Containment Team
Research, Policy and Containment Unit
Department of Polio Eradication

CAG
June 2017
Report

Report of the First Meeting of the Containment Advisory Group

Geneva
19 – 20 June 2017

Abbreviations

BSC	Biosafety cabinet
BSL	Biosafety level
CAG	Containment Advisory Group
CC	Certificate of Containment
CCS	Containment Certification Scheme to support the WHO Global Action Plan for Poliovirus Containment
CP	Certificate of participation
ECBS	Expert Committee on Biological Standardization
ESG	Expert Support Group
GAPIII	Global Action Plan III for Poliovirus Containment
GCC	Global Commission for the Certification of the Eradication of Poliomyelitis
GDG	Guidance Drafting Group
GPEI	Global Polio Eradication Initiative
GPLN	Global Polio Laboratory Network
HEPA	High-efficiency particulate arresting
ICC	Interim certificate of containment
IHR	International Health Regulations
IPV	Inactivated polio vaccine
NAC	National authority for containment
OPV	Oral polio vaccine
mOPV	Monovalent oral polio vaccine containing one type only
nOPV	New oral polio vaccine
PEF	Poliovirus-essential facility
POL	WHO's Polio Eradication Department
PPE	personal protective equipment
PRC	Polio Research Committee
SAGE	Strategic Advisory Group of Experts on Immunization
TC	Teleconference
TRS	Technical Report Series
VDPV	Vaccine-derived poliovirus
VLP	Virus-like particle
WHA	World Health Assembly
WHO	World Health Organization
WPV	Wild poliovirus

Report of the First Meeting of the Containment Advisory Group
19 – 20 June 2017
Geneva, Switzerland

CONTENTS

This page is intentionally left blank

SUMMARY RECORD

The Containment Advisory Group (CAG) held its first meeting on the 19 - 20 June 2017 in Geneva, Switzerland. The following are the recommendations that are linked to specific elements of GAP III, as detailed below:

Priority Group I: Issues submitted by the drafting group of TRS 926, Annex 2 'Safe Production and quality control of Poliomyelitis Vaccine' or the drafting group of 'Guidance for Non-Poliovirus Facilities to Minimize Risk of Sample Collections Potentially Infectious for Polioviruses'

Issue 1: Shower

GAP III, Annexes 2 and 3, **(changes to existing text are shown in bold)**:

Modify Subelement 12.3.1 (g) of Annexes 2 and 3 to read as follows: 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 **not mandatory, other than** in the event of an uncontrolled breach of the primary containment equipment.

Issue 2: Storage outside of containment

Storage of polioviruses must be performed under appropriate containment conditions, as determined by a risk assessment approved by the competent authority (NAC), in line with the approach detailed in the *Containment Certification Scheme to support the WHO Global Action Plan for Poliovirus Containment (GAPIII-CCS)*[1] for an interim certificate of containment (ICC) assessment. Any derogations applied for and accepted by the NAC will be reflected on the certificate scope and associated certificates.

Issue 3: Dedicated facilities, work on campaign basis

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.

Requirement 12.3.1 (c) '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.' of Annexes 2 and 3 was not changed.

Issue 4: RNA

GAPIII, Annex 1, **(changes to existing text are shown in bold)**:

Add the following definition:

Poliovirus nucleic acid: Nucleic acid* that has been extracted/purified using methods demonstrated to inactivate poliovirus can be handled outside of poliovirus containment under the condition that:

- **These materials will not be introduced into polio-permissive cells or animals (as defined in GAPIII and the "Guidance for Non-Poliovirus Facilities") with or without a transfection reagent, except under appropriate containment conditions as described in GAPIII Annex 2 or Annex 3;**

***"Nucleic acid" refers to RNA, cDNA and total nucleic acid, extracted from poliovirus infectious materials (e.g., a virus isolate) or potentially infectious materials (e.g., stool, respiratory specimen, sewage), or synthesized RNA or cDNA RNA/cDNA (e.g., cDNA clone, synthetic transcript).**

Modify the definitions as follows:

(a) Poliovirus infectious materials, wild (bullet point 7): full-length RNA or cDNA ~~that includes capsid sequences derived from wild poliovirus, unless viruses derived from them are demonstrably~~ **of viruses** proven to be safer than Sabin strains**, but that includes wild poliovirus capsid sequences**. The safety of **these** full-length RNA or cDNA ~~containing wild poliovirus capsid sequences~~ **and their containment**

[1] Containment Certification Scheme to support the WHO Global Action Plan for Poliovirus Containment (GAPIII-CCS) http://polioeradication.org/polio-today/preparing-for-a-polio-free-world/containment/containment-resources/

requirements will be assessed by an expert panel convened by WHO, on the basis of comparison to reference Sabin strains for (i) degree and stability of attenuation; (ii) potential for person-to-person transmission; and (iii) neurovirulence in animal models;

(a) Poliovirus infectious materials, OPV/Sabin (bullet point 7): full-length RNA or cDNA ~~that includes capsid sequences derived from OPV/Sabin strains~~ **of viruses proven to be safer than Sabin strains, but that includes OPV/Sabin poliovirus capsid sequences. The safety of these full-length RNA or cDNA and their containment requirements will be assessed by an expert panel convened by WHO, on the basis of comparison to reference Sabin strains for (i) degree and stability of attenuation; (ii) potential for person-to-person transmission; and (iii) neurovirulence in animal models.**

Priority Group II: Issues submitted by other stakeholders

Issue 5: Verification of Room Containment

GAPIII, Annexes 2 and 3:

Room pressure testing is not a GAPIII requirement unless the need to do so has been determined by a risk assessment, regulatory requirement or other similar instance.

Requirement 12.3.1 (d) 'The containment perimeter is a defined working area sealable for gaseous decontamination and with sealed penetrations to prevent uncontrolled outward airflow. The containment perimeter is required irrespective of the choice of primary containment.' of Annexes 2 and 3 was not changed.

Issue 6: Personal Protective Equipment (PPE)

GAPIII, Annexes 2 and 3:

Element 7 Clothing and Personal Protective Equipment (PPE) of Annexes 2 and 3 was not changed.

Issue 7: Risk Assessment *vs*. prescriptive requirements

GAP III, Annexes 2 and 3, **(changes to existing text are shown in bold)**:

Modify Subelement 12.3.1 (g) of Annexes 2 and 3 to read as follows: 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 **not mandatory, other than** in the event of an uncontrolled breach of the primary containment equipment.

Issue 8: Location of HEPA filters

GAPIII, Annexes 2 and 3:

Subelement 12.3.1 (h) '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.' of Annex 2 was not changed .

Issue 9: Dedicated ventilation

Ventilation systems shall be dedicated to the area defined as the poliovirus containment perimeter. These ventilation systems shall not serve other spaces which are not dedicated to the work with poliovirus. The dedicated ventilation systems shall include all supply and exhaust systems, including those serving primary containment isolators and other similar equipment to ensure these systems are not shared with areas beyond the poliovirus containment perimeter.

Subelement 12.3.1 (h) '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' of Annex 2 was not changed.

Issue 10: Backflow protection on gas services

GAP III, Annexes 2 and 3:

Subelement 12.3.1 (i) 'The decontamination of all effluent (including shower water, eyewash, unsterilized autoclave condensate) from within the containment perimeter is achieved through a validated inactivation procedure. Backflow prevention is implemented on all services/utilities entering the facility (water, gases)

and via measures to prevent release through traps, sinks and shower drains.' of Annex 2 was not changed.

Issue 11: Documented records

GAP III, Annexes 2 and 3:

Modify Subelement 1.4.2 to read as follows: Records, documents and data are handled in such a way that they remain legible, readily identifiable and retrievable.

Documented records are maintained in paper or electronic form for a minimum of 10 years from the day of withdrawal and should be available for review during national certification~~/WHO verification~~ procedures.

Priority Group III: Issues that need to be addressed by other groups first, before they are discussed by the CAG at the Second Meeting of the CAG

Issue 12: Issues that need to be addressed by other groups first

	Issue	Follow up action required	Actions taken and outcomes achieved (to be completed before 2nd CAG meeting)
12A	**Encourage newer safer technologies or newer strains for the production of polio vaccines and diagnostic reagents, and determine appropriate containment requirements for the handling of specific new strains (e.g. S-19 Sabin 2 containing Sabin 2 capsid sequence; nOPV strains)**		
	Create a CAG Expert Support Group (CAG-ESG) to consider containment requirements for the new strains and propose potential solutions to the CAG and other groups if necessary, for review and approval	CAG secretariat to organize selection of CAG-ESG members, organize appropriate communication channels (meetings/TCs), report on activities and CAG-ESG's recommendations	
12B	**Encourage new technologies for the production of polio vaccines (e.g. VLP)**		
	Encourage the Polio Research Committee (PRC) to pursue their consideration of other vaccine options, including the development of VLPs, and inform CAG of research progress and developments	CAG secretariat to engage PRC in discussions and report on exchanges	
12C	**Immunization of facility personnel: maintaining mucosal immunity in facility operators post-bOPV cessation**		
	Ensure that the SAGE polio WG addresses the consequences of reduced mucosal immunity in facility operators after OPV cessation and provides recommendations for the consideration of SAGE	CAG secretariat to ensure this discussion item is included in the agenda of the SAGE polio WG meeting of 12-13 Sep 2017 and report on SAGE polio WG's recommendations	
12D	**Clarify what activities will be allowed at poliovirus-non-essential facilities tasked with poliovirus surveillance post-eradication**		
	Ensure that appropriate guidance and relevant protocols are developed and published by the Global Polio Laboratory Network (GPLN)	CAG secretariat to follow up and report on progress	
12E	**Determine appropriate tests to demonstrate genetic stability of handled Sabin polioviruses, and define associated containment requirements**		
	Share this request with the	CAG secretariat to follow up	

	Expert Committee on Biological Standardization (ECBS) and specific Technical Report Series (TRS) working groups for consideration and action, before conclusions are shared with CAG for further advice on specific containment requirements	and report on progress	
12F	**Develop a protocol to identify and deal with individuals, including facility operators, exposed to poliovirus and becoming infected**		
	The CAG secretariat should approach the WHO Polio Eradication Department (POL) and the International Health Regulations (IHR) and ensure such guidance is developed and made available to stakeholders in due course	CAG secretariat to follow up and report on progress	
12G	**Guidance for the establishment of the National Authority for Containment (NAC)**		
	Guidance for the establishment of NACs is available in CCS	CAG secretariat to provide clarifications in consultation with individual countries	
12H	**Include in GAPIII 'Inventory, destruction or preparation for containment of poliovirus types 1 and 3'**		
	The CAG secretariat should ensure that GCC discusses and clarifies the timing to start and complete Phase I activities for poliovirus types 1 and 3	CAG secretariat to ensure GCC addresses this point at the GCC meeting of 4-5 July 2017	A containment-dedicated GCC meeting is planned to be organized before the 2nd CAG meeting so that GCC can appropriately address this request. CAG secretariat to further report on GCC's recommendations in due course

Priority Group IV: Issues that do not need input from the CAG, but require short clarification

Issue 13: Items under column 'guidance' in Annexes 2 or 3 of GAPIII

CAG provided the following clarification: Information in the column 'Guidance' of Annexes 2 and 3 does not constitute conformity requirements. This information should be read and understood by poliovirus-essential facilities (PEFs), but where appropriate, alternative measures may be set in place to demonstrate compliance against requirements. Where alternative measures have been selected or areas in guidance have not been proactively addressed, the PEF should be able to provide a relevant justification where necessary.

Issue 14: Outsourced work

NACs should ensure that all facilities retaining polioviruses are certified against GAPIII, whether or not the work has been outsourced.

Priority Group V: Issues for consideration at the Second Meeting of the CAG

Issue 15: Issues requiring 'Guidance for non-poliovirus facilities to minimize risk of sample collections potentially infectious for polioviruses'

Finalize the document *Guidance for non-poliovirus facilities to minimize risk of sample collections potentially infectious for polioviruses*, in view of its consideration and endorsement at the next CAG meeting, planned for end-November 2017.

Issue 16: Issues for the Second Meeting of the Containment Advisory Group

The CAG secretariat should collect feedback from other groups on issues described under Priority group III above, for discussions and deliberations at the next CAG meeting, planned for end-November 2017.

This page is intentionally left blank

Main Findings, Conclusions and Recommendations
NOTE FOR THE RECORD

Background

The Containment Advisory Group (CAG), nominated in March 2017, is an advisory body to the Director-General of WHO to make recommendations on technical issues related to the implementation of the Global Plan of Action for Poliovirus Containment (GAPIII)[2]. The function of the CAG is to provide:

1. Recommendations to WHO on technical issues arising from implementation of GAPIII;
2. Guidance on the handling of poliovirus-related materials for diagnosis, research and vaccine production (including production of VLPs, pseudoviruses, new OPV, etc.);
3. Guidance on the identification and categorization of poliovirus potentially infectious materials, their destruction, or handling and storage;
4. Guidance on the identification of acceptable alternative containment solutions in the interim period, before full eradication.

The First Meeting of the CAG was held on 19 – 20 June 2017 at WHO in Geneva, Switzerland.

The meeting was attended by the following CAG members: Professor David Heymann (Chair), Dr Mark Pallansch, Professor Shahina Tabassum, Professor George Griffin, Professor Yvonne (Bonnie) Maldonado, Dr Jagadish Deshpande, Dr Åsa Szekely Björndal, Dr Stephen McAdam, Dr Vibeke Halkjær-Knudsen, Dr Bernard Fanget, Mr Neil Godden and Mr Kenneth Ugwu. Dr Atef El-Gendy and Dr Janice Lo were unable to attend.

Additional participants included Dr Paul Huntly (WHO expert biorisk management consultant), Dr Philip Minor, Dr Konstantin Chumakov and Dr Tong Wu of the drafting group of the WHO Technical Report Series (TRS) 926, Annex 2, *Guidelines for the safe production and quality control of poliomyelitis vaccine*, and Dr Walter Dowdle and Dr Steve Oberste of the drafting group of the *Guidance for Non-Poliovirus Facilities to Minimize Risk of Sample Collections Potentially Infectious for Polioviruses*.

Observers included Professor David Salisbury and Dr Arlene King of the Global Commission for the Certification of the Eradication of Poliomyelitis (GCC), Dr King also representing the GCC Containment Working Group (GCC-CWG), and Dr Jeffrey Partridge of the Containment Management Group (CMG).

This note presents a summary of the main findings, conclusions and recommendations of the meeting.

Context, objectives and expected outcomes of the meeting

An open call for the submission[3] of technical issues to the CAG, linked to GAPIII was published on the Global Polio Eradication Initiative website from 17 May to 2 June 2017. The secretariat received 29 requests to the CAG covering 16 different issues. These issues were prioritized by the Containment Team into the following groups:

Priority Group

I Issues submitted by the

1. Drafting group of TRS 926, Annex 2
2. Drafting group of the Guidance for Non-Poliovirus Facilities to Minimize

[2] 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 (GAPIII) http://polioeradication.org/wp-content/uploads/2016/12/GAPIII_2014.pdf

[3] http://polioeradication.org/wp-content/uploads/2017/05/Request-to-CAG-Template-Template-May-2017-docx-2.docx

Risk of Sample Collections Potentially Infectious for Polioviruses

- **II** Issues submitted by other stakeholders
- **III** Issues that need to be addressed by other groups first, before they are discussed by the CAG at the Second CAG meeting
- **IV** Issues that do not need input from the CAG, but require short clarifications
- **V** Issues for consideration at the Second Meeting of the CAG

All 29 requests received were shared electronically with the CAG members one week ahead of the meeting and were addressed during the 1st CAG meeting that had the following:

Objectives:

1. Inform participants on progress with poliovirus containment activities and achievements
2. Discuss technical issues related to GAPIII, as submitted and prioritized
3. Develop recommendations for the Director-General of WHO

Expected outcomes:

1. Development of recommendations on:
   a. Issues for which consensus is reached
   b. Required next steps (e.g. additional research, collection of data, referral to other groups for consideration, and associated timelines) where insufficient data are available for CAG to make informed decisions, or for which consensus is not reached
2. Identification of issues that require clarifications rather than CAG's input
3. Identification of issues for consideration at the 2nd CAG meeting
4. CAG recommendations will specify by when a revision of GAPIII is expected and what changes are expected to be included
5. Rationale for accepting modifications to GAPIII
6. Identification of dates for the GAPIII orientation training and the 2nd CAG meeting

Priority Group I: Issues submitted by the drafting group of TRS 926, Annex 2 'Safe Production of Poliomyelitis Vaccine' or the drafting group of 'Guidance for Non-Poliovirus Facilities to Minimize Risk of Sample Collections Potentially Infectious for Polioviruses'

Issue No. 1: Containment exit shower

Relevant GAPIII section

Annexes 2 and 3:
Subelement 12.3.1 (g) of Annexes 2 and 3: Controlled exit from the containment perimeter is via a walk-through exit shower. Showering out is mandatory except for facilities employing fully functional Class III BSCs or similar isolators (in such facilities, showering out is required in the event of an uncontrolled breach of the primary containment equipment).

Statement of key issues raised

It is argued that the use of showers is not risk-based with regard to work with poliovirus, although it is a routinely applied control in other containment-related situations (e.g. high containment (BSL4) and some animal facilities). Taking a shower potentially multiple times per day is both costly and disruptive. The use of exit showers should only be mandated in case of incidents or accidents with routine controls provided by closed systems, work practices, PPE, etc. A published paper also questioned the value of soap and water in removal of virus from skin[4]. It is also argued that showers may create aerosols and increase the

[4] Schürmann W, Eggers HJ. (1985) An experimental study on the epidemiology of enteroviruses: water and soap washing of poliovirus 1--contaminated hands, its effectiveness and kinetics. Med Microbiol Immunol. 1985;174(5):221-36.

risk of ingestion or inhalation, although presumably this would also be the case in the home or other uncontrolled environment were an exit shower not taken.

Summary of requests to CAG:
Reconsider the need to install showers for use on exiting the containment perimeter, other than in the event of spill or other significant emergency.

Summary of CAG discussions and conclusions
GAPIII was developed in 2009 around a very low tolerance for risk of release of eradicated agents from facilities.

Large scale IPV vaccine production plants use closed systems, although accidents were admitted to happen. Vaccine manufacturers request that the need for showering-out of the containment perimeter on routine basis be guided by a risk assessment rather than being a prescriptive requirement. However, emphasis was placed on the need to demonstrate and validate primary containment.

A study in 1985 questioned the potential effectiveness of water and soap in removing poliovirus from the skin[5]. However, the recent Ebola outbreak showed that many of the Ebola healthcare-acquired infections were attributed to inadequate doffing procedures leading to the need for enhanced procedures which included chemical decontamination before doffing[5]. At present there is no GAPIII requirement for chemical decontamination of PPE, although such control measures may need to be addressed through risk assessments. It was also noted that it was not clear which disinfectants might be suitable for use in such situations, particularly given issues including potential risks to worker health, material compatibility issues, etc. While the need for chemical decontamination of PPE and other measures were considered potentially viable measures, such additional/alternative controls were considered also to be potentially problematical and would require careful consideration and further evidence to support their effectiveness in relation to removal of the need for showering.

While discussions raised the issue whether the shower increases the risk of poliovirus aerosolization, participants recognized that this same consideration would also apply if facility staff were to take their showers when they go home, possibly placing family members and the community at risks that may be otherwise controlled within the facility.

Based on the conflicting discussions and lack of evidence to make decisions against the current requirements of GAPIII, the precautionary approach of GAPIII was maintained, including in relation to manufacturing facilities which are not specifically addressed in GAPIII, the following modifications to GAPIII were recommended.

CAG recommendations
GAP III, Annexes 2 and 3, **(changes to existing text are shown in bold)**:
Modify Subelement 12.3.1 (g) of Annexes 2 and 3 to read as follows: 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 **not mandatory, other than** in the event of an uncontrolled breach of the primary containment equipment.

---

[5] Hersi M, Stevens A, Quach P, Hamel C, Thavorn K, Garritty C, et al. (2015) Effectiveness of Personal Protective Equipment for Healthcare Workers Caring for Patients with Filovirus Disease: A Rapid Review. PLoS ONE 10(10): e0140290. doi:10.1371/journal.pone.0140290

Issue No. 2: Storage of polioviruses outside of containment

Relevant GAPIII sections

Phase Implementation

The storage of mOPV2 stockpiles (frozen bulk and finished product, prepared in accordance with international requirements (15)) and the replenishment of mOPV2 stockpiles of filled vaccine vials must be performed under appropriate containment conditions, based on a risk assessment approved by the competent authority (NAC).

Annex 1 (Definition):

Facility, poliovirus-essential: A facility designated by the ministry of health or another designated national body or authority as serving critical national or international functions that involve the handling and storage of needed poliovirus infectious materials or potentially infectious materials post-eradication under conditions set out in GAPIII'.

Annexes 2 and 3:

Subelement 14.2.1: Inactivation of poliovirus. Procedures are established and maintained to ensure the complete inactivation of all poliovirus from all materials and solid waste streams leaving the containment perimeter.

Statement of key issues raised

GAPIII focuses on the storage and handling of polioviruses in containment, but does not address the need to only store polioviruses other than mOPV stockpiles, without any handling.

Summary of requests to CAG

Allow the secure storage of poliovirus (without handling) outside of poliovirus containment, including vaccine bulks following a validated inactivation procedure but before the completion of the residual live virus test.

Summary of CAG discussions and conclusions

The CAG recognized that there may be legitimate reasons why essential polio facilities wish to store live polio containing materials outside the poliovirus containment perimeter. Storage might be both for the medium or long term and would not involve manipulation of the samples outside of their primary containers. While this kind of storage may be associated with lower risk than the actual manipulation of samples in the facility environment there are still a range of biosafety and biosecurity risks that need to be managed. The CAG therefore proposed that storage areas should also conform to the requirements outlined in GAPIII including all 16 elements of Annexes 2 or 3. However if the PEFs identifies specific requirements that would not contribute to the reduction of biorisk in these storage areas (for example a number of the prescriptive requirements found in 12.3.1) then the PEFs should apply to the NAC for a derogation. This application should identify the specific requirements, in which facility or part of a facility they wish the derogation to apply, the rationale for the derogation as well as a risk assessment examining how the derogation might impact on biorisk.

TRS 926 describes a process for managing bulk IPV out of poliovirus containment once the inactivation process has been completed. This process includes a validated inactivation process and risk assessment and as such the CAG agreed it appeared consistent with the requirements of GAPIII including 14.2.1: procedures are established and maintained to ensure the complete inactivation of all poliovirus from all materials and solid waste streams leaving the containment perimeter.

CAG decisions/recommendations

Storage of polioviruses must be performed under appropriate containment conditions, as determined by a risk assessment approved by the competent authority (NAC), in line with the approach detailed in the *Containment Certification Scheme to support the WHO Global Action Plan for Poliovirus Containment*

(GAPIII-CCS)[6] for an interim certificate of containment (ICC) assessment. Any derogations applied for and accepted by the NAC will be reflected on the certificate scope and associated certificates.

Issue No. 3: Dedicated facilities, work on campaign basis

Relevant GAPIII section
Annexes 2 and 3:
Subelement 12.3.1 (c) of Annexes 2 and 3: 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.

Statement of key issues raised
Allow the use of multipurpose (non-dedicated) laboratory-type areas (e.g., quality control (QC), research and development (R&D) laboratories) for storage and handling of polioviruses.

Summary of requests to CAG
Allow laboratory scale areas such as Quality Control (QC), Research and Development (R&D) and other Manufacturing Technology laboratories to be exempt from being poliovirus-dedicated facilities or work on campaign basis, provided appropriate risk mitigation strategies are determined based on risk assessment. This request is not extended to manufacturing scale areas, for which the requirement for dedicated facilities would remain mandatory.

Summary of CAG discussions and conclusions
In the multi-campaign use, i.e. where multiple agents are tested, CAG would need to understand how the additional measures determined by risk assessment for a particular facility would be implemented to coincide whether derogation is possible. However, in terms of the wider containment scope, work in poliovirus-dedicated facilities or on a campaign basis does not only apply to QC and R&D facilities, but to any facilities planning to retain polioviruses. Agreement on the relaxation of the requirements described in Subelement 12.3.1 (c) was not met. However, CAG recognized that interim measures (as part of the ICC) may be approved by individual NACs following CCS.

CAG decisions/recommendations
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.
Requirement 12.3.1 (c) '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.' of Annexes 2 and 3 was not changed.

Issue No. 4: RNA

Relevant GAPIII section
Annex 1 (Definition):
(a) Poliovirus infectious materials, wild: These include: full-length RNA or cDNA that includes capsid sequences derived from wild poliovirus, unless viruses derived from them are demonstrably proven to be

[6] Containment Certification Scheme to support the WHO Global Action Plan for Poliovirus Containment (GAPIII-CCS) http://polioeradication.org/polio-today/preparing-for-a-polio-free-world/containment/containment-resources/

safer than Sabin strains. The safety of full-length RNA or cDNA containing wild poliovirus capsid sequences will be assessed by an expert panel convened by WHO, on the basis of comparison to reference Sabin strains for (i) degree and stability of attenuation; (ii) potential for person-to-person transmission; and (iii) neurovirulence in animal models;

Annex 1 (Definition):
(a) Poliovirus infectious materials, OPV/Sabin: These include: full-length RNA or cDNA that includes capsid sequences derived from OPV/Sabin strains;

Statement of key issues raised
Allow the storage and handling of nucleic acid materials, extracted from poliovirus infectious or potentially infectious materials, outside of poliovirus containment.

Summary of requests to CAG
Allow the extraction of RNA/cDNA from samples that are infectious or potentially infectious with polioviruses, including stool or respiratory collections, and handling of poliovirus RNA or cDNA outside of containment.

Summary of CAG discussions and conclusions
Molecular detection of pathogens in nucleic acid extracted from human clinical specimens is a routine activity in clinical and research laboratories worldwide. As such, maintaining the current containment restrictions for nucleic acid extracted from poliovirus potentially infectious materials will have a negative impact on other public health and research programs (e.g., those focusing on diarrheal diseases or acute respiratory illness). The need for facilities to implement Annex 2 or Annex 3 of GAPIII to handle and store RNA extracted from poliovirus isolates also impacts poliovirus genomic sequencing, a key component of poliovirus surveillance, in the WHO Global Polio Laboratory Network (GPLN). Very few GPLN laboratories—even those in a polio-essential facility—have space within their poliovirus containment perimeter for sequencing equipment.

By definition, full-length genomic RNA from any positive-strand RNA virus, including poliovirus, is considered “infectious,” in that it can be used to generate infectious virus if introduced into permissive cells[7,8]. However, the process is very inefficient, having low “specific infectivity” (amount of infectious virus produced per unit mass of RNA) unless enhanced through the use of transfection reagent. In the absence of transfection reagent, at least 2 µg of synthetic RNA is required to produce viral cytopathic effect in a monolayer of HEp-2C cells (human epithelial cell line that is highly permissive for poliovirus infection), whereas only 2 ng is required with transfection reagent highlighting the high amount of RNA needed to induce an infection[9]. It is therefore correct to assume that poliovirus potentially infectious material contains much less RNA compared to poliovirus cell culture isolates.

The storage and handling of such nucleic acid is suggested to be in line with the proposed risk mitigation strategies for Lowest Risk poliovirus potentially infectious materials (PIM) of the *Guidance* for Non-Poliovirus Facilities to Minimize Risk of Sample Collections Potentially Infectious for Polioviruses (draft of 10 June 2017).

[7] Colter JS, Bird HH, Moyer AW, Brown RA.(1957) Infectivity of ribonucleic acid from virus-infected tissues. Virology 4:522-532.

[8] Alexander HE, Koch G, Mountain IM, Sprunt K, Van Damme O. (1958) Infectivity of ribonucleic acid of poliovirus on HeLa cell monolayers. Virology 1958;5:172-173.

[9] Martin J. Excerpt from “Infectivity of poliovirus nucleic acids.” Presentation to the Ad Hoc Small Working Group of the WHO Global Polio Laboratory Network, 15 Jun 2016, Tokyo, Slides 1-6.

The CAG was asked to consent to the exclusion of poliovirus RNA and cDNA from the requirements of GAPIII but in line with the risk mitigation procedures described in the Guidance for Non-Poliovirus Facilities to Minimize Risk of Sample Collections Potentially Infectious for Polioviruses.

CAG decisions/recommendations

GAPIII, Annex 1, **(changes to existing text are shown in bold)**:

Add the following definition:

Poliovirus nucleic acid: Nucleic acid* that has been extracted/purified using methods demonstrated to inactivate poliovirus can be handled outside of poliovirus containment under the condition that:

- **These materials will not be introduced into poliovirus-permissive cells or animals (as defined in GAPIII and the "Guidance for Non-Poliovirus Facilities") with or without a transfection reagent, except under appropriate containment conditions as described in GAPIII Annex 2 or Annex 3;**

***"Nucleic acid" refers to RNA, cDNA and total nucleic acid, extracted from poliovirus infectious materials (e.*g*., a virus isolate) or potentially infectious materials (*e.g*., stool, respiratory specimen, sewage), or synthesized RNA or cDNA RNA/cDNA (*e.g*., cDNA clone, synthetic transcript).**

Modify existing definitions as follows:

(a) Poliovirus infectious materials, wild (bullet point 7): full-length RNA or cDNA ~~that includes capsid sequences derived from wild poliovirus, unless viruses derived from them are demonstrably~~ **of viruses** proven to be safer than Sabin strains, **but that includes wild poliovirus capsid sequences**. The safety of these full-length RNA or cDNA ~~containing wild poliovirus capsid sequences~~ **and their containment requirements** will be assessed by an expert panel convened by WHO, on the basis of comparison to reference Sabin strains for (i) degree and stability of attenuation; (ii) potential for person-to-person transmission; and (iii) neurovirulence in animal models;

(a) Poliovirus infectious materials, OPV/Sabin (bullet point 7): full-length RNA or cDNA ~~that includes capsid sequences derived from OPV/Sabin strains~~ **of viruses proven to be safer than Sabin strains, but that includes OPV/Sabin poliovirus capsid sequences. The safety of these full-length RNA or cDNA and their containment requirements will be assessed by an expert panel convened by WHO, on the basis of comparison to reference Sabin strains for (i) degree and stability of attenuation; (ii) potential for person-to-person transmission; and (iii) neurovirulence in animal models.**

Priority Group II: Issues submitted by other stakeholders

Issue No. 5: Verification of room containment

Relevant GAPIII section

Annexes 2 and 3:

Subelement 12.3.1 (d): The containment perimeter is a defined working area sealable for gaseous decontamination and with sealed penetrations to prevent uncontrolled outward airflow. The containment perimeter is required irrespective of the choice of primary containment.

Statement of key issues raised

Describe the room pressure testing parameters and recommended allowed room leakage rates.

Summary of requests to CAG

GAPIII recommends containment measures to minimize the risk of release of polioviruses from facilities. However, GAPIII does not require room pressure testing, and it does not specify which additional standards need to be followed.

Summary of CAG discussions and conclusions

In some countries, some additional standards for containment have to be followed. GAPIII however does not require the facility to apply any additional standard to demonstrate meeting the intent of 12.3.1 (d). GAPIII will not be changed to meet this request.

CAG decisions/recommendations
GAPIII, Annexes 2 and 3:
Room pressure testing is not a GAPIII requirement unless the need to do so has been determined by a risk assessment, regulatory requirement or other similar instance.
Requirement 12.3.1 (d) 'The containment perimeter is a defined working area sealable for gaseous decontamination and with sealed penetrations to prevent uncontrolled outward airflow. The containment perimeter is required irrespective of the choice of primary containment.' of Annexes 2 and 3 was not changed.

Issue No. 6: Personal Protective Equipment (PPE)

Relevant GAPIII section
Annexes 2 and 3:
Element 7 Clothing and Personal Protective Equipment (PPE)
Subelement 7.1.1: PPE needs are identified
Subelement 7.1.2: Suitable equipment is specified, made available, used and maintained appropriately within the facility.

Statement of key issues raised
Clarify which poliovirus-specific PPE is needed to meet GAPIII requirements.

Summary of requests to CAG
The same PPE requirements seem to be required for facilities holding WPV or OPV/Sabin strains, while in reality, based on risk assessment, the PPE used may be different.

Summary of CAG discussions and conclusions
The wording in the requirements of Annexes 2 and 3 is identical in terms of PPE identification and use. However, the ultimate choice of PPE should be based on risk assessment and may be different depending on local needs and circumstances. GAPIII assumes that the organization is best placed to ensure that staff is provided with the right tools to minimize potential exposures, and that they know how and when to use them.

CAG decisions/recommendations
GAPIII, Annexes 2 and 3:
Element 7 Clothing and Personal Protective Equipment (PPE) of Annexes 2 and 3 was not changed.

Issue No. 7: Risk assessment vs. prescriptive requirements

Relevant GAPIII section
Annexes 2 and 3:
Element 12: Facility physical requirements

Statement of key issues raised
GAPIII recommends identifying appropriate risk mitigation measures based on thorough risk assessments (RAs). However, especially in terms of Element 12 Facility physical requirements, GAPIII provides a number of prescriptive requirements.

Summary of requests to CAG
Reconsider the need for prescriptive requirements when addressing facility physical features.

Summary of discussions and conclusions
GAPIII expects designated PEFs to develop very detailed risk assessments following recognized methodologies. However, multiple agencies will look at and evaluate these RAs, and considerable variations may be possible in terms of what are considered to be acceptable risk levels by different parties. CCS requires an independent review of the RA in case of deviations from GAPIII requirements for issue of an ICC. Given the criticality of risk assessments and potential for differing interpretation, expectations on RAs for containment certification may benefit from the development of RA guidance, possibly by the WHO secretariat. However, guidance on RAs is already available from different sources, and WHO's mandate is to support GCC and NACs, not PEFs. For this reason, and until further experience is collected through the issuance of CPs and ICCs following CCS, CAG did not make a formal request for WHO to develop specific RA guidance for containment needs, and recommended modifications in 12.3.1 (g) only, as described under Issue No. 1 above.

CAG decisions/recommendations
The prescriptive requirements in GAP III, Element 12 will remain valid. The following modification was recommended for Subelement 12.3.1 (g):

GAP III, Annexes 2 and 3, **(changes to existing text are shown in bold)**:
Modify Subelement 12.3.1 (g) of Annexes 2 and 3 to read as follows: 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 **not mandatory, other than** in the event of an uncontrolled breach of the primary containment equipment.

Issue No. 8: Location of HEPA filters

Relevant GAPIII section
Annex 2:
Subelement 12.3.1 (h): 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.

Statement of key issues raised
Clarify if the intent of this requirement is to prevent reversal of supply leading to a loss of containment and whether terminal HEPA filters at the containment barrier (that effectively isolate the ventilation system) would be acceptable.

Summary of requests to CAG
Consider alternative options meeting the intent of GAPIII, including the installation of a HEPA filter on supply.

Summary of CAG discussions and conclusions
Unprotected reversal of airflow is not desirable and should be avoided to assist preventing a breach of microbiological containment. If the solution proposed to prevent release through ventilation reversal is better than or equal to the backflow/draught measures indicated in GAPIII, meets the GAPIII requirement for 'backflow protection', and does not affect the intent of GAPIII, then this may be acceptable.

CAG decisions/recommendations
GAPIII, Annexes 2 and 3:

Subelement 12.3.1 (h) '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.' of Annex 2 was not changed .

Issue No. 9: Dedicated ventilation system

Relevant GAPIII section
Annex 2:
Subelement 12.3.1 (h): 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.

Statement of key issues raised
Clarification was sought on the definition of dedicated ventilation system.

Summary of requests to CAG
Clarify whether supply and exhaust air systems can be combined with areas of lower containment when provided with effective backdraft protection.

Clarify whether GAPIII means that the facilities have to have their own dedicated fans or whether the fans can used for other contained spaces provided there is a means of isolation of the ductwork (HEPA or backdraft protection).

Summary of CAG discussions and conclusions
It was clarified that the request to CAG referred to the supply and extract ventilation system from inlet to outlet serving a laboratory which in turn is dedicated to the handling of poliovirus or products harbouring poliovirus.

While in terms of ventilation plants different solutions may be conceivable, the term 'dedicated' in the context of GAPIII was recognized as referring to a totally independent unit that no other unit should interfere with.

The following clarifications were provided, and modifications to Subelement 12.3.1 (h) were not approved.

CAG decisions/recommendations
Ventilation systems shall be dedicated to the area defined as the poliovirus containment perimeter. These ventilation systems shall not serve other spaces which are not dedicated to the work with poliovirus. The dedicated ventilation systems shall include all supply and exhaust systems, including those serving primary containment isolators and other similar equipment to ensure these systems are not shared with areas beyond the poliovirus containment perimeter.

Subelement 12.3.1 (h) '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' of Annex 2 was not changed.

Issue No. 10: Backflow protection on gas services

Relevant GAPIII section
Annex 2:

Subelement 12.3.1 (i): The decontamination of all effluent (including shower water, eyewash, unsterilized autoclave condensate) from within the containment perimeter is achieved through validated inactivation procedure. Backflow prevention is implemented on all services/utilities entering the facility (water, gases) and via measures to prevent release through traps, sinks and shower drains.

Statement of key issues raised
Clarification was sought on the need for backflow protection on pressurized gas services.

Summary of requests to CAG
Clarify if backflow protection is indeed necessary on gas services as these are pressurized eliminating the need for backflow protection

Summary of CAG discussions and conclusions
Gas lines are not always pressurized. For this reason, a backflow protection should always be there.

CAG decisions/recommendations
GAP III, Annexes 2 and 3:
Subelement 12.3.1 (i) 'The decontamination of all effluent (including shower water, eyewash, unsterilized autoclave condensate) from within the containment perimeter is achieved through a validated inactivation procedure. Backflow prevention is implemented on all services/utilities entering the facility (water, gases) and via measures to prevent release through traps, sinks and shower drains.' of Annex 2 was not changed.

Issue No. 11: Documented records

Relevant GAPIII section
Annexes 2 and 3:
Subelement 1.4.2: Records, documents and data are handled in such a way that they remain legible, readily identifiable and retrievable.
Documented records are maintained in paper or electronic form for a minimum of 10 years from the day of withdrawal and should be available for review during national certification/WHO verification procedures.

Statement of key issues raised
Clarification was sought on the duration of required storage of commissioning documents.

Summary of requests to CAG
Modify the requirement to indicate that all commissioning documents be kept on file for the lifetime of the PEF (until 2 or 5 years after the PEF is decommissioned).

Summary of CAG discussions and conclusions
A number of documents should be kept for longer periods, including commissioning documents, certificates, calibration and maintenance documents and no conflict with such needs was identified by the existing clause

As the intent of this element in GAPIII is to have a process to identify and keep control over what is necessary, and considering the need to delete the last part of the paragraph, referring to WHO verification procedures already superseded by CCS, the following modifications to Subelement 1.4.2 were recommended.

CAG decisions/recommendations
GAP III, Annexes 2 and 3:

Modify Subelement 1.4.2 to read as follows: Records, documents and data are handled in such a way that they remain legible, readily identifiable and retrievable.
Documented records are maintained in paper or electronic form for a minimum of 10 years from the day of withdrawal and should be available for review during national certification~~/WHO verification~~ procedures.

Priority Group III: Issues that need to be addressed by other groups first, before they are discussed by the CAG e.g., at the Second Meeting of the CAG

Issue No. 12: Issues that need to be addressed by other groups first

A. Encourage newer safer technologies or newer strains for the production of polio vaccines and diagnostic reagents, and determine appropriate containment requirements for the handling of specific new strains (e.g. S-19 Sabin 2 containing Sabin 2 capsid sequence; nOPV strains)

Relevant GAPIII section
Introduction (last paragraph):
GAPIII is an evolving document, subject to revisions as new information emerges relevant to achieving the appropriate balance between community risk and the systems and controls to manage that risk. The poliovirus "Biorisk management standard" (Annexes 2 and 3) provides the framework for facility certification based on the principles of a biorisk management system. This standard requires the institution/facility to understand the risks associated with its activities and to manage those risks in ways acceptable to the national and international bodies responsible for the oversight of work with polioviruses. National authorities are responsible for reviewing the application of these risk management standards and principles in local circumstances. Although Annexes 2 and 3 are written specifically for wild polioviruses and OPV/Sabin strains, respectively, as they exist at the present time, should novel strains emerge that are considered to be more attenuated, less pathogenic and safer than OPV/Sabin strains, the evidence will be reviewed by a panel of scientific experts convened by WHO to consider the controls applicable to their containment and safe handling.

Statement of key issues raised
Different strains are being developed to move away from the use of WPV or Sabin strains for the development of vaccines or diagnostic reagents.
For example, strain S19 is designed not to infect people, and 2 current candidate nOPV strains are designed to infect and immunize people. However, currently GAPIII classifies them as WPV.

Summary of requests to CAG
Clarify the containment requirements for the new strains[10].

Summary of CAG discussions and conclusions
The Polio Research Committee (PRC) had already considered these strains and determined that additional testing in humans was needed for further assessment. Clinical trials with nOPV are ongoing in Belgium under containment conditions and results will be available around the end of the year 2017.

The need for a process to define containment requirements for new poliovirus strains was discussed. The development of a CAG Expert Support Group (CAG-ESG) to address these issues was proposed. The following membership was proposed: Mark Pallansch, George Griffin, Steven McAdam, including

[10] Minor PD, et al. (2017) Scientific consultation on the safety and containment of new poliovirus strains for vaccine production, clinical/regulatory testing and research. Report of a meeting held at NIBSC, Potters Bar, Hertfordshire, UK, 6/7th July 2016, Biologicals (2017), http://dx.doi.org/10.1016/j.biologicals.2017.05.001

additional external polio experts to be further identified. A suggestion was put forward for the CAG WG to have a face-to-face meeting early November 2017.

CAG decisions/recommendations
Create a CAG Expert Support Group (CAG-ESG) to consider containment requirements for the new strains and propose potential solutions to the CAG and other groups if necessary, for review and approval

Follow on action required
CAG secretariat to organize selection of CAG-ESG members, organize appropriate communication channels (meetings/TCs), report on activities and CAG-ESG's recommendations.

Actions taken and outcomes achieved (to be completed before next CAG)

B. Encourage new technologies for the production of polio vaccines (e.g. VLP)

Relevant GAPIII section
Title page:
After type-specific eradication and containment of wild poliovirus and cessation of oral polio vaccination, minimizing the risk of poliovirus reintroduction is critical. To prevent reintroduction, the number of international poliovirus facilities will need to be reduced to the minimum necessary to perform critical functions of vaccine production, diagnosis and research.

Statement of key issues raised
CAG should encourage the development of other low transmission techniques for the production of safe and efficient vaccines.

Summary of requests to CAG
Encourage low risk poliovirus vaccine techniques, including virus-like particles (VLPs)

Summary of CAG discussions and conclusions
This request should be addressed by the WHO Poliovirus Research Group (PRC).

CAG decisions/recommendations
Encourage the Polio Research Committee (PRC) to pursue their consideration of other vaccine options, including the development of VLPs, and inform CAG of research progress and developments.

Follow on action required
CAG secretariat to engage PRC in discussions and report on exchanges

Actions taken and outcomes achieved (to be completed before next CAG)

C. Immunization of facility personnel: maintaining mucosal immunity in facility operators post-bOPV cessation

Relevant GAPIII section
Table 1, footnote 2:
Since the operator is considered to be one of the sources of poliovirus release from the facility, specific protection measures are required, including, for example, the use of personal protective equipment (PPE), the use of primary containment devices and vaccination.

Statement of key issues raised
Shedding of virus by infected facility workers is a real risk, as shown in the latest release of WPV2 from a facility in the Netherlands (April 2017)[11]. One way to reduce this risk is to induce mucosal immunity protection in facility operators. However, when the use of OPV will be ceased and only IPV will be administered, mucosal immunity will no longer be achieved.

Summary of requests to CAG
Determine a strategy to prevent shedding of poliovirus in infected facility operators no longer vaccinated with OPV.

Summary of CAG discussions and conclusions
Discussions focused around the question of the future of IPV if prevention of shedding is the goal. CAG recommended that the SAGE polio WG address this question and provide recommendations to SAGE for their consideration.

CAG decisions/recommendations
Ensure that the SAGE polio WG addresses the consequences of reduced mucosal immunity in facility operators after OPV cessation and provides recommendations for the consideration of SAGE.

Follow on action required
CAG secretariat to ensure this discussion item is included in the agenda of the SAGE polio WG meeting of 12-13 Sep 2017 and report on SAGE polio WG's recommendations

Actions taken and outcomes achieved (to be completed before next CAG

D. Clarify what activities will be allowed at poliovirus-non-essential facilities tasked with poliovirus surveillance post-eradication

Relevant GAPIII section
Table 1: GAPIII containment safeguards at a glance

Statement of key issues raised
The table does not clarify what activities facilities receiving samples from suspected polio cases will be allowed to carry out outside of containment, before samples are referred to PEFs for further testing.

Summary of requests to CAG
Clarify what activities will be allowed in poliovirus-non-essential facilities, and indicate specific protocols, including on PCR detection of poliovirus.

Summary of CAG discussions and conclusions
The table focuses on the needs of PEFs in Phases II and III of GAPIII, addressed in Annexes 2 and 3 of GAPIII. Guidance for activities allowed at poliovirus-non-essential facilities is available from the Global Poliovirus Laboratory Network (GPLN)[12].

CAG decisions/recommendations
Ensure that appropriate guidance and relevant protocols are developed and published by the Global Polio Laboratory Network (GPLN).

---

[11] Duizer E, Ruijs WL, van der Weijden CP, Timen A. Response to a wild poliovirus type 2 (WPV2)-shedding event following accidental exposure to WPV2, the Netherlands, April 2017. Euro Surveill. 2017;22(21):pii=30542. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2017.22.21.30542

[12] Global Polio Laboratory Network, Guidance Paper 1 For safe handling and storage of type 2 poliovirus in GPLN laboratories (July 2016)

Follow on action required
CAG secretariat to follow up and report on progress.

Actions taken and outcomes achieved (to be completed before next CAG

E. Determine appropriate tests to demonstrate genetic stability of handled Sabin polioviruses, and define associated containment requirements

Relevant GAPIII section
Definitions:
Poliovirus, Sabin (OPV/Sabin strains): Attenuated poliovirus strains (approved for use in oral polio vaccines by national regulatory authorities, principally Sabin strains).

Poliovirus, OPV-like (last paragraph): The attenuated phenotype of viruses resulting from manufacture based on the OPV/Sabin seeds must be assured and cannot rely on the lack of sequence drift alone.

Statement of key issues raised
The statements in the definitions of Sabin strains affect how IPV based on OPV/Sabin strains should be produced and controlled. Sabin-IPV producers have to ensure that what they are using are effectively Sabin strains.

Summary of requests to CAG
Clarify what specific tests will demonstrate the genetic stability of master seeds, working seeds and production bulks.

Summary of CAG discussions and conclusions
This question of seed validation and required tests to be performed at different production stages should be submitted to ECBS and addressed by a TRS document first. Once the tests are determined, CAG can recommend containment requirements.

CAG decisions/recommendations
Share this request with the Expert Committee on Biological Standardization (ECBS) and specific Technical Report Series (TRS) working groups for consideration and action, before conclusions are shared with CAG for further advice on specific containment requirements.

Follow on action required
CAG secretariat to follow up and report on progress

Actions taken and outcomes achieved (to be completed before next CAG)

F. Develop a protocol to identify and deal with individuals, including facility operators, exposed to poliovirus and becoming infected

Relevant GAPIII sections
Annexes 2 and 3:
Subelement 10.2.2: Emergency planning covers all aspects of biorisk and includes general safety, security and medical issues.
A system is established to effectively manage a confirmed facility-associated poliovirus infection until the individual is free of poliovirus in stools for three consecutive days. This includes procedures for:

1. isolating infected individuals, particularly from children and the unimmunized;
2. collecting and disinfecting stool and associated waste;

3. educating families and frequent contacts on the risk posed by poliovirus infection and the procedures for isolation;
4. communicating with relevant national and local officials to evaluate the needs to implement community immunization response plans;
5. notifying WHO;
6. disinfecting areas potentially contaminated by infected individuals.

Subelement 10.3.1: Biorisks are taken into account when preparing and implementing emergency plans. A system is established to effectively manage incidents that are determined by the evaluation/response team to be significant poliovirus exposures, including:

1. implementing full preventive measures by isolating individuals under evaluation from children and the unimmunized in particular, and securing stool and associated waste;
2. educating individuals under investigation, their family and close contacts on the risk of poliovirus infection to the community, the procedures for diagnosis and the precautionary measures required to prevent possible transmission;
3. initiating procedures to determine whether individuals are infected, by collecting and testing nose, throat and stool specimens daily for a minimum of seven days post-exposure.

Statement of key issues raised
An infected individual could shed virus into the sewage system and infect close family contacts

Summary of requests to CAG
Address the timing and legality of interventions recommended in GAPIII.

Summary of CAG discussions and conclusions
While the management and control of infected individuals post-infection is under the ultimate responsibility of the country hosting the facility, this issues was raised based on the release of WPV through an infected facility operator in the Netherlands (April 2017)[13]. The WHO Polio Eradication programme (POL) is developing a post-exposure protocol to address such situations. In addition, IHR could be consulted to develop generic recommendations and guidance.

CAG decisions/recommendations
The CAG secretariat should approach the WHO Polio Eradication Department (POL) and the International Health Regulations (IHR) and ensure such guidance (post-exposure protocol) is developed and made available to stakeholders in due course.

Follow on action required
CAG secretariat to follow up and report on progress

Actions taken and outcomes achieved (to be completed before next CAG)

G. Guidance for the establishment of the National Authority for Containment (NAC)

Relevant GAPIII section
Phase implementation:
Countries or concerned facilities may apply through their national authorities for WHO verification of poliovirus-essential facilities, certified by the MoH or another designated national authority, and declared to meet all biorisk management criteria consistent with Annex 2 or 3 (Annex 4).

[13] Duizer E, Ruijs WL, van der Weijden CP, Timen A. Response to a wild poliovirus type 2 (WPV2)-shedding event following accidental exposure to WPV2, the Netherlands, April 2017. Euro Surveill. 2017;22(21):pii=30542. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2017.22.21.30542

Statement of key issues raised
GAPIII does not address the establishment of the NAC, responsible for containment certification of PEFs against GAPIII.

Summary of requests to CAG
Provide additional guidance on the establishment of the NAC and on options for PEFs if such an authority cannot be nominated.

Summary of CAG discussions and conclusions
CCS was endorsed by SAGE and published in October 2016 and supersedes Annex 4 of GAPIII. This means that NACs are fully responsible for containment certification of their designated PEFs. Currently, WHO does not have a specific mandate to inspect facilities and verify the implementation of GAPIII. Through GAPIII, WHO recommends that countries that cannot nominate a NAC and cannot take on the responsibility of containment certification of facilities retaining polioviruses against GAPIII, should not host such facilities.

CAG decisions/recommendations
Guidance for the establishment of NACs is available in CCS.

Follow on action required
CAG secretariat to provide clarifications in consultation with individual countries

Actions taken and outcomes achieved (to be completed before next CAG)

H. Include in GAPIII 'Inventory, destruction or preparation for containment of poliovirus **types 1 and 3'**

Relevant GAPIII section
Overview of phases

Statement of key issues raised
GAPIII does not specify Phase I activities in preparation for containment of poliovirus types 1 and 3.

Summary of requests to CAG
Consider the inclusion of a Phase I for poliovirus types 1 and 3.

Summary of CAG discussions and conclusions
The timing to start surveys and inventory activities in search for WPV1 and 3, and VDPV1 and 3, needs to be defined.

CAG decisions/recommendations
The CAG secretariat should ensure that GCC discusses and clarifies the timing to start and complete Phase I activities for poliovirus types 1 and 3.

Follow on action required
CAG secretariat to ensure GCC addresses this point at the GCC meeting of 4-5 July 2017

Actions taken and outcomes achieved (to be completed before next CAG)
A containment-dedicated GCC meeting is planned to be organized before the 2nd CAG meeting so that GCC can appropriately address this request. CAG secretariat to further report on GCC's recommendations in due course

Priority Group IV: Issues that do not need input from CAG, but require short clarification

Issue No. 13: Items under column 'Guidance' in Annexes 2 and 3

Relevant GAPIII section
Annexes 2 and 3:
Items described in the column 'Guidance'

Statement of key issues raised
Some of the items listed in the column 'Guidance' of Annexes 2 and 3 on GAPIII cannot be followed or implemented

Summary of requests to CAG
Revise the 'requirements' under the column 'Guidance'

Summary of CAG discussions and conclusions
As the title of the column suggests, information provided in the column 'Guidance' of Annexes 2 and 3 is made available for guidance purposes only, and should not be considered as a requirement. PEFs will not be assessed against the implementation of items listed in the column 'Guidance'.

CAG decisions/recommendations
CAG provided the following clarification: Information in the column 'Guidance' of Annexes 2 and 3 does not constitute conformity requirements. This information should be read and understood by PEFs, but where appropriate alternative measures may be set in place to demonstrate compliance against requirements. Where alternative measures have been selected or areas in guidance have not been proactively addressed, the PEF should be able to provide a relevant justification where necessary.

Issue No. 14: Outsourced work

Relevant GAPIII section
Annexes 2 and 3:
Subelement 12.3.1

Statement of key issues raised
Organizations, including contract testing organizations supplying services for which the use of live poliovirus is necessary, may not be able to meet GAPIII requirements.

Summary of requests to CAG
Clarify which facilities have to comply with GAPIII, and who, in the absence of containment-certified QC facilities, should perform QC tests in specific countries.

Summary of CAG discussions and conclusions
GAPIII specifies requirements for all facilities retaining polioviruses, irrespective of the activities these facilities intend to carry out. All facilities handling polioviruses, including contract testing organizations, QC labs, etc. are requested to meet GAPIII requirements and are expected to be certified against GAPIII implementation.

CAG decisions/recommendations
NACs should ensure that all facilities retaining polioviruses are certified against GAPIII, whether or not the work has been outsourced.

Priority Group V: Issues for consideration at the Second Meeting of the CAG

Issue No. 15: Issues requiring "Guidance for non-poliovirus facilities to minimize risk of sample collections potentially infectious for polioviruses"

Relevant GAPIII sections

Definitions:

Poliovirus potentially infectious materials, wild: These include:

- faecal or respiratory secretion samples collected for any purpose in a time and geographic area of wild poliovirus (including VDPV) circulation;
- products of such materials from poliovirus permissive cells or animals;
- uncharacterized enterovirus-like cell culture isolates from countries known or suspected to have circulating wild poliovirus or VDPV at the time of collection;
- respiratory and enteric virus stocks handled under conditions where poliovirus contamination or replication is possible.

Poliovirus potentially infectious materials, OPV/Sabin: These include:

- faecal or respiratory secretion samples collected for any purpose in a time and geographic area of OPV use;
- products of such materials from poliovirus permissive cells or animals;
- respiratory and enteric virus stocks handled under conditions where OPV/Sabin strain contamination or replication is possible.

Rationale:

Most countries will have no need to retain live polioviruses in the post-eradication and post-OPV era. Facility-associated risks in these countries can be eliminated by a thorough nationwide search for and destruction of all WPV and all OPV/Sabin infectious and potentially infectious materials.

Strategy:

Risk elimination in poliovirus-non-essential facilities is achieved through the destruction, or transfer to poliovirus-essential facilities, of:

1. infectious and potentially infectious WPV materials;
2. OPV/Sabin materials

Statement of key issues raised

Revise the definitions of poliovirus PIM in light of their implications and impacts on PEFs and NACs. Address the issue and the evidence supporting the request to eliminate or contain respiratory samples potentially infected with poliovirus. Develop and endorse guidance to help non-polio facilities identify and appropriately handle and store poliovirus potentially infectious materials, in support of the completion of Phase I of GAPIII.

Summary of requests to CAG

Clarify requirements for destruction or containment of samples potentially infectious with poliovirus.

Summary of CAG discussions and conclusions

A brief presentation was provided of the draft Guidance for non-poliovirus facilities to minimize risk of sample collections potentially infectious for polioviruses that is being finalized to assist non-poliovirus facilities identify poliovirus PIM in their possession and implement appropriate risk reduction consistent with GAPIII. It was explained that next steps for this document would include the following:

a) Include CAG recommendations on the handling of poliovirus genetic materials into a next draft
b) Post the next draft on the web for public comments and pilot testing
c) incorporate comments and pilot test results into a further revised draft
d) submit to CAG for endorsement at the Second CAG Meeting planned in Nov 2017

e) publish the final document.

CAG decisions/recommendations
Finalize the document *Guidance for non-poliovirus facilities to minimize risk of sample collections potentially infectious for polioviruses*, in view of its consideration and endorsement at the next CAG meeting, planned for end-November 2017.

Issue No. 16: Issues to be addressed at the 2nd CAG meeting

Statement of key issues raised
CAG agreed that some of the questions submitted to the first CAG meeting for consideration need to be addressed by different groups first, as described under Priority group III above.
At the next CAG meeting, priority is expected to be given to discussions on containment requirements for new poliovirus strains described under Issue 12A above.

Summary of requests to CAG
At the 2nd CAG meeting, address issues described under Priority group III above, based on feedback received from the identified 'other groups'.

Summary of CAG discussions and conclusions
CAG agreed for the secretariat to share issues raised under Priority group III above with the identified 'other groups', and provide feedback to CAG in advance of discussions planned at the next CAG meeting

CAG decisions/recommendations
The CAG secretariat should collect feedback from other groups on issues described under Priority group III above, for discussions and deliberations at the next CAG meeting, planned for end-November 2017.

Other Issues discussed at the 1st CAG meeting

Working relationship between the Global Commission for the Certification of Poliomyelitis Eradication (GCC), its Containment Working Group (GCC-CWG) and the Containment Advisory Group (CAG)
According to the selection criteria for CAG and GCC CWG, members of one group cannot be members of the other group. For this reason, representatives from GCC and GCC-CWG will be invited to attend CAG meetings in the capacity of observers or liaison officers, but not as full CAG members.

Dates for the Second Meeting of the CAG
The following dates and location have been identified and agreed for the Second Meeting of the CAG: 28-30 Nov 2017, WHO, Geneva, Switzerland. The three-day meeting will allow to provide additional orientation to members in terms of GAPIII and CCS, and the broader context and wider implications of requests submitted to the CAG.