre-switch tOPV SIAs	High	Low
2	2-3years	General immunity still reasonably high, but overall mucosal immunity declining and absent in new birth cohorts	Medium	Medium
3	≥4 years	Mucosal immunity declines sharply	Low	High

Occurrence of aVDPV2s is historically less responsive to immunity conditions and may be more difficult to predict in the context of rapidly decreasing population immunity to transmission after OPV2 cessation; however, a minimum of four aVDPVs could be expected in the first year following OPV2 cessation.[36]

ii) Place—(country or sub-national region w/ >10 million population)
What is the scope of the outbreak affected area and extent of epidemiologically linked populations?

The geographic scope under consideration for a response should take into account epidemiologically-linked populations, including defined areas of ongoing circulation as well as other areas of high risk. The scope may include an entire country, or for large countries, could include a sub-national region/urban area with at least 10 million population. Note that in some situations, epidemiologic links may include homogenous populations who regularly inter-mix and cross international borders so that areas of multiple countries may need to be included in the scope of the response.

The scope and scale of response may also be influenced by characteristics of the place such as environmental factors (e.g. poor sanitation and high force-of-infection), geo-political challenges (e.g. insecurity) and other geographic factors (e.g. transport links to high risk communities with immunity gaps).

[35] Institute for Disease Modeling, Unpublished data, January 2016.
[36] Institute for Disease Modeling. Unpublished data, January 2016.

iii) Characteristics of the affected population.

What are the estimated immunity levels of the population in the area where the poliovirus was detected? Does the community in which the virus was discovered have particular characteristics which may signal low immunity and/or an increased risk for transmission?

Although the greatest risk factor for emergence of a VDPV2 is low overall population immunity to type 2 poliovirus transmission, other risk factors include high birth rate, high population size and density, low routine immunization coverage, failure to reach unvaccinated children in pre-switch SIAs, and other conditions associated with high levels of fecal-oral transmission.

Vaccination coverage rates from both routine immunization programs and any SIAs in the area can be useful input, but this data must be analyzed in the context of any known information on the immunogenicity of OPV in order to provide an indication of population immunity. In many situations, vaccination coverage may be unknown but other population characteristics (e.g. marginalized or underserved, conflict-affected, history of immunization refusal, etc.) in the affected community may be indicative of low immunity. Detection of poliovirus in a mobile community or conflict zone may be of special concern for further spread.

Factors such as past epidemiologic history, location, and population characteristics may determine three general "transmission risk zones" that reflect the risk for any type 2 transmission (see **Table 3**).

Table 3. "Transmission risk zones" based on population risk for type 2 poliovirus transmission

Zone	Country/area and Population Characteristics	Risk for further transmission
1	Clear history of sustained WPV or reported **cVDPV2** since 2005; OR affected community with other risks for low immunity* or high mobility links to susceptible communities	High
2	Consistently low DTP3 coverage <80% in the previous 3 years; OR history of imported WPV or **any cVDPV or aVDPV2** in the previous 3 years; OR with DTP3 coverage <90% and adjacent to affected area	High-Medium
3	DTP3 coverage consistently >80%; affected community with few risk factors for sustained transmission	Low

*E.g. high birth rate, high population size and density, low routine immunization coverage, failure to reach unvaccinated children in pre-switch SIAs, and other conditions associated with high levels of fecal-oral transmission

c- Response strategies for phase 1

See **Table 4** (page 24) for a summary comparison of the standard strategies for responding to any polio outbreak and steps required following detection of a type 2 isolate post-cessation of OPV2. Further details and comments on these strategies are provided below.

- **Vaccine choice:** Utilize mOPV2 as the vaccine of choice for response to stop type 2 poliovirus circulation during Phase 1, but there are specific targeted roles for the use of inactivated polio vaccine (IPV).

Special circumstances: Although tOPV and mOPV2 have similar immunogenicity against type 2,[37] use of tOPV in the post-switch era is not feasible due to logistical concerns and containment imperatives. Simultaneous bOPV and mOPV2 might be considered in areas at risk for WPV1 or WPV3. If an outbreak response to cVPDV2 requires multiple SIAs that overlap the switch, initiate any pre-switch SIAs with tOPV and request release of mOPV2 from the global stockpile to implement any SIAs planned post-switch.

mOPV2. Modeling suggests that a mOPV2 response sufficient to interrupt the live poliovirus transmission that caused the outbreak will not create new cVDPVs within the same population.[38] However, exportation of the OPV-related virus to other susceptible neighboring populations remains a concern. In addition, an inadequate response with mOPV2 long after initial SIAs have controlled an outbreak also creates the potential for vaccine virus transmission. Nevertheless, the risk of remaining cVPDV2 circulation far outweighs the risk of seeding type 2 virus through mOPV2 SIAs.

IPV. While modeling has shown that a single IPV dose (such as given during routine immunization) may have only a modest impact on the probability of cVDPV emergence, a second IPV dose given in an outbreak response is expected to rapidly boost individual antibody titers.[39] Further indication of the potential role for IPV was demonstrated by a recent field study showing that one dose of IPV given to OPV-primed children significantly boosted intestinal mucosal immunity for types 1 and 3 compared to no vaccine and this boost was higher than what was achieved with an additional dose of bOPV.[40] The full impact on transmission of these clinical trial findings demonstrating an increase in mucosal immunity remains to be determined. However, preliminary analyses of polio case data in both Pakistan and Nigeria from March 2014 to October 2015 promisingly suggest that combined use of IPV + tOPV in endemic settings is associated with a measurable decrease in incidence of both wild and vaccine-derived poliovirus.[41]

Based on the evidence of IPV boosting of previously-OPV immunized individuals, IPV use along with mOPV2 in the outbreak response area may aid in preventing paralytic cases and limiting transmission--particularly within the first 12 months after the switch from tOPV. Additional use of IPV alone can boost individual immunity in surrounding high risk populations to mitigate the risk of mOPV2 exportations beyond the initial outbreak zone. On a smaller scale, IPV may also be utilized in selected individuals to

[37] Duintjer Tebbens RJ, Pallansch MA, Cochi SL, Wassalik SGF, Thompson KM. Characterization of outbreak response strategies and potential vaccine stockpile needs for the polio endgame. BMC Infectious Diseases 2016; 16:137, doi: 10.1186/s12879-016-1465-7.
[38] Thompson KM and Duintjer Tebbens RJ. Modeling the dynamics of oral poliovirus vaccine cessation. J Infect Dis. (2014) 210 (suppl 1): S475-484; and Duintjer Tebbens RJ, Pallansch MA, Cochi SL, Wassalik SGF, Thompson KM. Characterization of outbreak response strategies and potential vaccine stockpile needs for the polio endgame. BMC Infectious Diseases 2016; 16:137, doi: 10.1186/s12879-016-1465-7.
[39] See Duintjer Tebbens RJ and Thompson KM. Modeling the potential role of inactivated poliovirus vaccine to manage the risk of oral poliovirus vaccine cessation. J Infect Dis. (2014) 210 (suppl 1): S485-497.
[40] Jafari H, et al. Efficacy of inactivated poliovirus vaccine in India. Science. August 2014; 345:922-925.
[41] Imperial College. Unpublished data, December 2015.

provide protection for long distance travelers to infected areas (see section on IHR below) or close contacts of iVDPV or WPV2 cases.

Due to the projected limited global IPV supply through at least the end of 2017, full dose IPV will most likely not be available for outbreak response. Multiple studies have demonstrated the efficacy and operational feasibility of using fractional dosing through intradermal (ID) administration for IPV.[42] Therefore, full or fractional dose IPV (preferably administered with an ID device rather than a needle and syringe) may be used depending on vaccine availability.

***Other tools*.** The most common form of treatment for persons with primary immune deficiency disorders that may lead to an iVDPV is replacement therapy with intravenous immunoglobulin (IVIG). Polio anti-viral compounds and monoclonal antibodies have demonstrated therapeutic value in limited studies, but additional research is being conducted urgently to make these options widely available as potentially useful prevention measures.[43]

- **Vaccine Stockpile**. Request mOPV2 for type 2 outbreak response through WHO for allocation from the global stockpile managed in collaboration with UNICEF Supply Division. Member States that decide to establish a national poliovirus vaccine stockpile should maintain the stockpile in conditions of containment that are verified by the Regional Certification Commission for Polio Eradication to be compliant with the containment Global Action Plan and also seek authorization of the Director-General (DG) of WHO before release and use of mOPV2[44] (See **Response Scenarios** and **Annex A** for further details).

In order to maximize the containment of type 2 poliovirus, the WHA has urged countries to rely on a global stockpile of mOPV2 managed under the authority of the WHO Director-General. Accordingly, WHO, in collaboration with UNICEF Supply Division and vaccine manufacturers, has established a stockpile of mOPV2 which can be rapidly provided to Member States based on an established request procedure[45] in case of a type 2 outbreak. In line with the guidelines for a type 2 outbreak response in this protocol, countries should file a request for mOPV2 (and IPV if indicated for a SIA)[46] to WHO. A global advisory body will review the request and make a recommendation to the WHO Director-General who can authorize the release of mOPV2. Due to global supply constraints of IPV, UNICEF will coordinate shipments from available supplies of IPV when targeted to an outbreak response. Appropriate syringes and intradermal delivery devices will also be provided for fractional dosing of IPV.

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[42] Estıvariz CF, et al. Poliovirus vaccination options for achieving eradication and securing the endgame. Current Opinion in Virology 2013, 3:309–315. And Okayasu H, et al. Affordable inactivated poliovirus vaccine: strategies and progress. J Infect Dis. (2014) 210 (suppl 1): S459-464.

[43] Puligedda RD et al. Human monoclonal antibodies that neutralize vaccine and wild-type poliovirus strains. Antiviral Res. 2014 Aug; 108:36-43. doi: 10.1016/j.antiviral.2014.05.005. Epub 2014 May 10.

[44] 68th WHA. Poliomyelitis. http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R3-en.pdf.

[45] link/reference to be included

[46] If only a very limited number of doses of IPV are required (i.e. to vaccinate household contacts) countries should use their own national stocks.

- **Optimal number of Supplemental Immunization Activities (SIAs):** Conduct a minimum of four SIAs in response to *confirmed type 2 transmission*; however five (or more) SIAs may be needed in high risk settings (e.g. Transmission Risk Zones 1 or 2). Evidence of *probable transmission* will require a more situational response, but in most circumstances at least one initial SIA should be conducted while further investigation continues (See **Response Scenarios** below for further details and recommended SIAs).

- **Speed of Supplemental Immunization Activities (SIAs):** Conduct the first 'rapid response' SIA (e.g. SIA1) within 14 days of initial sequencing results provided by the GPLN.

Modeling[47] and multiple years of experience in responding to prior outbreaks of WPV and cVDPV have demonstrated that conducting an immunization response quickly even with moderate coverage for the first round will stop transmission in fewer rounds than waiting to intervene later in hopes of maximizing coverage through better organization. The implications are even greater in responding to an emergence of type 2 poliovirus given the potential ramifications of spread.

- **Interval of SIAs:** After SIA1, conduct subsequent SIAs (if required) within 2-3 week intervals as long as coverage is not compromised. Plan to begin the combined mOPV + IPV SIA (if required) no later than 45 days post outbreak confirmation. If additional time for planning or logistics is required, continue with mOPV2 alone in SIA2 and add the IPV to SIA3 in order not to delay any of the outbreak response. Local operational feasibility based on environmental, infrastructure, security, and programmatic factors should ultimately determine the intervals required to ensure safety and effectiveness.

- **Target age group:** During the first year after tOPV cessation, target **all** children under 5 years of age. To minimize the use of mOPV2 in the population, expanded age groups are not routinely recommended for a type 2 immunization response unless there is evidence of circulation among older persons.

- **Target population:** Target 500,000 children for SIA1 in the "rapid response area." Subsequent SIAs should include this group and increase the full "outbreak affected area" to cover a minimum of 2 million children. Where 2 million children do not exist within a reasonable radius, all children, or children of 10 million total population could be targeted. Consider increasing the scope further in densely populated areas or if there is evidence of extensive circulation (e.g. higher number of nucleotide changes) or if there is potential for extensive circulation (e.g. outbreak population well-connected to a major urban area). However, in all situations, the target population should not be increased beyond the capacity of the program to attain high coverage.

A global retrospective analysis in 13 countries with recent VDPVs found an average of 100,000 potentially exposed children (and likely less than 300,000 children) under 5 years of age prior to

[47] See Thompson KM, Duintjer Tebbens RJ, Pallansch MA. Evaluation of response scenarios to potential polio outbreaks using mathematical models. Risk Analysis 2006; 26(6):1541-1556. Risk Anal, 2006

detection.[48] For the initial response to a VDPV after tOPV cessation, most of which will likely have 6-10 nucleotide changes, a conservative vaccination target up to 500,000 children should maximize the chances of containing transmission. Practical field experience to date has also demonstrated that this target represents the upper boundary of the number of children that can be effectively vaccinated through a rapidly organized SIA. Even if a cVDPV shows evidence of prolonged circulation, the priority for the initial SIA is to begin vaccination within 14 days of sequencing results using the 500,000 target, unless circumstances clearly suggest otherwise.

The minimum target for the second and subsequent SIAs needs to balance the requirement to stop transmission while minimizing the chances of reseeding the vaccine virus elsewhere. Related modeling shows that the exportation risk is very low during the period that population immunity remains high (e.g. during Phase 1) in most countries.[49] The target of 2 million reflects successful experience in the pre-cessation era. With high coverage, this target should be adequate to stop transmission in most areas, but could be expanded based on analysis of local risk factors.

Supplies permitting, the recommended target for the use of IPV in the expanded high risk area surrounding the outbreak is also 2 million children. While in general this intervention should target geographic areas adjacent to the outbreak affected area, the key objective is to raise individual immunity levels in populations that mix with or surround those receiving mOPV. Therefore, the size and location of the expanded high risk area to vaccinate may vary depending on the assessed risk of neighboring populations and degree of interaction with the affected community. Especially for highly mobile populations such as migrants, the targeted area may include non-adjacent pockets or transmission corridors.

d- Response scenarios for phase 1

The general GPEI performance standards and planning steps for any poliovirus outbreak response are detailed elsewhere.[50] **Figure 1** (page 26) summarizes these steps and includes the specific measures required for a type 2 outbreak response. Depending on the situation, an outbreak or an event may trigger a vaccination response.

VDPVs (See **Figure 3a,** page 28)**.** Initial sequencing results of a **cVDPV** should prompt a rapid, small scale SIA response (e.g. SIA1) in all risk zones. For Transmission Risk Zones 1 or 2 one SIA after the first round (SIA2 if logistically practical) should use mOPV2+IPV in the outbreak affected area, and if IPV supply is

[48] See Institute for Disease Modeling and the National Institute for Viral Disease Control and Prevention, China CDC. Unpublished data, January 2016.
[49] Institute for Disease Modeling. Unpublished data, January 2016.
[50] See GPEI. Responding to a poliovirus outbreak or event: Standard Operating Procedures for non-endemic countries. Geneva. April 2016.
http://www.polioeradication.org/Portals/0/Document/Resources/PolioEradicators/1a.PolioOutbreakGuideline20150220.pdf

adequate[51], target an additional 2 million children with IPV only in an "extended area" for high-risk populations. Other SIAs in the outbreak affected area should use mOPV2. For Transmission Risk Zone 3, target 2 million children with mOPV2 for SIAs 2 to 4.

Given the risks involved with a delayed response, proceed with an initial SIA following detection of a **'new VDPV'** even before final classification can be obtained.[52] **NOTE: implementing a rapid response SIA should not wait for full case or community investigation or for laboratory testing to rule out an iVDPV.**

If further contact tracing finds additional VDPV cases linked to the original isolate, classify as a '**new cVDPV'** and continue with *confirmed transmission* response SIAs for the appropriate transmission risk zone. If an **iVDPV** individual is discovered, treat the individual with IVIG and/or antivirals (when available) plus give IPV for any household members or close contacts. SIAs are not routinely recommended in response to iVPDVs whether the classification is made based on initial sequencing or after identification of an immunocompromised individual. However, one to three SIAs (each with a target of 500,000 children) may be considered in high-risk areas around the immunodeficient case, especially if the iVDPV is detected late in Phase 1 when type 2 immunity will have declined.

If further investigation does not discover either a new cVDPV or iVDPV, consider the isolate an **aVDPV**. Historically, most aVDPVs have occurred in isolation, but in the context of decreasing population immunity a higher fraction of aVDPVs may go on to become cVDPVs . Therefore, classification of an aVDPV should lead to close monitoring of surveillance performance standards for the next 3-6 months. Additionally, a more aggressive vaccination response to an aVDPV may be required if it meets one of several criteria: i) interval from the switch is >6 months; or ii) occurrence in an area with prior cVDPV emergence; or iii) substantial genetic deviation from a parent Sabin virus (e.g. evidenced by nucleotide deviations or recombination with class C enterovirus). In these situations or in an area otherwise considered high risk for transmission, after the initial rapid response SIA, proceed with at least two more SIAs each targeting 2 million children with mOPV2.

WPV (See **Figure 3b,** page 29)**.** In the unlikely event of detecting a **WPV2 human/AFP case**, promptly determine whether the individual has a known type 2 exposure due to a containment breach. In the instance of known, documented exposure, vaccinate close contacts with IPV; but no further vaccination response is required unless active surveillance provides evidence of other cases. If no exposure can be documented, respond aggressively according to the *confirmed transmission* scenarios for a cVDPV.

For a single **WPV2 ES sample**, rapidly assess the community for evidence of an individual excreting virus (e.g. a polio compatible AFP case or a WPV case). Multiple ES samples with sequencing which indicates

[51] In the face of limited IPV supply, the first priority for use of IPV is to target children in the outbreak affected area.

[52] Proceed with the rapid response SIA before final classification unless there is strong indication of very low risk of transmission (e.g. very high immunity, few nucleotide changes in the isolate, etc.) or if initial sequencing shows an iVDPV in a low risk area.

>1 infected individual[53] may also demonstrate virus excretion in the community. If evidence of excretion is found, respond according to the WPV2 case scenario. If no evidence is found, consider at least one rapid response SIA especially in Transmission Risk Zone 1 or any area deemed to be at high risk.

Sabin ES sample or individual (See **Figure 3c,** page 30). Detection of Sabin type 2 poliovirus in stool within 3 months or in sewage within 4 months of the switch (and/or mOPV2 response immunization) should encourage continued monitoring for Sabin type 2 poliovirus, but does not need to automatically trigger a search for OPV2-containing vaccine in the community. However, if there are any nearby laboratories or vaccine production facilities, prompt investigation should be undertaken to discover any breach in containment, to test workers as possible sources of poliovirus, and to review safety protocols, particularly in light of the deadline for all Sabin type 2 polioviruses globally to be contained or destroyed within 3 months of the switch.[54]

Detection of Sabin type 2 poliovirus more than 3 months after the switch in stool and more than 4 months of the switch in sewage suggests possible containment breach or continued use of tOPV after the switch. The sequencing of the isolated Sabin type 2 poliovirus and, if there are multiple isolates, analysis of trends in the detection of Sabin type 2 polioviruses, should guide further action. If the detected isolate sequence is ≥99.7% similar to the parent Sabin type 2 poliovirus sequence, the isolate probably originated from tOPV administered after the switch or a breach in containment and a search should be conducted for tOPV in use or storage in the area in which the Sabin type 2 poliovirus was found. If the detected isolate sequence is <99.7% similar to the parent Sabin type 2 poliovirus sequence, the isolate may have originated from tOPV administered prior to the switch and may represent an outlier in excretion descended from polio vaccine viruses. A search for tOPV may still be warranted unless sequencing results compared to prior Sabin type 2 samples demonstrate a continued decline in similarity to the parent Sabin strain.

Primary actions required by national public health authorities:

- Based on the risk assessment (Tables 2 and 3) and strategies noted above, implement the recommended response according to the appropriate scenario of type 2 virus classification (Table 1).
- If indicated, request mOPV2 (and IPV) for type 2 outbreak response through WHO for allocation from the global stockpile. Requests should be submitted in two stages. Submit the Stage 1 request for vaccines required for SIA1 within 24 hours of validation of sequencing results. The Stage 2 request covering vaccines needed for all subsequent SIAs should be submitted within the two weeks following outbreak/event confirmation. (See **Annex A** for details.)

[53] E.g. samples 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.

[54] WHO. GAPIII: WHO Global Action Plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of oral polio vaccine use. http://www.polioeradication.org/Portals/0/Document/Resources/PostEradication/GAPIII_2014.pdf

3.5 Travelers and quarantine

Due to the high likelihood of ongoing undetected poliovirus circulation in the situations of confirmed or probable poliovirus type 2 transmissions, strict quarantine of individual polio cases will have limited impact on stopping the outbreak unless there is a documented exposure to a type 2 poliovirus. On a population wide basis, travel and migration patterns in and out of affected communities can have a significant impact on the risk and extent of poliovirus circulation, but even in the face of major epidemics enforcing local travel restrictions has proved challenging. Nevertheless, in the situation of a type 2 poliovirus outbreak, local epidemiologic, geographic, and population mobility factors should be used to determine the specific boundaries of the outbreak affected area.

***Primary actions required by national public health authorities*:**

- Consider imposing a local quarantine in situations where a single individual has a documented exposure to poliovirus type 2 (e.g. in a laboratory or vaccine production facility). Continue further investigation and close surveillance of family members and/or co-workers for at least 60 days post initial case detection.
- Based on local feasibility and assessed risk, consider implementing local travel restrictions and/or proof of polio vaccination for travelers of any age into/out of the outbreak area. This is in addition to the IPV SIA recommended for adjacent high risk populations in the scenario of confirmed transmission. Community organizers may be mobilized to engage the population in risk reduction behaviors, including vaccination and voluntarily restricting travel.

On 5 May 2014, the Director-General declared the international spread of wild poliovirus a public health emergency of international concern under the International Health Regulations (2005).[55] Since then, The *IHR Emergency Committee* has met regularly to issue advisories to polio-affected countries regarding measures they should undertake to restrict the international spread of poliovirus, including heightened surveillance and traveler vaccination. [56]

Primary actions required by WHO and national public health authorities:

- In accordance with national regulations and IHR (2005) Articles 30-32[57] WHO and national health authorities should collaborate to implement international travel restrictions as necessary. International traveler verification of IPV vaccination should follow guidance in the IHR (2005).

[55] WHO statement on the meeting of the International Health Regulations Emergency Committee concerning the international spread of wild poliovirus. http://www.who.int/mediacentre/news/statements/2014/polio-20140505/en/.
[56] See http://www.who.int/ihr/ihr_ec_2014/en/
[57] See IHR (2005) http://whqlibdoc.who.int/publications/2008/9789241580410_eng.pdf?ua=1

3.6 Outbreak/event response assessment and follow-up steps

The urgency of stopping any type 2 poliovirus transmission as soon as possible underscores the need to follow up the initial response steps with ongoing evaluation of the impact. Since poliovirus transmission has been declared a public health emergency of international concern, specific oversight and reporting requirements will be required under IHR (2005).

***Primary actions required by national public health authorities*:**

- As with any SIA, institute adequate supervision, lot quality assurance, and independent monitoring of immunization activities to ensure the quality of the interventions.[58]
- Submit regular updates to the *IHR Emergency Committee* as requested.

Primary actions required by GPEI[59]:

- Conduct Independent Monitoring at least by SIA2. Also conduct outbreak/event response assessments by the third month from day 0 and continuing quarterly thereafter until 12 months have passed without a type 2 poliovirus identification.
- Confirm the end of the outbreak by validating the absence of poliovirus type 2 in the population and the environment 12 months after the onset date of the most recent case plus one month to account for case detection, investigation, laboratory testing and reporting period.[60] The final assessment should be submitted to the GCC for final verification that the outbreak has ended.
- Develop a six month plan for strengthening surveillance which should be monitored quarterly.
- Provide 'surge' technical support graded to risk of transmission and local response capacity.

[58] See Global Guidelines for Independent monitoring of polio SIA. http://www.polioeradication.org/Portals/0/Document/Resources/PolioEradicators/IndependentMonitoringGuidelines_20101124.pdf

[59] For further details see: GPEI. Responding to a poliovirus outbreak or event: Standard Operating Procedures for a new polio outbreak in a polio-free country. Geneva. April 2016. http://www.polioeradication.org/Portals/0/Document/Resources/PolioEradicators/1a.PolioOutbreakGuideline20150220.pdf.

[60] For details, see Statement on the Seventh IHR Emergency Committee. http://www.who.int/mediacentre/news/statements/2015/ihr-ec-poliovirus/en/

Additional tables and figures

Table 4: Comparison of the standard strategies for responding to any polio outbreak and steps required post detection of a type 2 isolate post-cessation of OPV2

	Standard ***(e.g. response to detection of any type 1 or 3)***	***Response to detection of type 2***
General		
Objective	To provide standard operating procedures to respond to any polio outbreak or event	To provide strategy and guidance for detecting, notification, and response specifically to a type 2 poliovirus after OPV2 cessation
Target application	Any non-endemic country (previously free from polio for at least 6 months)	General strategies apply to any country. Response guidelines are directed to countries with prior use of tOPV within 1 year prior to OPV2 cessation.
Time frame	Ongoing	Begins with OPV2 cessation-1May2016. Response guidelines limited to Phase 1 (e.g. ≤12 months post OPV2 cessation).
Detection	AFP surveillance supplemented by environmental surveillance (ES). If outbreak, enhance target to >3 NPAFP/100,000 pop<15yrs for 12 months in every 1st level sub-national area.	In addition, polio laboratories should prioritize processing any type 2 isolate.
Notification	Report all poliovirus isolation to WHO w/in 24 hours regardless of isolate (WPV, VDPV) or source (clinical case or ES sample).	Detection of any type 2 poliovirus (including Sabin2 >4 months post OPV2 cessation and/or mOPV2 response) reportable under IHR.
Rapid Assessment	Conduct rapid clinical and epidemiologic investigation of case and affected community.	In addition, investigate possible containment breaks for any Sabin2 isolation or post-switch use of tOPV (>4 months post OPV2 cessation).
Response		
Classification of response scenarios	Event (no evidence of transmission) or Outbreak (evidence of transmission).	Further classifies by status of type 2 transmission (See Table 1); -Outbreak=confirmed transmission; -Event= probable or possible transmission (includes detection of Sabin2 poliovirus)
SIAs	Required for outbreaks; typically not required for events (e.g. VDPV1 or 3) -SIA for WPV in ES based on situation	Required for outbreaks and some events. Based on all confirmed and most situations of probable type 2 transmission (e.g. VDPV2); -SIA for WPV2 depends on +/- known exposure and local situation
Vaccine of choice	Vaccine choice based on consultation with WHO; bOPV for WPV1 or 3 bOPV for cVDPV1 or 3	mOPV2 (+ IPV for confirmed transmission in a high risk area). Country must submit application to WHO for release of mOPV2 from global stockpile under authority of WHO DG
Number of rounds	≥3 SIAs	Confirmed transmission: min 4 SIAs, 5+ in high risk areas; Probable transmission: 1-3 SIAs depending on situation

Initial SIA	Within 14 days from sequencing results	Within 14 days from sequencing results
Interval between SIA rounds	First three rounds should be 2-3 weeks apart	2-3 week intervals; if SIA2 includes mOPV2 + IPV may require up to 4 weeks
Target age	All children under 5 years of age + an expanded age group in ≥1 SIAs	All children under 5 years of age unless there is evidence of circulation among older persons
Target population scope	Based on local situation, as advised by WHO and GPEI partners	500,000 for SIA1; minimum of 2 million for subsequent SIAs
Travellers	Travel restrictions and quarantine may be recommended by IHR EC.	In addition, consider quarantine of polio cases + possible local traveller vaccination requirements
Follow-up	Independent Monitoring (IM) within 1 month; outbreak response assessments (OBRA) every 3 months and continuing quarterly thereafter until 6 months without any further detection of the outbreak virus, with documentation of high quality eradication activities, and with evidence of sensitive and enhanced surveillance. In the absence of such activities, the outbreak is not considered closed until at least 12+2 months pass without detection of the outbreak virus. IHR EC may request longer follow-up.	Institute IM and OBRA. Outbreak cannot be considered closed until 12 months after the onset date of the most recent case PLUS 2 months to account for case detection, investigation, laboratory testing and reporting period. IHR EC must confirm closure status.

Figure 1: Timeline and responsibility for actions following detection of type 2 poliovirus

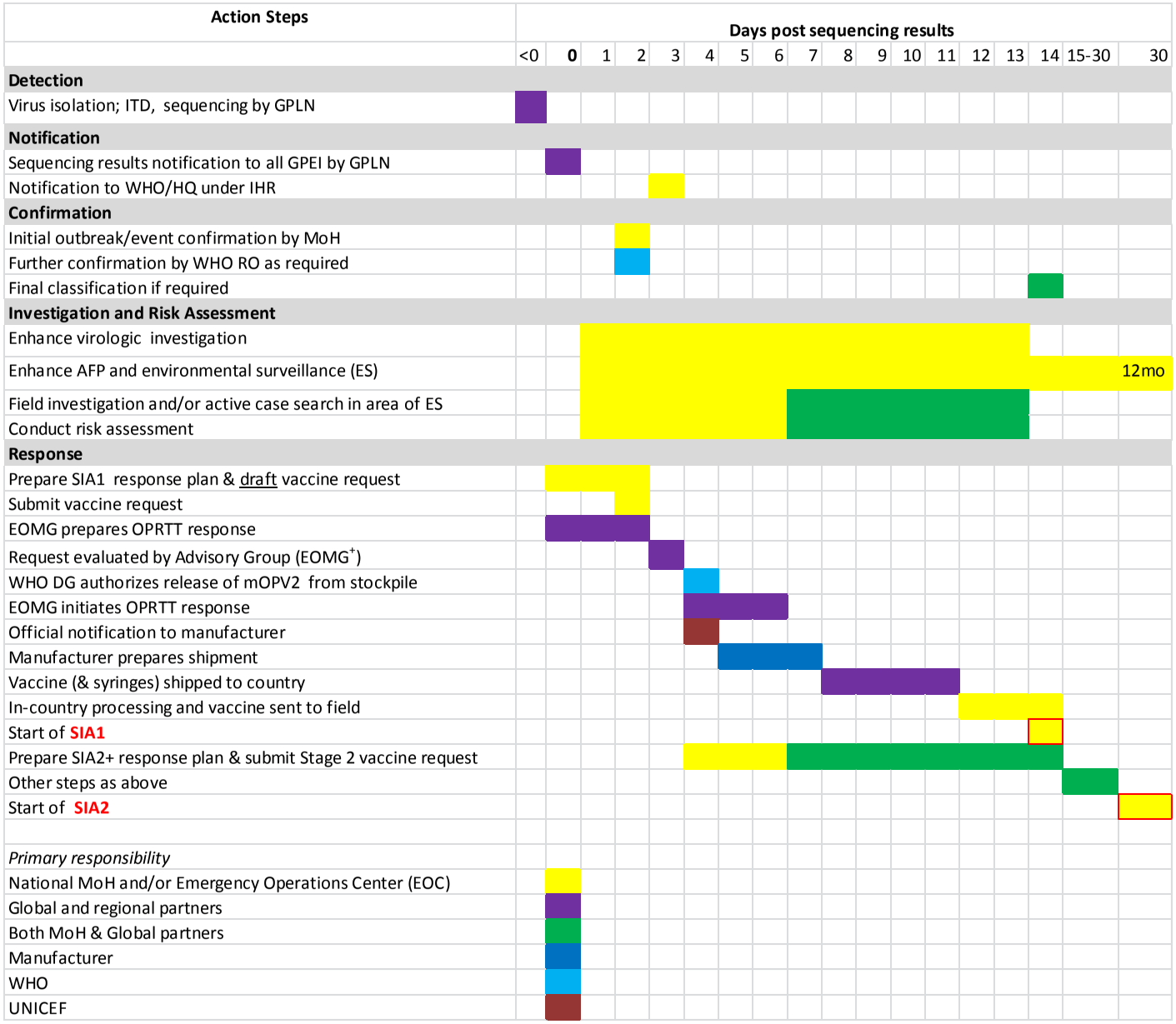
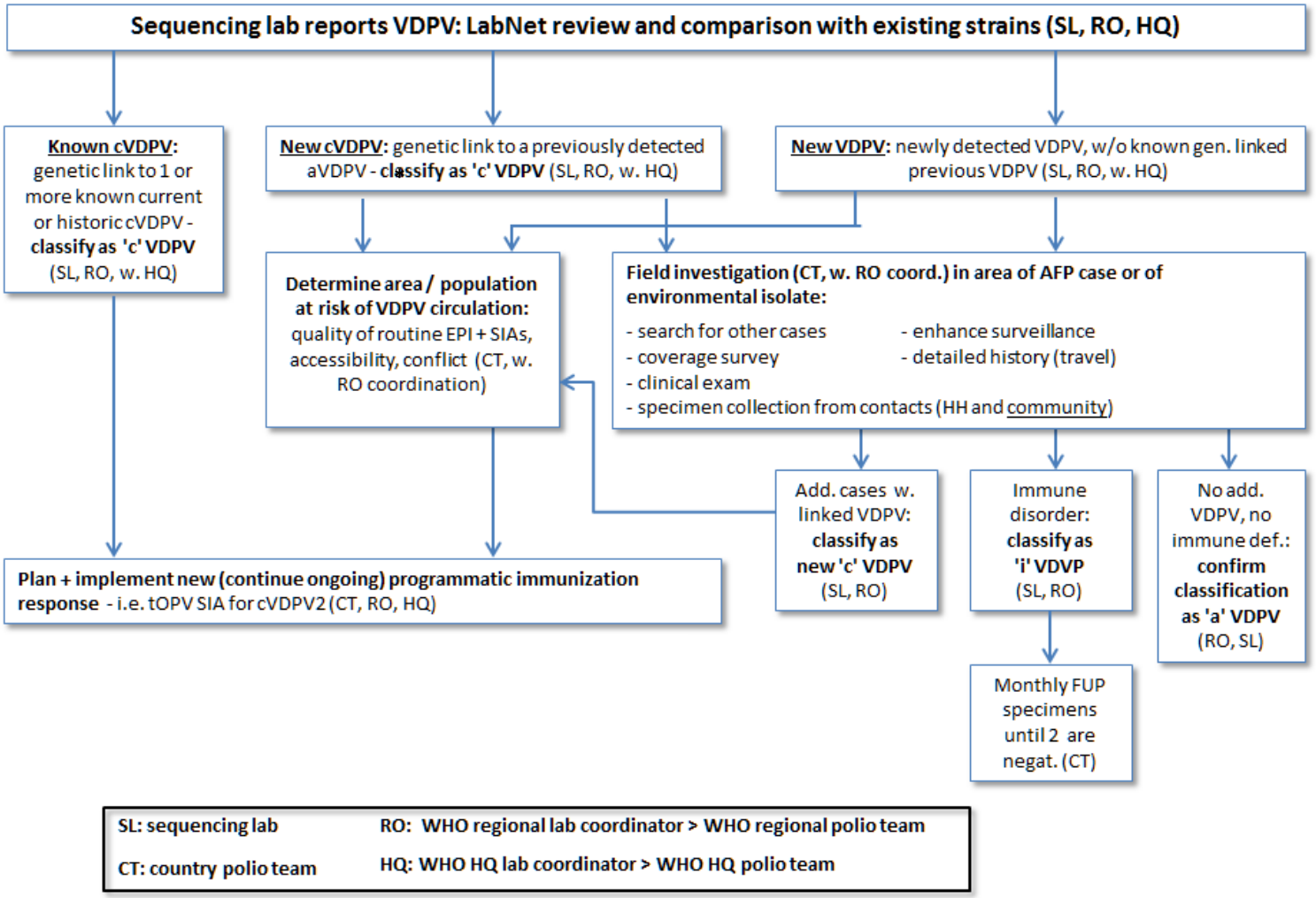


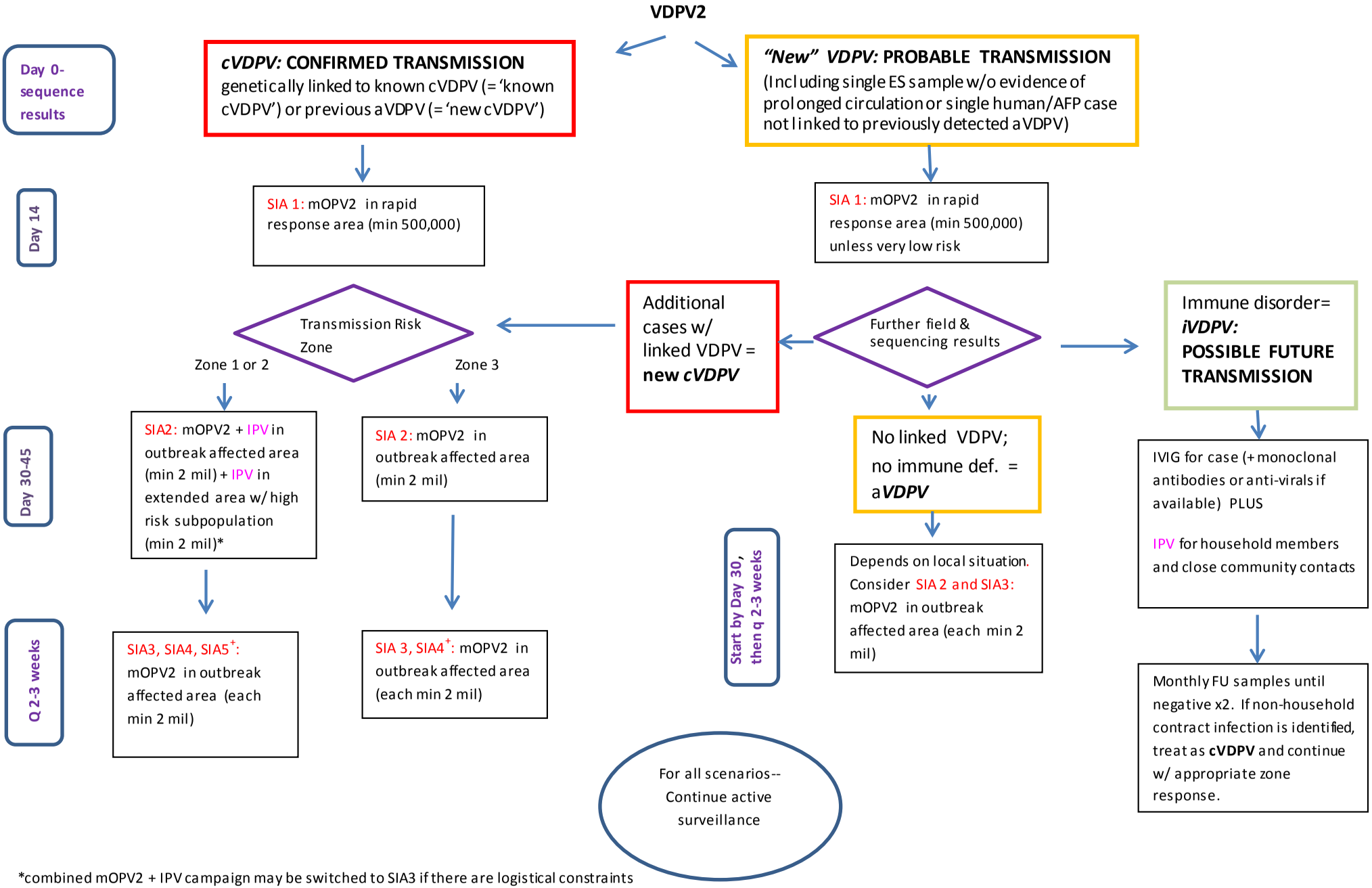
Figure 2: Classification of and response to reported VDPV isolates



*or a single VDPV isolate with genetic features indicating prolonged circulation. See page 11.

Source: GPEI. Reporting and classification of vaccine-derived polioviruses. July 2015. http://www.polioeradication.org/Portals/0/Document/Resources/VDPV_ReportingClassification.pdf

Figure 3a: General response strategies by detection scenarios of a VDPV2 isolate during Phase 1 for countries with use of OPV within 1 year prior to type 2 OPV withdrawal



*combined mOPV2 + IPV campaign may be switched to SIA3 if there are logistical constraints

Figure 3b: General response strategies by detection scenarios of a <u>WPV2</u> isolate during Phase 1 for countries with use of OPV within 1 year prior to type 2 OPV withdrawal

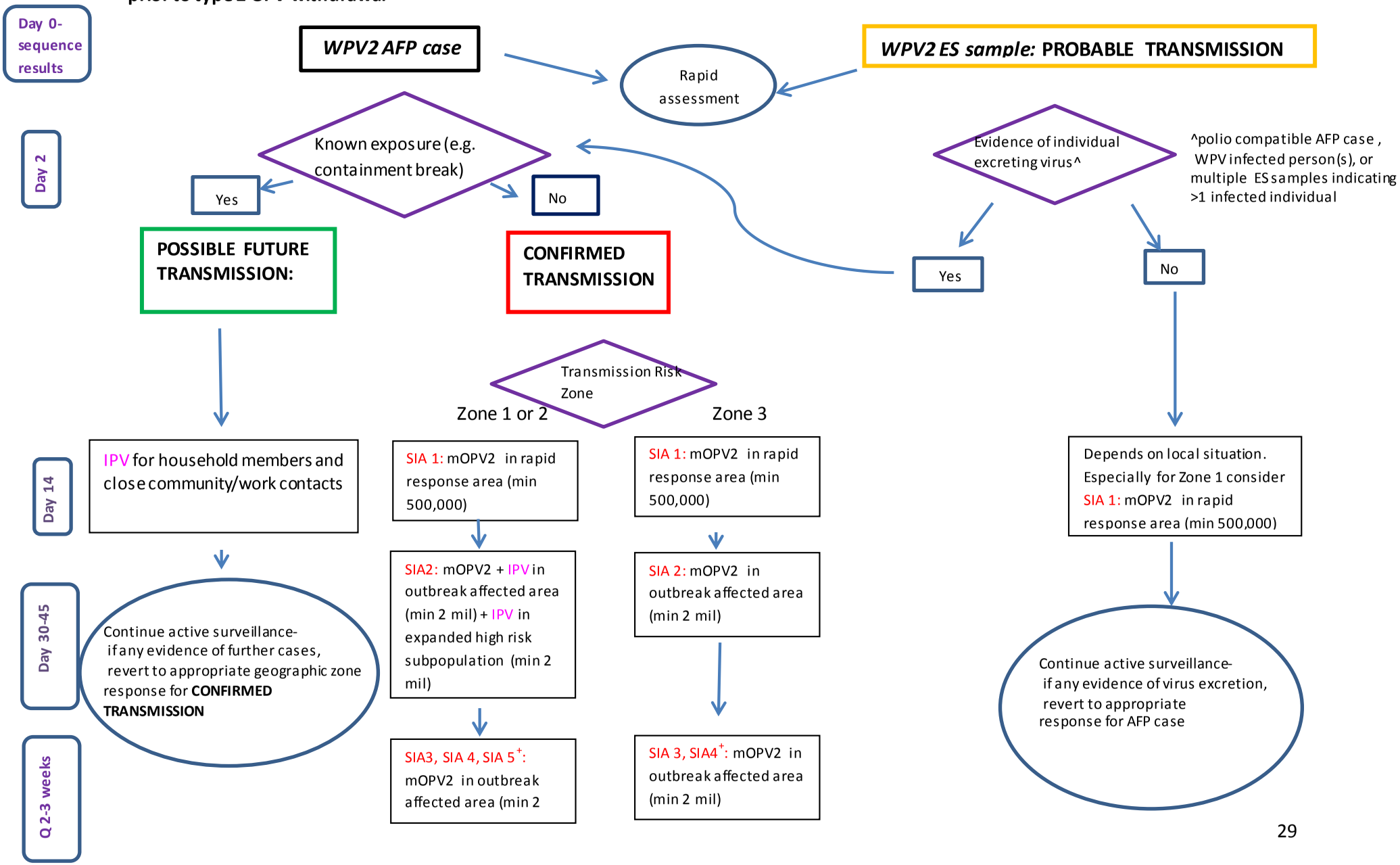
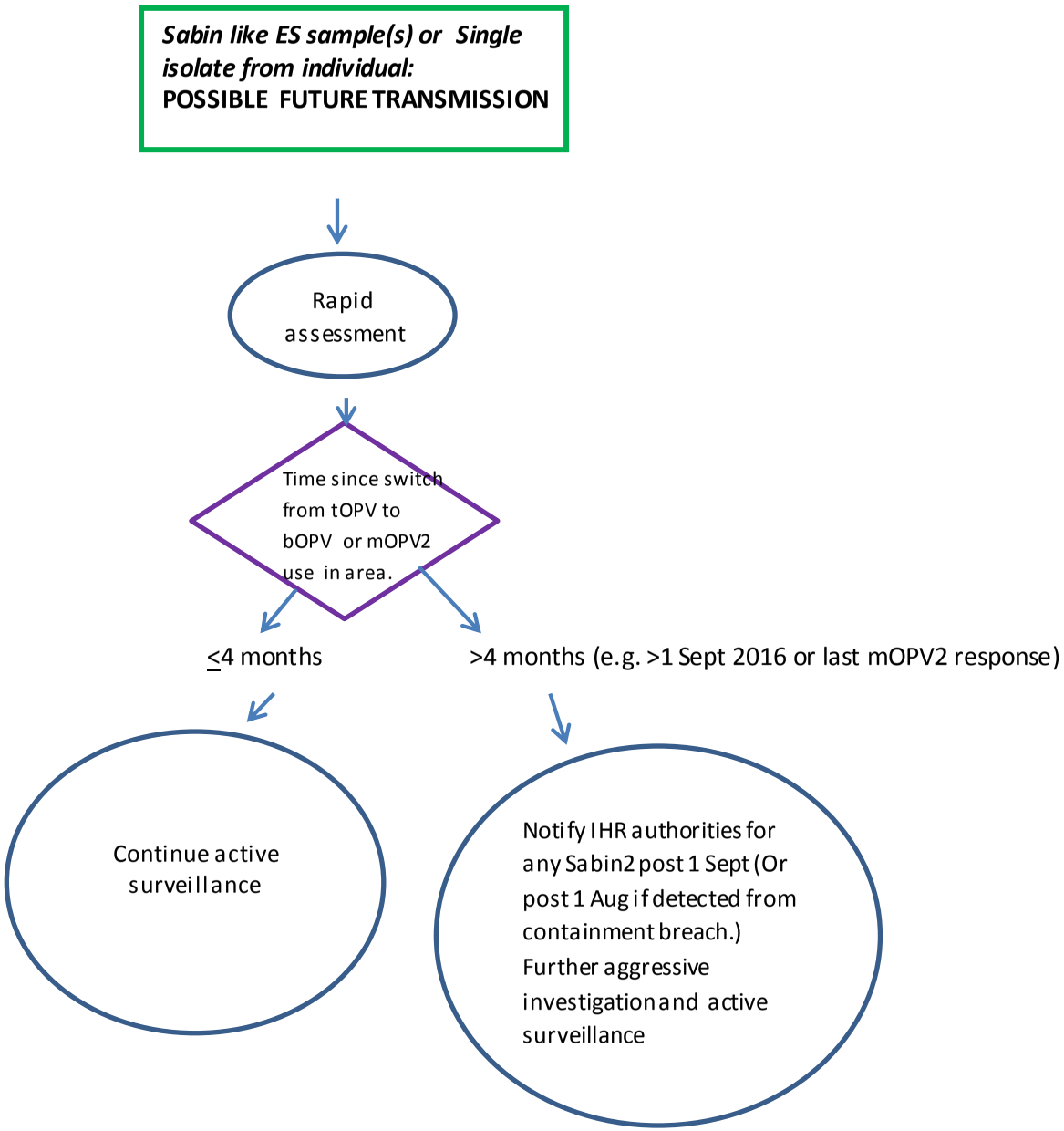


Figure 3c: General response strategies by detection scenarios for a Sabin2 isolate during Phase 1 for countries with use of OPV within 1 year prior to type 2 OPV withdrawal



Annexes

Annex A. Operational Framework for monovalent oral poliovirus type 2 (mOPV2) stockpile deployment and replenishment after OPV2 cessation

1 Stockpile Objectives

In May 2014, the WHA endorsed the SAGE recommendation to establish a global stockpile of mOPV2 for responding to type 2 outbreaks post OPV2 cessation.[61] The primary objectives of the stock pile are: 1) to ensure rapid, universal supplies of mOPV2 for countries experiencing outbreaks of VDPV2 or WPV2; and 2) to maximize the containment of Sabin type 2 poliovirus. Specific quantities of vaccine will be released upon authorization of the WHO Director General.

2 Eligibility

All countries, whether or not they have previously received vaccines through UNICEF, are eligible to access the stockpile.

The SAGE has strongly advised that all countries should rely on this global stock. In May 2015, the WHA directed that any country that decides to establish their own national stock of mOPV2 should maintain the stockpile in conditions of containment that are verified by their Regional Certification Commission for Polio Eradication to be compliant with the GAPIII guidelines[62] and to seek authorization from the Director-General of WHO before its release and use.[63]

3 Stockpile content

WHO and the UNICEF Supply Division have collaborated with two vaccine manufacturers to establish a stockpile of bulk mOPV2. Both manufactures of mOPV2 vaccines have been licensed in the country of origin and their vaccines are pre-qualified by WHO.[64]

As of March 2016, the stockpile contains 519 million doses of mOPV2: 419 million doses of bulk vaccine (shelf life of 20 years), 50 million doses finished product ready for deployment by April 2016 and 50 million doses in semi-finished product (vials without labels) available by July 2016 which can be converted to finished product between September and December 2016. Vaccine will be processed to replenish the supply of finished product upon request from the GPEI to maintain stock levels.

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[61] See World Health Assembly. Poliomyelitis: intensification of the global eradication initiative. Report by the Secretariat. Geneva: World Health Organization, 2014 http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_38-en.pdf; and Meeting of the Strategic Advisory Group of Experts on immunization, November 2013 – conclusions and recommendations. Weekly Epidemiological Record, 2014; 89(1):1–16. http://www.who.int/wer/2014/wer8901.pdf

[62] WHO. GAPIII: WHO Global Action Plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of oral polio vaccine use. http://www.polioeradication.org/Portals/0/Document/Resources/PostEradication/GAPIII_2014.pdf

[63] 68th WHA. Poliomyelitis. http://apps.who.int/gb/ebwha/pdf_files/WHA68/A68_R3-en.pdf.

[64] World Health organization list of prequalified vaccines. http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/

4 Stockpile location, management, and governance

The roles and responsibilities of each party (e.g. manufacturers, WHO, UNICEF) are outlined in a contract for services with the manufacturers which builds on a Letter of Agreement between WHO and UNICEF. WHO maintains ownership of the stockpile. The manufacturers are responsible for storing and maintaining the stockpile under appropriate containment and quality assurance standards as well as preparing the vaccine for delivery in line with the agreed lead times. UNICEF has responsibility for procuring and coordinating the delivery of the vaccine to recipient countries when authorized by the WHO Director General based on national requests.

5 Decision making for release of vaccine

The objective of establishing the stockpile is to manage stocks of mOPV2 which will be required in all vaccination responses. (See **Response Strategies for Phase 1**, page 16). Countries (even those with their own national stocks) should submit a request for mOPV2 to a global advisory committee[65] who will make a recommendation to the Director-General of WHO (DG). The DG's authorization permits release of mOPV2 from a national or global stockpile and initiates the process for shipping the vaccine to the requesting country as necessary.

Evidence of confirmed type 2 transmission in high risk countries will also require a response with IPV. Due to severe constraints in the global availability of IPV vaccine through at least the end of 2017 use of this vaccine for a type 2 outbreak response will need to be closely monitored and managed. Countries may use the same form to request both mOPV2 and IPV. As it does for IPV used for routine immunization, UNICEF in close coordination with global partners will manage the procurement and supply of IPV targeted for response to a type 2 outbreak in any non-producing country. If only a very limited number of doses of IPV are required (i.e. to vaccinate household contacts) countries should use their own national stocks.

See **Table 5** (page 33) for a summary of the steps required for notification, confirmation, and response to a type 2 outbreak/event. Note that the steps and time frame may be revised based on experience and implementation of new laboratory procedures.

6 Stages in Accessing Vaccine Stockpile *(See also Figure 2, page 26)*

Vaccine will be requested in two stages: Stage 1 covers only the mOPV2 vaccine required for SIA1; Stage 2 covers vaccines (mOPV2 and if necessary, IPV) for all further planned SIAs.

Stage 1: In order to ensure a rapid response, the initial request (**see Annex B**) should be prepared within 24 hours of validation of sequencing results and include:

- Relevant laboratory and epidemiologic information of the investigation to date
- Basic profile of the affected population (e.g. vaccination coverage rates, summary of other risk factors, etc.)
- General response plan for SIA1 only, including requested quantities of mOPV2 vaccine
- Authorization for emergency use of mOPV2 based on WHO prequalification (See **Regulatory Considerations** below.)

Stage 2: Planning for subsequent response strategies will usually require further field investigation. Submit request for all subsequent SIAs together. Stage 2 request form should contain:

- Results of any further laboratory and epidemiologic investigation

[65] The Eradication and Outbreak Management Group (EOMG) plus other technical experts

- Response plan for all further SIAs (including specific number of vaccine doses required) and number of doses of any existing stocks of mOPV2 from SIA1
- If IPV is required (and not already licensed in the country), confirmation that the recipient country will accept the vaccine and has the regulatory procedure in place to authorize its anticipated use.

Table 5. Steps for notification, confirmation, and response to a type 2 outbreak/event [+]

Step	Action	Comments	Responsibility	Time frame@	Data or decision reported to	Days > Notification of Sequencing Results
Notification and Response Preparation						
1	Laboratory Notification of type 2 poliovirus isolate sequencing results		Global Polio Laboratory Network (GPLN)	-Complete w/in 14 days of initial isolation -Report w/in 24 hours of results	Notification to MoH, GPEI partners (including UNICEF SD)	Day 0
2a	Initial confirmation of outbreak/event & risk assessment *-national level*	Conduct rapid case confirmation and risk assessment. Further investigation should continue to aid in final classification (*see step 14*)	-MoH/EOC*(with local GPEI support if needed and available). -If outbreak/event is confirmed, IHR focal point has reporting responsibility	-Complete in <48 hours; report findings asap. -If outbreak/event is confirmed to meet IHR criteria, report in <24 hours of completing assessment through IHR protocol	-Report initial findings to WHO country and Regional Office. - Report to WHO IHR contact point	Day 0-2
2b	Confirmation of outbreak/event - *regional-global level*	Follow-up with MoH upon receiving lab notification. If any concerns, verify lab results with GPLN regional reference lab	WHO Regional Office polio focal point	Report immediately or in <24 hours of completing assessment	Notification to regional & global GPEI partners	Day 2
3a	Response preparation *-global level*	Prepare OPRTT^ response -Identify potential TA -Prepare funding	EOMG **	Begin <24 hours from lab notification		Days 0-2
3b	Response preparation *-national level*	Draft response plan & vaccine request simultaneously with rapid investigation	MOH/EOC (with GPEI if needed & available)	Begin <24 hours from lab notification; complete within 48 hours		Days 1-2
Stage 1 – Response Implementation						
4	Submit SIA1 vaccine request upon confirmation of outbreak/event	Complete initial risk assessment; finalize vaccine requirements per response plan	MoH/EOC (consult with WHO/UNICEF in-country)	<24 hours from confirmation of outbreak or event	EOMG**	Day 2
5	Vaccine request evaluated at global level	Assisted by WHO/POL as secretariat	Advisory Group (EOMG[+])	<24 hours	WHO Director General (DG)	Day 3
6	Vaccine stockpile release authorized	DG reviews Advisory Group recommendation	WHO DG	<24 hours	Authorization sent to UNICEF, MoH	Day 4

7	GPEI Response initiated	OPRTT^ support implementation -Grading -TA staff deployed -No regret funds released	EOMG**/OPRTT^	<72 hours from DG authorization	Communicates w/ other GPEI partners at all levels & MoH	Days 4-6
8	Official notification to prepare vaccines for delivery	Purchase Order issued to manufacturer	UNICEF Supply Division (SD)	<24 hrs from receipt of DG's authorization	Vaccine manufacturer	Day 4
9	Prepare shipment		Manufacturer-vaccine; UNICEF (or WHO)-syringes and safety boxes if required	3 working days	UNICEF	Days 4-6
10	Ship to recipient country		UNICEF SD (or WHO)	≤72 hours	Recipient MoH	Days 7-9
11	In-country processing and transport	Includes customs clearances; delivery to field level	MoH/EOC	≤5 days		Days 10-14
12	**SIA 1**		MoH/EOC +EOMG Rapid Response Team	3-5 days		Day 14+
Stage 2 - Response Preparation and Implementation						
13	Conduct further field + laboratory investigation to reach final classification	Simultaneous with Stage 1. Includes contact tracing, further labs to rule out immunodeficiency.	MoH/EOC + EOMG Rapid Response Team	7-14 days; further time may be required in some circumstances		Day 0-13
14	Prepare further response plans (SIA2+) & Stage 2 vaccine request	Simultaneous with Stage 1. Request should include vaccines required for all additional planned SIAs.	MoH/EOC + EOMG Rapid Response Team	7-14 days	WHO HQ	By day 14
	Repeat steps 4-12	Delivery may take longer than in Stage 1 when syringes required.	All	16 Days		Days 15-30
	Implement **SIA 2 and additional SIAs**		MoH/EOC + EOMG support as necessary			By day 30-45; then q2-3 wks
	Proper containment & disposal of mOPV2	Should take place after each SIA w/ validation after last SIA.	MoH w/ assistance of GPEI	Final stock report w/in 2 weeks of last SIA		

+NOTE: Steps and time frame may be revised based on experience and implementation of new laboratory procedures
@: All time frames indicate intended targets. Some steps may be accomplished quicker; others, particularly for logistics, may take longer depending on local conditions, flight schedules, etc. *EOC-Emergency Operations Center; **EOMG-Eradication & Outbreak Management Group; ^OPRTT-Outbreak Preparedness and Response Task Team; ^^NRA-National Regulatory Authority

7 Logistics

a. Shipping

UNICEF will coordinate with the supplier to organize shipment of mOPV2 and IPV. Depending on supplier, UNICEF or WHO will organize shipment of and syringes/ID devices and safety boxes as appropriate for the outbreak response.

b. Documentation

The list of documents in the packing list to accompany each vaccine consignment is listed in the contract for services with the manufacturer and includes: (a) Invoice; (b) Air Waybill; (c) Release certificate issued by the National Regulatory Authority of the country of manufacture for each lot of vaccine supplied; and (e) Vaccine Arrival Report (VAR). Temperature recorders will be including in the consignment as per guideline for international shipping of vaccine. A vaccine vial monitor (VVM) will be placed on each vaccine vial as for any WHO pre-qualified OPV vaccine. Any additional documentation requirements from recipient countries will not be accommodated and will need to be waived to ensure timely delivery.

c. Vaccine specifications and storage at country level

WHO and UNICEF will work closely with the recipient country to assess the storage volume required for the outbreak response vaccine and ensure sufficient cold room space at -20°C or 2°C to 8°C at the national level as well as adequate capacity at all relevant links of the cold chain. Vial sizes will depend on available supply. Refer to the request form for estimated volumes and storage requirements for both mOPV2 and IPV.

d. Management of unused stocks

The program should rigorously manage and monitor utilization of mOPV2 stocks.[66] After each SIA, all vaccine doses utilized and balance stock remaining (unopened vials) should be reported to district level within 2 days of completion of round. These unopened vials should be retrieved by the district level cold store within 5 days of completion of round. The district level cold store should report mOPV2 stock levels to the national EPI manager within one week of SIA completion. Supplies to the district for the next mOPV2 SIA round should be adjusted against these available stocks.

The district level cold chain manager should clearly segregate and store any retrieved mOPV2 vials separately from bOPV stocks. Open vials of mOPV2 remaining after each SIA should be securely disposed at the local level using the same guidelines issued for disposal of tOPV.[67]

[66] GPEI. Cold Chain and Logistics Guidelines for mOPV2 and IPV in post switch SIAs. *Draft*, April 2016.

[67] See GPEI. Managing the switch: Supply and logistics guide for the switch. August 2015. http://www.who.int/immunization/diseases/poliomyelitis/endgame_objective2/oral_polio_vaccine/implementation/en/

Within two weeks of completing the last SIA required in the response plan, countries must report their remaining stock levels of mOPV2 to WHO and UNICEF as outlined in the revised Standard Operation Procedures for Vaccine Management (SOP-VM2).[68]

All district stores should take remaining unopened mOPV2 vials out of the cold chain, label, and mark them clearly as explained in tOPV-bOPV switch guidelines. These vials should then be collected at regional stores and disposed of properly as per national regulatory procedures.

Further detailed guidance for country programs is being developed by GPEI.

8 Regulatory Considerations

a. Role of National Regulatory Authorities (NRA) in licensing and oversight

The 68th WHA urged all member states to establish procedures to authorize the importing and use of mOPV2 in the event of a type 2 outbreak. Since the procedure to license vaccine even in the case of a fast track procedure may be time consuming, high risk countries (e.g. those in transmission risk zones 1 and 2) should take steps in advance to ensure that mOPV2 can be rapidly deployed if necessary. WHO will provide technical support for these countries to facilitate implementation of this authorization procedure. Recipient countries may preemptively authorize use of mOPV2 based on licensure issued by the stringent NRA process in the producing country and the knowledge that the vaccine is prequalified by WHO. If not already completed, this authorization should be included as part of the vaccine request and will confirm that the recipient country will accept the vaccine and has the regulatory procedure in place to sanction its intended use.

If IPV response is recommended, the recipient country will also need to confirm it will accept the vaccine and has the regulatory procedure in place to authorize its intended use.

b. Prequalification

The mOPV2 products in the stockpile and IPV provided for outbreaks are licensed in the country of origin and WHO-prequalified. As for any vaccine supplied through UNICEF, the manufacturers are responsible for submission for WHO prequalification and for maintaining the prequalification status to cover the period of the stockpile contract.

[68] GPEI. Standard Operating Procedures for Vaccine Management version 2 (SOP-VM2). Draft, April 2016.

Annex B: Vaccine request form

Refer to GEPI website (under publication)

www.polioeradication.org