World Health Organization

Third Meeting of the Containment Advisory Group

13 – 14 December 2018
Geneva, SWITZERLAND

Note for the Record

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List of abbreviations

CAG	Containment Advisory Group
CAG1	First Meeting of the CAG, 19-20 June 2017
CAG2	Second Meeting of the CAG, 28-30 November 2017
CAG3	Third Meeting of the CAG, 13-14 December 2018
CAG TC1	Teleconference of the CAG on Showers, 25 January 2018
CAG TC2	Teleconference of the CAG on Novel Poliovirus Strains, 8 March 2018
CAG TC3	Teleconference of the CAG TC3 on nOPV2 candidate vaccines and S19 – poliovirus type 2 strains, 7 June 2018
CAG TC4	Ad hoc Teleconference of the CAG on Tertiary Safeguards, 14 August 2018
CAVA	Cold-Adapted Viral Attenuation - Poliovirus strains
CC	Certificate of Containment
CCS	Containment Certification Scheme to support the WHO Global Action Plan for Poliovirus Containment
CP	Certificate of participation
ESG	Expert Support Group of CAG on Novel Poliovirus Strains
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 or WHO Global Action Plan for Poliovirus Containment (3rd ed; 2014)
GCC	Global Commission for the Certification of the Eradication of Poliomyelitis
GPEI	Global Polio Eradication Initiative
GVAP	Global Vaccine Action Plan 2011-2020
ICC	Interim certificate of containment
IPV	Inactivated poliovirus vaccine
MOH	Ministry of Health
NAC	National authority for containment
NCC	National Committee for the Certification of the Eradication of Poliomyelitis
OPV	Oral poliomyelitis vaccine
bOPV	Bivalent oral poliomyelitis vaccine containing type 1 and type 3
mOPV2	Monovalent oral poliomyelitis vaccine type 2
nOPV2	Novel oral poliomyelitis vaccine type 2
PEF	Poliovirus-essential facility
PIM	Potentially infectious materials, poliovirus
PV	Poliovirus (PV1: Poliovirus serotype 1, PV2: Poliovirus serotype 2 and PV3: Poliovirus serotype 3)
PVSRIPO	Neuro-attenuated recombinant poliovirus; live attenuated Sabin serotype 1 poliovirus with heterologous internal ribosomal entry site (IRES) of human rhinovirus type 2
RCC	Regional Commission for the Certification of the Eradication of Poliomyelitis
SAGE	Strategic Advisory Group of Experts on Immunization
VDPV	Vaccine-derived poliovirus (VDPV1: VDPV serotype 1, VDPV2: VDPV serotype 2 and VDPV3: VDPV serotype 3)
aVDPV	Ambiguous vaccine-derived poliovirus (aVDPV1: aVDPV serotype 1, aVDPV2: aVDPV serotype 2 and aVDPV3: aVDPV serotype 3)
cVDPV	Circulating vaccine-derived poliovirus (cVDPV1: cVDPV serotype 1, cVDPV2: cVDPV serotype 2 and cVDPV3: cVDPV serotype 3)
iVDPV	Immunodeficiency-associated vaccine-derived poliovirus (iVDPV1: iVDPV serotype 1, iVDPV2: iVDPV serotype 2 and iVDPV3: iVDPV serotype
VLP	Virus-like particle
WHA	World Health Assembly
WHO	World Health Organization
WPV	Wild poliovirus (WPV1: WPV serotype 1, WPV2: WPV serotype 2 and WPV3: WPV serotype 3)
WSH	Water, Sanitation and Hygiene

List of recurring references used in this report:

CAG meeting reports

First meeting of the Containment Advisory Group, 19-20 June 2017, Geneva, Switzerland. Available at: http://polioeradication.org/wp-content/uploads/2017/08/CAG1-Report-30082017.pdf

Second meeting of the Containment Advisory Group, 28-30 November 2017, Geneva, Switzerland. Available at: http://polioeradication.org/wp-content/uploads/2018/02/poliovirus-containment-advisory-group-meeting-20171130.pdf

Teleconference of the Containment Advisory Group (CAG TC1) on Showers, 25 January 2018. Available at: http://polioeradication.org/wp-content/uploads/2018/05/containment-advisory-group-teleconference-1-on-showers-25-january-2018-20180523.pdf

Teleconference of the Containment Advisory Group (CAG TC2) on Novel Poliovirus Strains, 8 March 2018. Available at: http://polioeradication.org/wp-content/uploads/2018/05/containment-advisory-group-novel-poliovirus-strains-8-march-2018-20180518.pdf

Criteria for the evaluation of improved 'safety' of novel poliovirus strains to determine the containment requirements for their storage and handling. Available at: http://polioeradication.org/wp-content/uploads/2017/08/criteria-evaluation-novel-pv-june-2019-eng.pdf

Teleconference of the Containment Advisory Group (CAG TC3) on nOPV2 candidate vaccines and S19 – poliovirus type 2 strains, 7 June 2018. Available at: http://polioeradication.org/wp-content/uploads/2017/08/CAG-TC3-20180630-EN.pdf

> Addendum to the Report of the Teleconference of the Containment Advisory Group (CAG TC3) on nOPV2 candidate vaccines and S19 – poliovirus type 2 strains, 14 December 2018. Available at: http://polioeradication.org/wp-content/uploads/2017/08/Addendum-CAG-TC3-Dec-2018-EN-1.pdf

Ad hoc Teleconference of the Containment (CAG) on alternative measures of compliance with the requirements of Tertiary Safeguards in GAPIII, 14 August 2018. Available at: http://polioeradication.org/tools-and-library/policy-reports/advisory-reports/containment-advisory-group/

Containment resources

http://polioeradication.org/polio-today/preparing-for-a-polio-free-world/containment/containment-resources/

Summary of Recommendations
Third Meeting of the Containment Advisory Group

The Containment Advisory Group (CAG) met for the third time on 13-14 December 2018 at the Starling Hotel, Geneva, SWITZERLAND. These are the recommendations:

Global update on poliomyelitis eradication and poliovirus containment

Global progress on poliomyelitis eradication, and updates on research activities to maximize the impact of eradication and long-term risk management in the post-eradication era.

1. CAG expressed their concern on the continued use of mOPV2 for VDPV2 events and outbreaks which has now been shown to cause the emergence of other VDPV2 especially in areas with suboptimal vaccine coverage. The CAG recommends that more conserved approach be given by the mOPV2 Advisory Group when making decisions for its deployment. When approved to be deployed, it is also recommended by CAG, that the documentation to the country, including the EPI focal point, NPCC or equivalent, NAC and the NCC include the guidance for the removal, handling and disposal of unused mOPV2.

Global progress on containment implementation and issues or decisions relevant to CAG from recently concluded meetings (e.g., 18th GCC, 2nd meeting between GCC-CWG and NACs, etc)

1. The CAG commends the CWG on the critical work of the review of CCS application and noted that as facilities are not in full compliance with GAPIII yet, there will be numerous issues where the acceptability of alternative measures being put in place will require some guidance. The CAG, in its TORs, has been mandated to perform this function and is ready to assist as needed. The Fourth Meeting of the CAG will be an opportunity to determine and roll-out the operational aspects of this collaboration. This would also entail a coordinated effort from both the CAG and CWG secretariat.

Secondary (population immunity) and tertiary (facility location and environmental controls) safeguards requirements in GAPIII

Tertiary safeguards (definition, purpose, intent and ownership). Water, sanitation and hygiene controls to support GAPIII tertiary safeguards implementation

1. The CAG commends the secretariat for reaching out to the WSH unit at WHO and urges the secretariat to continue to collaborate with WSH to develop clear guidance on the acceptable alternative measures of compliance with tertiary safeguards, including clear definitions, expectations and standardized documentation/evidence expected from NACs for this requirement in the certification application process. Although likely to be challenging to implement from a containment perspective, the secretariat is urged to continue collaboration with the WSH unit in considering piloting the implementation of the WHO Sanitation safety planning in some PEF-hosting countries to determine its feasibility and appropriateness,

2. Considering the purpose of secondary (population immunity) and tertiary safeguards (facility and environment controls) which is to minimize the consequences of a release of poliovirus, the possibility of an alternative approach i.e., the use of a risk-based approach rather than a prescriptive approach that takes into consideration the basic (R_0) or effective (R) reproductive rate of poliovirus in an area which depends on factors such as population density and movements, sanitation and hygiene conditions (population, environment, sewage systems and treatment), population immunity, susceptible persons, etc) should also be explored.

3. Although not limited to this issue alone, there is a need to develop clear risk-based guidance, dialogues or discussions between NACs and PEFs on the potential failures of primary containment (hazard e.g., facility-associated release of poliovirus through untreated effluent, risk e.g., exposure to community, likely consequences e.g., re-establishment of transmission and expected responses). The guidance should include recommendations to mitigate risk that provide barriers to limit the consequences of the release (e.g., population immunity or secondary safeguards) or those that limit the re-establishment of WPV transmission (facility location and associated environmental controls or tertiary safeguards). The guidance may also include clear concise, one-page descriptions of the safeguard and its components that can be used both as reference and communication tool (see Annex 4 for an example).

Implementing the revised secondary safeguard requirements

1. CAG has noted the concerns raised and will consider options for requesting the SAGE Polio Working Group to consider additional flexibility in assessment criteria for secondary safeguards.

2. Similarly, the possibility of an alternative approach i.e., the use of a risk-based approach rather than a prescriptive approach that takes into consideration the basic (R_0) or effective (R) reproductive rate of poliovirus in an area which depends on factors such as population density and movements, sanitation and hygiene conditions (population, environment, sewage systems and treatment), population immunity, susceptible persons, etc) should also be explored.

Issue associated with the 'Guidance to minimize risks for facilities collecting, handling or storing materials potentially infectious for polioviruses'

Harmonizing containment requirements for all poliovirus potentially infectious materials

1. The PIM guidance should not be modified at this stage, but further evidence should be sought on the challenges faced by non-polio laboratories planning to retain WPV/VDPV PIM or from their national containment focal points including NACs on the number of potential facilities that would fall under this category.

Issues associated with the implementation of facility physical requirements in GAPIII

Alternative measures for walk-through exit shower

1. CAG considered the need for controlled exit from the containment perimeter via a walk-through exit shower during the First CAG TC on Showers (25 January 2018) and recommended not to further change the recommendations from the said TC[1] until more information and evidence was made available. In

[1] Subelement 12.3.1 (g) of Annex 2 and 3 of GAPIII: Controlled exit from the containment perimeter is via a walk-through exit shower. Showering out is mandatory except for facilities employing closed systems demonstrating validated primary containment. Such systems may include contained lines for use in vaccine production and/or facilities employing fully functional Class III BSCs or similar isolators. For such facilities, showering out is required as a precautionary measure, in the event of an uncontrolled breach of the primary containment equipment, during the period when further assessment of the effectiveness of showering is being undertaken. Additional recommendations: For other facilities, the requirement for mandatory showering should be left to the discretion of the National Authority, after review of a risk assessment submitted by the PEF. Risk mitigation measures will be proposed by the PEF and approved by the National Authority for the interim period of at least two years during which evidence for-or-against-mandatory showering out will be generated. The CAG urged the secretariat to commission a study to collect information on the use, effectiveness and risks associated with showering, including in facilities where showering is currently being used. The CAG will undertake further discussion on showers when the secretariat has collected the information necessary to make an evidence-based recommendation or has shown that it is not feasible to collect such information.

line with this, the compliance with routine showering-out is left up to the discretion of the NACs following the submission of a detailed risk assessment with risk mitigation steps by the PEF for consideration and approval by the NAC.

2. CAG acknowledges the value of the proposed concept note 'Concept and design of evidence-based efficacy study of showering as protective measure to prevent facility associated release of poliovirus' and urges the secretariat to facilitate the submission of a proposal with funding and other requirements for CAG's review as soon as possible.

Effluent decontamination

1. CAG recommends that the requirement for facilities handling WPV2 and/or OPV2/Sabin2 in Phase II as well as OPV/Sabin poliovirus materials in Phase III to follow the requirements for effluent decontamination as applicable for final containment of all WPV in Phase III be raised at the next CAG meeting.

Poliovirus-dedicated facility

1. CAG's previous recommendation on the issue of non-dedicated poliovirus facilities is not changed[2]. However, CAG urges the secretariat to reach out to the submitting NAC to gather additional information on this request in time for the next CAG meeting.

Dedicated ventilation system

1. CAG recognises that use of supply-side HEPA filters directly on the containment barrier in the absence of interconnections (supply connections to other spaces or return exhaust from other spaces) between the supply-side HEPA filter and the exhaust-side, if correctly maintained and routinely tested, are functionally equivalent to providing a dedicated heating, ventilation and air-conditioning (HVAC) system. While this meets the intent of being dedicated, the other requirements must also be in place e.g., airflow is controlled to maintain supply-to-exhaust unidirectional flow, with all passageway for distribution or extraction of air ('ductwork') sealable for gaseous decontamination, has an exhaust-side HEPA filter and supply-side, backflow prevention e.g., damper and has detectors to monitor the unidirectional airflow,

Novel poliovirus strains and innovation in polio vaccine production

S-19 - Poliovirus strains ± N8S in protein 2A

1. Sufficient data has been provided to conclude the series of S19-poliovirus strains (S19 with capsid region, P1 of wild-type and Sabin vaccine strain polioviruses of all serotypes) and the parallel series of viruses with the substitution of an asparagine by a serine at amino acid 18 in the non-structural protein 2A to allow better growth in Vero cells could be considered for use, outside of the containment requirements of Annex 2 or Annex 3 of GAPIII, as applicable for IPV production, rat neutralization IPV

[2] Subelement 12.3.1 (c) of Annex 2 and 3 as it appears in the current version of GAPIII is recommended to remain as is i.e., 'Poliovirus facilities are either poliovirus dedicated or used on a campaign basis with documented effective decontamination procedures between periods of work with agents other than poliovirus'. However, to facilitate its implementation, the use of non-dedicated facilities (e.g. QC laboratories) may be permissible under a CP/ICC during poliovirus type 2 containment phase of GAPIII in association with CCS. In such instances, risk assessments must be provided to demonstrate that the risk of breach of containment, cross-contamination, unauthorized access to materials and other factors have been fully evaluated and addressed. All non-poliovirus related practices and personnel within the containment perimeter shall also adhere to all GAPIII requirements and be included in the scope of GAPIII audits and certification activities.

potency assays, human serum neutralization test for poliovirus antibody determination and potency testing for immunoglobulin (human) lot control and release.

nOPV2

1. The production of nOPV2 and quality control using the candidate vaccine strains (S2/cre5/S15domV/rec1/hifi3 and S2/S15domV/CpG40) may occur outside the containment requirements of GAPIII but should always be in line with prevailing biorisk management institutional practices, national legislations, international standards, etc. CAG may review this decision on receipt of data on virus transmission and environmental behaviour from clinical trials currently underway. While the handling of stool samples from nOPV2 vaccine recipients is not subject to the containment requirements of GAPIII, the implementation of some form of institutional, national or international biorisk management standard or good laboratory practices is appropriate.

Neuro-attenuated recombinant poliovirus; live attenuated Sabin serotype 1 poliovirus with heterologous internal ribosomal entry site (IRES) of human rhinovirus type 2 (PVSRIPO)

1. CAG approves the use of PVSRIPO in Phase II clinical trials but requests more information be provided to CAG on the occupational risk associated with exposure of operators during the production phase of PVSRIPO and the mitigation and public health safeguards put in place to protect production workers and the wider community.

CAG's mandate and collaboration

Applicable CAG recommendations that constitute amendments/revision of GAPIII, endorsement and publication and CAG's mandate of GAPIII

1. CAG welcomes the endorsement of the Polio SAGE Working Group of the transfer of the oversight function for issues related to containment and containment documents e.g., GAPIII, GAPIII-CCS, PIM guidance, etc from Strategic Advisory Group of Experts (SAGE) on immunization to CAG. In line with that, CAG recommends that the Secretariat coordinates a detailed decision review meeting of CAG recommendations, implications of such recommendations on other requirements and to undertake the revision process of GAPIII taking into consideration all applicable recommendations and to coordinate a detailed review of the draft revised GAPIII by CAG to ensure consistency of approach to all safeguards as soon as possible. The CAG also welcomes a period of public consultation for the revised GAPIII.

Other Issues

CAG Membership

1. On 14 December 2018, CAG member Dr Bernard FANGET informed the CAG Chair, members and secretariat his intention to resign as a member of CAG – Dr Fanget's contribution to the CAG is gratefully acknowledged.

CAG Secretariat

1. The CAG took the opportunity to welcome Dr Daphne MOFFETT as the incoming Team Lead, Poliovirus Containment. This follows Dr Jacqueline CARUANA-FOURNIER who is retiring soon after many years of service.

Fourth Meeting of the Containment Advisory Group

1. The CAG agreed that the Fourth Meeting of the Containment Advisory Group should take place in the next six months (mid-2019)

Note for the Record

Background

The Containment Advisory Group (CAG) met for the third time on 13-14 December 2018 at the Starling Hotel, Geneva, Switzerland.

The meeting was attended by the following:

CAG members:	Professor David HEYMANN (Chair), Professor George E GRIFFIN (also CAG-ESG member) Dr Stephen MCADAM (also CAG-ESG member), Dr Mark PALLANSCH (also CAG-ESG member), Dr Atef EL-GENDY, Dr Vibeke HALKJÆR-KNUDSEN, Dr Janice LO, Mr Kenneth UGWU, Dr Jagadish DESHPANDE, Professor Shahina TABASSUM, Dr Åsa SZEKELY BJÖRNDAL and Dr Bernard FANGET. Unable to attend: Mr Neil GODDEN
Invited participants:	Session 3: Dr Bruce GORDON and Dr Kate MEDLICOTT from the Department of Public Health, Environmental and Social Determinants of Health, WHO Headquarters, Session 5: Dr Tjeerd KIMMAN, Wageningen Bioveterinary Research Institute, Netherlands (by phone), and Session 6: Dr Andrew MACADAM, National Institute for Biological Standards and Control (NIBSC).
Representatives of other containment supporting groups:	Dr Arlene KING, Containment Working Group of the Global Commission for the Certification of the Eradication of Poliomyelitis (GCC-CWG) Unable to attend: Professor David SALISBURY, Chair, GCC and Dr Jeffrey PARTRIDGE, Co-Chair, Containment Management Group (CMG)

The agenda and list of participants in indicated in Annex 1 and 2.

Session 1: Introduction
Context, objectives and expected outcomes of the meeting

The time since the certification of the eradication of wild-type poliovirus serotype 2 (WPV2) and the global synchronized switch from trivalent oral polio vaccine (tOPV) to bivalent polio vaccine (bOPV) in April 2016, increase the importance of the implementation of inventory, destruction, preparation-for and containment-of PV2 activities as a matter of urgency. The process of designation and certification of facilities retaining polioviruses post-eradication is the responsibility of National Authorities for Certification (NACs) in collaboration with the Global Certification Commission for the Eradication of Poliomyelitis (GCC). Applications from facilities to be recognized as suitable candidates to become poliovirus-essential facilities (PEFs) are now being submitted by NACs to the Containment Working Group (CWG) of the GCC for endorsement. In line with the terms of reference of CAG[3], several technical questions on the requirements or acceptable alternative measures of compliance with the requirements in the Global Action Plan for Poliovirus Containment (GAPIII) have been received by CAG from NACs, facilities retaining polioviruses and other containment supporting groups for guidance.

Face-to-face meetings of the CAG provide the opportunity for CAG members to review and discuss these questions and provide recommendations. As such the Third Meeting of the CAG had the following objectives:

1. Provide updates to CAG members on poliomyelitis eradication and poliovirus containment
2. Discuss and provide recommendations on the implementation of the following issues:

[3] Terms of Reference of the Containment Advisory Group (CAG). Available at: http://polioeradication.org/wp-content/uploads/2016/12/CAG.TOR_.122016.pdf

   a. Secondary (population immunity) and tertiary (facility location and environmental controls) safeguard requirements in GAPIII
   b. Facility physical requirements in GAPIII
   c. 'Guidance to minimize risks for facilities collecting, handling or storing materials potentially infectious for polioviruses'
   d. Containment requirements for the handling of novel poliovirus strains and innovation in polio vaccine production
   e. Alternative measure of compliance with GAPIII
3. To discuss CAG's mandate of GAPIII, its amendments and collaboration with other containment supporting groups

A summary list of issues discussed at the Third Meeting of the CAG is provided in Annex 3.

Session 2: Global update on poliomyelitis eradication and poliovirus containment

Global progress on poliomyelitis eradication, and updates on research activities to maximize the impact of eradication and long-term risk management in the post-eradication era

Roland SUTTER, Special Adviser to the Director of Polio Eradication, WHO

WPV serotype 1 continues to be widespread in Pakistan and Afghanistan with an increase in the number of cases reported till date over the same period in 2017. The number of WPV1 environmental isolates from these two countries also continues to be reported. There is ongoing virus circulation in three separate transmission zones, with frequent re-introduction of the virus into areas temporarily cleared. Community-based vaccination has been expanded in southern Pakistan, and supplementary immunization activities (SIAs) are continuing in the major transmission zones but ensuring high quality immunization activities in these areas remains a challenge. It is of concern that access to susceptible populations, particularly in Afghanistan is decreasing, with more than one million children now inaccessible to immunization services.

VDPV2 outbreaks have been reported from Nigeria, the Democratic Republic of the Congo, Niger, and Somalia while a VDPV1 outbreak has been reported from Papua New Guinea, and VDPV3 reported in Somalia. There is growing concern over the use of monovalent OPV type 2 (mOPV2) used in response to VDPV2 outbreaks or events, as evidence indicate that mOPV2 use can lead to the emergence of VDPV2 in under-vaccinated populations.

The main activities in poliovirus research and product development, which are key components in the acceleration of eradication and to provide options and contingencies should they be needed was outlined. A high priority of the programme is the development of 'safer' polio vaccines that are hyper-attenuated and genetically stable and could be used in place of the current mOPV2. Two novel OPV2 (nOPV2) candidate vaccines have been developed and subjected to phase I clinical trials under containment conditions and currently two phase 2 trials are being conducted in open populations. Other safe poliovirus strains have also been developed to replace the existing use of live polioviruses for laboratory testing and vaccine quality control [4].

[4] See also: Criteria for the evaluation of improved 'safety' of novel poliovirus strains to determine the containment requirements for their storage and handling and Report of the Teleconference of the Containment Advisory Group on nOPV2 candidate vaccines and S19 – poliovirus type 2 strains. Available at: http://polioeradication.org/tools-and-library/policy-reports/advisory-reports/containment-advisory-group/

To mitigate the impact of IPV supply shortages, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) has recommended the use of fractional doses of IPV[5]. Studies have shown that, in terms of seroconversion and antibody titres raised, two doses of intradermal IPV (1/5th of a dose) are more immunogenic than a single intramuscular IPV dose (full dose). Development of suitable devices for the delivery of intradermal doses of polio vaccine is also continuing.

Global progress on containment implementation and issues or decisions relevant to CAG from recently concluded meetings (e.g., 18th GCC, 2nd meeting between GCC-CWG and NACs, etc)
Daphne MOFFETT, Technical Adviser - Poliovirus Containment, WHO

The World Health Assembly (WHA) resolution 71.16 (2018)[6] adopted by all WHO Member States aims to accelerate progress in poliovirus containment and provides a timeline for the completion of national inventories of poliovirus materials and for the certification of facilities retaining poliovirus materials as described in the Containment Certification Scheme (CCS). There are currently 79 facilities in 27 countries designated for the continuation of critical functions requiring the retention of needed PV2 materials. Of these 27 countries, only 24 have established NACs and only seven applications from such facilities to be recognised as suitable candidates to become PEFs [i.e., Certificate of Participation (CP)] have been received by the CWG. Guidance to minimize risks for facilities collecting, handling or storing materials potentially infectious for polioviruses (PIM Guidance) was published in April 2018 along with reporting forms and other resources[7].

Major challenges in the implementation of containment include meeting the GCC deadline to complete PV2 inventories one year after the publication of the PIM guidance i.e., April 2019, updating national inventories to include WPV1 and WPV3 materials and the establishment of a verification mechanism for the data collection process and validation of data from the inventory, destruction and preparation for the containment of poliovirus activities carried by countries[8]. WHO and partners, namely CDC are currently supporting the implementation of the PIM guidance in countries. Support activities include training of national poliovirus containment focal points on the implementation of the PIM guidance, deployment of consultants to work together with the national poliovirus containment focal points to update their inventories to include poliovirus PIM materials and WPV1 and WPV3 infectious materials, development of global reporting forms, regional reporting formats and other resources. Other challenges include meeting the containment certification timelines of establishment of NACs by end-2018 and the submission of CP applications from facilities retaining polioviruses to their NACs by end-2019 as described in resolution WHA71.16.

A study is underway to assess the cost implications to facilities and their governments in achieving activities and full implementation of GAPIIII and the associated CCS activities over a five-year period i.e., achieving certification for full compliance with GAPIII requirement [Certificate of Containment (CC)]. This study does not take into consideration the cost associated with maintaining the requirements nor the CCS activity cost associated with the conduct of a full scope audit every three years. The preliminary data from this study

[5] Meeting of the Strategic Advisory Group of Experts on immunization, April 2017 – conclusions and recommendations. Weekly Epidemiological Record 2017; 92:301–20. Available at: http://apps.who.int/iris/bitstream/10665/255611/1/WER9222.pdf?ua=1

[6] Resolution WHA71.16 (2018) Poliomyelitis – containment of polioviruses. Available at: http://apps.who.int/gb/ebwha/pdf_files/WHA71/A71_R16-en.pdf

[7] Guidance to minimize risks for facilities collecting, handling or storing materials potentially infectious for polioviruses (PIM Guidance), associated annexes, FAQs, SOP and reporting forms. Available at: http://polioeradication.org/polio-today/preparing-for-a-polio-free-world/containment/containment-resources/

[8] Recommendations from the Special Meeting of the Global Commission for the Certification of the Eradication of Poliomyelitis on Poliovirus Containment, 23-25 October 2017, Geneva, Switzerland. Available at: http://polioeradication.org/wp-content/uploads/2018/03/polio-global-certification-commission-report-2017-10-20180314-en.pdf

estimates the cost to be approximately USD 10 M for production facilities, and 90% less for laboratories. Projected costs for NACs in the implementation to certification activities can range from a few hundreds of thousands to several millions USD for a full certification cycle. Full details of the study will be made available sometime in the future.

Session 3: Secondary (population immunity) and tertiary (facility location and environmental controls) safeguards requirements in GAPIII

Issue: Tertiary safeguards (definition, purpose, intent and ownership)

Sanitation and associated environmental controls to support GAPIII tertiary safeguards implementation

Harpal SINGH, Technical Officer - Poliovirus Containment, WHO
Bruce GORDON, Coordinator and Kate MEDLICOTT, Technical Officer, Public Health, Environment and Social Determinants (HQ/CED/PHE), WHO

Relevant GAPIII section (or other reference, as appropriate)	
GAPIII:	Strategy, Table 1, Phase Implementation, Annex 1 (Definition), Sublement 12.3.1 of Annex 2
Other reference:	CCS (Definition) and CAG TC4 report on tertiary safeguards

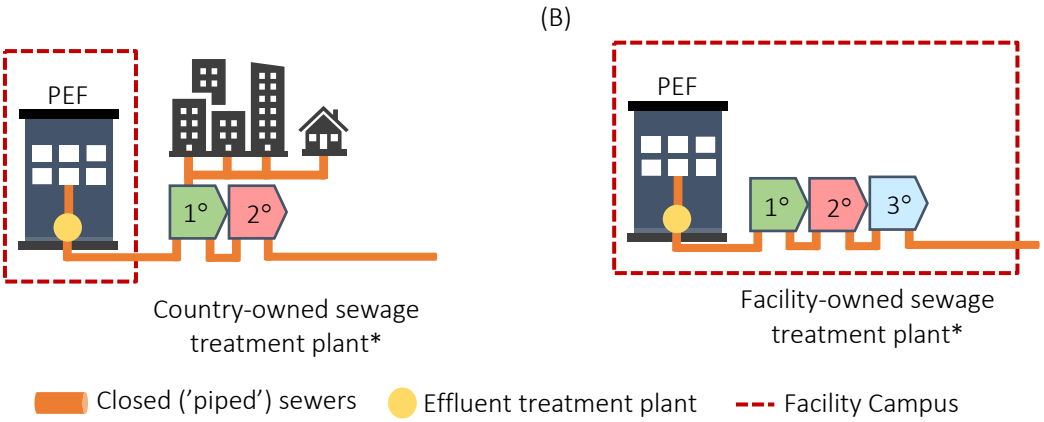
Background of issue raised:

Following a request for CAG guidance from the CWG on alternative measure of compliance with tertiary safeguards in GAPIII of a CP-applicant facility, a CAG TC4 was held in August 2018 (report from CAG TC4 is pending publication due to issues brought forward to this CAG3 meeting).

Definition of tertiary safeguard of facility location and environmental controls as described in GAPIII or GAPIII-CCS (left) and the proposed alternative measures of compliance (right)

The sanitation and hygiene conditions (good personal, domestic and environmental hygiene standards and closed sewage systems with secondary or greater effluent treatment) that minimize the risk of re-establishing the circulation of highly transmissible wild poliovirus in the event of reintroduction. The country hosting the poliovirus-essential facility is responsible for the implementation of the tertiary safeguards, a prerequisite for the containment certification of facilities retaining wild poliovirus in Phase III.	• Area surrounding the facility has no government entity-owned sewage system. The government has no plans to do so soon • Facility has its own 'open' sewage system with tertiary effluent treatment performed on campus • Inactivated effluents from its PEF will be conveyed in a 'closed' piped sewage system to its effluent treatment plant, undergo up to tertiary effluent treatment on campus before being discharged (Figure 1) • If compliant, the responsibility for implementation of tertiary safeguards of facility location will be transferred from the country to the facility

Figure 1: GAPIII tertiary safeguards of facility location requires the siting of facilities in areas with low transmission potential (R_0) for WPV i.e., in areas with closed sewage systems with a minimum of secondary treatment of effluents (A) and alternative measure of compliance with this requirement based on type and ownership of the sewage system (B)



* Sewage treatment levels: 1° (physical - settlement of suspended solids); 2° (biological - aerobic e.g., aeration tanks or anaerobic) and 3° (advanced – various types exist depending on requirements for receiving water e.g., UV, filter membranes) treatment levels. All treatment levels may include some part of the treatment process occuring in areas exposed to air e.g., aerated grit chamber, aeration tanks, aerators, etc.

A recommendation from CAG TC4 was for the secretariat to explore with the Water, Sanitation and Hygiene (WSH) Unit at WHO to provide clarity on the present definition, purpose and intent of this requirement for deliberation at this meeting.

The intent of tertiary safeguards was to require inactivation of effluent on-site (as part of facility-based primary safeguards), followed by the transfer of inactivated effluent through some form of 'closed' or 'piped' system to a government entity-owned public or community sewage treatment plant with secondary or greater effluent treatment i.e., in the event of failure of primary safeguards, untreated effluent from the facility would not be released into the local environment but would have to undergo sewage treatment prior to its release. There has been little attempt to engage WSH or public health engineers to provide clear definitions of the terms used in GAPIII, which has resulted in some ambiguity resulting in challenges to providing clear guidance on risk assessment criteria and risk mitigation requirements.

An overview of the WHO water, sanitation and hygiene strategy 2018-2025[9] which sets out WHO directions within the context of SDG 6 ('Ensure availability and sustainable management of water and sanitation for all'), the WHO Guidelines on Sanitation and Health[10] which provides a framework for health-protecting sanitation (policy, governance, use of sanitation technologies, risk-based management, etc) and the WHO Sanitation safety planning: Manual for safe use and disposal of wastewater, greywater and excreta[11] which is a risk based management tool that provides a risk-based approach to identify and manage health risk along the sanitation chain usually performed in collaboration with multiple sector stakeholders (health, utilities, private sector, environment, agriculture, etc). Options for future collaboration were discussed, including the training of a small number of facilities retaining polioviruses, NACs, staff sewage operators and relevant sectors in sanitation safety planning and in the piloting and auditing of safety plans.

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[9] WHO water, sanitation and hygiene strategy 2018-2025. Available at: https://apps.who.int/iris/bitstream/handle/10665/274273/WHO-CED-PHE-WSH-18.03-eng.pdf?ua=1

[10] WHO Guidelines on Sanitation and Health. Available at: https://www.who.int/water_sanitation_health/publications/guidelines-on-sanitation-and-health/en/

[11] WHO Sanitation safety planning: Manual for safe use and disposal of wastewater, greywater and excreta. Available at: https://www.who.int/water_sanitation_health/publications/ssp-manual/en/

Summary of CAG discussions and conclusions

Assessing sanitation effectiveness around a facility using the sanitation safety planning tool, is highly labour intensive, but is possible. It would identify risks to the surrounding community and allow the development, implementation and monitoring of appropriate control measures. This approach may be necessary as some of the requirements for tertiary safeguards as described in GAPIII which will be difficult to meet in some PEF-hosting countries. In addition, the use of the terms 'onsite' and 'offsite' treatment is more consistent with engineering terms than 'closed' or 'open' sewage systems and in many cases 'onsite ('facility') treatment may even perform better than offsite (government) treatment due to better management responsibility and oversight.

CAG recommendations

1. The CAG commends the secretariat for reaching out to the WSH units at WHO and urges the secretariat to continue to collaborate with WSH to develop clear guidance on the acceptable alternative measures of compliance with tertiary safeguards, including clear definitions, expectations and standardized documentation/evidence expected from NACs for this requirement in the certification application process. Although likely to be challenging to implement from a containment perspective, the secretariat is urged to continue collaboration with the WSH unit in considering piloting the implementation of the WHO Sanitation safety planning in some PEF-hosting countries to determine its feasibility and appropriateness.

2. Considering the purpose of secondary (population immunity) and tertiary safeguards (facility and environment controls) is to minimize the consequences of a release of poliovirus, the possibility of an alternative approach i.e., the use of a risk-based approach rather than a prescriptive approach that takes into consideration the basic (R_0) or effective (R) reproductive rate of poliovirus in an area which depends on factors such as population density and movements, sanitation and hygiene conditions (population, environment, sewage systems and treatment), population immunity, susceptible persons, etc) should also be explored.

3. Although not limited to this issue alone, there is a need to develop clear risk-based guidance, dialogues or discussions between NACs and PEFs on the potential failures of primary containment (hazard e.g., facility-associated release of poliovirus through untreated effluent, risk e.g., exposure to community, likely consequences e.g., re-establishment of transmission and expected responses. The guidance should include recommendations to mitigate risk that provide barriers to limit the consequences of the release (e.g., population immunity or secondary safeguards) or those that limit the re-establishment of WPV transmission (facility location and associated environmental controls or tertiary safeguards). The guidance may also include clear concise, one-page descriptions of the safeguard and its components that can be used both as reference and communication tool (see Annex 4 for an example).

Issue: Implementing the revised secondary safeguard requirements
Harpal SINGH, Technical Officer - Poliovirus Containment, WHO

Relevant GAPIII section (or other reference, as appropriate)	
GAPIII:	Strategy, Table 1, Phase Implementation, Annex 1 (Definition), Sublement 12.3.1 of Annex 2 and 3
Other reference:	Meeting of the Strategic Advisory Group of Experts on immunization, April 2018 – conclusions and recommendations[12]

[12] Meeting of the Strategic Advisory Group of Experts on immunization, April 2018 – conclusions and recommendations, Weekly Epidemiological Record 2018;93:329–44. Available at: http://apps.who.int/iris/bitstream/handle/10665/272782/WER9323.pdf?ua=1

Background of issue raised:

To align the GAPIII and SAGE recommendations on IPV immunization schedules, SAGE at its meeting in April 2018 reviewed and endorsed the proposal to align the recommendations of the future IPV schedule for countries hosting-PEFs and SAGE recommendations on IPV immunization schedules. SAGE in April 2018 recommended: 'Countries with PEFs and currently using a single dose of IPV are recommended to adjust their IPV schedule, coverage targets and geographical scope as soon as possible and no later than at the time of all OPV cessation, to:

1. Implement a routine immunization schedule with a minimum of 2 IPV doses (full or fractional, standalone or in combination vaccines), with the first dose administered at 4 months and second dose at an interval of at least 4 months after the first dose.
2. Maintain high population immunity with ≥90% of IPV2 coverage in infants in the area surrounding the PEF defined as within a 100km commutable distance from the PEF. Maintain the GVAP target coverage (90% national coverage and 80% in every district or equivalent administrative unit with all vaccines in national programmes, unless otherwise recommended) beyond the immediate zone of 100 km from the PEF.
3. Have an outbreak plan specifying response to containment breach and conduct outbreak simulation exercises'

Summary of CAG discussions and conclusions

Issues associated with this revised requirement is presented in the table below. In the event of breach in poliovirus containment, populations at risk include those at risk of exposure from an infected PEF worker (e.g., family members, community, etc), those at risk of exposure to contaminated effluent released into the local environment (e.g., community, sewage operators, etc) and those who may be exposed following the shedding of poliovirus from an infected individual into the local environment. At present, the IPV2 indicator disaggregated by age i.e., infants and the availability of coverage data of all administrative area level 2 within 100 km of the PEF is not routinely collected.

The recommendation of maintaining ≥90% coverage within 100 km of the PEF lacks supporting evidence and has now shown to be impractical in some instances. Appropriate alternatives to the 100 km criterion should be investigated, including active mapping of PEF workers and members of the surrounding community, and systematic environmental and sewage monitoring programmes.

With regard to the risk of transmission in a population that can be mitigated by immunization, additional guidance is needed on assessing and documenting coverage to demonstrate that 90% threshold has been achieved. Coverage data will be required at district level (second administrative level) which can aid in the identification of at-risk sub-populations and be demonstrably heterogeneous. Differences in the inherent risk of transmission in different locations and circumstances makes it very difficult to develop a single standard that is equivalent for all populations.

Concerns have been expressed over the quality and extent of data available and the need to validate and document the quality of information provided relative to the criteria. Different estimation methods are known to produce coverage estimates for sub-national populations that differ significantly from the national administrative data and there should be some guidance on how to validate these estimates. There may be a role for the collection and analysis of trend data.

Issues associated with the implementation of the revised secondary safeguard requirement

Issues associated with IPV2 admin2 ('district') coverage data[13].
1. Data availability • None of the countries-hosting PEFs reported admin2 coverage data for the second dose of IPV (IPV2). IPV2 is not routinely collected
2. Data accuracy • If proxy or closest fit indicators are reported, these are collected using the 'administrative method' which are always prone to errors
3. Age-disaggregated data • Coverage data for infants is not available
Other issues
4. Cross-border collaboration when geographical extent (100 km) includes part of another country • Responsibility to maintain population immunity requirements (IPV doses and coverage) when the 100 km extends into another country i.e., PEF- or non-PEF hosting country. Current polio immunization policy after global OPV withdrawal (2-doses IPV in EPI) is applicable for a minimum of 10 years only (for countries not hosting PEFs) and as long as mandated by GAPIII (for countries hosting PEFs) (Figure 2)[14].
5. Management of admin2 area (to consider part or entire admin2) when geographical extent (100 km) includes only a part of an admin2 area • Total area that falls within the 100 km commutable distance surrounding the PEF is almost always lesser than the total area of all admin2 areas that the 100 km extends into i.e., is there is a need to include the entire admin2 even if only a part of it falls within the 100 km commuting distance (Figure 3).
6. Interim recommendations for countries-hosting PEFs before full implementation of secondary safeguards (no later than bOPV cessation) to support the implementation of CCS • A prerequisite to the CCS is the demonstration of compliance with secondary safeguards in GAPIII i.e., a certificate of participation can only be awarded to facilities in countries that have demonstrated compliance with the required secondary and tertiary safeguards described in GAPIII. Although countries are expected to begin implementing these revised requirements as soon as feasible, SAGE recommendation provides a different timeline for countries to achieve full implementation of this prerequisite as described in the CCS i.e., 'secondary safeguard is a pre-requisite to begin the CCS' to 'during the time of bOPV cessation'.

[13] Subnational immunization coverage data reported through the WHO/UNICEF Joint Reporting Form on Immunization. Available at: https://www.who.int/immunization/monitoring_surveillance/data/subnational/en/

[14] Meeting of the Strategic Advisory Group of Experts on immunization, April 2017 – conclusions and recommendations. Weekly Epidemiological Record 2017;92:301–20. Available at: http://apps.who.int/iris/bitstream/10665/255611/1/WER9222.pdf?ua=1

Figure 2: The extension of the commuting distance of 100 km from a PEF- into a neighboring PEF-hosting or non-hosting country. Non-PEF hosting countries may decide to drop IPV 10 years after certification of eradication.

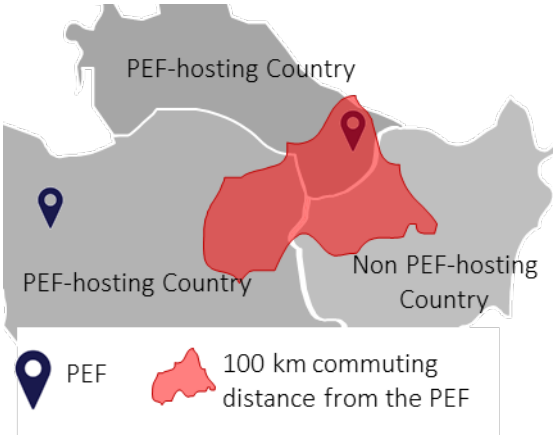
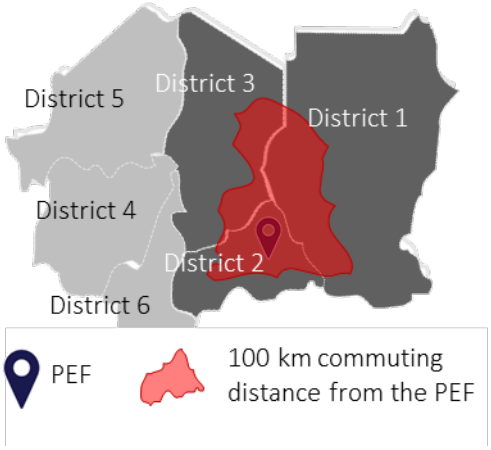


Figure 3: PEF-hosting country with boundaries of its districts ('admin2'). The extension of the commuting distance of 100 km into only parts of a districts e.g., Districts 1, 2 and 3 implies the requirement for continous resources to maintain population immunity in these entire district.



Way forward

1. CAG has noted the concerns raised and will consider options for requesting the SAGE Polio Working Group to consider additional flexibility in assessment criteria for secondary safeguards.

2. The possibility of an alternative approach i.e., the use of a risk-based approach rather than a prescriptive approach that takes into consideration the basic (R_0) or effective (R) reproductive rate of poliovirus in an area which depends on factors such as population density and movements, sanitation and hygiene conditions (population, environment, sewage systems and treatment), population immunity, susceptible persons, etc should also be explored by the Secretariat.

Session 4: Issue associated with the 'Guidance to minimize risks for facilities collecting, handling or storing materials potentially infectious for polioviruses'

Issue: Harmonizing containment requirements for all poliovirus potentially infectious materials (WPV/VDPV and Sabin PIM)

Harpal SINGH, Technical Officer - Poliovirus Containment, WHO

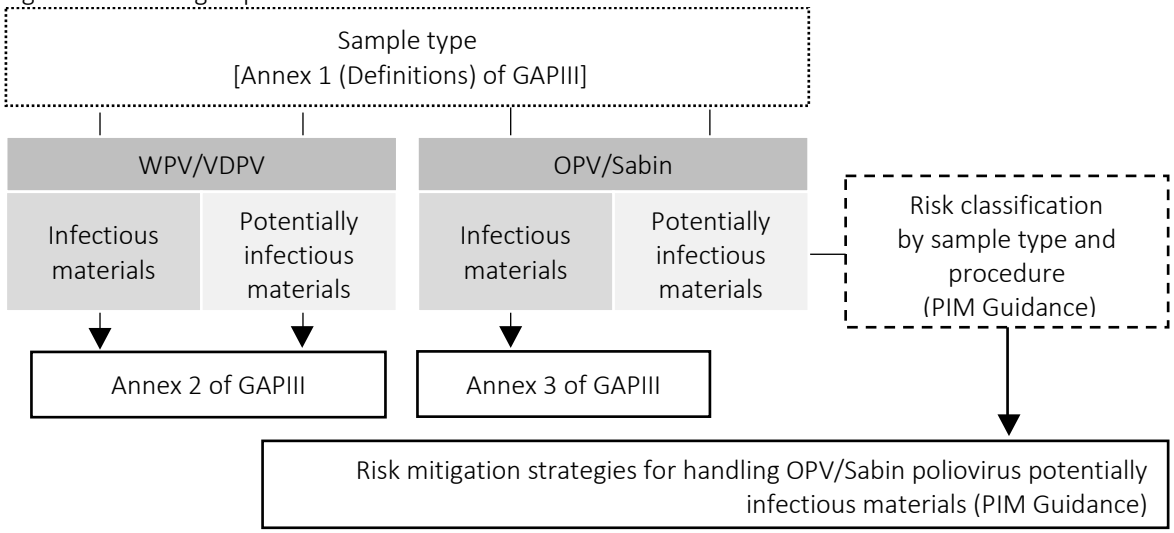
Relevant GAPIII section (or other reference, as appropriate)	
GAPIII:	Annex 1 (Definition)
Other reference:	Guidance to minimize risks for facilities collecting, handling or storing materials potentially infectious for polioviruses (PIM Guidance)

Summary of issues raised

In its current version, GAPIII requires all materials potentially infectious for polioviruses (PIM) to be handled according to conditions described in Annex 2 (WPV/VDPV) or Annex 3 (Sabin/OPV) of GAPIII. The current PIM guidance does not subject Sabin/OPV PIM to Annex 3 of GAPIII but rather that a risk determination be conducted based on both the sample type and nature of the work to be performed, and specific mitigation measures taken to minimize the risk of handling and storing such material. The PIM guidance continues to require WPV/VDPV PIM be subjected to Annex 2 of GAPIII. A submission has been received requesting that the requirements for WPV/VDPV PIM be subjected to a risk determination process and the containment

requirements for handling and storing WPV PIM also be in line with the risk mitigation approach by risk stratification as was done for Sabin PIM as per PIM Guidance (Figure 4).

Figure 4: Handling of poliovirus materials as described in GAPIII and the PIM Guidance



Summary of CAG discussions and conclusions

Laboratories operating in accordance with recommended biosafety standards and guidelines (e.g., WHO Laboratory Biosafety Manual, 3rd Edition; CDC/NIH Biosafety in Microbiological and Biomedical Laboratories, 5th Edition) are expected to provide effective protection to both public health and environment. It is also of concern that many non-poliovirus laboratories remain unaware of GAPIII or that the containment requirements apply to them. The last WPV2 case was reported in 1999 and there are probably only a number of laboratories housing historical collections who will always remain at a risk of release. There are potentially a larger number of laboratories housing potentially infectious materials, WPV1 and WPV3 i.e., samples that fall under Annex 1 (Definitions) of GAPIII that were collected at a time and place where WPV/VDPV1 or WPV3/VDPV3 was in circulation and yet are at risk but unaware of that risk. Concerns have been raised that the number of facilities handling WPV/VDPV PIM might be too many – the requirement for them to become PEFs might be too much of a burden for the country-hosting them. By definitions used in GAPIII, the handling and storage of WPV and VDPV infectious and potentially infectious materials must be in line with Annex 2 of GAPIII.

The current PIM guidance is now being implemented and should not be modified without further strong evidence that modification is required. Further details should be sought from the submitting NAC to determine the estimated number of facilities that would be handling WPV/VDPV PIM and that would require them to become PEFs.

CAG recommendation

The PIM guidance should not be modified at this stage, but further evidence should be sought on the challenges faced by non-polio laboratories planning to retain WPV/VDPV PIM or from their national containment focal points including NACs on the number of potential facilities that would fall under this category.

Session 5: Issues associated with the implementation of facility physical requirements in GAPIII

Issue: Alternative measures for walk-through exit shower

Harpal SINGH, Technical Officer - Poliovirus Containment, WHO

Relevant GAPIII section (or other reference, as appropriate)	
GAPIII:	Subelement 12.3.1 of Annex 2 and 3
Other reference:	CAG TC1 report on showers

Summary of issues raised

CAG considered the need for controlled exit from the containment perimeter via a walk-through exit shower during the First CAG TC on Showers (25 January 2018) [15]. The acceptability of alternative measures of compliance showering-out especially during the period until evidence for or against showering is being generated is left up to the NACs after review of a risk assessment submitted by PEFs. A submission was subsequently received from a NAC requesting CAG to consider the proposal of allowing either the use of a shower upon egress, or removal of an outer layer of PPE as an alternative. Showering out of many containment level 3 (CL3) facilities is only required in the event of a spill or contamination event.

Summary of CAG discussions and conclusions

The current interpretation of the First CAG TC on Showers is that the compliance with routine showering-out is left up to the discretion of the NAC. If routine showering-out is not to be implemented by the PEF, the PEF will have to provide a detailed risk assessment with risk mitigation steps for consideration and approval by the NAC. Further evidence will be collected through a study (see also next issue) regarding the need for showering-out and how these will be interpreted. The proposed study will include a risk assessment study to evaluate showering as a stand-alone or part of a regime of protective measures to prevent facility-associated release of poliovirus.

CAG recommendation

CAG considered the need for controlled exit from the containment perimeter via a walk-through exit shower during the First CAG TC on Showers (25 January 2018) and recommended not to further change the recommendations from the said TC[16] until more information and evidence was made available. In line with

[15] Report of the Teleconference of the Containment Advisory Group (CAG TC1) on Showers. Available at: http://polioeradication.org/wp-content/uploads/2018/05/containment-advisory-group-teleconference-1-on-showers-25-january-2018-20180523.pdf

[16] Subelement 12.3.1 (g) of Annex 2 and 3 of GAPIII: Controlled exit from the containment perimeter is via a walk-through exit shower. Showering out is mandatory except for facilities employing closed systems demonstrating validated primary containment. Such systems may include contained lines for use in vaccine production and/or facilities employing fully functional Class III BSCs or similar isolators. For such facilities, showering out is required as a precautionary measure, in the event of an uncontrolled breach of the primary containment equipment, during the period when further assessment of the effectiveness of showering is being undertaken.
Additional recommendations: For other facilities, the requirement for mandatory showering should be left to the discretion of the National Authority, after review of a risk assessment submitted by the PEF. Risk mitigation measures will be proposed by the PEF and approved by the National Authority for the interim period of at least two years during which evidence for-or-against-mandatory showering out will be generated.

this, the compliance with routine showering-out is left up to the discretion of the NACs following the submission of a detailed risk assessment with risk mitigation steps by the PEF for consideration and approval by the NAC.

Concept and design of evidence-based efficacy study of showering as protective measure to prevent facility associated release of poliovirus

Tjeerd KIMMAN, Wageningen Bioveterinary Research Institute, Netherlands

Relevant GAPIII section (or other reference, as appropriate)	
GAPIII:	Subelement 12.3.1 of Annex 2 and 3
Other reference:	CAG TC1 report on showers

Summary of issues raised

The CAG discussed in depth the GAPIII requirement of subelement 12.3.1 (g) of Annex 2 and 3 at the First CAG TC (CAG TC1) on Showers on 25 January 2018 and urged the secretariat to commission a study on the use, effectiveness and risks associated with showering for an evidence-based recommendation to be made or has shown that it is not feasible to collect such information. Upon request from the Secretariat, the Wageningen Bioveterinary Research Institute in the Netherlands submitted the document 'Concept and design of evidence-based efficacy study of showering as protective measure to prevent facility-associated release of poliovirus'. The proposed project will be composed of three work streams:

1. literature search
2. experimental work to generate quantitative data
3. risk assessment study to evaluate showering as a stand-alone or part of a regime of protective measures to prevent facility-associated release of poliovirus

Summary of CAG discussions and conclusions

With respect to the literature search, contributions from CAG members with experience and expertise in this are area of work would be welcome. Suggestions to include the aerosolization potential of showering in the experimental design was also provided. Although practical aspects of the experimental design have not yet been finalised, the proposed scope will include showering-out as an integrated component and a standalone component of protective measures to prevent facility-associated release of poliovirus. The development of a brief proposal which would detail these points is underway and would be submitted to CAG for review.

CAG recommendation

CAG acknowledges the value of the proposed concept note 'Concept and design of evidence-based efficacy study of showering as protective measure to prevent facility associated release of poliovirus' and urges the secretariat to facilitate the submission of a proposal with funding and other requirements for CAG's review as soon as possible.

The CAG urged the secretariat to commission a study to collect information on the use, effectiveness and risks associated with showering, including in facilities where showering is currently being used. The CAG will undertake further discussion on showers when the secretariat has collected the information necessary to make an evidence-based recommendation or has shown that it is not feasible to collect such information.

Effluent decontamination

Harpal SINGH, Technical Officer - Poliovirus Containment, WHO

Relevant GAPIII section (or other reference, as appropriate)	
GAPIII:	Subelement 12.3.1 of Annex 2 and 3
Other reference:	CAG2 report

Summary of issues raised

At the Second Meeting of the CAG[17], CAG recommended the inclusion of a new requirement on effluent decontamination: 'Facilities handling WPV2 and/or OPV2/Sabin2 in Phase II as well as OPV/Sabin poliovirus materials in Phase III need to follow the requirements for effluent decontamination as applicable for final containment of all WPV in Phase III i.e., effluent decontamination is required in Phase II (PV2 containment phase) and Phase III (Final containment of all PV) of GAPIII. The current interpretation of this requirement is all facilities will require decontamination of effluent and in most cases, it would be an effluent decontamination system (EDS). For those facilities that continue handling WPV and VDPV viruses and materials post-eradication (or in the containment of all poliovirus phase of GAPIII), the EDS must be dedicated to the PEF alone. In line with this, the proposed amendments to Table 1 of GAPIII recommended by CAG at the Second Meeting of the CAG are:

	Poliovirus type 2 containment period	Final poliovirus containment period	
	All type 2 polioviruses	All OPV/Sabin polioviruses	All wild Polioviruses
1° safeguards: Prevent infection & release of contaminated materials			
Dedicated effluent treatment plant	No[3]	No[3]	Yes [4]

[3] Untreated release into a closed sewage system with secondary effluent treatment in the facility location (all waste from facilities, potentially containing live poliovirus, should be inactivated prior to release through adequate and validated inactivation procedures. In facilities without a dedicated effluent treatment plant, this would normally be done by applying heat or chemicals as part of a validated treatment process. Under no circumstances should raw poliovirus containing effluents be discharged to drains, unless the effluent treatment plant has been designed and validated to handle such effluents, effectively acting as part of the primary containment system)

[4] Facility effluent treatment before release into a closed sewage system with secondary or greater effluent treatment in the facility location.

EDS are used to treat large amounts of biologically contaminated liquid effluents from containment facilities i.e., large scale production plants, animal holding facilities and research laboratories. Biologically contaminated effluents originate typically from sinks, showers, autoclave chambers and floor drains. The EDS when used must ensure inactivation of all viable micro-organisms including survival structures (e.g., spores) and in that respect the process must be validated by microbial challenge testing[18].

[17] Second meeting of the Containment Advisory Group, 28-30 November 2017, Geneva, Switzerland. Available at: http://polioeradication.org/wp-content/uploads/2018/02/poliovirus-containment-advisory-group-meeting-20171130.pdf

[18] Effluent Decontamination System. Design, Operation and Safety. Biosafety and Biotechnology Unit, Scientific Institute of Public Health, Belgium (2012). Available at: https://www.biosafety.be/sites/default/files/2012_effluentdeconsystems_sbb_2505_58.pdf

However, this recommendation is not an amendment to an existing GAPIII requirement but is considered an additional requirement. There have been calls for GAPIII amendments or revision to be subjected to a period of public consultation prior to finalization and publication.

Summary of CAG discussions and conclusions

CAG members expressed the need for a more systematic approach to making recommendations that includes a review of primary, secondary and tertiary safeguards to provide clear guidance to NACs on assessment of facility-associated risk of release of polioviruses of PEFs and the CWG with technical guidance on assessing submissions from NACs following review of documentation submitted by PEFs.

CAG recommendation

CAG recommends that the requirement for facilities handling WPV2 and/or OPV2/Sabin2 in Phase II as well as OPV/Sabin poliovirus materials in Phase III to follow the requirements for effluent decontamination as applicable for final containment of all WPV in Phase III be raised at the next CAG meeting.

Poliovirus-dedicated facilities

Harpal SINGH, Technical Officer - Poliovirus Containment, WHO

Relevant GAPIII section (or other reference, as appropriate)	
GAPIII:	Subelement 12.3.1 of Annex 2 and 3
Other reference:	CAG1 and CAG2 report

Summary of issues raised

GAPIII requires that poliovirus materials be handled in a poliovirus-dedicated facility but makes no distinction between facilities handling high titre or volumes (e.g., vaccine production facilities) and those handling low titre or volumes (e.g. diagnostic, research and QA/QC laboratories). A request has been received that the requirement be dependent on the scale and use of poliovirus materials and to recognize the distinction between laboratory scale (diagnostic, QC/QA) work and production scale risk mitigation i.e., at laboratory scale, where all materials, equipment and waste are treated as though they contain poliovirus and are all subject to GAPIII requirements, a dedicated facility may not be required.

Summary of CAG discussions and conclusions

To facilitate the implementation of this requirement, CAG previously recommended[19,20] that the use of non-dedicated facilities (e.g. QC laboratories) may be permissible under a CP/ICC during Phase II of GAPIII in association with CCS. In such instances, risk assessments must be provided to demonstrate that the risk of breach of containment, cross-contamination, unauthorized access to materials and other factors have been fully evaluated and addressed. All non-poliovirus related practices and personnel within the containment perimeter shall also adhere to all GAPIII requirements and be included in the scope of GAPIII audits and certification activities.

This submission requests that an extension of this requirement is made to include diagnostic laboratories. However, relaxation of this requirements would extend to any laboratory (e.g., research, academic, etc) in which while titre and volume of materials are considered lower, the number of manipulations are considered

[19] First meeting of the Containment Advisory Group, 19-20 June 2017, Geneva, Switzerland. Available at: http://polioeradication.org/wp-content/uploads/2017/08/CAG1-Report-30082017.pdf

[20] Second meeting of the Containment Advisory Group, 28-30 November 2017, Geneva, Switzerland. Available at: http://polioeradication.org/wp-content/uploads/2018/02/poliovirus-containment-advisory-group-meeting-20171130.pdf

higher than vaccine production sites. Further explanation from the submitting NAC is therefore needed to understand the exact nature of the request.

CAG recommendation

CAG's previous recommendation on the issue of non-dedicated poliovirus facilities is not changed[21]. However, CAG urges the secretariat to reach out to the submitting NAC to gather additional information on this request in time for the next CAG meeting.

Dedicated ventilation systems

Harpal SINGH, Technical Officer - Poliovirus Containment, WHO

Relevant GAPIII section (or other reference, as appropriate)	
GAPIII:	Subelement 12.3.1 of Annex 2 and 3
Other reference:	CAG2 report

Summary of issues raised

According to GAPIII[22], ventilation systems must be dedicated to the area defining the containment perimeter and should not be shared or serve areas that are not dedicated to the work with polioviruses. The dedicated ventilation system includes all supply and exhaust side systems including those serving primary containment devices e.g., biosafety cabinets, isolators and local exhaust system, where appropriate. In other words, there are no interconnected parts between the supply and exhaust-side system i.e., not interconnected with any other exhaust or return and does not extend beyond the containment perimeter.

The CAG previously commented that a facility that works with polioviruses must have its own dedicated air-handling fans, and these cannot be shared with spaces not dedicated to poliovirus work, even if ductwork, exhaust-side HEPA filters or other backflow protection devices are provided. However, a supply-side terminal HEPA filters placed at the containment barrier meets the intent of this requirement from a performance perspective i.e., no interconnections from supply to exhaust (Figure 4A). A request has been submitted on the use of supply-side terminal HEPA filters that are placed directly on the containment barrier which effectively work to isolate the ventilation system, ensuring no facility-associated poliovirus release occurs by the ductwork or ventilation system.

[21] Subelement 12.3.1 (c) of Annex 2 and 3 as it appears in the current version of GAPIII is recommended to remain as is i.e., 'Poliovirus facilities are either poliovirus dedicated or used on a campaign basis with documented effective decontamination procedures between periods of work with agents other than poliovirus'. However, to facilitate its implementation, the use of non-dedicated facilities (e.g. QC laboratories) may be permissible under a CP/ICC during poliovirus type 2 containment phase of GAPIII in association with CCS. In such instances, risk assessments must be provided to demonstrate that the risk of breach of containment, cross-contamination, unauthorized access to materials and other factors have been fully evaluated and addressed. All non-poliovirus related practices and personnel within the containment perimeter shall also adhere to all GAPIII requirements and be included in the scope of GAPIII audits and certification activities.

[22] Subelement 12.3.1 (h) of Annex 2 and 3 of GAPIII 'the controlled air system maintains directional airflow via a dedicated ventilation system with ductwork sealable for gaseous decontamination, HEPA filtration on exhaust, backflow protection on supply, and monitors/alarms to ensure directional airflow can be readily validated'

Summary of CAG discussions and conclusions

The absence of any interconnections to other laboratory suites or spaces between the supply side and exhaust side of the ventilation system of the containment perimeter is defined as being 'poliovirus dedicated'. In addition, the airflow is controlled to maintain supply-to-exhaust unidirectional flow, with all passageway for distribution or extraction of air ('ductwork') sealable for gaseous decontamination, has an exhaust-side HEPA filter and supply-side, backflow prevention e.g., damper and has detectors to monitor the unidirectional airflow. The placement of a supply-side terminal HEPA filter on the containment barrier would functionally isolate the ventilation system thus still making it functionally equivalent to a PEF-dedicated ventilation system and is acceptable (Figure 5). Concerns were raised, however, over the risks associated with HEPA filter failure, requirement for routine maintenance, testing and validation of these filters. A risk assessment should be made for HEPA filter failure, both on the supply- and exhaust-side.

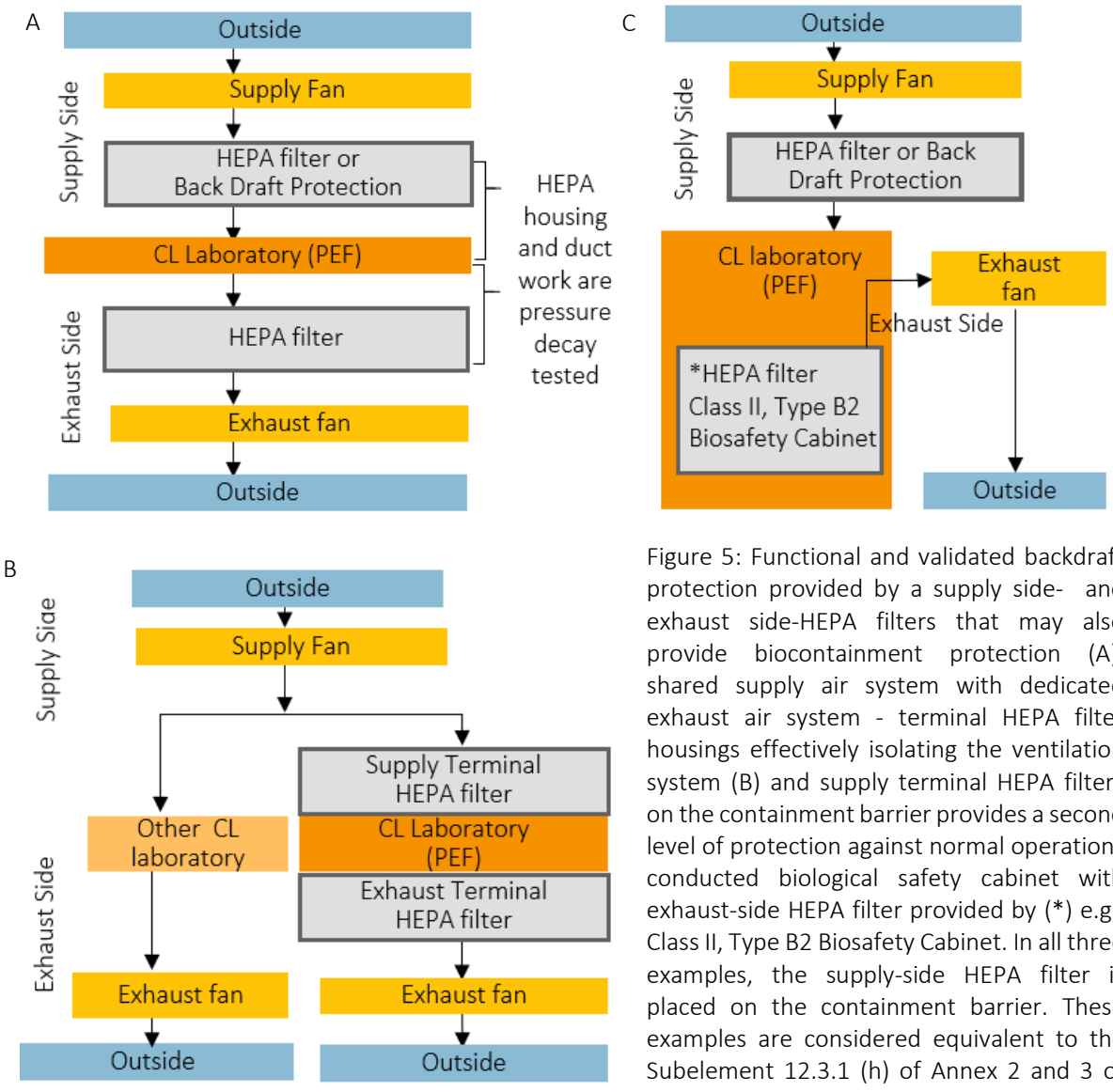


Figure 5: Functional and validated backdraft protection provided by a supply side- and exhaust side-HEPA filters that may also provide biocontainment protection (A), shared supply air system with dedicated exhaust air system - terminal HEPA filter housings effectively isolating the ventilation system (B) and supply terminal HEPA filters on the containment barrier provides a second level of protection against normal operations conducted biological safety cabinet with exhaust-side HEPA filter provided by (*) e.g., Class II, Type B2 Biosafety Cabinet. In all three examples, the supply-side HEPA filter is placed on the containment barrier. These examples are considered equivalent to the Subelement 12.3.1 (h) of Annex 2 and 3 of GAPIII mentioned above.

(Graphics courtesy of Mr Kenneth Ugwu, CAG Member)

CAG recommendation

CAG recognises that use of supply-side HEPA filters directly on the containment barrier in the absence of interconnections (supply connections to other spaces or return exhaust from other spaces) between the supply-side HEPA filter and the exhaust-side, if correctly maintained and routinely tested, are functionally equivalent to providing a dedicated heating, ventilation and air-conditioning (HVAC) system. While this meets the intent of being dedicated, the other requirements must also be in place e.g., airflow is controlled to maintain supply-to-exhaust unidirectional flow, with all passageway for distribution or extraction of air ('ductwork') sealable for gaseous decontamination, has an exhaust-side HEPA filter and supply-side, backflow prevention e.g., damper and has detectors to monitor the unidirectional airflow.

Session 6: Novel poliovirus strains and innovation in polio vaccine production

Issues addressed in this report: Development of novel polio strains and summary of findings of the CAG-Expert Support Group (ESG) on the containment requirements of novel poliovirus strains and their proposed use for consideration of CAG

1. Containment requirements of recombinant oncolytic poliovirus PVS-RIPO in cancer immunotherapy
2. nOPV2 vaccine strains for nOPV2 production and control
3. S19 – poliovirus strains (± N18S substitution in non-structural protein 2A) for IPV production and laboratory assay (IPV potency, neutralization test, human immunoglobulin lot control and release)

See Annex 5 for a list of CAG-ESG issues related to novel poliovirus strains under specific terms of usage and status of their deliberation

Summary of issue raised

An overview of the concept, development process, characteristics and potential uses of the S19 poliovirus strains was presented to CAG. These highly attenuated, genetically stable viruses have been developed as alternatives to the use of live viruses in laboratory testing and for IPV production. Viruses based on S19 were initially constructed to include the N18S substitution (substitution of asparagine by serine at amino acid no. 18 of protein 2A) that allows better growth in Vero cells, but this substitution is not necessary for growth in other common cell lines. Thus, strains without the N18S substitution have also been produced. The CAG previously concluded that the S19-poliovirus type 2 strain can be use outside of GAPIII containment[23] based on the 'criteria for the evaluation of improved 'safety' of novel poliovirus strains to determine the containment requirements for their storage and handling' as developed by CAG[24]. A request was submitted to extend this recommendation, subject to review of available data, to all Wild- and Sabin vaccine virus-serotypes 1 to 3, with or without the N18S substitution (Table below and Figure 6) for IPV production, rat neutralization IPV potency assays, human serum neutralization test for poliovirus antibody determination and potency testing for immunoglobulin (human) lot control and release.

[23] Teleconference of the Containment Advisory Group (CAG TC3) on nOPV2 candidate vaccines and S19 – poliovirus type 2 strains, 7 June 2018. Available at: http://polioeradication.org/wp-content/uploads/2017/08/CAG-TC3-20180630-EN.pdf and Addendum to the Report of the Teleconference of the Containment Advisory Group (CAG TC3) on nOPV2 candidate vaccines and S19 – poliovirus type 2 strains, 14 December 2018. Available at: http://polioeradication.org/wp-content/uploads/2017/08/Addendum-CAG-TC3-Dec-2018-EN-1.pdf

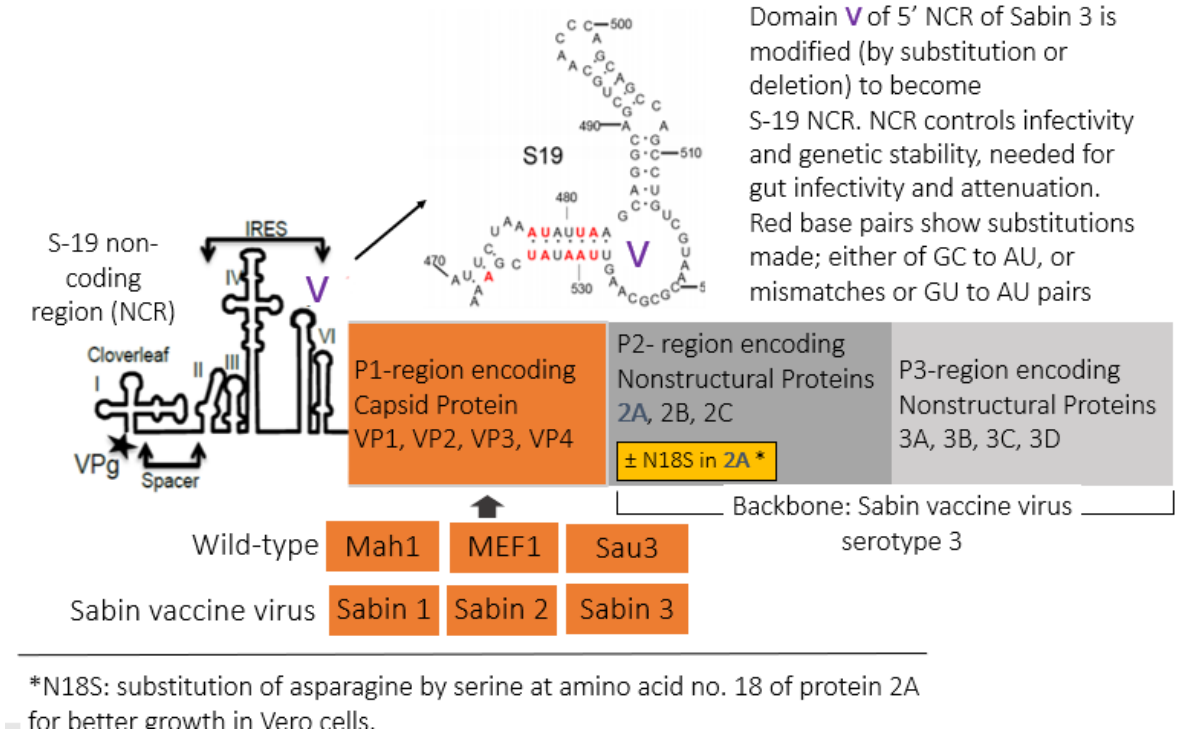
[24] Criteria for the evaluation of improved 'safety' of novel poliovirus strains to determine the containment requirements for their storage and handling. Available at: http://polioeradication.org/tools-and-library/policy-reports/advisory-reports/containment-advisory-group/

Series of genetic cassettes of S19 and capsid protein encoding P1-region of polioviruses

	S19		S19/N18S*	
Capsid region	Wild-type	Sabin	Wild-type	Sabin
Poliovirus Serotype 1	S19/Mah1P1	S19/S1P1	S19/Mah1/N18S	S19/S1/N18S
Poliovirus Serotype 2	S19/MEF1P1	S19/S2P1	S19/MEF1P1/N18S	S19/S2P1/N18S
Poliovirus Serotype 3	S19/Sau3P1	S19/S3P1	S19/Sau3P1/N18S	S19/S3P1/N18S

Abbreviations: (Wild-type): Mah1: Mahoney serotype 1; MEF1: Middle East Forces serotype 2; Sau3: Saukett serotype 3; (Sabin strains): S1: Sabin serotype 1; S2: Sabin serotype 2; S3: Sabin serotype 3 and P1: region of the poliovirus genome encoding the structural (capsid) polypeptides
*N18S is a mutation (substitution) of an asparagine by a serine at amino acid 18 in the non-structural protein 2A to allow better growth in Vero cells.

Figure 6: Series of genetic cassettes of S19 with capsid protein encoding P1-region of polioviruses with and without N18S in protein 2A*

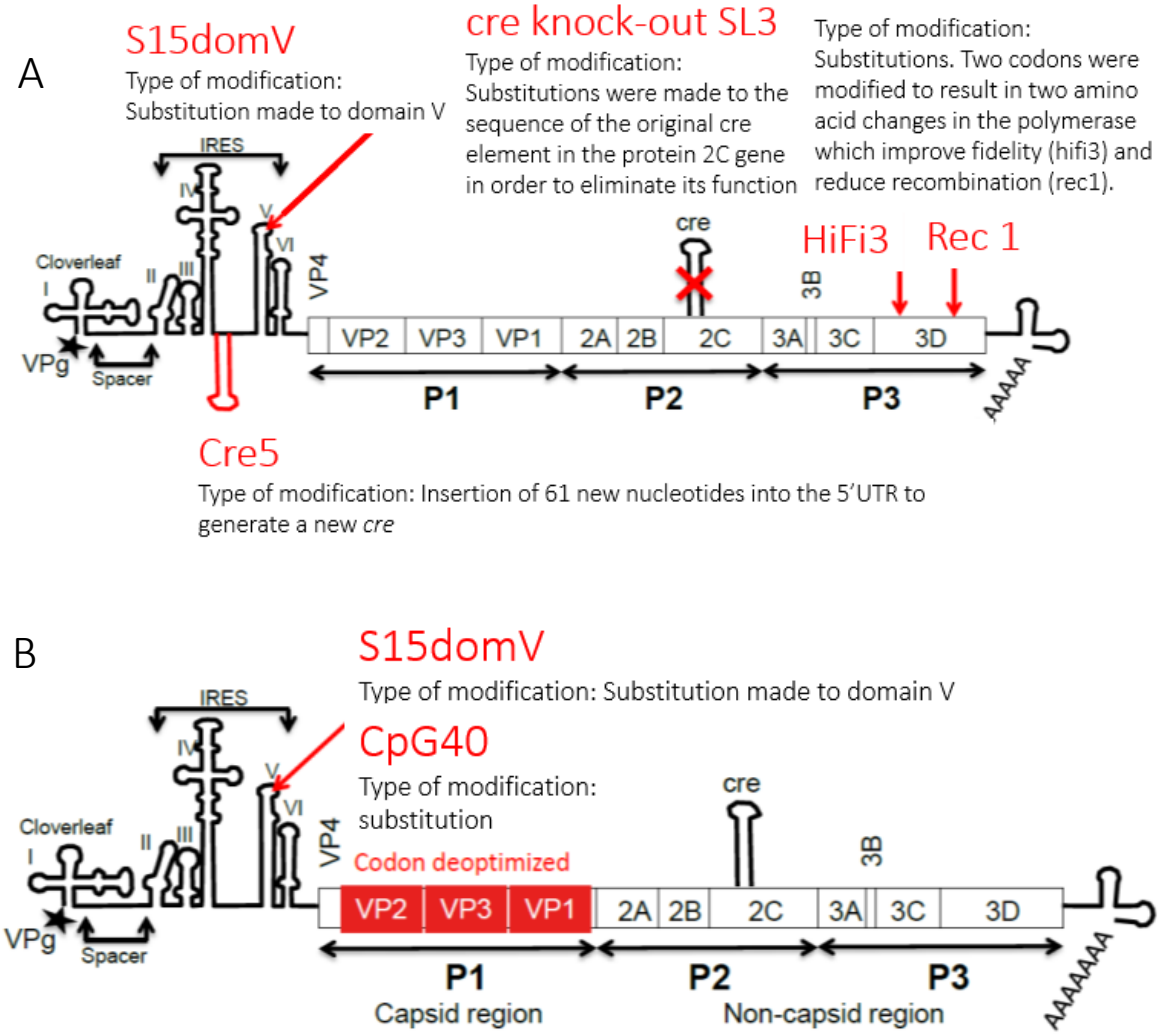


The CAG-ESG provided a summary of their findings on containment requirements for genetically modified poliovirus strains. Genetic stability and neurovirulence are the most important characteristics that determine the safety of novel strains, but not all data on the new strains were comparable due to experimental designs and the selection of data. The level of replicative fitness (considered a proxy for infectiousness) is important for the novel oral polio vaccines' candidate strains (S2/cre5/S15domV/rec1/hifi3 and S2/S15domV/CpG40) but at present data generated will need to be reviewed as it becomes available. There is relatively little information yet available on transmissibility of the vaccine viruses – a proxy of which is 'duration and amount of shedding' and the behaviour of these novel vaccine viruses in the environment. The CAG previously concluded that the handling of nOPV2 candidate vaccines can occur outside the containment requirements of GAPIII for clinical trials, stockpile and for outbreak response[25]. Two clinical

[25] Teleconference of the Containment Advisory Group (CAG TC3) on nOPV2 candidate vaccines and S19 – poliovirus type 2 strains, 7 June 2018. Available at: http://polioeradication.org/wp-content/uploads/2017/08/CAG-TC3-20180630-EN.pdf and Addendum to the Report of the Teleconference of the Containment Advisory Group (CAG TC3) on nOPV2 candidate vaccines and S19 – poliovirus type 2

phase II trials are currently underway involving adolescents and adults and children and infants under deliberate release procedure. A related request was received by the ESG to determine the containment requirements for the production of nOPV2 and for quality control testing using the candidate vaccines' strains (S2/cre5/S15domV/rec1/hifi3 and S2/S15domV/CpG40) (Figure 7). A related request was received for guidance on the containment requirements when handling stool samples taken from nOPV2 vaccine recipients during the ongoing phase II clinical trials.

Figure 7: nOPV2 Candidate 1 or S2/cre5/S15domV/rec1/hifi3 (A) and nOPV2 Candidate2 or S2/S15domV/CpG40 (B), both of which are based on a series of modifications that have been made to a Sabin vaccine virus serotype 2



PVSRIPO is a type 1 live-attenuated (Sabin) poliovirus vaccine containing an internal ribosomal entry site (IRES) of human rhinovirus type 2 (HRV2). Poliovirus: HRV2 IRES chimeras i.e., PVSRIPO is under investigation for use in cancer immunotherapy in patients with recurrent malignant glioma. A request for guidance from CAG is sought on the containment requirement of PVSRIPO to be evaluated for use in a multi-institutional phase-2 clinical trial against GBM. Clinical trials in children with recurrent high-grade malignant glioma; adults with nonresectable malignant melanoma; and triple-negative breast cancer are currently open, with multiple new trials in preparation. In most of these trials, it is assumed that trial subjects will be provided

strains, 14 December 2018. Available at: http://polioeradication.org/wp-content/uploads/2017/08/Addendum-CAG-TC3-Dec-2018-EN-1.pdf

hospital-based treatment allowed to go home with periodic hospital-based follow-ups ('deliberate release setting').

Summary of CAG discussions and conclusions

Once validated and readily made available, the S19 strain is seen as one strategy to reduce the number of facilities intending to become PEFs e.g., PEFs performing only serology work or QC requiring the use of live poliovirus may substitute the use of live virus with S-19 strains. The S-19 strains have been demonstrated to be highly attenuated, genetically stable and immunogenic in animal models. There is no evidence that the S19- poliovirus serotypes 1 or 3 type 1 and 3 strains, with or without the N18S substitution, pose any greater risk than S19 - poliovirus serotype 2 which have met the criteria for handling outside the containment requirements of GAPIII. Efforts should now be made to complete the validation of the use of these strains in assays otherwise requiring the use of live virus, to increase the availability of these strains so as to encourage its use over live virus. A seed-lot system for distribution of these strains are currently proposed, with deep-sequencing of seed-strains used to validate stocks and monitor for potential genetic reversion.

Clinical trials with nOPV2 strains have already taken place and trials outside of containment were already planned before CAG was requested for guidance. Similarly, there was little if any discussions with CAG on the containment requirements to produce nOPV2 that is ongoing in one vaccine producer.

The CAG would like to commend the parties submitting this request for the thorough, detailed, complete and evidence-based responses using the submission template. Data on attenuation, genetic stability and shedding have been provide that indicate the risks to persons other than patients receiving treatment with PVSRIPO are very low. However, little information was provided on the current and future production aspects of PVSRIPO and concerns that might be to production workers. Additional discussion on the prevention of coinfection and potential recombination would be welcomed.

CAG recommendations

Sufficient data has been provided to conclude the series of S19-poliovirus strains (S19 with capsid region, P1 of wild-type and Sabin vaccine strain polioviruses of all serotypes) and the parallel series of viruses with the substitution of an asparagine by a serine at amino acid 18 in the non-structural protein 2A to allow better growth in Vero cells (Table below) could be considered for use, outside of the containment requirements of Annex 2 or Annex 3 of GAPIII, as applicable for IPV production, rat neutralization IPV potency assays, human serum neutralization test for poliovirus antibody determination and potency testing for immunoglobulin (human) lot control and release.

The production of nOPV2 and quality control using the candidate vaccine strains (S2/cre5/S15domV/rec1/hifi3 and S2/S15domV/CpG40) may occur outside the containment requirements of GAPIII but should always be in line with prevailing biorisk management institutional practices, national legislations, international standards, etc. CAG may review this decision on receipt of data on virus transmission and environmental behaviour from clinical trials currently underway. While the handling of stool samples from nOPV2 vaccine recipients is not subject to the containment requirements of GAPIII, the implementation of some form of institutional, national or international biorisk management standard or good laboratory practices is appropriate.

CAG approves the use of PVSRIPO in Phase II clinical trials but requests more information on the risk associated with production and the mitigation and public health safeguards put in place to protect production workers and the wider community.

Session 7: CAG's mandate and collaboration

Issue: Applicable CAG recommendations that constitute amendments/revision of GAPIII, endorsement and publication and CAG's mandate of GAPIII

Daphne MOFFETT, Technical Adviser - Poliovirus Containment, WHO
Harpal SINGH, Technical Officer - Poliovirus Containment, WHO

The list of applicable CAG recommendations that constitute amendments to GAPIII also makes the revision process of GAPIII timely. The oversight body for issues related to containment and containment documents e.g., GAPIII, GAPIII-CCS, PIM guidance, etc has been the function of the Strategic Advisory Group of Experts (SAGE) on immunization. The CAG, established in early 2017, is better placed to perform this role since it functions as an advisory body to the Director-General of WHO to make recommendations on technical issues related to the implementation of GAPIII and other issues related to containment. In October 2018, the Polio SAGE Working Group endorsed the transfer of this function to CAG thus providing CAG with the mandate on all issues associated with GAPIII (amendments, revision, endorsement, etc).

CAG recommendation:

CAG recommends that the Secretariat coordinates a detailed decision review meeting of CAG recommendations, implications of such recommendations on other requirements and to undertakes the revision process of GAPIII taking into consideration all applicable recommendations and to coordinate a detailed review of the draft revised GAPIII by CAG to ensure consistency of approach to all safeguards as soon as possible. The CAG also welcomes a period of public consultation for the revised GAPIII.

Other Issues

CAG Membership

On 14 December 2018, CAG member Dr Bernard FANGET informed the CAG Chair, members and secretariat his intention to resign as a member of CAG – Dr Fanget's contribution to the CAG is gratefully acknowledged.

CAG Secretariat

The CAG took the opportunity to welcome Dr Daphne MOFFETT as the incoming Team Lead for the Poliovirus Containment. This follows Dr Jacqueline CARUANA-FOURNIER who is retiring in a few weeks from the organization after many years of service.

Dr Moffett has over 20 years of public health experience and holds the rank of Captain in the United States Public Health Service (USPHS). Prior to joining WHO, she was the CDC Central Asia Regional Director with leadership and oversight of CDC programs in Kazakhstan Uzbekistan, Kyrgyzstan, Tajikistan, and Turkmenistan. Dr Moffett is approachable, friendly and most especially she spends time listening.

Fourth Meeting of the Containment Advisory Group

The CAG agreed that the Fourth Meeting of the Containment Advisory Group should take place in the next six months (mid-2019).

Annexes

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Annex 1: Agenda

World Health Organization

Third Meeting of the Containment Advisory Group
13 – 14 December 2018
Starling Hotel, Geneva, Switzerland

Thursday, 13 December 2018 Chair: Professor David HEYMANN, CAG Chair

Time	Session	Purpose of the session	Duration
Session 1: Introduction			
8:00 – 8:30	Welcome coffee/tea		30 min.
8:30 - 8:40	Welcome and opening remarks David HEYMANN, CAG Chair		10 min.
8:40 – 8:45	Declarations of Interests (information by the Secretariat on any declared interests and discussion, update by CAG members) Caroline NAKANDI, Assistant to the Team - Poliovirus Containment	• CAG members are invited to report changes in circumstances, if any, to their previously disclosed conflict of interest(s) and confidentiality agreement	5 min.
8:45 – 9:45	Terms of reference and rules of procedure of CAG Daphne MOFFETT, Technical Adviser - Poliovirus Containment, WHO	For information only (Pages 5 and 6) • CAG members are invited to take note of the established TORs and rules of procedure for CAG and associated activities (e.g., meetings, collaborations)	60 min.

Time	Session	Purpose of the session	Duration
Session 2: Global update on poliomyelitis eradication and poliovirus containment			
9:45 – 10:15	Global progress on poliomyelitis eradication, and updates on research activities to maximize the impact of eradication and long-term risk management in the post-eradication era Roland SUTTER, Special Adviser on Research, Policy and Containment to the Director of Polio Eradication, WHO	For information only	30 min.
10:15 – 10:30	Discussion		15 min.
10:30 – 10:45	Coffee/Tea Break	• Break	15 min.
10:45 – 11:05	Global progress on containment implementation and issues or decisions relevant to CAG from recently concluded meetings (e.g., 18th GCC, 1st meeting between GCC-CWG and NACs, etc) Daphne MOFFETT, Technical Adviser - Poliovirus Containment, WHO	For information only	20 min.
11:05 – 11:15	Discussion		10 min.
Session 3: Secondary (population immunity) and tertiary (facility location and environmental controls) safeguards requirements in GAPIII			
11:15 – 11:25	Tertiary safeguard requirements in GAPIII Harpal SINGH, Technical Officer - Poliovirus Containment, WHO	• This agenda item is associated with the next presentation	10 min.
11:25 – 12:05	Sanitation and associated environmental controls to support GAPIII tertiary safeguards implementation Bruce GORDON, Coordinator, Public Health, Enviroment and Social Determinants (HQ/CED/PHE), WHO Headquarters Kate MEDLICOTT, Technical Officer, Public Health, Enviroment and Social Determinants (HQ/CED/PHE), WHO Headquarters	For decision • As follow up from CAG's decision at CAG TC4 to provide clarity on the definition, purpose and intent of tertiary safeguards to facilitate country level achievement and maintenance	30 min.
12:05 – 12:30	Discussion		30 min.
12:30 – 13:30	Lunch		60 min.

Time	Session	Purpose of the session	Duration
13:30 – 13:50	Implementation of the revised secondary safeguard requirements Harpal SINGH, Technical Officer - Poliovirus Containment, WHO	For information and discussion	20 min.
13:50 – 14:00	Discussion		10 min.
Session 4: Issue associated with the Guidance to minimize risks for facilities collecting, handling or storing materials potentially infectious for polioviruses			
14:00 – 14:15	Harmonizing containment requirements for all poliovirus potentially infectious materials Harpal SINGH, Technical Officer - Poliovirus Containment, WHO	For decision	15 min.
14:15 – 14:30	Discussion		10 min.
Session 5: Issues associated with the implementation of facility physical requirements in GAPIII			
14:30 – 15:45	• Alternative measures for walk-through exit shower • Effluent decontamination Harpal SINGH, Technical Officer - Poliovirus Containment, WHO	For decision	75 min.
15:45 – 16:00	Coffee/Tea Break	• Break	15 min.
16:00 – 16:30	Concept and design of evidence-based efficacy study of showering as protective measure to prevent facility associated release of poliovirus Tjeerd KIMMAN, Wageningen Bioveterinary Research Institute, Netherlands	For decision • Research concept note to support the generation of evidence on the effectiveness of GAPIII requirement of walk-through exit shower	30 min.
16:30 – 17:00	Discussion		30 min.
17:00 – 17:10	Summary for the day Daphne MOFFETT, Technical Adviser - Poliovirus Containment, WHO		10 min.

Friday, 14 December 2018 Chair: Professor David HEYMANN, CAG Chair

Time	Session	Purpose of the session	Duration
Session 5: Issues associated with the implementation of facility physical requirements in GAPIII			
08:00 – 10:00	• Poliovirus-dedicated facilities Harpal SINGH, Technical Officer - Poliovirus Containment, WHO • Dedicated ventilation systems Ken UGWU, CAG Member	<u>For decision</u> <u>For decision</u>	120 min.
Session 6: Novel poliovirus strains and innovation in polio vaccine production			
10:00 – 10:30	Development of S19 novel poliovirus strains, their use and containment considerations Andrew MACADAM, Principal Scientist, Division of Virology, National Institute for Biological Standards and Control (NIBSC)	<u>For information only</u>	30 min.
10:30 – 10:45	Discussion		15 min.
10:45 – 11:00	Coffee/Tea break		15 min.
11:00 – 12:00	Presentation of findings on the Expert Support Group (ESG) on the containment requirements of novel poliovirus strains and their proposed use, genetically-modified polioviruses used in cancer immunotherapy and newer technologies for poliomyelitis vaccine production for consideration of CAG Mark PALLANSCH, Stephan McADAM, George GRIFFITH ESG and CAG members	<u>For decision</u> • Summary of findings of CAG-Expert Support Group to CAG for recommendations on the containment requirements of genetically-modified poliovirus strains and their proposed use	60 min.
12:00 – 12:30	Discussion		30 min.
12:30 – 13:30	Lunch		60 min.
Session 7: CAG's mandate and collaboration			

Time	Session	Purpose of the session	Duration
13:30 – 13:50	Summary on the progress and outcome (CAG recommendations) of issues addressed till date, issues for the 3rd CAG meeting and other pending issues Harpal SINGH, Technical Officer - Poliovirus Containment, WHO	<u>For information only</u> - Summary of applicable CAG's recommendation on issues already discussed - issues for discussion/decision at CAG3 - summary of pending issues • CAG members are invited to identify other issues of concerns not already raised	20 min.
13:50 – 14:10	Applicable CAG recommendations that constitute amendments of GAPIII, endorsement and publication and CAG's mandate of GAPIII Daphne MOFFETT, Technical Adviser - Poliovirus Containment, WHO Harpal SINGH, Technical Officer - Poliovirus Containment, WHO	<u>For information and discussion</u>	20 min.
14:10 – 14:40	Collaboration with other groups on guidance on alternative measure of compliance with GAPIII Daphne MOFFETT, Technical Adviser - Poliovirus Containment, WHO Harpal SINGH, Technical Officer - Poliovirus Containment, WHO	<u>For information and discussion</u>	30 min.
14:40 – 15:00	Wrap-up and Closing David HEYMANN, CAG Chair		20 min.

Annex 2: List of Invited Participants

Third Meeting of the Containment Advisory Group
13 – 14 December 2018
Starling Hotel, Geneva, Switzerland

Containment Advisory Group

1. Professor David HEYMANN
Chair, Containment Advisory Group and
Professor of Infectious Disease Epidemiology,
London School of Hygiene and Tropical Medicine; and
Head, Centre on Global Health Security, Chatham House,
London, United Kingdom

2. Dr Mark PALLANSCH
Director, Division of Viral Diseases,
National Centre for Immunization and Respiratory Diseases,
Centres for Disease Control and Prevention,
Atlanta, Georgia, United States of America

3. Professor Shahina TABASSUM
Professor and Chairman, Department of Virology,
Bangabandhu Sheikh Mujib Medical University (BSMMU),
Dhaka, Bangladesh

4. Dr Atef M. ELGENDY
Retired [former Head, Bacteriology Section and Biological Safety Coordinator, United States Naval Medical Research Unit (NAMRU-3), Cairo, Egypt]

5. Professor George E GRIFFIN
Emeritus Professor of Infectious Diseases and Medicine,
St George's University of London, London, United Kingdom

6. Dr Jagadish DESHPANDE
Scientific Consultant, Indian Council of Medical Research (ICMR) and Technical Consultant, National Task Force on Laboratory Containment of Polioviruses

7. Dr Åsa Szekely BJORNDAL
Chair, National Authority for Containment of Sweden and
Senior Expert Advisor/Specialist; Biosafety Professional and Microbiologist at the Department of Microbiology,
Public Health Agency of Sweden (PHAS), Solna, Sweden

8. Dr Stephen McADAM
Global Healthcare Director, DNV GL Business Assurance,
Oslo, Norway

9. Dr Vibeke HALKJÆR-KNUDSEN
Principal Member of Technical Staff,
Engineering Program/Project Lead, International Biological and Chemical Threat Reduction Program (SNL/IBCTR),
Sandia National Laboratories, Albuquerque, New Mexico,
United States of America

10. Dr Bernard FANGET
CEO, Bernard Fanget Consulting SAS, Chateauneuf, France

11. Dr Janice LO
Head and Consultant Medical Microbiologist,
Public Health Laboratory Services Branch,
Centre for Health Protection, Department of Health,
Hong Kong SAR China.

12. Mr Kenneth UGWU
Senior Biocontainment Advisor, Global Affairs Canada,
Ottawa, Ontario, Canada

13. Mr Neil GODDEN (Unable to attend)
High Containment Specialist, Science Strategy and Laboratory Engineering, Commercial, Estates and Knowledge Directorate,
Department for Environment, Food and Rural Affairs (DEFRA),
Herefordshire, United Kingdom

Resource Persons/Experts

1. Mr Bruce GORDON
Coordinator, Public Health, Enviroment and Social Determinants (HQ/CED/PHE), WHO, Geneva, Switzerland
[*Session 3: Secondary (population immunity) and tertiary (facility location and environmental controls) safeguards requirements in GAPIII]

2. Ms Kate MEDLICOTT
Technical Officer, Public Health, Enviroment and Social Determinants (HQ/CED/PHE), WHO, Geneva, Switzerland
[*Session 3: Secondary (population immunity) and tertiary (facility location and environmental controls) safeguards requirements in GAPIII]

3. Dr Tjeerd KIMMAN (by phone)
Wageningen Bioveterinary Research Institute (Central Veterinary Institute), Lelystad,
the Netherlands
(*Session 5: Issues associated with the implementation of facility physical requirements in GAPIII)

4. Dr Andrew MACADAM
   Principal Scientist, Division of Virology,
   National Institute for Biological Standards and Control (NIBSC),
   Department of Health and Social Care
   South Mimms, Potters Bar, Herts, EN6 3QG, United Kingdom
   (*Session 6: Novel poliovirus strains and non/infectious platforms for polio vaccine production)

Representatives of other containment supporting groups

1. Dr Arlene KING
   Chair, GCC - Containment Working Group and
   Adjunct Professor, Dalla Lana School of Public Health,
   University of Toronto, Ontario, Canada

2. Professor David SALISBURY (unable to attend)
   Chair, Global Commission for the Certification of the Eradication of Poliomyelitis (GCC) and Associate Fellow, Centre on Global Health Security, Royal Institute for International Affairs, Chatham House, London, United Kingdom

3. Dr Jeffrey PARTRIDGE (unable to attend)
   Co-Chair, Containment Management Group and
   Senior Program Officer, Bill & Melinda Gates Foundation,
   Seattle, Washington, United States

WHO Secretariat

1. Mr Michel ZAFFRAN
   Director, HQ/WSI/POL

2. Dr Roland SUTTER
   Special Adviser to the Director, Polio Eradication
   HQ/WSI/POL/RPC

3. Dr Jacqueline FOURNIER-CARUANA
   a.i. Team Lead, HQ/WSI/POL/RPC/CNT

4. Dr Daphne MOFFETT
   Technical Adviser, HQ/WSI/POL/RPC/CNT

5. Dr Harpal SINGH
   Technical Officer, HQ/WSI/POL/RPC/CNT

6. Ms Caroline A NAKANDI
   Assistant to the Team, HQ/WSI/POL/RPC/CNT

Rapporteur

Dr Ray SANDERS
United Kingdom

Annex 3: Summary List of Issues at CAG3

Issue	Status	Relevant GAPIII section (or other reference, as appropriate)	
Tertiary safeguards (definition, purpose, intent and ownership)	Ongoing, Follow-up from CAG TC4	GAPIII:	Strategy, Table 1, Phase Implementation, Annex 1 (Definition), Sublement 12.3.1 of Annex 2
		Other reference:	CAG TC4 report on tertiary safeguards
Implementing the revised secondary safeguards requirements	Ongoing; Feedback to CAG on implementation of revised requirements proposed by SAGE	GAPIII:	Strategy, Table 1, Phase Implementation, Annex 1 (Definition), Sublement 12.3.1 of Annex 2 and 3
		Other reference:	Meeting of the Strategic Advisory Group of Experts on immunization, April 2018 – conclusions and recommendations
Harmonizing containment requirements for all poliovirus potentially infectious materials (WPV/VDPV and Sabin PIM)	New submission	GAPIII:	Annex 1 (Definition)
		Other reference:	Guidance to minimize risks for facilities collecting, handling or storing materials potentially infectious for polioviruses (PIM Guidance) (available as separate document)
Alternative measures for walk-through exit shower	New submission	GAPIII:	Sublement 12.3.1 of Annex 2 and 3
		Other reference:	CAG TC1 report on showers
Effluent decontamination	New submission	GAPIII:	Sublement 12.3.1 of Annex 2 and 3
		Other reference:	CAG2 report
Concept and design of evidence-based efficacy study of showering as protective measure to prevent facility associated release of poliovirus	Submission requested by the Secretariat	GAPIII:	Sublement 12.3.1 of Annex 2 and 3
		Other reference:	CAG TC1 report on showers
Poliovirus-dedicated facilities	New submission; Issue raised at CAG1 and CAG2	GAPIII:	Sublement 12.3.1 of Annex 2 and 3
		Other reference:	CAG1 and CAG2 report
Dedicated ventilation systems	New submission; Issue raised at CAG2	GAPIII:	Sublement 12.3.1 of Annex 2 and 3
		Other reference:	CAG2 report
Containment requirements of novel poliovirus strains and their proposed use of the following: - Recombinant oncolytic poliovirus PVS-RIPO for use in Phase II clinical trials (cancer immunotherapy) - nOPV2 vaccine strains (S2/cre5/S15domV/rec1/hifi3 and S2/S15domV/CpG40) for nOPV2 production and QC - S19 – poliovirus strains (± N18S substitution in PV 2A gene) for IPV production, laboratory assay (IPV potency, neutralization test, Human immunoglobulin lot control and release of: S19/MEF1P1, S19/S2P1; S19/Mah1P1, S19/S1PI; S19/Sau3P1, S19/S3P1 - Cold-Adapted Viral Attenuation (CAVA)-Poliovirus strains - Containment requirements for handling of stools from nOPV2 vaccine recipients			

Annex 4: Risk-based guidance for country-hosting PEFs on failure of primary, consequences and risk mitigation (secondary and tertiary) safeguards. Implementation as per GAPIII (Fig A4.1), risk-management based identification of failure of selected primary safeguards (Table A4.1) and selected one-page summary of safeguard (Table A4.2).

Figure A4,1: Implementation of primary, secondary and tertiary safeguards as described in GAPIII.

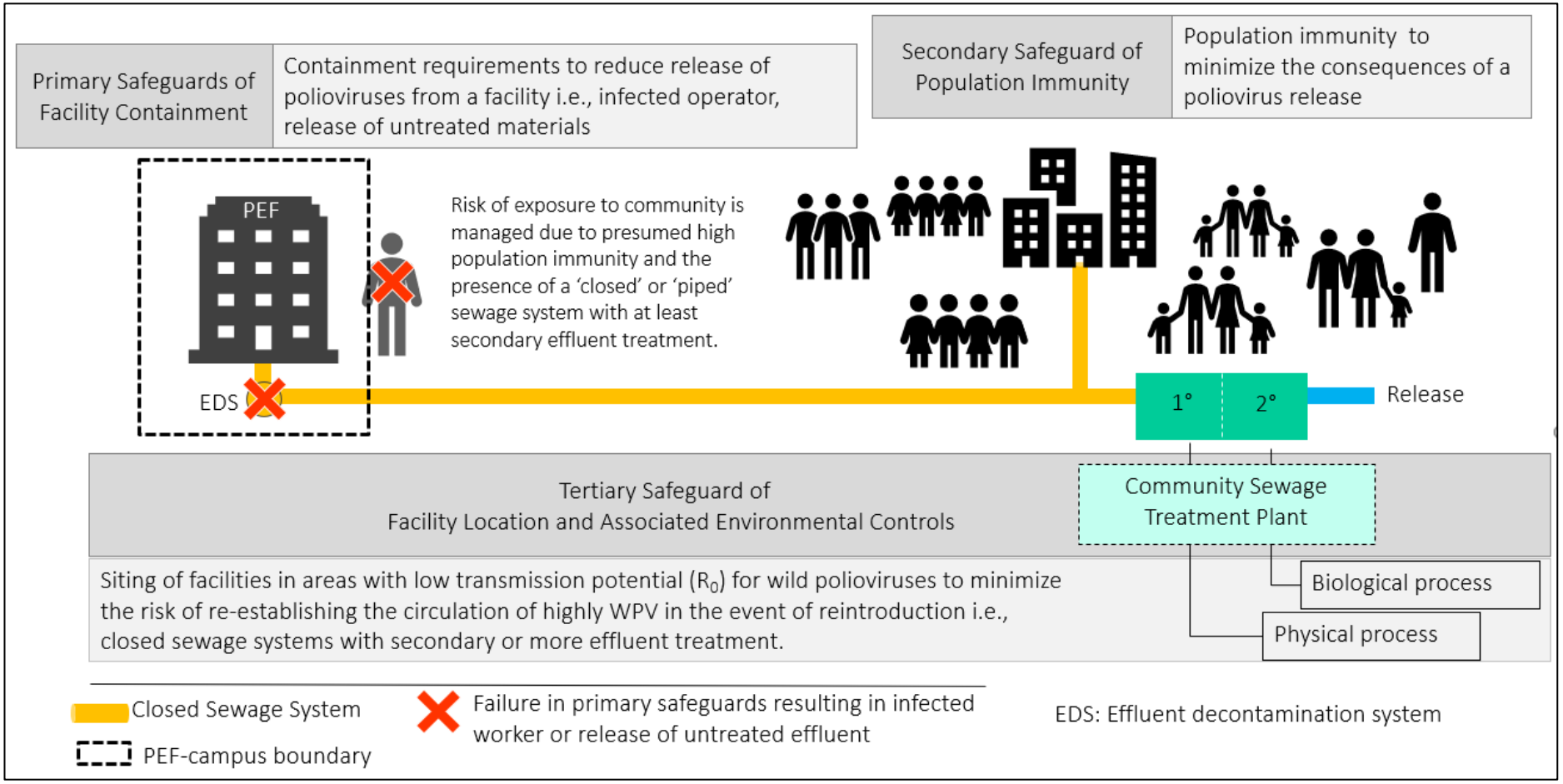

Table A4.1: Risk-based identification of failure of primary safeguards, consequences and other risk mitigation strategies (THIS IS A NON-EXHAUSTIVE EXAMPLE ONLY)

		Hazard	Risk	Primary Safeguard	Secondary Safeguard*	Tertiary Safeguard
Failure of facility-based primary safeguards	Untreated effluent release	Poliovirus in effluent waste, manual handling	Exposure of poliovirus to the community	Validated inactivation/ decontamination procedure, etc.	Population immunity requirements (IPV doses and IPV coverage)	Areas with closed sewage systems with a minimum of secondary treatment of effluents.
	Infected worker	Spills in poliovirus vaccine production facility	Exposure of facility operator, recognized spill, skin exposure	PPE, facility physical requirements, immunization of operators, etc.	Population immunity requirements (IPV doses and IPV coverage)	Areas with closed sewage systems with a minimum of secondary treatment of effluents.

*Current recommendations for countries-hosting PEFs:[26]
To align GAPIII and SAGE recommendations on IPV immunization schedules, countries with PEFs using a single dose of IPV should adjust their IPV schedule, coverage targets and geographical scope as soon as possible and no later than at the time of all OPV cessation, as follows:

- At least 2 IPV doses in routine immunization, IPV1 at 4 months and IPV2 at least 4 months after IPV1 (full or fractional, standalone or in combination vaccines)
- ≥90% of IPV2 coverage in infants within a 100 km of the PEF.

Table A4.2: One-page summary of a safeguard (THIS IS AN EXAMPLE ONLY – THE RESPONSES PROVIDED MAY NOT NECESSARILY BE ACCURATE OR EXHAUSTIVE)

Safeguard	Community sewage treatment plant
Why	As tertiary safeguard in case of failure of facility effluent inactivation
When	Always
Capacity	Large enough to worst case load (volume / concentration), should include at least secondary treatment
How	Closed piped system from facility to community sewage treatment plant, with at least secondary or more sewage treatment steps.
Ownership	Government, government-entity, private sector
Operating-entity	Government utilities personnel, local government authority, private contractor
Operator requirements	Trained, vaccinated, skilled
Entity responsible for SOP development	Operating-entity

[26] Meeting of the Strategic Advisory Group of Experts on immunization, April 2018 – conclusions and recommendations, Weekly Epidemiological Record 2018;93:329–44. Available at: http://apps.who.int/iris/bitstream/handle/10665/272782/WER9323.pdf?ua=1

Table A4.2: One-page summary of a safeguard (THIS IS AN EXAMPLE ONLY – THE RESPONSES PROVIDED MAY NOT NECESSARILY BE ACCURATE OR EXHAUSTIVE)

Safeguard		Community sewage treatment plant
Operator training		Training in operation, shut-down/start-up, maintenance, notification process of accidents, incidents and near-misses.
Maintenance		Operating-entity facility engineers or private contractors
Entity performing the risk assessment		Operating-entity or the entity with insight into plant operations. May involve PEFs, NACs and relevant authorities*
Entity reviewing the risk assessment		NAC, GCC and CAG should additional guidance be needed*
Entity approving the risk assessment		NAC and GCC*
Entity responsible for compliance		Government of the PEF-hosting country in close collaboration with the NAC*
Validation. If yes, frequency.		Yes, twice a year
Entity performing audit*		Appropriate government agency- or entity
Frequency of audit**		After construction, during start up, after changes, at least yearly
Audit** scope and performance		Treatment procedure trend data, maintenance data of tanks, test sample results, accidents and near misses. Piping system from PEF to sewage treatment plant. Physical condition of the plant
Performance indicators (PI)		Biological burden on different steps, during rainy days, during draught, different seasons, when sewage composition changes drastically
Trend analyses		Yes, quarterly review of PI's
Security		Treatment plant must be secured from non-authorized personnel. Security details to be decided in risk assessment and mitigation rationale. Approved by NAC and relevant authorities. *
GAPIII	Section	Annex 1 (Definition)
	Statement	The sanitation and hygiene conditions (good personal, domestic and environmental hygiene standards and closed sewage systems with secondary or greater effluent treatment) that minimize the risk of re-establishing the circulation of highly transmissible wild poliovirus in the event of reintroduction. The country hosting the poliovirus-essential facility is responsible for the implementation of the tertiary safeguards, a prerequisite for the containment certification of facilities retaining wild poliovirus in Phase III.

* The involvement of the PEF, NAC, GCC or CAG in the development, review, approval, monitoring and guidance of the risk assessment is within the context of tertiary safeguards described in GAPIII and CCS.

**audits in the context above refers to compliance verification of sewage treatment plants within a national regulatory context of protecting public health or the environment and does not refer to a GAPIII-CCS audit.

Annex 5: List of CAG-ESG issues related to novel poliovirus strains under specific terms of usage and status of their deliberations

Issue	Status	Report
Criteria for the evaluation of improved 'safety' of novel PV strains to determine the containment needs for their storage and handling	Completed	http://polioeradication.org/wp-content/uploads/2017/08/criteria-evaluation-novel-pv-june-2019-eng.pdf
Containment requirements: nOPV2 vaccine candidates (S2/cre5/S15domV/rec1/hifi3 and S2/S15domV/CpG40) for clinical trials, stockpile and for outbreak response	Completed	http://polioeradication.org/wp-content/uploads/2017/08/CAG-TC3-20180630-EN.pdf
Containment requirement nOPV2 vaccine strains (S2/cre5/S15domV/rec1/hifi3 and S2/S15domV/CpG40) for novel OPV2 production and quality control testing	Completed	http://polioeradication.org/wp-content/uploads/2017/08/Addendum-CAG-TC3-Dec-2018-EN-1.pdf
S19 – poliovirus strains (± N18S substitution in protein 2A) for IPV production, laboratory assay (IPV potency, neutralization test, Human immunoglobulin lot control and release. - N18S • S19/Mah1P1, S19/MEF1P1, S19/Sau3P1 • S19/S1PI, S19/S2P1, S19/S3P1 + N18S • S19/Mah1P1/N18S, S19/MEF1P1/N18S, S19/Sau3P1/N18S • S19/S1PI/N18S, S19/S2P1/N18S, S19/S3P1/N18S	Completed	http://polioeradication.org/wp-content/uploads/2017/08/CAG-TC3-20180630-EN.pdf http://polioeradication.org/wp-content/uploads/2017/08/Addendum-CAG-TC3-Dec-2018-EN-1.pdf
Containment requirements of Cold-Adapted Viral Attenuation (CAVA)-Poliovirus strains and other novel strains under specific terms of usage	To be addressed	-
Use of PVSRIPO, type 1 poliovirus (Sabin) vaccine carrying a heterologous internal ribosomal entry site (IRES) of human rhinovirus type 2, in cancer immunotherapy.	Ongoing	This report
Containment requirements for handling of stools from nOPV2 vaccine recipient	Completed	This report

Annex 6: Notable changes in the membership of the CAG and CAG Secretariat

Table A 6.1: Changes brought about by the appointment of new leadership for the containment team

Containment Team, Department of Polio Eradication, WHO (wef 1 January 2019)	The CAG took the opportunity to welcome Dr Daphne MOFFETT as the incoming Team Lead for the Poliovirus Containment. Dr Moffett has 20+ years of public health experience and holds the rank of Captain in the United States Public Health Service (USPHS). Prior to joining WHO, she was the CDC Central Asia Regional Director with leadership and oversight of CDC programs in Kazakhstan Uzbekistan, Kyrgyzstan, Tajikistan, and Turkmenistan. Dr Moffett takes over the portfolio of Dr Jacqueline CARUANA-FOURNIER who is retiring in a few weeks from the organization after many years of service. Dr Moffett will also take on the role as Co-Chair to the Containment Management Group. The CAG and the secretariat express their appreciation to Jackie for support to the CAG, her leadership, her vision, her expertise and her openness to constructive criticism.

List of WHO staff serving in the containment (HQ/DGO/POL/CNT) team (wef 1 January 2019)		
DR. MOFFETT, Daphne Team Lead, Containment +41 22 791 4269 moffettd@who.int	MRS. BOUALAM, Liliane Dalila Technical Officer +41 22 791 21639 boualaml@who.int	DR. SINGH, Harpal Technical Officer – Poliovirus Containment +41 22 791 1067 hsingh@who.int
MR. SWAN, Joseph Sinclair Communications Officer +41 22 791 3708 swanj@who.int	MISS NAKANDI, Caroline Ann Assistant to the Containment Team +41 22 791 4671 nakandic@who.int	Containment also maintains a generic mailbox. If you have question or require clarification you may send your email to containment@who.int

Table A 6.2: Secretariat to the Containment Advisory Group (CAG)

Secretariat to the Containment Advisory Group (effective from 1 January 2019)			Supporting Member of the CAG Secretariat
DR MOFFETT, Daphne Team Lead, Containment and Head of the CAG Secretariat. (supports the CAG both technically and administratively, provide support and guidance, vision and direction to members of the secretariat in the screening of CAG submissions, development of agenda) +41 22 791 4269 moffettd@who.int	DR. SINGH, Harpal Technical Officer – Poliovirus and Technical Focal Point on Issues related to implementation of the containment requirements of GAPIII, PIM Guidance, Containment requirements for newer strains of poliovirus, and acceptability of alternative measure of compliance with GAPIII. +41 22 791 1067 hsingh@who.int	MISS NAKANDI, Caroline Ann Assistant to the Containment Team and Management focal point for CAG meetings and activities. +41 22 791 4671 nakandic@who.int	MRS. BOUALAM, Liliane Dalila Technical Officer and Responsible for ensuring that funds are available for the implementation of CAG activities. +41 22 791 21639 boualaml@who.int

Table A 6.3 Containment Advisory Group (as of 14 December 2018)

On December 14, 2018, CAG Member, Dr Bernard FANGET informed the CAG and its secretariat his intention to resign as a member of the CAG – the CAG Chair, its members and the secretariat express their appreciation for contributions to the CAG.

Current members of CAG (wef 15 December 2019)

1. Professor David HEYMANN, Chair, CAG and Professor of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine; and Head, Centre on Global Health Security, Chatham House, London, United Kingdom of Great Britain and Northern Ireland
1. Dr Mark PALLANSCH, Director, Division of Viral Diseases, National Centre for Immunization and Respiratory Diseases, Centres for Disease Control and Prevention, Atlanta, Georgia, United States of America
2. Professor Shahina TABASSUM, Professor and Chairman, Department of Virology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh
3. Dr Atef M. ELGENDY, Retired [former Head, Bacteriology Section and Biological Safety Coordinator, United States Naval Medical Research Unit (NAMRU-3), Cairo, Egypt]
4. Professor George E. GRIFFIN, Emeritus Professor of Infectious Diseases and Medicine, St George's University of London, London, United Kingdom of Great Britain and Northern Ireland
5. Dr Jagadish DESHPANDE, Scientific Consultant, Indian Council of Medical Research (ICMR) and Technical Consultant, National Task Force on Laboratory Containment of Polioviruses, Mumbai, India
6. Dr Åsa Szekely BJORNDAL, Chair, National Authority for Containment of Sweden and Senior Expert Advisor/Specialist; Biosafety Professional and Microbiologist at the Department of Microbiology, Public Health Agency of Sweden (PHAS), Solna, Sweden
7. Dr Stephen McADAM, Global Healthcare Director, DNV GL Business Assurance, Oslo, Norway
8. Dr Vibeke HALKJÆR-KNUDSEN, Principal Member of Technical Staff, Engineering Program/Project Lead, International Biological and Chemical Threat Reduction Program (SNL/IBCTR), Sandia National Laboratories, Albuquerque, New Mexico, United States of America
9. Mr Neil GODDEN, High Containment Specialist, Science Strategy and Laboratory Engineering, Commercial, Estates and Knowledge Directorate, Department for Environment, Food and Rural Affairs (DEFRA), Herefordshire, United Kingdom of Great Britain and Northern Ireland
10. Mr Kenneth UGWU, Senior Biocontainment Advisor, Global Affairs Canada, Ottawa, Ontario, Canada
11. Dr Janice LO, Head and Consultant Medical Microbiologist, Public Health Laboratory Services Branch, Centre for Health Protection, Department of Health, Hong Kong SAR China.

CAG members are considered experts in their area of work. While serving as CAG members, they represent themselves and not their host agencies, institutions or governments.